



**REPUBLIC OF TURKEY
ADANA ALPARSLAN TÜRKESİ SCIENCE AND TECHNOLOGY
UNIVERSITY**

**GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF BIOENGINEERING**

**INTEGRATIVE AND COMPARATIVE OMIC APPROACHES TO
IDENTIFY MOLECULAR SIGNATURES OF
RHEUMATOID ARTHRITIS**

**BETUL COMERTPAY
MASTER OF SCIENCE**



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**SUPERVISOR
ASST. PROF. DR. ESRA GÖV**

ADANA 2020

Integrative and Comparative Omic Approaches to Identify Molecular Signatures of Rheumatoid Arthritis

submitted by **Betul COMERTPAY** in partial fulfillment of the requirements for the degree of **Master of Science in Department of Bioengineering, Adana Alparslan Türkeş Science and Technology University** by,

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I hereby declare that all information in this thesis has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all information that is not original to this work.

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Betul COMERTPAY

ABSTRACT

INTEGRATIVE AND COMPARATIVE OMIC APPROACHES TO IDENTIFY MOLECULAR SIGNATURES OF RHEUMATOID ARTHRITIS

Betul COMERTPAY

Department of Bioengineering

Supervisor: Asst. Prof. Dr. Esra GÖV

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Rheumatoid arthritis (RA) frequently seen chronic synovial inflammation causing joint destruction, chronic disability, and reduced life expectancy. The pathogenesis of RA is not completely known. In this study, several gene expression data including synovial tissue and macrophages cells, blood cells, T, CD4⁺ T, CD8⁺ T cells, natural killer T (NKT) cells, natural killer (NK) cells, neutrophils, and monocytes were analyzed with a holistic and comparative perspective and the molecular targets and signatures in RA were determined. Differentially expressed genes (DEGs) were identified from each dataset by comparing diseased and healthy samples. Afterward, the RA-specific protein-protein interaction (PPI) and hub proteins were identified. Molecular signatures were determined through a statistical test employing the hypergeometric probability density function by using the physical interactions of transcriptional regulators and PPI. Reporter metabolites of each tissue with RA were determined by using genome-scale metabolic networks and DEGs. It was determined the common hub proteins, novel reporter biomolecules (i.e. receptor, transcription factors, and miRNAs), metabolites in two or more tissue types. It was identified SOCS2 Cullin family members CUL1 and CUL3, HDAC family members HDAC2, HDAC4, HDAC9, RAS members KRAS, HRAS and NRAS, OCS family members SOCS1 and SOCS2, as hub proteins, AR, FOXP3 and GATA2 as TFs, NADP⁺ NADPH, ADP, pyruvate, and Acetyl-CoA members as a reporter biomolecule. Importantly, miR-155-5p is common miRNAs in all tissues.

Our findings could be a crucial resource for the understanding of RA molecular mechanisms and may be considered as drug targets and development of novel diagnostic strategies. Corresponding genes and miRNAs should be validated via experimental studies.

Keywords: Rheumatoid arthritis, omics approaches, network medicine, transcriptome



ÖZET

ROMATOİD ARTRİT HASTALIĞINDA MOLEKÜLER İŞARETÇİLER BELİRLEMEDE BÜTÜNCÜL VE KARŞILAŞTIRMALI OMİK YAKLAŞIMLAR

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Romatoid artrit (RA) sıklıkla kronik sinovyal inflamasyonun eklem yıkımına, kronik sakatlığa ve yaşam beklentisinin azalmasına neden olduğu görülür. RA'nın patogenezi tam olarak bilinmemektedir. Bu çalışmada, sinovyal doku ve makrofaj hücreleri, kan hücreleri, T hücreleri, CD4⁺ T hücreleri, CD8⁺ T hücreleri, doğal öldürücü T (NKT) hücreleri, doğal öldürücü (NK) hücreleri, nötrofiller ve monosit hücreleri dahil olmak üzere çeşitli gen ekspresyon verileri bütüncül bir bakış açısıyla analiz edilerek RA'daki moleküler hedefler ve imzalar belirlendi.

Farklı olarak ifade edilen genler (DEG'ler), hastalıklı ve sağlıklı numunelerin karşılaştırılmasıyla her bir veri kümesinden tanımlandı. Daha sonra, RA'ya özgü protein-protein etkileşimi (PPI) ve hub proteinler tanımlandı. Moleküler imzalar, transkripsiyonel düzenleyiciler ve PPI 'in fiziksel etkileşimleri kullanılarak hipergeometrik olasılık yoğunluk fonksiyonunu kullanan bir istatistiksel test yoluyla belirlendi. RA'lı her dokunun raportör metabolitleri, genom ölçekli metabolik ağ ve DEG'ler kullanılarak belirlendi. Ortak hub proteinleri, yeni raportör biyomolekülleri (yani reseptör, transkripsiyon faktörleri ve miRNA'lar), veya daha fazla doku tipindeki metabolitler belirlendi. SOCS2 Cullin ailesi üyeleri CUL1 ve CUL3, HDAC ailesi üyeleri HDAC2, HDAC4, HDAC9, RAS üyeleri KRAS, HRAS ve NRAS, OCS aile üyeleri SOCS1 ve SOCS2, hub protein olarak, AR, FOXP3 ve GATA2, TFs olarak NADP, NADPH, muhabir biyomolekül olarak ADP, piruvat ve Asetil-CoA üyeleri belirlendi. Önemli olarak, miR-155-5p tüm dokularda ortak miRNA' dır.

Bulgularımız, RA' nın moleküler mekanizmasının anlaşılması için çok önemli bir kaynak olabilir ve ilaç hedefleri ve yeni tanı stratejilerinin geliştirilmesi olarak düşünülebilir. İlgili genler ve miRNA'lar deneysel çalışmalarla doğrulanmalıdır.

Anahtar Kelimeler: Romatoid artrit, omik yaklaşımlar, ağ tıbbı, transkriptom





dedication

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NOMENCLATURE

ACPA	:	Autoimmunity to citrulline proteins
circRNAs	:	Circular RNAs
DEG	:	Differentially expressed gene
DNA	:	Deoxyribonucleic acid
ELMO1		Engulfment and Cell Motility Protein-1
FLS	:	Fibroblast-like synoviocytes
GEO	:	Gene Expression Omnibus
GWAS	:	genome-wide association studies
HLA	:	human leukocyte antigens
HTRIdb	:	Human Transcriptional Regulation Interactions database
IFN- γ	:	Interferon-gamma
IL	:	Interleukin
KEGG	:	Kyoto Encyclopedia of Genes and Genomes
MEGs		Multiple evidence genes
mRNA	:	Messenger ribonucleic acid
NK	:	Natural killer
NKT	:	Natural killer T
OA	:	Osteoarthritis
PPI	:	protein-protein interaction
RA	:	Rheumatoid arthritis
RNA-seq	:	RNA sequencing
SF	:	Synovial fibroblasts
SOCS	:	Suppressors of cytokine signal
SuppTl		Supplementary Table
TF	:	Transcription factor

1. INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease characterized by polyarthritis and causes chronic synovial inflammation that eventually leading to joint destruction and disability (Deodhar & Woolf, 1996). RA affects 0.5% to 1% of the world's population and causes severe pain, stiffness, functional limitation, poor quality of life, and work disability (Mertens & Singh, 2009). Recently, despite the rapid advances in RA treatment, the etiology of RA has not been fully understood (Maeda & Takeda, 2019). RA is a complex disease, with variable clinical outcomes and pathogenetic mechanisms involved between patients with the similar diagnosis or different disease stages (Smolen et al., 2018). Rapid diagnosis and effective treatment are crucial to prevent functional disability, joint disruption, and adverse disease consequences. The effective treatment strategy in RA is generally required within 3-6 months after the onset of the disease. Therefore, it is difficult to achieve remission with this disease. Genetics, autoimmunity and environmental factors create the "Bermuda triangle" of RA, which triggers the formation of the underlying synovitis. Inheritance of RA is estimated to be approximately 60%. According to Kurko and co-worker, genetic factors, including MHC class II cell surface receptor/ human leukocyte antigens (HLA-DR) and non-HLA genes play a role in the progression of RA (Kurkó et al., 2013). Besides, combinations of genetic and environmental factors have been reported in the development of RA. The compliance rates for RA in studies in monozygotic twins are ~ 15%. This suggests that environmental factors are crucial for the development of RA (Maeda & Takeda, 2019). Exposure to many environmental factors such as microbiota, smoking, infections, and, hormones can play a role in the induction of the RA (Tracy et al., 2017). Studies in mice have shown that, among the environmental factors, gut microbiota plays an crucial role in the pathogenesis of arthritis (Kim et al., 2017). Besides, antimicrobial drugs such as minocycline or salazosulfapridine are reported as an effective drugs in some RA patients. This supports the relationship between RA, oral microbiota, and gut (Maeda & Takeda, 2019). High levels of anti-cyclic citrullinated peptide antibodies in individuals indicate a high risk for RA and correlated with the radiographic progression of patients (Venrooij et al., 2008). Biomarkers determined from peripheral blood such as rheumatoid factor and anti-cyclic citrullinated peptide antibodies have been reported to be generally specific and predict RA development in 70-80% of asymptomatic people (Orr et al., 2017). Furthermore, HLA and some non-HLA

genes have been associated with autoimmunity to citrulline proteins (ACPA) as well as smoking. Environmental factors, smoking, and lifestyle factors can trigger ACPA production and the formation of ACPA seropositive RA, at least in some cohorts, and need to do with the disease results and prognosis of some genes (Kurkó et al., 2013).

In recent years, a lot of researches have been made to understand the pathogenesis of RA mechanism and to identify diagnostic and prognostic gene or protein targets. However, disease-specific and prognostic and therapeutic biomarkers were still not available, and the interactions and relationships between gene products have been ignored in many studies. The integration of biological data with biomolecular omic- networks at any level provides valuable information about the illumination of disease mechanisms and the identification of molecular signatures of human disease.

Here, we analyzed eleven gene expression datasets including synovial tissues, macrophage cells, blood, CD4⁺T, CD8⁺ T, T, NK, NKT cells, monocytes, and neutrophils with RA patients by comparing healthy group. Advanced statistical approaches were performed each dataset to identify DEGs. Common DEGs in all datasets were identified which was named as core DEGs and PPI, transcriptional regulatory networks were reconstructed through these core genes. Molecular signatures (i.e.: receptor, TFs, miRNAs) were determined via a statistical test employing the hypergeometric probability density function by using the physical interactions of biomolecules and PPI. Gene set enrichment analyses were performed to determine the biological insights of the resultant DEGs. It was presented that the novel molecular signatures might give crucial directions for RA disease diagnosis and treatment strategies.

2. Literature Review

2.1. Expression profiling of mRNAs and miRNAs

Transcriptomic studies measure the mRNA levels of all genes and identify genes that are differentially expressed between two conditions such as health and disease. Recently, tissues with RA have been analyzed at the transcriptome level such as Ye et al. analyzed gene expression of CD4 positive T cells in healthy and diseased samples (Ye et al., 2015). Their study showed that CD4 positive T cells are highly related to the STAT3 signalling and Wnt signalling pathway in the RA pathogenesis. Also, their results suggest that ZEB1, ZNF292, and ZNF644, zinc finger transcription factors (TFs), may be taken an active role in the development of RA. In another study, Ekwall et al. demonstrated that LBH is a key candidate gene in synovial tissues with RA and it is highly correlated with growth factors by using microarray techniques (Ekwall et al., 2015). Ouyang et al. worked on five circular RNAs (092516, 003524, 103047, 104871, and 101873) via microarray screening in healthy individuals and patients with RA. It was determined that they were significantly elevated in peripheral blood mononuclear cells with RA (Ouyang et al., 2017). Transcriptional regulators of gene expression act a pivotal role in the regulation of many fundamental cellular processes. Disease-specific transcriptional regulators give crucial information about key gene expression profiles. Some of the TFs were considered as molecular signatures or drug targets in the treatment of RA. In a study, it was demonstrated that expression of NFAT5 which is a TF in macrophages supports apoptotic resistance to activated macrophages by inducing secretion of CCL2 that is a chemokine in both human and murine macrophages (Choi et al., 2017). In another study, they determined that YY1, a TF, was up-regulated in RA patients and collagen-induced arthritis mice. Furthermore, they observed that blocking of YY1 decreased IL-6 production and downregulation of the Th17 population (Lin et al., 2017).

Recent decades, studies have shown that miRNAs play a major role in several important biological processes involves early cell growth, differentiation, apoptosis, death, fat metabolism, aging, signal transduction, viral infection, etc (Bartel, 2004; Y. Huang et al., 2011). Many studies have reported that miRNAs are highly connected to many complex human diseases including RA. Considering the regulatory role of miRNAs in disease states is very crucial to understand the molecular mechanism of RA. In the past years, miRNAs are dysregulated in RA patients. In the study of Mu and colleagues, NF- κ B / YY1 / microRNA10a

regulatory circuit in fibroblast-like synoviocytes (FLS) has been shown to regulate inflammation in RA (Mu et al., 2016). In another study, MicroRNA-143 and -145 have modulated the phenotype of synovial fibroblasts in RA (Hong et al., 2017). Besides, Rajasekhar and co-workers show that MicroRNA-155 has patients with RA contribute to increased resistance to apoptosis in monocytes (Rajasekhar et al., 2017). Therefore, it might be an important resource that accumulates disease-related miRNAs that could be used for the diagnosis, treatment, and prevention of RA disease.

2.2. Significant biological pathways in RA

Understanding the underlying signal pathways is essential in disease research because of the significant regulatory roles these pathways play in a great number of cellular events, including RA pathogenesis and formation.

In the recent study of Wei and co-workers reported that, the deletion of Notch3 gene or blockade of the NOTCH3 signalling pathway reduces inflammation and prevent joint damage in mice with inflammatory arthritis. These comes about show that synovial fibroblasts show a positional identity regulated by endothelium-derived Notch signaling pathway and stromal relationship is about inflammation and inflammatory arthritis (Wei et al., 2020). Guo and co-workers have demonstrated that the immune checkpoint inhibitor PD-1 pathway is down-regulated in the synovium at various stages of the pathogenesis of RA disease. RA patients have been shown to express PD-1 in most synovial tissues infiltrating CD4 and CD8⁺ T cells. Enrichment of gene signatures has been resulted in inflammatory arthritis and RA, this demonstrated that the PD-1 pathway was downregulated during the progression of RA disease. Also, serum-soluble PD-1 were altered as higher level in autoantibody-positive early RA patients. Besides, lots of the early RA synovium tissue sections have been shown to have negative PD-L1 staining via immunohistochemistry. The results supported downregulation in PD-1 inhibitory signals in RA, increased connectivity to serum sPD-1, and decreased PD-L1 levels in synovial tissues (Guo et al., 2018).

2.3. Integrative computational biology approaches in RA

The development and advances of high-throughput technologies that provide functional genomic datasets provides an opportunity to make an integrated analysis in RA research. However, to date, the available literature does not include the integrative analysis for tissue-

specific-RA. A few studies have utilized integrative network analyses to present context-specific network models in RA.

Ma and co-workers used the weighted gene co-expression network analysis method, which aims to identify RA-related genes based on microarray data, with 26 RA and 17 control groups. A total of 599 gene signatures were determined. These genes are mainly inflammatory response (CD97, C3AR1, CXCL1, CCR1, LYZ, etc.) immune response (CD97, CCR1, CXCL1, FYB, IKBKE, etc.), and homeostasis (C3AR1, CCR1, CCL19, PLN, PPT1), etc. Besides, sanguinarine and papaverine, small-molecule drugs, were determined as therapeutic potential of RA (Ma et al., 2017). In another study, to clarify the main role of miRNAs in the rheumatoid cytokine network, it was shown that miR-155 participates to regulation of TNF- α and IL-6 mediated inflammatory pathways in RA. It was also shown that TNF- α modulates miRNA expressions in rheumatoid synovial fibroblasts. Besides, miR-155 which is highly induced by TNF- α stimulation, inhibited IL-6 mediated JAK2 / STAT3 activation in rheumatoid synovial fibroblasts (Migita et al., 2017). Another example, Traylor et al., in their study combined with seven genome-wide association studies (GWAS) (2,775 RA cases of a series of ancestors) in this meta-analysis, RA associated genetics with radiological damage. The single nucleotide polymorphism relationships with radiological damage were tested at a single time point through regression models. As a result of meta-analysis, HLA-RB1 confirmed the known relationship between shared epitope and RA radiological damage (Traylor et al., 2019).

In the study of the identification of novel candidate genes for RA, RNA sequencing- (RNA-seq) -based expression analysis of 377 genes from previously confirmed RA-related loci was performed in the blood cells of 5 newly diagnosed patients, untreated RA patients, 7 patients with treated RA, and 12 healthy controls. The study showed the integration of RNA-seq data with findings from association studies and the resulting path analysis showed novel candidate genes, TP53, ERBB2, and THOP1 in the RA (Shchetynsky et al., 2017). Afroz et al. performed a meta-analysis of the gene expression data set of 8 studies (107 patients with RA and 76 healthy controls). Common 33 differently expressed genes were significantly identified in all data sets. The meta-analysis revealed the upregulation of several novel gene signatures, such as CYFIP2, EIF4E2, PLCG2, HLA-DOB, and HLA-F validated in peripheral blood mononuclear cells with RA. Also, functional enrichment analysis demonstrated the disruption of several common genes involved in the hypoxia, inflammatory, antigen presentation, and apoptosis signaling pathways

in RA. Besides, PLCG2 has been proposed as a potential therapeutic target to control the excessive inflammation during RA (Afroz et al., 2017).

2.4. RA meet integrative multi-omics science

Numerous molecules organized in cells perform specific biological functions in living organisms. Each multicellular organism contains different types of cells in organs and tissues during development. The basic instructions for each organism are encoded in the DNA sequence consisting of adenine, guanine, thymine, and cytosine nucleotide type in eukaryotic organisms. DNA is a double helix structure that contains a linear sequence of approximately 3 billion nucleotide bases in humans. DNA molecules are arranged as chromosomes inherited from parents after molecular recombination of parental chromosomes in the meiosis division process. Approximately 1% of the genome encodes the sequence for about 20,000 genes that indicate proteins. Messenger ribonucleic acid (mRNA) is copied from the DNA of these protein-coding genes. mRNA is translated into proteins composed of amino acids; proteins are the primary building blocks of cells. Thus, the central dogma of molecular biology: DNA is copied to RNA and converted into RNA protein.

To determine a comprehensive set of interactions between genes and proteins, it is important to develop large-scale datasets that capture the biological activities of cells (Figure1.1). All of these -omic approaches require substantial bioinformatics support and advanced statistical analysis.

Transcriptomics was made feasible by microarray assays, which allowed the identification of thousands of expressed transcripts in one experiment. A probe attached to an array of platforms is used to query selected RNA types. Various mRNA types are the focus of these assays, but microRNA and other RNA types can also provide valuable information. Transcriptomic studies are conducted with RNA-seq, which does not require the capture of specific RNA transcripts to perform quantitation (Loscalzo et al., 2017).

Proteomic studies can supply integral information to transcriptomics because the correlation between mRNA and protein levels in one cell or another biological sample is generally surprisingly low. In addition to measuring protein levels, post-translational protein modifications can be evaluated (Loscalzo et al., 2017; Rolland et al., 2014).

The development of reliable, highly efficient assay systems for large metabolite panels has allowed metabolomic studies. Metabolomics can reflect most of the cellular functional activities and provide information about dynamic changes in a biological system, such as metabolite transformation events known as “flux”. While untargeted, comprehensive metabolomics typically contain quantitative evaluations of a large number of metabolites, including unidentified analytes, while targeted metabolomics focus on measuring a pre-selected set of metabolites (Loscalzo et al., 2017).

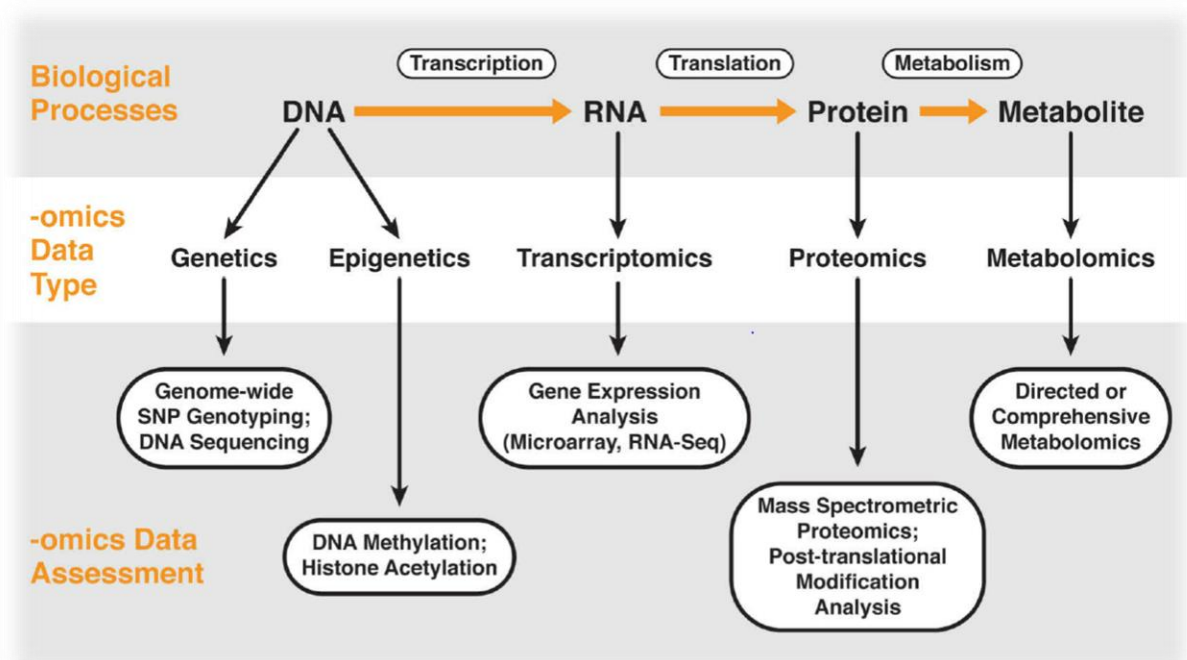


Figure1.1 Demonstration of basic biological processes and related omics data types (Loscalzo et al., 2017)

2.5. Human transcriptional regulatory network

Transcriptomic studies measure the mRNA levels of all genes and identify genes that are differentially expressed between two conditions such as health and disease. RA has been increasingly analyzed at the transcriptome level.

In the RA transcriptomic study to investigate the similarities and differences between tissue lines, Harshan et al., constructed a network that captured signal flow leading to osteoclast differentiation, and based on gene expression analysis, demonstrated potential mechanisms responsible for the phenotype in the synovium affected by RA. This network displays the progression about the activation of the neutrophil cytosolic factor complex concerning osteoclastogenesis, the canonical pathway of NF- κ B activation in the synovium with RA. It was

also showed that the upregulation of the T cell receptor signal and downregulation of the transforming growth factor-beta signaling pathway triggers osteoclastogenesis in RA (Harshan et al., 2018). Such as, Ye and co-worker analyzed CD4⁺ T cell transcriptome in a healthy and diseased group of RA. Their study shows that in the RA patients CD4⁺ T cells are highly related to STAT3 signalling and Wnt signalling. Also, their results suggest that ZEB1, ZNF292, and ZNF644 zinc finger transcription factors may be an active role in the pathogenesis of RA (Ye et al., 2015). In another study, Ekwall et al., have used three different data sets (i.e: risk genes in RA, differentially expressed genes, and differential DNA methylation) in RA versus osteoarthritis (OA). Firstly, synovial tissue samples taken from patients with RA and with OA were collected. Then, LBH (limb bud and heart development) expression was silenced by using small interfering RNA or overexpressed in the primary FLS using an LBH expression vector. Moreover, the altered LBH expression were investigated via experiments. As a result of the study, LBH was determined as the candidate gene in RA (Ekwall et al., 2015).

2.6. Protein-protein interaction in RA

Protein-protein interaction (PPI) is significant for almost every biological process in a cell and disease-specific PPI has a crucial role in the comprehending of disease progression and pathogenesis (Barabási et al., 2011).

Malavia et al. compared the lists of single nucleotide polymorphisms with significant genetic relationships for schizophrenia and RA. It was determined that single nucleotide polymorphisms that determined as risk for both schizophrenia and RA were only placed into to the extended HLA region. The majority of single nucleotide polymorphisms were localized in HLA-B, HLA-C, TNXB, NOTCH4, HCP5, PSORS1C1, MICB and C6orf10. The PPI was reconstructed by using these genes and PPI information. Single nucleotide polymorphisms of the resultant genes were determined that are closely related to RA and schizophrenia-related genes via common interacting partners (Malavia et al., 2017). In another study, Panga et al. examined the involvement of mitochondria cell organelle in dysfunction when moving the nuclear DNA encoded protein to mitochondria during RA. By analyzing six synovial transcriptome datasets of RA patients and samples of healthy people, identified differentially expressed nuclear DNA genes which encode mitochondrial proteins. Then, by employing gene co-expression from gene expression data formed the mitochondrial PPI network that was specific to the RA synovial joint tissue identified differentially expressed neighbors of the hub

proteins. The results demonstrated that nDNA-encoded proteins are crucial for the elevation of mitochondrial reactive oxygen species and take a role in metabolism, membrane potential, transport processes, and apoptosis during RA (Panga et al., 2019). Moreover, Hayashi and colleagues conducted an HPLC/mass spectrometry-based proteomic analysis on laser-micro-dissected synovial tissues with RA and osteoarthritis as the control. Network analyses of PPI were applied and the ribosome pathway and p53 signalling were enriched. As a result of the study, it was supported that known RA biomarkers such as stromelysin-1 and S100-A8 and S100-A9 proteins as well as leukocyte antigens such as HLA-DRB1 were included. Besides, it was observed that in the network analysis of PPI for proteins significantly important for RA, the dominant involvement of the ribosome pathway and interestingly p53 signaling. Additively, it was suggested that the resultant proteins, including CD14, S100-A8, S100-A9, can function as an activation of the NF- κ B / MAPK signal pathway (Hayashi et al., 2015). In another study, Whitaker, and co-worker, independently coordinated gene groups involved in RA pathogenicity through three GWAS and differential methylation in fibroblast-like synoviocytes (FLS). The integrated analysis of these datasets determined that multiple evidence genes (MEGs) enriched significantly in the pathways associated with RA pathogenicity. Engulfment and Cell Motility Protein-1 (ELMO1) was identified as a MEG was not previously considered a therapeutic target in RA- FLS. In RA-FLS, ELMO1 has been shown to promote cell migration and invasion, and regulate Rac1 activity. It was reported that the association between ELMO1 and RA pathogenicity, ELMO1 could be a therapeutic biomolecules in RA (Whitaker et al., 2015).

2.7. Metabolome in RA

A metabolic network uses metabolic data to understand the physiological and biochemical properties of a biospecimen, end in metabolic pathways give rise to a disease state. The metabolome is a complement to tinny molecular weight (<2000 amu) molecules in a biological sample or organism. Metabolomic molecules contain carbohydrates, sugars, fatty acids, lipids, nucleotides, amino acids, and short peptide chains. The amount in number to metabolites is still unknown and changes by the biological sample. As technology improves and sensitivity grows, the number of identified metabolites keeps going to increase (Loscalzo et al., 2017).

Carlson et al. analyzed the metabolomic profiles of 3 RA synovial and 5 healthy synovial fluids to test the use of metabolomics by liquid chromatography-mass spectrometry for clinical

analysis of synovial fluid. A total of 1018 metabolites were appointed by LC-MS analysis in synovial fluid in RA and healthy patients, and 162 metabolites were significantly different between diseased and healthy. The upregulated pathways with the disease included alpha-linolenic acid metabolism, ibuprofen metabolism, glucocorticoid, and mineralocorticoid metabolism, and steroid hormone biosynthesis. Downregulated pathways including purine and pyrimidine metabolism, arginine and proline metabolism, biological oxidation, glutathione metabolism and citrulline-nitric oxide cycle were determined in the RA. The recipient operating characteristic analysis had defined 30 metabolites as default RA biomarkers including various phospholipids, diol, and its derivatives, oleananoic acid acetate, arsonoacetate, docosahexaenoic acid methyl ester, inolenic acid and eicosatrienoic acid derivatives (Carlson et al., 2019). In the study by Ahn et al., gas chromatography/flight time mass spectrometry (GC / TOF-MS) was used to define the metabolic profile of RA- FLS. A metabolite enrichment analysis was performed to determine which pathways were affected. A total of 129 metabolites have been identified. The levels of 35 metabolites belonging to the amine, fatty acids, phosphates, and organic acids class have been shown to increase significantly in RA-FLS compared to OA-FLS. Also, 26 metabolite levels belonging to the class of amino acids, sugars, and sugar alcohols have been observed to decrease significantly in RA-FLS compared to OA-FLS. Sugar metabolism (i.e: glycolysis and pentose phosphate pathway) and amino acid metabolism (i.e: tyrosine and catecholamine biosynthesis and protein biosynthesis) have been shown to be severely impaired in RA-FLS compared to OA-FLS. Metabolic results suggest that the change in sugar metabolism, amino acid metabolism and lipolysis in RA-FLS which is associated with synovial hyperplasia and inflammation (Ahn et al., 2016). Another example is Fu et al., developed a bovine liver- β glucuronidase hydrolyzing sample preparation method, using liquid chromatography coupled to tandem mass spectrometry to analyze the total urinary oxidized lipid profile including the isoprostanes, prostaglandins, hydroxy fatty acids, etc. The method of forming a total oxidized lipid profile was developed and validated for human urine and was also shown for urine samples from RA patients. Proinflammatory mediators, PGF2a and PGF3a, and oxidative stress markers, 11-HETE, 14-HDoHE and iPF2a-IV, had been positively related to improving the RA disease activity. Besides, anti-inflammatory nitro-fatty acids had been shown to be negatively associated with the initial disease activity (Fu et al., 2016).

2.8. Immunological cells affected by RA disease

The purpose of tissue-specific RA, synovial tissues, macrophages, blood cells, CD4⁺T cells, CD8⁺T cells, T cells, NK cells, NKT cells, monocytes and neutrophils, analysis is to examine and explain the similarities and differences between genomic and cellular changes found in different tissue types. The distribution of genomic signatures among RA tissues is unknown. When many samples from different tissue types specific to RA were examined by integrative and comparative analysis, it was observed that some tissue types had common features.

RA is a complicated immune-mediated disease in which primarily involving inflammation of synovial tissues and joint damage. The main target tissue of autoimmune arthritis such as RA is synovial tissue. In recent years, there has been a large study to analyze molecular and cellular alteration in synovial tissue obtained from RA patients to identify biomarkers in RA. Synovium take two main roles in homeostasis: (I) produce to lubricants which enable to operate in a low-friction environment in cartilage surface and ensure nutrients to the cartilage that lacks its blood flow. It is an overly sensitive structure with an intimal lining consisting of healthy synovium, macrophage-like synoviocytes and FLS, and a sub-lining consisting of adipocytes, fibroblasts, diffused immune cells and blood vessels. FLS contributes to the pathogenesis of RA and is epigenetically imprinted in RA with an aggressive phenotype. Also, synovial fibroblasts, including FLS, may have different phenotypes with different functional properties. Moreover, FLS-related epigenetic mechanisms that suppress RA include changes in histone modifications, DNA methylation and microRNA expression (Dakin et al., 2018; Nygaard & Firestein, 2020; Orr et al., 2017). The principal target of inflammation in synovium of RA and established FLSs play a role in the pathogenesis of synovitis, so investigate to biomarkers in inflamed synovial tissues can be a promising approach (Orr et al., 2017). Using a combination of proposed methodologies, together with high-throughput omic data sciences, represent a novel perspective in the search of these biomarkers.

In a genome-wide gene expression analysis study to characterize RA pathogenesis at the molecular level and reveal pathomechanisms; pairwise comparisons were made between RA and osteoarthritis (OA) patients, RA and normal donors, or OA and normal donors, and 1,054 gene clusters were identified. Correlation analysis was revealed that the secreted phosphoprotein 1 (SPP1) was significantly up-regulated in RA compared to the normal donors.

Also, the genes associated with PRG4 and PRG4 have shown that they can be valuable targets for assessing the regenerative and protective status of a particular patient and eventually opening up new ways for therapeutic intervention (Ungethuem et al., 2010). Human intestinal microbiota can mediate the development of arthritis. Investigations show that some bacterial nucleic acids may be present in synovial fluid and may be involved in arthritis, although the arthritis mechanism is still unknown. To characterize potential synovial fibroblast (SF) bacterial nucleic acids, Zhao and co-workers used 16S rRNA gene amplicon sequencing to assess bacterial nucleic acid communities in synovial tissue and SF samples from 125 patients with RA and synovial tissue and SF samples from 58 patients with osteoarthritis. They reported, abundant bacterial nucleic acid diversity, including the presence of *Porfirromonas* and *Bacteroids* in all samples. In addition, *Agrobacterium*, *Comamonas*, *Kocuria*, *Meiothermus*, and *Rhodoplanes* were more abundant in RA synovial tissues. Moreover, *Haemophilus parainfluenzae*, *Veillonella dispar*, *Treponema amylovorum* and *Prevotella copri* have been found to be quite abundant in RA synovial fluid (Y. Zhao et al., 2018).

While RA sometimes indicate thyroidal illness, the role of thyroid hormones in inflamed synovial tissue is still unknown. In the study examining the hypothesis that the nodes of the thyroid hormone network reconstructed in synovial tissue, biodegradation was observed especially in RA, as a result of superfusion experiments with synovial tissue from patients with RA and osteoarthritis. Moreover, RA synovial tissue / SFs were showed a local thyroid hormone network. Furthermore, thyroid hormones have undergone strong biodegradation in the synovium and bioactive T3 does not affect gene expression of SFs, while SFs have a key function in the role of thyroid hormones (Pörings et al., 2019).

Circular RNAs (circRNAs) form a large class of RNA which can be used as biomarkers and molecular signatures in human blood samples. In the study aiming to identification of the expression profiles of circRNAs in peripheral blood mononuclear cells obtained from RA patients to determine new biomarkers for RA screening applications; microarray screening of circRNA changes in peripheral blood mononuclear cells from RA patients and healthy controls were performed. Besides, using real-time quantitative reverse transcription-polymerase chain reaction verified circRNA alters selected in peripheral blood mononuclear cells from RA patients and healthy controls. Spearman correlation test was executed to evaluate the correlation between circRNA and clinical variables, and the receiver operating characteristic curve was

calculated to evaluate the diagnostic performance of the resultant circRNAs. The results of the study showed that circRNA (003524, 103047, 104871, 101873) expression of significantly increased in peripheral blood mononuclear cells may be potential diagnostic biomarkers in RA (Ouyang et al., 2017). Imbalance in pro-inflammatory and anti-inflammatory cytokines is reported to take a part the tissue damage in RA. In the study, which defines cytokine expression patterns may be accepted as possible indicators in disease activity, plasma cytokine, and peripheral blood mononuclear cells secreting cytokines were calculated in RA patients and healthy controls. Pro-inflammatory cytokine (TNF- α , IFN- γ , IL-6, IL-12, IL-17) and anti-inflammatory cytokine (IL-4, IL-10, IL-13) analysis were performed in a ELISA. It was also observed that patients with RA had higher plasma levels of IL-12, IL-4 and TNF- α , compared to healthy controls. In addition, mitogen-activated peripheral blood mononuclear cells was secreted at levels higher than pro-inflammatory cytokines TNF- α , IFN- γ , IL-17, and IL-12 in RA. However, in RA, anti-inflammatory cytokine was observed to be secreted at lower levels compared to healthy controls. In conclusion, IFN- / IL-13, IL-17 / IL-10, TNF- α / IL-10, IFN- γ / IL-10, IL-12 / IL-10, and ratios in RA patients compared to healthy ones it was found to be significantly higher. Also, the cytokines expression were obtained higher in peripheral blood mononuclear cells than in plasma in all groups examined (Azizieh et al., 2017). Another recent study analyzed the profile of chemokine receptor expression of T cell subtypes in the blood in untreated early RA patients compared to healthy controls. Peripheral blood was obtained from early RA patients meeting the ACR 2010 criteria and sex and age-matched healthy controls. In the analysis, the ratios of T helper cells in the blood, including Th0, Th1, Th2, TFh, Th17, Th1Th17, and regulatory T cells, were identified via flow cytometry. Fifteen chemokines, containing several CXCL and CCL chemokines related to T cell subtypes and other large immune cells in blood plasma were also measured using flow cytometry based immunoassay or ELISA. The data were analyzed using multivariate factor analysis and then univariate analysis. Multivariate discriminant analysis showed that early RA patients are different from healthy controls in terms of the blood plasma chemokine profile. CCL4, CXCL9, CXCL10, CXCL13, and CCL22 were identified to be significantly higher in early RA compared to healthy controls by univariate analyses. Also, in the analysis of chemokines, CDAI, CXCL10, DAS28-CRP, DAS28-ESR, correlated with multiple disease activity measures of 66 joints. Among the chemokines analyzed, only CXCL10 was found to be correlated with multiple disease activity measures (Pandya et al., 2017).

Macrophages are particularly crucial in the disease mechanism of RA. The higher number of sublining macrophages in the synovium is an early onset of active rheumatic disease. Macrophages produce what they produce cytokines that increase inflammation and contribute to the destruction of cartilage and bone and decrease after effective treatment. Also, macrophages can quickly respond to many stimuli and make them potentially very crucial in the progression of many diseases. Research has revealed a high level of heterogeneity in the origin and function of macrophage and environmental factors have demonstrated their importance in determining the unique identity and function of macrophages residing in the tissue by regulating transcription factors and creating tissue-specific enhancers. The origin of macrophages in human tissues is not yet known. The seeding and self-renewal of macrophages in the mouse synovium have not yet been determined, but immunophenotyping represents that macrophages in the synovial tissue contain bone marrow-derived and embryonically derived populations. Treatments that target specific macrophage subsets for RA can be targeted, but it is not yet known whether such treatments interfere with host preservatives or remedies (Udalova et al., 2016). In the study of macrophages primary effector cells in IL-7-induced arthritis, RA, increased IL-7R / CD127 expression is the hallmark of M1 macrophages and these cells are highly susceptible to interleukin-7 (IL-7) -riven osteoclastogenesis. Lipopolysaccharide, interferon- γ , and tumor necrosis factor- α , which are the classic M1 macrophage mediators, have been shown to increase IL-R expression in RA and murine macrophages. The expression of IL-7 increased arthritis, mainly by increasing the number of F480⁺ iNOS⁺ cells instead of CD3⁺T cells, and ectopic LPS injection stabilizes IL-7-induced arthritis by partially increasing IFN γ induction by myeloid IL-7R expression. In a study on mice, RAG - / - mice were shown to suppress IL-7 mediated arthritis due to a decrease in myeloid IL-7R expression due to a deficiency of IFN γ . This study reported that IL-7-induced arthritis is due to F480⁺ iNOS⁺ IL – 7R⁺ CCL5⁺ cell function, which activates TH-1 cells to increase myeloid IL-7R expression and disease severity (S. Jae Kim et al., 2019). Osteoclasts play an important role in bone remodeling and arthritis bone erosion and have the capacity to destroy the bone. In the study showing that osteoclasts in pannus originate exclusively from circulating bone marrow-derived cells and not from locally resident macrophages, Tamoxiphenylated Foxm1 deletion suppressed the ability of osteoclastogenic macrophages associated with arthritis to separate into osteoclasts in vitro and in vivo. As a result, synovial samples from RA patients were found to contain CX₃CR1⁺HLA-DR^{hi}CD11c⁺CD80⁻CD86⁺ cells corresponding to arthritis-related osteoclastogenic macrophages in mice and inhibit

FoxM1 inhibitor thiostreptone, which is a potential target for RA treatment (Hasegawa et al., 2019).

T cells regulate the disease process in RA at many levels. T cells promote lymphoid organogenesis and neoangiogenesis in the inflamed joint and stimulate synoviocyte proliferation and the development of bone-eroding osteoclasts (Weyand & Goronzy, 2006). In the autoimmune inflammation site, proinflammatory mediators interfere with T-cell regulation and can induce T-cell plasticity. Regulatory T cells are less functional in an autoimmune inflammatory environment or may even be pathogenic. The resistance of effector T cells to suppression significantly contributes to the disturbing immune balance in the inflamed joints of RA patients. In autoimmune inflammation, antigen-presenting cells have a cycle in which they instruct T cell function and differentiation, and effector T cells promote the infiltration and differentiation of antigen-presenting cells (Wehrens et al., 2013). The chemokine receptor CXCR5 is primarily expressed on B cells and T follicular helper cells and facilitates their migration into B cell follicles. Moschovakis et al reported that the role of the CXCL13 / CXCR5 axis in the pathogenesis of RA in mice, CXCR5-mediated co-localization of T follicular helper cells and B cells in secondary lymphoid organs is essential for RA induction and identifies CXCR5 and T follicular helper cells as promising therapeutic targets for RA treatment. As a result, the study showed that T cell-specific CXCR5 deficiency prevents RA disease (Moschovakis et al., 2017). In the study investigating the frequencies of Th1, Th17 and Th22 cells and related cytokine levels in the subchondral bone marrow in patients with RA; peripheral blood and bone marrow samples were taken from patients with RA and with osteoarthritis and healthy controls. The frequencies of Th1, Th17 and Th22 cells were examined via flow cytometry, and IL -22, IL-17 and IFN- γ levels were examined by ELISA. Disease activity score was analysed in joints of RA patients. Each T cell subset in the bone marrow is elevated in RA patients compared to that in the peripheral blood. Consistently, IL-22 and IL-17 plasma levels in RA patients are elevated, and this increase is more pronounced in the bone marrow than peripheral blood. In addition, the percentages of Th22, Th17 and Th1 cells and bone marrow IL-22 and IL-17 levels correlated positively with DAS28. These results showed that local pro-inflammatory T helper cells are elevated in the bone marrow and associated with disease severity (S. Li et al., 2017).

CD4⁺ T cells play an important role in the development and maintenance of protective immunity and tolerance against diseases. Imbalances in these processes can cause autoimmune diseases (Hughes & Choubey, 2014). RA is autoimmune-destructive arthritis associated with CD4⁺ T cell-mediated immunity (Ishigaki et al., 2015). It has been demonstrated that B cells have an effect in regulating the first proliferation of CD4⁺ T cells and in CD4⁺ T cell memory responses (Lund & Randall, 2010). In addition, in the relationship of B cells with CD4⁺ T cells; the combination of B cells with dendritic cells has also been shown to maximize memory CD4⁺ T cell recall response to the herpes simplex virus (Iijima et al., 2008; Lund & Randall, 2010). Ishigaki, et al., investigated cell clones by examining the peripheral blood from 5 RA patients and the synovium from 1 RA patient, using a combination of single-cell analysis and next-generation sequencing in TCR repertoire analysis. When the single-cell transcript of the most enlarged clones in CD4⁺ T cells in RA-peripheral blood was examined, aging-related transcripts were upregulated, which showed that circulating cell clones were constantly stimulated. In addition, monitoring of transcriptome shifts in the same memory CD4⁺ T cells between peripheral blood and synovium revealed increased senescence-related gene expression and upregulation of synovium-homing chemokine receptors in synovium. The indepth characterization of cell clones in RA showed the presence of specific immunological selection pressure that determined the phenotype of the cell clones (Ishigaki et al., 2015). The cytokine IL-6 controls the effector characteristics of lymphocytes, proliferation and survival through activation of the STAT1 and STAT3 which are transcription factor. STAT3 activity is characteristic of IL-6 signaling in CD4⁺ T cells. Also, STAT3 activity and prior activation via the T cell antigen receptor limits the STAT1 control in the effector and memory populations of IL-6. This study represent that phosphorylation of STAT1 in response to IL-6 was regulated through the tyrosine phosphatases PTPN2 and PTPN22 and activation of naïve CD4⁺ T cells (Twohig et al., 2019).

CD8⁺ T cells are known cytotoxic cells due to their ability to induction of cell death via the release of cytolytic granules or to induce the Fas-mediated apoptosis. CD8⁺ T -cell homeostasis is differed in the peripheral blood of patients with autoimmune arthritis (Petrelli & Van Wijk, 2016). The role of CD8⁺ T cells in RA has been less defined. However, Tripathy et al. showed that these cells are activated in RA patients, where the expression of cytolytic granules and inflammatory mediators increases, thereby modulating immune responses that contribute to disease severity. In addition, in the study, they showed that TLR4 expression increased on

peripheral CD8⁺ T cells of RA patients and that surface expression of TLR4 on CD8⁺ T cells was directly related to disease severity. Additionally, in the study, they showed that TLR4 expression increased on peripheral CD8⁺ T cells of RA patients and that surface expression of TLR4 on CD8⁺ T cells was directly related to disease severity. Also, the LPS linkage of functional TLR4 expressed on their surface activates these lymphocytes, thereby reporting that it directly contributes to the preservation of chronic inflammatory processes in RA (Tripathy et al., 2017). Although somatic mutations occur in all proliferating cells, in the study investigating their accumulation under non-tumor conditions such as 25 RA patients and 20 healthy controls were examined. While newly diagnosed RA expanded CD8⁺ T cell clones, somatic mutations were seen in CD8⁺ T cells in 20% of patients, while CD4⁺ was not seen in T cells. In healthy controls, only one mutation was identified in the CD8⁺ T cell pool. The mutations were found only in the extended CD8⁺ effector-memory subgroup. As a result of the analyses, PADI4, PROM1, C5, IRF1, SLAMF6, and SEC14L3 are some of the mutated genes. It is known that variation genes SLAMF6, IRF1 was previously associated with autoimmunity (Savola et al., 2017).

Natural killer T (NKT) cells are a distinct class of lymphocytes that can rapidly secrete huge amounts of cytokines, including IFN- γ , IL-2, IL-4, and IL-12, and co-express the TCR and NK cell receptors. Numerous studies represent that NKT cells can have an impact on the differentiation of CD4⁺ T cells through cytokines in vitro. These findings suggest that NKT cells may take a role in RA by polarizing Th1, Th2, Treg cells and Th17 (J. Chen et al., 2016). NKT cells are significant regulatory lymphocytes, which have been shown to play an important role in increasing immunity to tumors, bacteria, and viruses and suppressing cell-mediated autoimmunity in mouse studies (Berzins et al., 2011). NKT1 cells are also present in the synovial fluid of arthritis patients. However, while various subsets of invariant NKT cells with different cytokine production are known to develop in the mouse thymus, the factors that direct their differentiation remain uncertain. In the Zhao and co-workers' study, Zap70 mutant mice develop IL-17-dependent arthritis. In the mouse experimental arthritis model, NKT17 cells increased as the disease progressed, while NKT1, whose NKT1 numbers depend on IFN- γ expressions, showed a negative correlation between this protective effect and disease severity (M. Zhao et al., n.d.).

Natural killer (NK) cells are known as bone marrow-derived granular lymphocytes that play a crucial role in immune defense mechanism against bacterial and viral infections and malignancies. Because NK cells lack recombination-activating gene recombinase-dependent clonal antigen receptors, they have traditionally been identified as cells of the innate immune response. Also, some studies suggest that specific subsets of mouse NK cells can still develop a long-lived and highly specific memory for various antigens (Paust & Andrian, 2011). RA is associated with an increased risk of lymphoma due to the activity of the disease. Since NK cells have recently been shown to participate in anti-lymphoma immunosurveillance, Nocturne et al. investigated whether anti-TNF will affect anti-lymphoma activities. NK cells were evaluated ex vivo in RA patients treated with methotrexate with or without anti-TNF. Phenotype flow cytometry was cultured for 6 days in the presence of function NKp30-crosslinking and NK, anti-TNF, TNF-R inhibitors or controls, and the phenotype was studied. Then, cytotoxicity was evaluated against the 2B non-Hodgkin lymphoma cell line. As a result, exposure to Anti-TNF has been observed to be associated with reduced activation of NK cells. Therefore, in the study, a meta-analysis of randomized controlled trials and recordings has drawn attention to this possible side effect in patients with long-term anti-TNF exposure, even though the risk of lymphoma with increased anti-TNF to date (Nocturne et al., 2017). Another study that characterized NK cell populations found in the blood and synovial fluids of patients with deformative RA and non-deformed RA. It has been shown that a separate population of activated synovial fluids NK cells has been shown to forms a large number of immune cells, found in synovial fluids of deformative RA patients. In both deformative RA and non-deformative RA patients, synovial fluid NK cells were examined to have different functions, although they had similar phenotypes. It has been reported that deformative RA releases more TNF α and IFN γ when exposed to synovial fluid NK, IL-2 and IL-15. They also suggested that 'synovial fluid NK cells may be a marker for more severe destructive RA disease (Yamin et al., 2019).

Monocytes originate from progenitors in the bone marrow and pass into the peripheral tissues through the bloodstream. They have long been considered as a source for tissue macrophages, however recent studies show more complex roles for monocytes, both in circulation and after migration to tissues and lymphoid organs. During both homeostasis and inflammation, circulating monocytes abandon the bloodstream and migrate to tissues where they are divided into macrophage or dendritic cell populations after conditioning with local growth factors, pro-

inflammatory cytokines, and microbial products (Jakubzick et al., 2017; Shi & Pamer, 2011). It is important to take monocytes to ensure effective control and clearance of fungal, viral, bacterial and protozoal infections, but monocytes also contribute to the pathogenesis of degenerative and inflammatory diseases (Shi & Pamer, 2011). The migration and infiltration of mononuclear cells into inflammatory sites play a key role in the pathogenesis of RA. Monocyte chemo attractive protein-1 (MCP-1 / CCL2) is the important chemokine that regulates the migration and infiltration of monocytes and Cysteine-rich 61 (Cyr61 or CCN1), is a significant proinflammatory cytokine. In the experimental RA study in mice, the role of CCN1 in monocyte migration and CCL2 expression in osteoblasts were investigated. In the synovial fluid of RA patients, higher levels of CCN1 and CCL2 were found compared to the levels of non-RA controls, and it was observed that the CCP-induced positively alteration in CCL2 expression mediated the MAPK signaling pathway and that the miR-518a-5p expression was down regulated by CCN1 via the MAPK cascade. (C. Chen et al., 2017). Molecules that induce chemokine synergy appears as regulatory factors in cell migration. While the alarm HMGB1, in its reduced form, can complex with CXCL12, which enhances its activity on monocytes via the chemokine receptor CXCR4, the form containing the disulfide bond initiates a series of events that bind TLR2 or TLR4 to produce cytokines and chemokines. Recently, the possibility of maintaining CXCL12 / HMGB1 heterocomplex in chronic inflammation has been discussed due to the release of reactive oxygen species. In the study by Cecchinato and colleagues, they examined whether heterocomplex can remain active in RA and its relation to disease assessment. Monocytes from RA patients required a low concentration of HMGB1 to increase migration from CXCL12 compared to monocytes from patients in clinical remission or healthy donors. Hetero-complex activity depends on the activity of RA disease. The presence of an active thioredoxin system in RA is associated with increased cell migration and the presence of heterocomplex in synovial fluid. Prostaglandin E2 stimulation of monocytes from healthy donors is sufficient to recapitulate the response observed in patients with active RA. Mechanism activation which counteract oxidative stress in the extracellular compartment protects, HMGB1 in its reduced form and contributes to increasing the flow of inflammatory cells (Uguccioni, 2018).

Neutrophils (also known as polymorphonuclear cells) are the most abundant leukocyte population in humans. Neutrophils are among the shortest-lived cells in mammals, despite their constant regeneration from bone marrow. These are terminally differentiated cells with

extremely limited transcription activity. Neutrophils, as effector cells of the innate immune system, participate in a variety of immunological and inflammatory processes. It is the first line of defense against bacterial and fungal infections. They contain an armament of antimicrobial agents (including reactive oxygen species (ROS) and hydrolytic enzymes) that can eliminate invading pathogens. Neutrophils also play an important role in the coordination of general immunity and inflammatory response (Németh et al., 2020). It has the greatest cytotoxic potential from all cells involved in RA pathology due to its ability to release neutrophils, degrading enzymes, and reactive oxygen species. Neutrophils also contribute to cytokines and chemokine cascades accompanying inflammation and regulate immune responses through cell-cell interactions. Recent evidence has shown that neutrophils can release not only extracellular microorganisms but also neutrophil extracellular traps, which also provide a source of autoantigen. Neutrophils from RA patients show an increased tendency to form neutrophil extracellular traps containing citrullinated proteins. Serums from RA patients contain autoantibodies that recognize these proteins. Therefore, in addition to the cytotoxic and immunoregulatory roles in RA, neutrophils may be the source of autoantigens that direct the autoimmune processes of this disease (Wright et al., 2014). In the experimental study of Rivera et al., The molecular mechanisms of neutrophil extracellular traps promoting proinflammatory phenotypes in synovial fibroblasts and whether these interactions produce adaptive immune responses in pathogenic antitrulline. They have internalized neutrophil extracellular traps containing citrulline peptides by synovial fibroblasts via a RAGE-TLR9 pathway that supports the synovial fibroblast inflammatory phenotype and upregulation of MHC class II. After internalization, arthritogenic neutrophil extracellular traps-peptides synovial fibroblasts are loaded into MHC class II and presented to Ag-specific T cells. Vaccinated with mouse synovial fibroblasts loaded with neutrophil extracellular traps, HLA-DRB1 * 0401 transgenic mice have developed specific antibodies specific to cartilage damage, as well as related RA autoantigens involved in RA pathogenesis (Rivera et al., 2017).

3. MATERIALS AND METHODS

3.1. Gene expression datasets of tissue-specific RA

The raw data of high throughput gene expression datasets associated with rheumatoid arthritis (RA) from a total of eleven studies (GSE1919, GSE55235, GSE55457, GSE77298, GSE10500, GSE97779, GSE93776, GSE93272, GSE93777, GSE65010, GSE56649) have been obtained from Gene Expression Omnibus (GEO) (Barrett et al., 2013) which is a public functional genomics data repository supporting MIAME-compliant data submissions and analyzed to characterize gene expression profiles in RA. The samples in these datasets were taken from synovial tissues, blood cells, T cells, CD4⁺ T cells, CD8⁺ T cells, NK cells, NKT cells, macrophage cells, monocytes, and neutrophils. A total of 283 samples were explored, including 133 healthy control and 150 RA diseases. According to the synovial tissue classification, GSE1919, GSE55235, GSE55457, and GSE77298 datasets were examined and a total of 5, 10, 13, 16 diseased samples were compared to 5, 10, 10, 7 control samples, respectively. From RA blood cell (20 samples) and control cells (30 samples) (GSE93272), were examined. Considering the heterogeneous nature of RA, we focused on immune cells which might be affected by RA pathogenesis. Data sets (GSE65010, GSE56649, and GSE93776) containing samples of T cells, CD4⁺ T cells, CD8⁺ T cells, NK cells, NKT cells from the RA naïve cell population and control tissues were taken into account. T immune response group raw data consisting of a total of 84 samples (45 RA and 39 control samples) were obtained from GEO. Macrophages were examined from 14 RA diseased cells and 8 control cells (GSE10500, GSE97779) and Monocyte 18 RA diseased cells and 18 control cells (GSE93776). Also, the neutrophils cells and control group, GSE93776 dataset gene expression profiles were downloaded from the GEO database. (Table3.1)

Table 3.1. Gene expression datasets in the present study.

Data Sets	Examples	# number of control samples	# number of diseased samples	Array Type	References
GSE1919	Synovial tissues from RA patients and normal donors	5	5	Affymetrix HG- U95A Array	(Ungethuem et al., 2010)
GSE55235	Synovial tissue from healthy joints and RA joints.	10	10	Affymetrix HG- U133A Array	(Woetzel et al., 2014)
GSE55457	RA Synovial tissue from the patient and RA healthy controls	10	13	Affymetrix HG- U133A Array	(Woetzel et al., 2014)
GSE77298	RA synovium and from subjects without a joint disease	7	16	Affymetrix HG- U133 Plus 2.0 Array	(Broeren, et al., 2016)
GSE93272	Transcriptome of whole blood from RA patients with or without drug treatments and healthy volunteers	30	20	Affymetrix HG- U133 Plus 2.0 Array	(Tasaki et al., 2018)
GSE65010	Gene expression profiling of effector and regulatory T-cells from peripheral blood of RA patients and healthy volunteers.	6	6	Affymetrix HG- U133 Plus 2.0 Array	(Walter et al., 2016)
GSE56649	The highly purified peripheral blood CD4 T cells were isolated	9	13	Affymetrix HG- U133 Plus 2.0 Array	(Ye et al., 2015)
GSE93776	CD4T(Transcriptome of sorted immune cells from patients with RA and healthy volunteers.)	6	6	Affymetrix HG- U133 Plus 2.0 Array	(Tasaki et al., 2018)

GSE93776	CD8T (Transcriptome of sorted immune cells from patients with RA and healthy volunteers.)	6	6	Affymetrix HG- U133 Plus 2.0 Array	(Tasaki et al., 2018)
GSE93776	NKT (Transcriptome of sorted immune cells from patients with RA and healthy volunteers.)	6	7	Affymetrix HG- U133 Plus 2.0 Array	(Tasaki et al., 2018)
GSE93776	NK (Transcriptome of sorted immune cells from patients with RA and healthy volunteers.)	6	7	Affymetrix HG- U133 Plus 2.0 Array	(Tasaki et al., 2018)
GSE10500	Macrophages from RA synovial fluids were compared to primary human blood-derived macrophages.	3	5	Affymetrix HG- U95 Version 2 Array	(Broeren, et al., 2016)
GSE97779	Macrophages from RA synovial fluids and primary human monocyte-derived macrophages	5	9	Affymetrix HG- U133 Plus 2.0 Array	(Kang et al., 2017)
GSE93776	Monocyte-macrophages (Transcriptome of sorted immune cells from patients with RA and healthy volunteers.)	18	18	Affymetrix HG- U133 Plus 2.0 Array	(Tasaki et al., 2018)
GSE93776	Neutrophils (Transcriptome of sorted immune cells from patients with RA and healthy volunteers.)	6	9	Affymetrix HG- U133 Plus 2.0 Array	(Tasaki et al., 2018)

3.2. Identification of Differentially Expressed Genes

To identify differentially expressed genes (DEGs), an affy package of R/Bioconductor platform (version 3.6) was used. Each dataset was normalized via Robust Multi Array (RMA) techniques (Irizarry et al., 2003). DEGs were identified from the normalized log-expression values using the multiple testing options of linear models for microarray data (LIMMA) (Smyth, 2005) was used in the statistical analysis of each dataset by compared with the diseased vs control group to identify DEGs. They were selected according to computed p-values < 0.05 with a fold-change cut-off of > 1.5 and < 0.67 was used to determine the statistical significance of differential expression.

3.3. Gene set overrepresentation analyses

To identify functional annotations (i.e., biological processes, molecular functions, signaling, and metabolic pathways) significantly associated with the core genes of RA, overrepresentation analyses were performed using the ConsensusPathDB bioinformatics tool (Kamburov et al., 2009). In the analyses, the Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2014) and Reactome (Croft et al., 2011) used as the pathway databases. Gene Ontology (GO) terminology (Blake et al., 2015) was employed as the source for annotating the molecular functions and biological processes. P-values representing the significance of enrichment analyses were obtained via Fisher's Exact Test. Tissues were divided into synovial, blood, T groups (T, $CD4^+$ T, $CD8^+$ T, NKT, and NK), macrophages and monocytes, neutrophils to find common pathways in all tissues. The pathways common to at least three data sets in each group were taken and created core paths separately according to up and down-regulated DEGs. The common pathways to at least four tissues were accepted as seed pathways.

3.4. PPI network reconstruction and analysis

The physical protein-protein interaction dataset of homo sapiens was obtained from the BioGRID database (Chatr-Aryamontri et al., 2017). 43,219 physical interaction associated with proteins corresponding to DEGs were identified and PPI networks were reconstructed. The visualization and topological analysis of the PPI network was used via Cytoscape (Shannon et al., 1971). The biological descriptions of hub genes were obtained from Gene Cards (Safran et al., 2010).

3.5. Biomolecule data interaction retrieval

To identify key regulators, TFs and miRNAs, the TF-target gene, and miRNA- target gene interactions were used. Experimentally validated TF-target gene interactions were obtained from our previous study of the combined human transcriptional regulatory interaction network (Gov et al., 2016) and the Human Transcriptional Regulation Interactions database (HTRIdb) (Bovolenta et al., 2012) to identify reporter TFs. Experimentally validated miRNA-target gene interactions from our previous study and miRTarBase database (version 6.0) (Chou et al., 2016) were used to identify reporter miRNAs. Receptor-protein interaction data were obtained from DAVID (Huang et al., 2007), where proteins have receptor activity (GO: 0004872), PANTHER (Thomas et al., 2003), and Genecodis (Carmona-Saez et al., 2007) databases and their physical interactions were extracted from extensive human protein interaction. Eventually, TF-target gene interactions, miRNA-target gene interactions, and receptor–protein interactions used in this study contain 51871 interactions involving 284 TFs and 22808 genes, 322133 interactions contain as a part of 2599 miRNA and 22808 genes, 20120 interactions involving 916 receptors and 22808 genes. Biomolecule interaction data employed here consist of 284 TFs, 2599 miRNAs, 916 receptors, and 22808 genes.

3.6. Identification of reporter biomolecules

Reporter biomolecules were identified through a statistical test employing the hypergeometric probability density function by using the physical interaction of transcriptional regulators (i.e. TFs and miRNAs) and receptors with core DEGs obtained from each specific tissue with RA datasets. Reporter biomolecules (i.e. miRNAs, TFs, and receptors) were identified by using biomolecule data interactions and gene expression profiles. Similarly, the procedure was adopted to gene expression data of RA was used in our previous study (Comertpay & Gov, 2020) and was used to predict molecular signature in disease progression. Hypergeometric probability represents the probability that an n-trial hypergeometric experiment results in exactly k successes, when the population consists of N items, K of which are classified as successes. Hypergeometric probability formula:

$$p = \frac{\binom{K}{k} \binom{N-K}{n-k}}{\binom{N}{n}} \quad (a)$$

Here, p represents the estimated probability of the association of biomolecules with core DEGs. N is the number of total genes in the interactions, whereas n is the number of core DEGs. K is the number of genes interacting with each biomolecule (i.e. TF, miRNA, and receptor), whereas k is the number of core DEGs interacting with each biomolecule. K and k have a variable number for each biomolecule. Here, n / N refers to the ratio of RA-related genes representing core DEGs between the human genome, and k / K refers to the ratio of core DEGs that interact with the key biomolecule and human genes that interact with the key biomolecule. Reporter molecules specific to each tissue were considered statistically significant to calculated p values $<.05$.

3.7. Identification of reporter metabolites

Human Metabolic Reaction (HMR 2.00) (Mardinoglu et al., 2014) resource was used to identify reporter metabolites in RA pathogenesis. That informs metabolic reactions and the genes that encode enzymes catalyzing these reactions.

The Benjamini correction was applied to the BioMet Toolbox (Agren et al., 2013) by using up and down-regulated DEGs of each tissue-specific of RA to identify reporter metabolites. The P-value threshold ($p < 0.05$) was used to determine statistical significance. The top 5 reporter metabolites were taken into consideration. Also, the biological roles of metabolites and related KEGG pathways were explored through the MBRole bioinformatics tool (López-Ibáñez et al., 2016).

4. RESULTS AND DISCUSSIONS

4.1. Differentially expressed genes across several tissues with RA

In this study, eleven gene expression datasets were analyzed by using non-RA and RA tissue-cell samples. The impressions of RA at gene expression levels were different in various tissues, indicating that genomic reprogramming depends on the type of tissue. However, synovial tissues, blood cells, macrophages, and monocytes a common signature was that most of the core DEGs were upregulated. Also, in the T group, core DEGs were upregulated in CD4⁺ T cells, CD8⁺ T cells, NKT cells, and NK cells, while T cells were also equal. In contrast to the majority, in the neutrophil cells, the core genes were down-regulated. These core genes might be crucial information about RA pathogenesis. Therefore, the result of statistical analyses of all datasets yielded a total of 7131 genes as DEGs, 2792 of which were downregulated, while 4339 were upregulated (Figure 4.1-4.7).

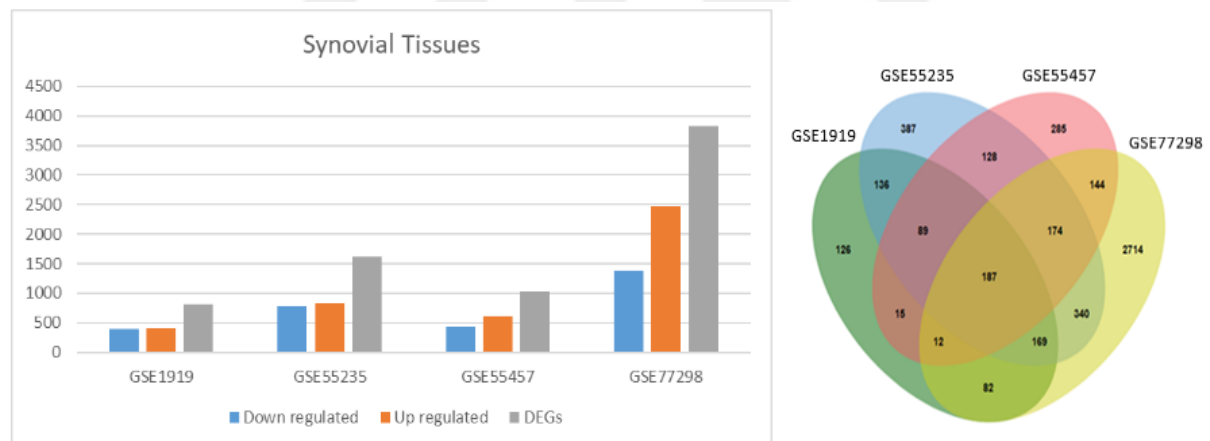


Figure 4.1 Gene expression profiles in synovial tissues with RA.

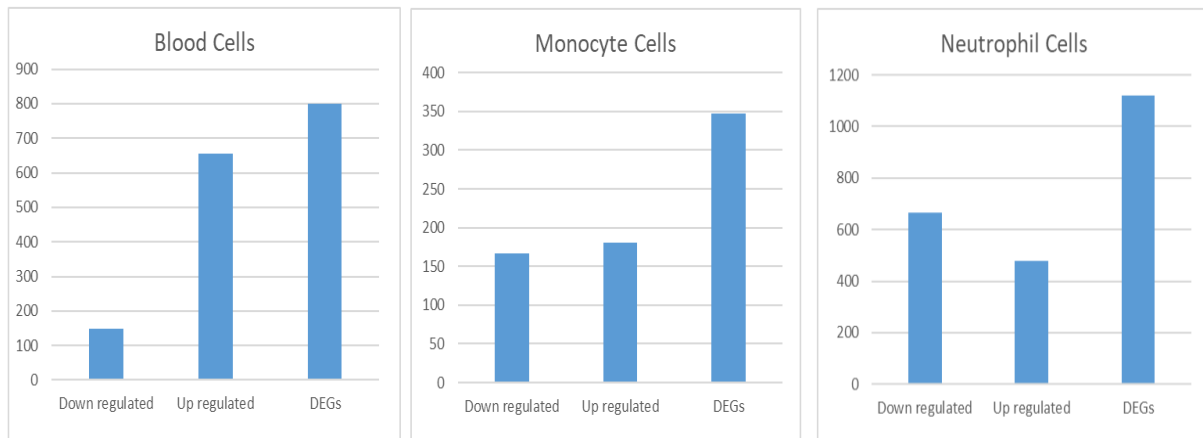


Figure 4.2 Gene expression profiles in blood cells, monocyte cells and neutrophils cells with RA.

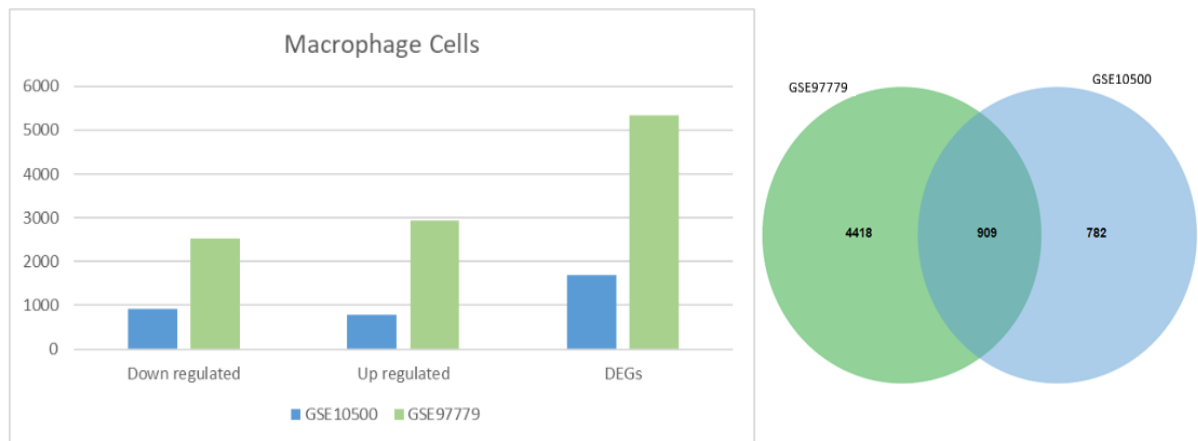


Figure 4.3 Gene expression profiles in macrophage cells with RA

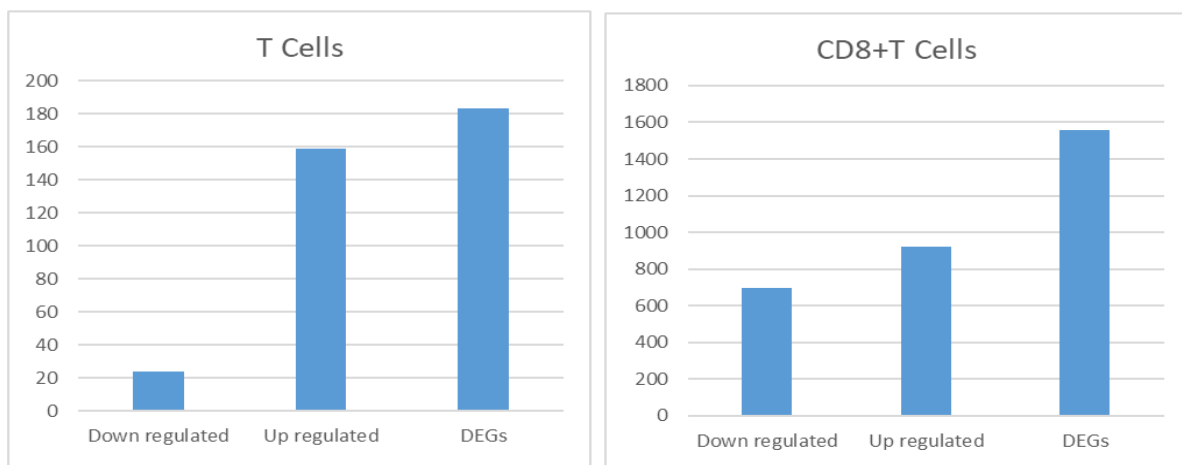


Figure 4.4 Gene expression profiles in T cells and CD8⁺ T cells with RA.

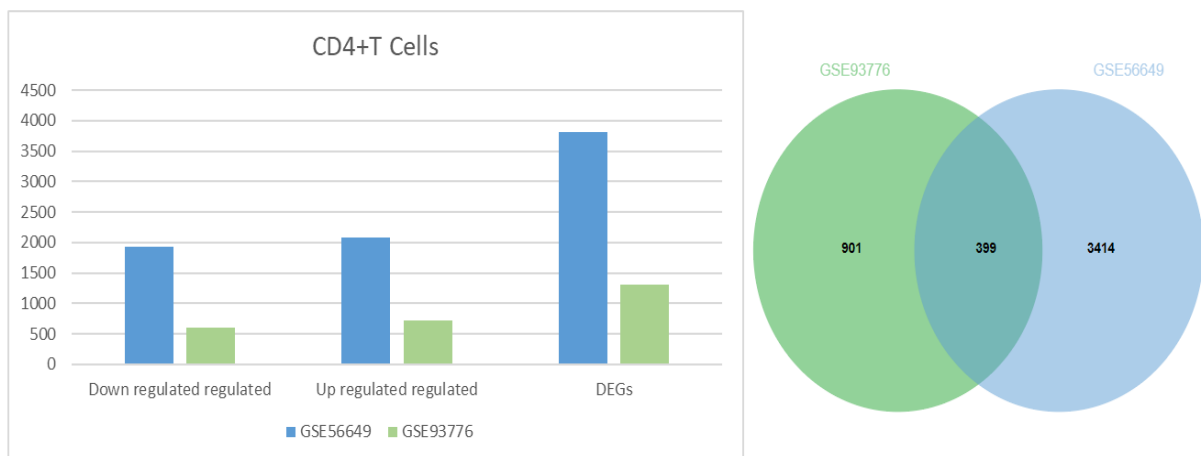


Figure 4.5 Gene expression profiles in CD4⁺ T cells with RA.

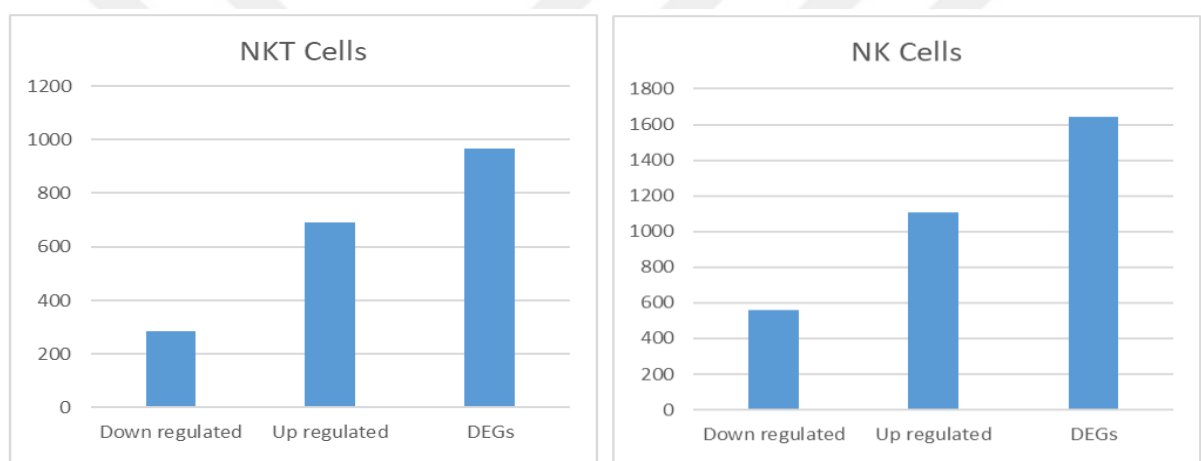


Figure 4.6 Gene expression profiles in NKT cells and NK cells with RA.

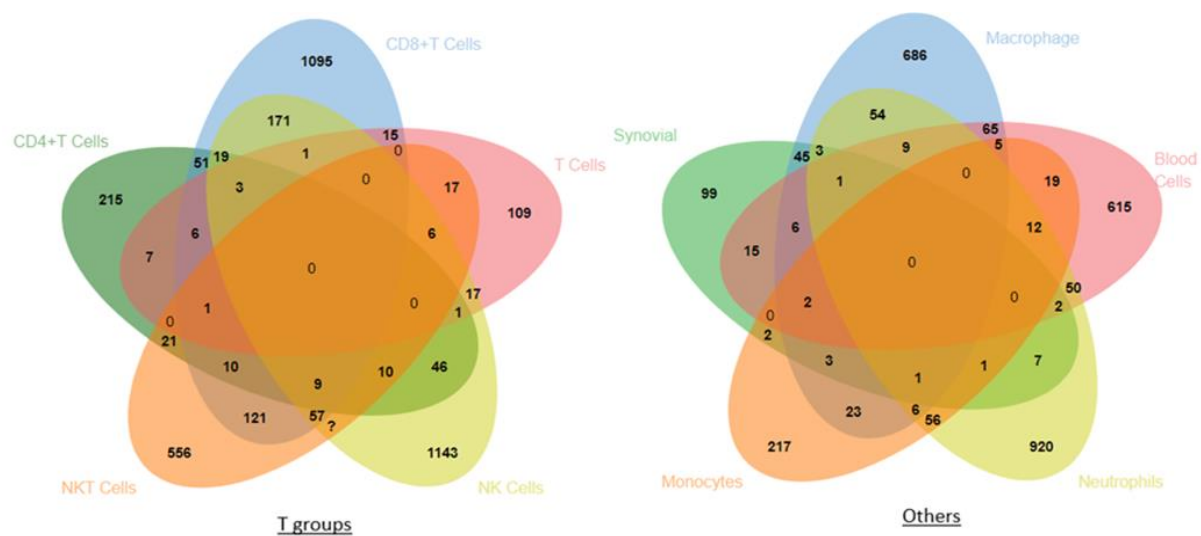


Figure 4.7 Comparative analysis of gene expression profiles in all tissues.

Despite a large number of DEGs in the RA datasets, the comparative analysis of DEG sets did not demonstrate core DEG in all. For instance, the expressions of the SOX4 gene were altered in four tissue types in T group: T cells, CD8⁺ T cells, NKT cells, and CD4⁺ T cells. Besides, ERICH1, LST1, SOCS3 were also common core DEG in T, CD4⁺ T cells, CD8⁺ T cells, and NK cells. Furthermore, common core DEGs in CD4⁺ T cells, CD8⁺ T cells, NKT cells, and NK cells were EMC3-AS1, HCG18, ICOS, OCLN, OXR1, TMCC1, WNK1, ZHX2, and ZNF32. On the other side for other tissues, it was identified SEL1L3 common core DEGs between both synovial, macrophages, monocyte, and neutrophils cells associated datasets. For synovial tissues, blood cells, macrophage cells, and neutrophil cells KIAA0101 was common core DEG. Besides this, AIM2, TNFSF10 genes were common DEGs in synovial tissues, blood cells, macrophages cells, and monocyte cells.

4.2. Biological insights of DEGs

Over-representation analysis based on DEGs for each tissue-specific of RA showed significant results for predominantly immune system associated pathways such as a cytokine, antigen processing, and infection-related pathways (Figure 4.8).

According to the results of the analysis, the pathways associated with interferon-gamma signaling were enriched in all tissues except T cells and CD8⁺ T cells. Interferon characteristics depend on the immune context (infectious or non-infectious) and cellular microenvironment (containing immune and stromal cells) (Nehmar et al., 2018). Interferon-gamma (IFN- γ) plays important role in immune responses and bone metabolism. IFN- γ improves macrophage activation and antigen presentation. In addition, IFN- γ is a significant pathogenetic factor in some immune-mediated bone diseases including RA, postmenopausal osteoporosis, and acquired immunodeficiency syndrome (Tang et al., 2018). Second, predominantly, the RA-associated tissue-specific enrichment pathway in cytokine signaling in the immune system. The cytokine signal is an important occurrence of the immune system, which depends on the pathogenesis of RA. Several cytokines are known to be expressed in synovial tissues or fluid after the onset of RA. When the synovial fluid samples of RA patients are examined; remarkably, a wide level of stromal cell range has increased T cell and macrophage-related cytokines such as interleukins (IL - 1, IL - 6, IL- 10, IL - 17, IL - 18, and IL - 21), epidermal growth factor and fibroblast growth factor are prominent (Sharma et al., 2016).

Besides, infection association pathways such as RA, Epstein Barr virus infection, influenza A, viral myocarditis, hepatitis C, staphylococcus aureus infection, systemic lupus erythematosus, and transcriptional misregulation in cancer pathways were enriched. In the literature, researches are showing the relationship of RA with various diseases, such as systemic lupus erythematosus (Jin et al., 2016), influenza A (Ciccacci et al., 2019), viral myocarditis (Li et al., 2018), Primary Sjogren Syndrome (Galarza-Delgado et al., 2018), hepatitis C (Sebastiani et al., 2019), Staphylococcus aureus bacteremia (Joost et al., 2017), etc.

On the other side, the top five pathways we found in tissue-specific pathway analysis are as follows (Table 4.1). All enriched pathways of the resultant DEGs were tabulated in Supplementary Table 1-10.



Table 4.1 Top five enriched tissue-specific biological pathways

Synovial tissue enriched pathway-based sets

Pathway	p-value	Source
Immune System	1.04E-19	Reactome
Cytokine Signaling in Immune system	8.38E-15	Reactome
Adaptive Immune System	2.26E-14	Reactome
Epstein Barr virus infection	5.43E-11	KEGG
Leishmaniasis	8.93E-11	KEGG

Blood cells enriched pathway-based sets

Pathway	p-value	Source
Ribosome	5.56E-12	KEGG
Interleukin-7 signaling	6.35E-12	Reactome
Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)	1.06E-11	Reactome
Nonsense-Mediated Decay (NMD)	1.06E-11	Reactome
Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex (EJC)	4.18E-11	Reactome

Macrophage cells enriched pathway-based sets

Pathway	p-value	Source
Immune System	9.98E-25	Reactome
Innate Immune System	1.96E-18	Reactome
Neutrophil degranulation	6.38E-17	Reactome
Pathways in cancer	1.56E-12	KEGG
Lysosome	8.16E-12	KEGG

T cells enriched pathway-based sets

Pathway	p-value	Source
Growth hormone receptor signaling	3.30E-05	Reactome
Cytokine Signaling in Immune system	1.95E-04	Reactome
Eicosanoid ligand-binding receptors	4.08E-04	Reactome
Immune System	8.98E-04	Reactome
Signaling by Interleukins	1.02E-03	Reactome

CD4⁺ T cells enriched pathway-based sets

Pathway	p-value	Source
Antigen processing: Ubiquitination & Proteasome degradation	1.72E-05	Reactome
Class I MHC mediated antigen processing & presentation	2.19E-04	Reactome
Epstein-Barr virus infection	5.91E-04	KEGG
Measles	1.11E-03	KEGG
Interleukin-7 signaling	1.54E-03	Reactome

CD8⁺ T cells enriched pathway-based sets

Pathway	p-value	Source
RNA Polymerase II Transcription	6.59E-08	Reactome
Gene expression (Transcription)	6.89E-08	Reactome
Transcriptional regulation by RUNX1	6.74E-07	Reactome
Generic Transcription Pathway	8.20E-07	Reactome
Chromatin modifying enzymes	4.38E-06	Reactome

NKT cells enriched pathway-based sets

Pathway	p-value	Source
Systemic lupus erythematosus	2.83E-15	KEGG
RNA Polymerase I Promoter Opening	1.98E-13	Reactome
Meiotic recombination	2.25E-12	Reactome
Amyloid fiber formation	2.89E-12	Reactome
DNA methylation	4.15E-12	Reactome

NK cells enriched pathway-based sets

Pathway	p-value	Source
Hematopoietic cell lineage	1.70E-13	KEGG
Antigen processing and presentation	2.16E-10	KEGG
Leishmaniasis	4.03E-10	KEGG
Immune System	6.53E-10	Reactome
Allograft rejection	9.21E-10	KEGG

Neutrophil cells enriched pathway-based sets

Pathway	p-value	Source
Synthesis of PIPs at the early endosome membrane	8.97E-05	Reactome
Estrogen-dependent gene expression	9.10E-05	Reactome
RNA Polymerase II Transcription	1.01E-04	Reactome
Gene expression (Transcription)	1.12E-04	Reactome
ESR-mediated signaling	1.92E-04	Reactome

Monocyte cells enriched pathway-based sets

Pathway	p-value	Source
Intestinal immune network for IgA production	1.95E-08	KEGG
Allograft rejection	4.46E-08	KEGG
Translocation of ZAP-70 to Immunological synapse	8.26E-08	Reactome
Type I diabetes mellitus	1.56E-07	KEGG
Asthma	1.82E-07	KEGG

Core pathway	Synovial	Blood	Macrophages	T	CD4+T	CD8+T	NKT	NK	Neutrophils	Monocytes
Interferon gamma signaling	↑ 4.98E-06	↑ 5.73E-04	↑ 5.73E-04		↑ 1.04E-02		↔ 7.24E-05	↑ 7.71E-05	↔ 8.33E-03	↔ 9.99E-07
Cytokine Signaling in Immune system	↑ 8.38E-15	↔ 2.03E-11	↑ 2.03E-11	↑ 1.95E-04			↔ 2.43E-05	↑ 2.80E-05		↓ 6.78E-03
Epstein-Barr virus infection	↑ 3.00E-06	↑ 1.64E-06	↑ 1.64E-06		↑ 5.91E-04		↓ 5.41E-03	↑ 8.69E-06		↓ 8.66E-03
Immune System	↑ 5.81E-09	↑ 9.98E-25	↑ 9.98E-25	↑ 8.98E-04	↔ 1.94E-03			↑ 6.53E-10		↔ 7.37E-03
Influenza A	↑ 1.00E-03	↑ 1.59E-05	↑ 1.59E-05		↑ 6.64E-03		↔ 1.21E-05	↑ 7.78E-08		↔ 7.03E-06
Interferon Signaling	↑ 6.01E-08	↑ 9.30E-08	↑ 9.30E-08		3.63E-02		↑ 1.33E-05	↑ 6.28E-04		↔ 9.94E-05
Downstream TCR signaling	↑ 1.04E-19	↑ 1.19E-02	↑ 1.19E-02				↑ 3.53E-03	↑ 1.23E-06	↔ 4.05E-03	↔ 8.03E-06
Generation of second messenger molecules	↑ 3.38E-09	↑ 3.05E-03	↑ 3.05E-03				↑ 1.60E-04	↑ 5.65E-09	↔ 9.51E-04	↔ 1.76E-06
MHC class II antigen presentation	↑ 1.76E-05	↑ 9.39E-03	↓ 9.39E-03				↔ 1.52E-05	↑ 5.70E-08	↔ 9.86E-03	↔ 2.15E-05
PD-1 signaling	↑ 8.25E-09	↑ 2.30E-03	↑ 2.30E-03				↔ 1.87E-05	↔ 5.26E-09	↔ 7.91E-04	↔ 2.33E-07
Phagosome	↑ 8.14E-06	↓ 4.70E-05	↔ 4.70E-05				↔ 1.77E-06	↑ 4.58E-05		↔ 6.80E-05
Phosphorylation of CD3 and TCR zeta chains	↑ 5.09E-03	↑ 3.41E-04	↑ 3.41E-04				↑ 1.26E-04	↑ 3.46E-08	↔ 6.40E-04	↔ 1.82E-07
Staphylococcus aureus infection	↑ 1.95E-06	↑ 1.83E-02	↑ 1.83E-02				↔ 7.49E-06	↑ 8.13E-05	↔ 1.73E-03	↔ 1.13E-06
Translocation of ZAP-70 to Immunological synapse	↑ 2.88E-06	↑ 9.64E-04	↑ 9.64E-04				↑ 6.09E-05	↑ 7.06E-09	↔ 3.19E-04	↔ 8.26E-08
Viral myocarditis	↑ 1.59E-06	↑ 1.72E-04	↑ 1.72E-04				↔ 1.98E-06	↑ 2.55E-07	↔ 8.91E-03	↔ 1.91E-05
Costimulation by the CD28 family	↑ 1.39E-04	↑ 5.75E-05	↑ 5.75E-05				↔ 4.14E-05	↔ 7.55E-09	↔ 5.64E-03	↔ 1.22E-04
NOD-like receptor signaling pathway	↑ 3.64E-07	↑ 3.38E-03	↑ 3.38E-03		↑ 1.78E-02					3.54E-02
Hepatitis C	↑	↑ 6.01E-08	↑ 6.01E-08		↔ 3.51E-03					
Interferon alpha/beta signaling	↑ 1.25E-10	↑ 1.76E-05	↑ 1.76E-05				↑ 5.87E-03			Up&Down ↔
Programmed Cell Death	↑ 1.83E-05	↑ 1.39E-04	↑ 1.39E-04			↓ 1.05E-03			↑ 3.11E-02	Up ↑
Systemic lupus erythematosus	↑ 3.68E-08	↔					↓ 2.83E-15		↔ 3.06E-03	Down ↓
Transcriptional misregulation in cancer	↔	↔ 1.25E-10	↑ 1.25E-10				↑ 1.13E-03			

Figure 4.8 Mutual pathways across studied all tissues with RA.

4.3. Central biomolecules: Hub proteins in RA

The PPI network was constructed around proteins encoded by the core DEGs of several type tissues with RA through their physical interactions obtained from the previous study. The first neighbor enriched PPI network was constructed for core DEGs of each tissue (Figure 4.9-4.18). Macrophages-related PPI network was reconstructed consisting of 3572 nodes and 7030 edges and neutrophils related to the PPI network including 3383 nodes and 6386 edges. However, in another phagocytic cells monocytes, less number of proteins and interactions were obtained, it has consisted of 966 nodes and 1041 edge. In the T group tissues, NK cells have the highest number of interactions in the PPI network was constructed including 3468 nodes and 6331 edges. Secondly, 2367 nodes and 3453 edges interacted with NKT cells related to the PPI network formed. Next, CD8⁺ T cells were formed including 3914 nodes and 8194 edges. However, the number of interactions in the PPI networks constructed in T cells and CD4⁺ T cells was relatively low, including respectively 824 nodes-933 edges and 1835 nodes- 2479 edges. On the other side, blood cell and synovial tissue-related PPI networks were constructed including sequentially 3354nodes- 6779 edge and 2597 nodes- 4506 edges.

In the topological analysis of the PPI networks, degree (local-based) and betweenness centrality (global-based) metrics were used to identify highly bound proteins, i.e. hub proteins that may play an important role in disease pathogenesis (Calimlioglu et al., 2015; Gov et al., 2017). According to degree metrics, the top ten genes as hub proteins were determined. Among tissue-specific hubs, LMNA came into prominence in NKT cells, macrophages, and monocytes. LMNA (Lamin A and C) is essential form the normal development of the peripheral nervous system and skeletal muscle and muscle satellite cell proliferation, osteoblastogenesis, and bone formation. In addition, it helps maintain the volume and strength of skeletal muscle and bone by preventing fat infiltration of the muscle and bone marrow (Safran et al., 2010). Similarly, HDAC family members HDAC2, HDAC4, and HDAC9 were the hub proteins observed in NK, NKT, and monocyte, respectively. HDAC2 and HDAC4 knockdown rescues miR-138-regulated expression of inflammatory cytokines in fibroblast-like synoviocytes of RA (Shao & Hou, 2019). HDAC9 acts as a strong immune enhancer (Liya Li et al., 2018). Ras family of protein members KRAS and HRAS were hub protein observed in macrophages, besides NRAS observed as the hub protein in the blood cells. Homologous in mammals, HRas, NRas, and KRas isoforms are rapidly activated on ligation of the t-cell receptor, but it is largely unknown whether each isoform plays particular roles in T cells (Messina, 2018). The decreased

expression of let-7a can enhance ACPA-mediated phosphorylation of ERK and JNK and increase expression of IL-1 β through increased expression of Ras proteins in the monocyte of RA (Article, 2019). Besides, suppressors of cytokine signal (SOCS) proteins are cytokine, and growth factor signal modulators also, it has been linked to various inflammatory and neoplastic diseases. SOCS family members SOCS1 and SOCS2 were hub protein seen in mutually CD4⁺ T cells and synovial tissues. Several single nucleotide polymorphisms have been identified in RA patients associated with SOCS1 mRNA expression (Lamana et al., 2020). SOCS2 Cullin family members CUL1 and CUL3 were hub protein observed in mutually, macrophages, CD4⁺ T cells. CUL1 alters lymphocyte signal transduction with a possible effect on RA (Kawaida et al., 2005). Reducing CUL3 mRNA expression may cause fibroblast-like synoviocyte proliferation (Tanaka et al., 2016). Also, Protein Ser/Thr phosphatases group member PPP1CA has observed hub gene in CD8⁺ T cells, and neutrophils, another member PPP2CA was the hub protein in NKT cells. PPP1CA has been shown to be effective in autoimmunity diseases such as type 1 diabetes and multiple sclerosis (Safari-alighiarloo et al., 2020). Next, CDKN1A was the hub protein in synovial tissue, macrophage cells, and NK cells. CDKN1A over-expression could be enhanced by miR-146a suppression, inhibited the proliferation of invasion in fibroblast-like synoviocytes of RA (Gang et al., 2018). Another observed hub protein was JUN proto-oncogene in synovial tissue and CD4⁺ T cells. In the experimental study in mice, c-Jun regulates the activation state of macrophages (Hannemann et al., 2017). Next, observed hub protein was LARP7 in blood cells and CD8⁺ T cells. The knockdown of LARP7 increases neutrophilic inflammation in zebrafish in vivo (Hoodless et al., 2016). In addition, CTBP1 was the hub gene in CD4⁺ T cells and neutrophils cells. increased CTBP1 levels were shown to disrupt skin homeostasis (Deng et al., 2014). MDM2 was observed in NK cells and CD8⁺ T cells. MDM2 promotes RA via activation of MAPK and NF- κ B (Zhang et al., 2016). SQSTM1 was observed in members of NK cells and NKT cells hub protein. Finally, HGS was the hub protein in T cells and monocytes cells. That gene regulates endosomal sorting and plays an important role in the recycling and degradation of membrane receptors also, involved in intracellular signal transduction mediated by cytokines and growth factors.

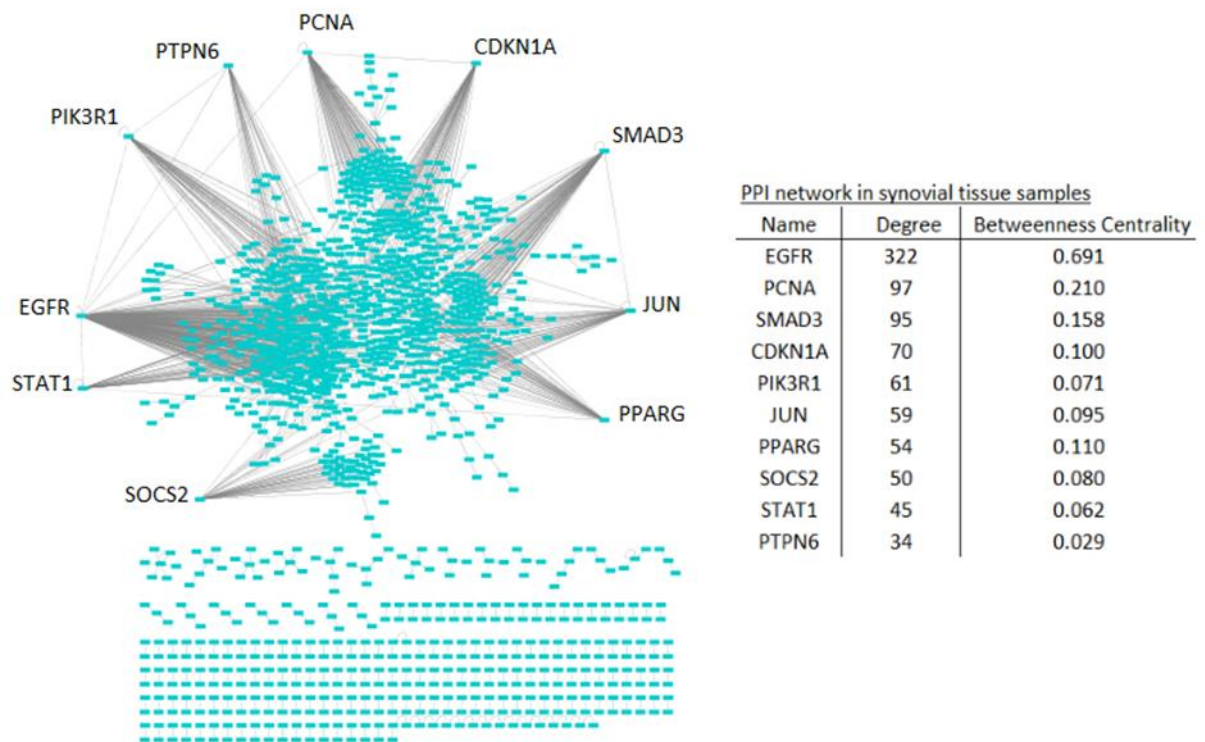


Figure 4.9 Synovial tissue related to PPI network and hub proteins

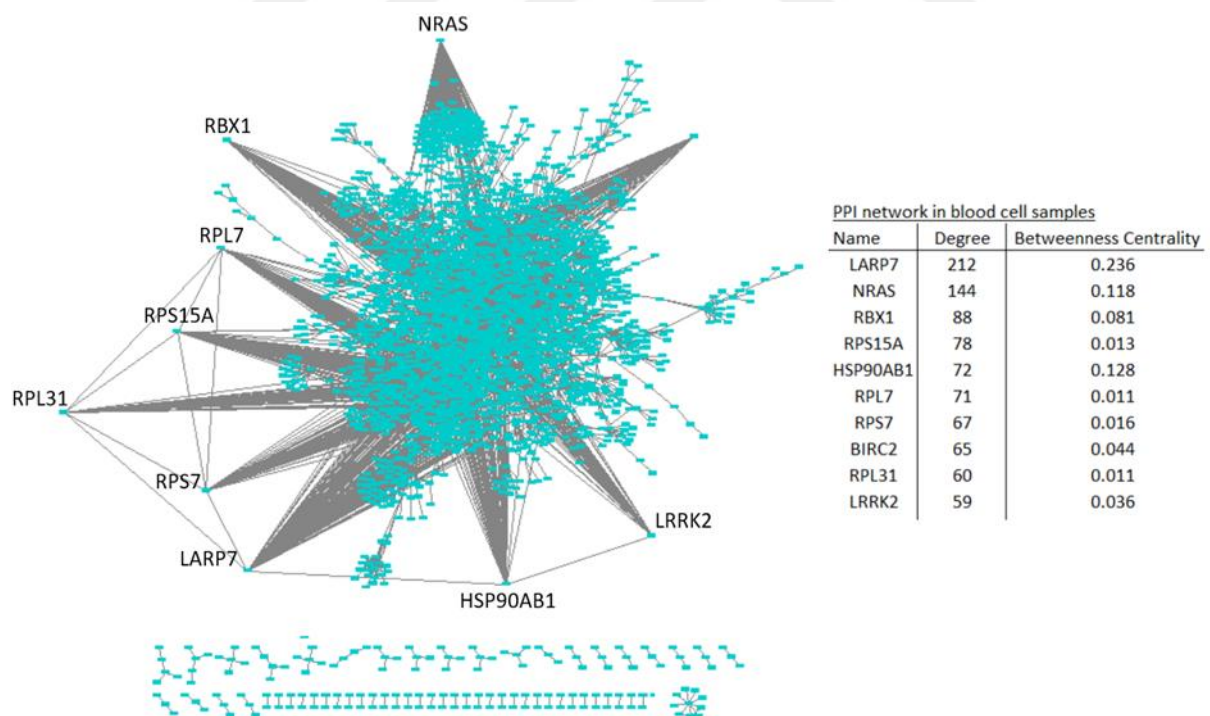


Figure 4.10 Blood cells related to PPI network and hub proteins

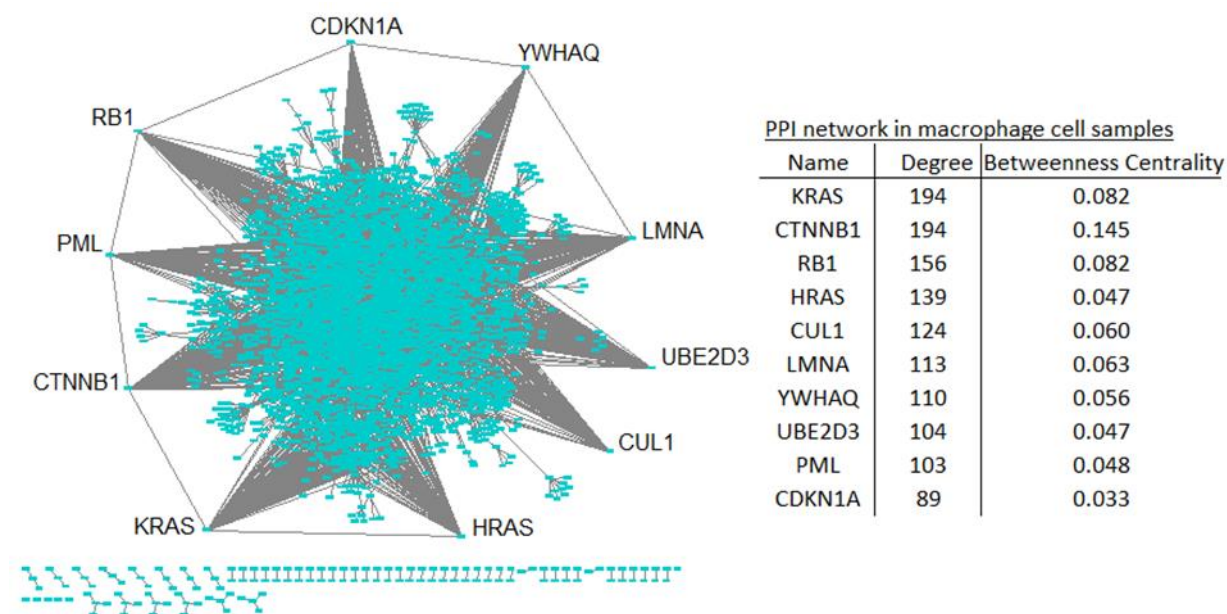


Figure 4.11 Macrophage cells related to PPI network and hub proteins

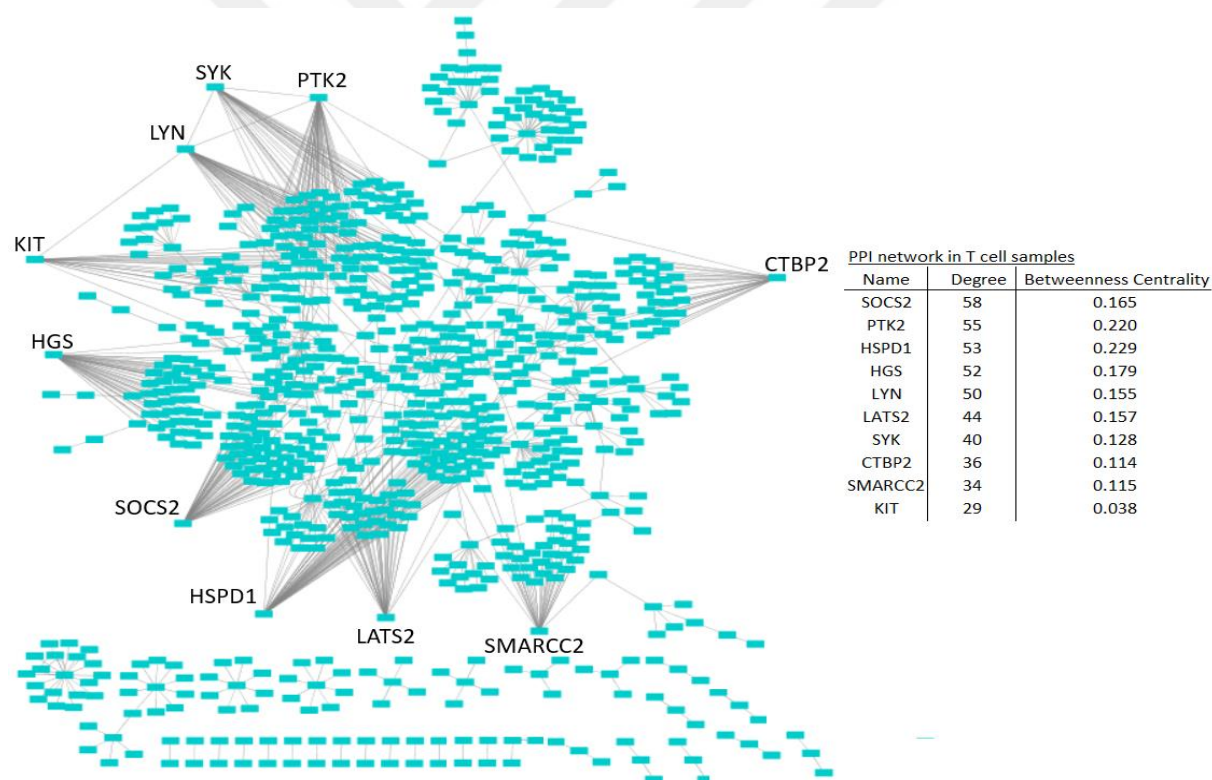


Figure 4.12 T cells related to PPI network and hub proteins

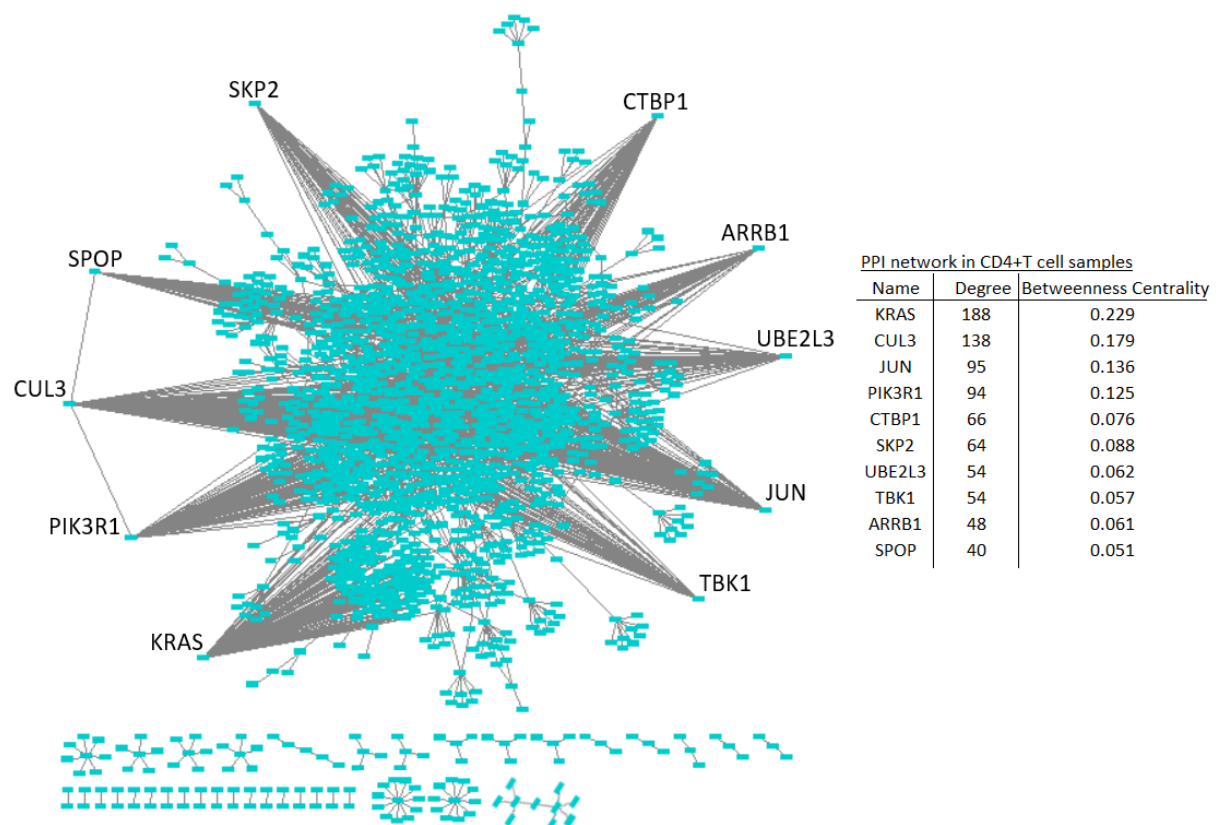


Figure 4.13 CD4⁺ T cells related to PPI network and hub proteins

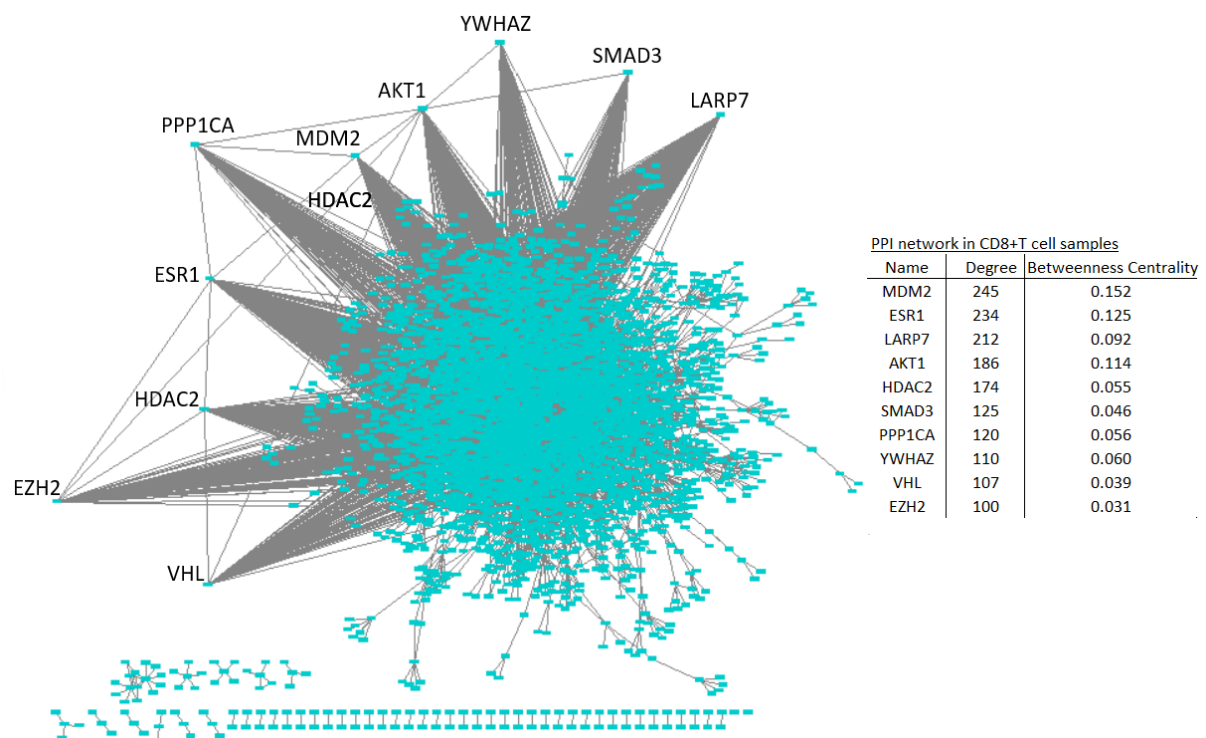


Figure 4.14 CD8⁺ T cells related to PPI network and hub proteins

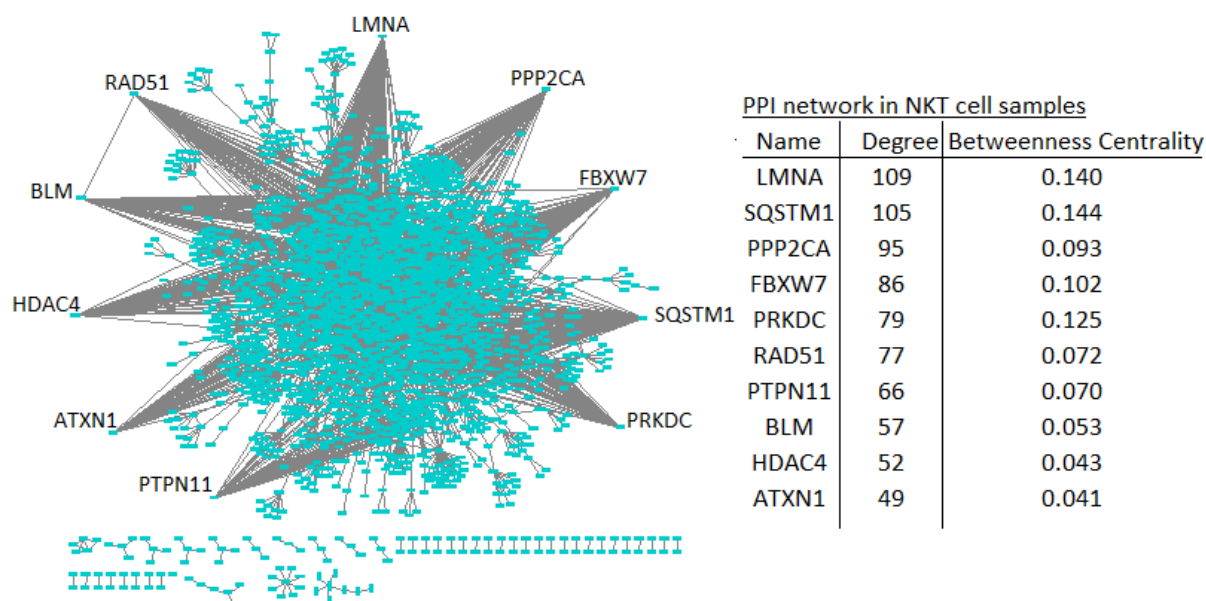


Figure 4.15 NKT cells related to PPI network and hub proteins

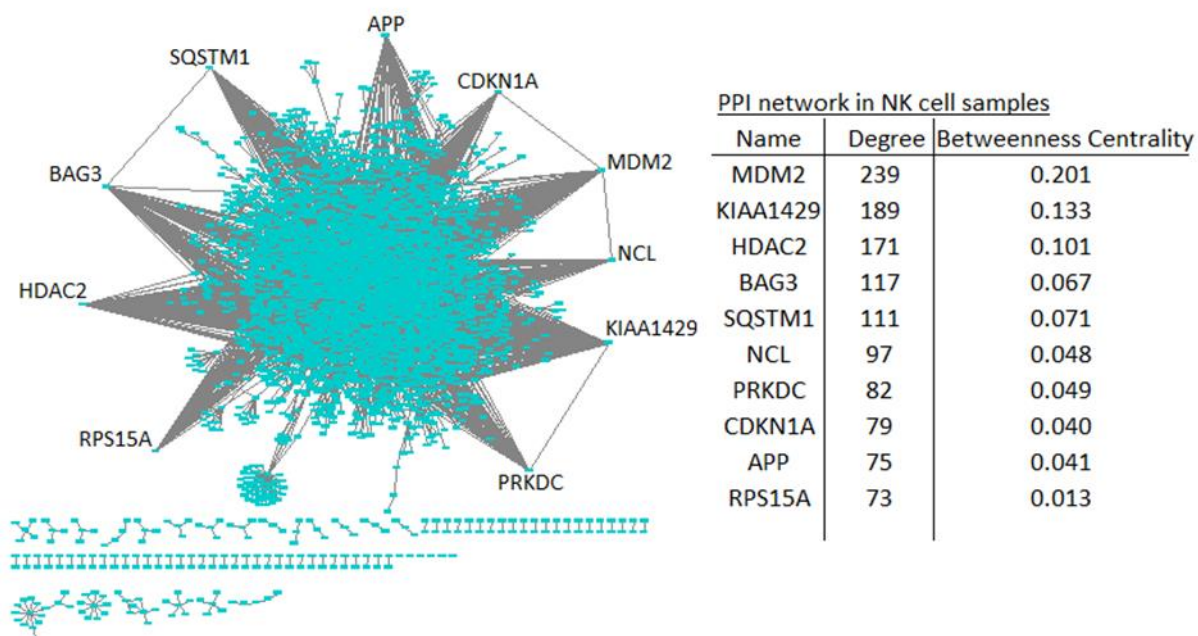


Figure 4.16 NK cells related to PPI network and hub proteins

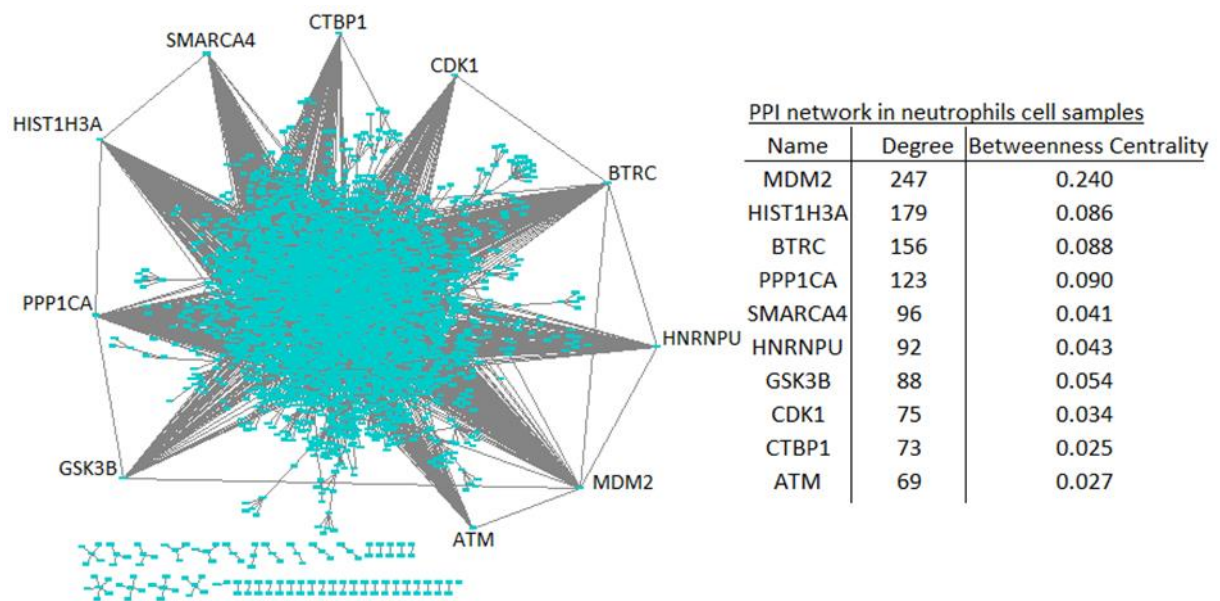


Figure 4.17 Neutrophils cells related to PPI network and hub proteins

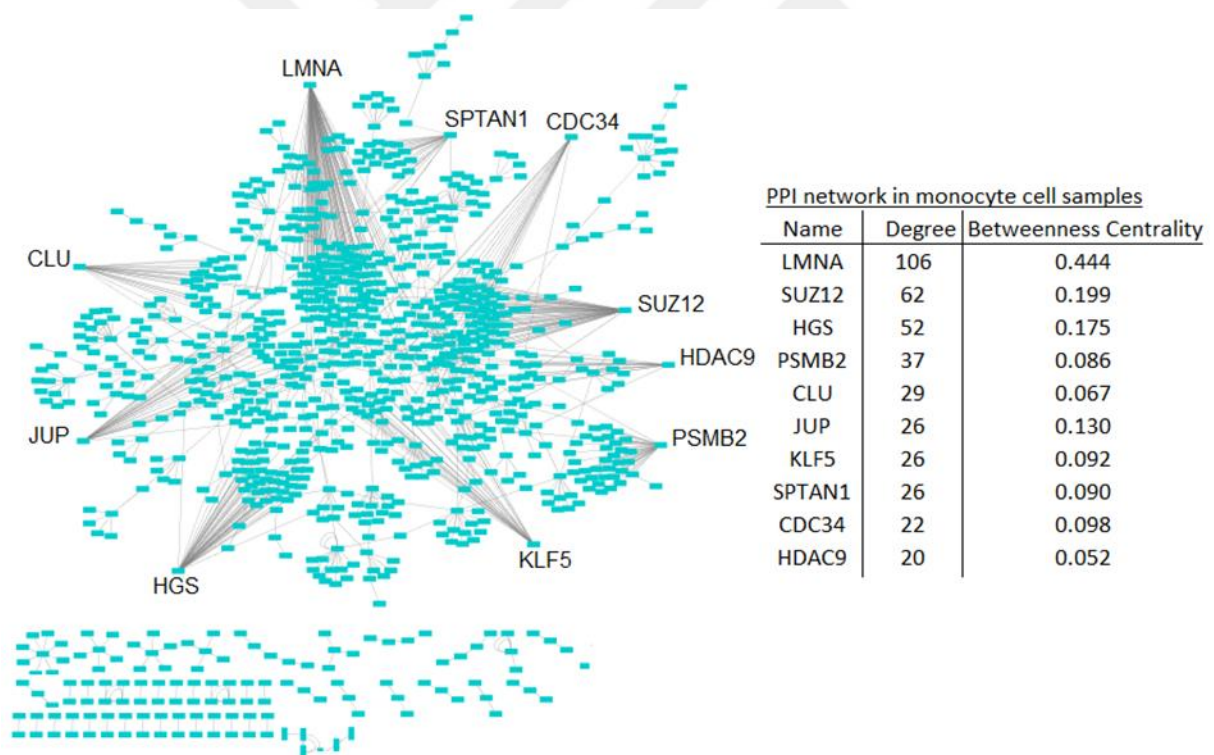


Figure 4.18 Monocyte cells related to PPI network and hub proteins

4.4. Reporter biomolecules in RA

Reporter TFs and miRNAs, which are transcriptional and post-translational regulatory components, have been identified based on transcriptomic alterations and extensive interaction data through analysis of hypergeometric probability in disease states. The highly significant TFs, miRNAs, and receptors were identified as reporter biomolecules (Table 4.2).

There were no common reporter TFs in all tissues. AR was identified in all T group cells (T cells, CD4⁺ T cells, CD8⁺ T cells, NKT cells, NK cells) as well as blood cells, macrophage cells, and neutrophils cells. FOXP3 was highlighted in all tissues except NKT and monocyte cells. Therefore, GATA2 was a common TF in all tissues except T-group cells. The protein functions of AR are a steroid hormone activated TF and it was reported that C- AR (Clematichinenoside AR) may play a role in myofibroblast activation by blocking the cross-talk between inflammation and fibrosis (Y. Li et al., 2016). In the association of FOXP3 and RA, the polymorphism of the FOXP3 gene affects the frequency of regulatory T cells function and disease activity in patients with RA (Hashemi et al., 2018). GATA2 is the GATA family of zinc-finger transcription factors. Recently, it was pointed out that, rheumatological manifestations and immune dysregulation are common in GATA2 deficiency (Amarnani et al., 2020).

Results of reporter miRNA analysis were represented miR-155-5p is mutual miRNAs in all tissues. Besides, miR-192-5p, miR-30a-5p, miR-155-5p, and miR-218-5p was identified in all T group cell tissues. miR-155 plays a critical role in the inflammatory process and RA (Kolarz et al., 2020). On the other side, miR-192 were determined in a few autoimmune disease types such as RA (Zheng et al., 2020), HIV-1 (Hernández-Walias et al., 2020), Type1 diabetes (Tesovnik et al., 2020) as well as Behcet Diseases (Puccetti et al., 2018). In addition, miR-30a-5p has played an important role in regulating autoimmune responses in RA by blocking the B cell activation factor (Alsaleh et al., 2014; Xu et al., 2013), which plays an important role in various biological processes such as cellular proliferation, differentiation, and apoptosis (Hwang & Mendell, 2006; Yates et al., 2013). miR-218-5p and RA association is not mentioned previously, this miRNA may be beneficial for understanding the biological mechanisms of RA. Another side, common miRNA in synovial tissues, blood cells, macrophage cells, and monocyte cells were miR-146a-5p. Besides, miR-3160-3p and miR-142-3p were common miRNAs in synovial tissues, blood cells, macrophage cells, and neutrophil cells.

Furthermore, there were not found common receptors in all tissues with RA. It may suggest that this result is not interesting because of tissue or cell differences. miRNAs, TF, and receptors were statistically significantly determined ($p < .01$). The rest of them were presented in (Supplementary Table 11-20)

Table 4.2 The top five reporter TFs, miRNAs and receptors

Tissue type	miRNA	p-value	TF	p-value	Receptor	p-value
Synovial Tissues	miR-146a-5p	1.18E-06	FOXP3	1.54E-10	LCK	9.40E-12
	miR-335-5p	1.25E-06	ESR1	2.59E-07	JAK2	3.70E-05
	miR-127-3p	3.32E-05	GATA3	6.58E-05	EPOR	1.59E-04
	miR-124-3p	3.72E-04	FOXA1	2.95E-04	CCR5	1.99E-04
	miR-558	4.12E-04	EGR1	8.17E-04	DPP4	3.29E-04
Blood Cells	miR-32-5p	2.42E-08	ETS1	6.57E-16	EP300	5.72E-03
	miR-146a-5p	8.89E-08	FOXP3	7.41E-09		
	miR-192-5p	1.71E-07	SPI1	3.88E-04		
	miR-215-5p	5.54E-07	AR	1.01E-03		
	miR-30a-5p	2.20E-06	CEBPA	1.79E-03		
Macrophage Cells	miR-26b-5p	3.82E-20	ETS1	1.07E-34	SRC	2.37E-05
	miR-155-5p	1.81E-15	GATA2	2.81E-32	ERBB2	1.15E-04
	miR-17-5p	1.33E-13	FOXP3	3.29E-30	HIPK3	2.00E-04
	miR-106a-5p	9.17E-13	ESR1	1.28E-26	CDK2	2.76E-04
	miR-16-5p	1.15E-12	AR	1.32E-24	IL1B	2.78E-04
T Cells	miR-19b-3p	1.07E-05	FOXP3	1.54E-06	EPOR	6.98E-06
	miR-4679	1.30E-04	AR	1.27E-05	CSF3R	4.34E-04
	miR-548c-3p	2.42E-04	ESR1	2.34E-04	PRLR	6.73E-04
	miR-187-5p	2.77E-04	EGR1	7.68E-04	ITPR1	1.23E-03
	miR-944	3.09E-04	GATA2	8.30E-04	GHR	3.74E-03
CD4 ⁺ T Cells	miR-21-5p	6.05E-10	ETS1	3.44E-83		
	miR-3938	1.05E-07	GATA2	3.10E-59		
	miR-221-3p	1.12E-06	AR	8.39E-48		
	miR-26a-5p	3.43E-06	YBX1	4.21E-41		
	miR-568	4.02E-06	FOXP3	7.43E-35		
CD8 ⁺ T Cells	miR-15b-5p	3.97E-08	ETS1	1.30E-15	CDK5	1.10E-03
	miR-21-5p	1.42E-07	YBX1	3.47E-06	KDM6B	1.93E-03
	miR-8485	2.80E-07	FOXP3	3.83E-06	KMT2B	2.20E-03
	miR-195-5p	4.75E-07	GATA2	1.15E-03	EHMT2	6.62E-03
	miR-19b-3p	5.67E-07	AR	3.69E-03	WDR5	9.75E-03
NKT Cells	miR-511-3p	2.17E-06	AR	5.28E-04	SRC	9.71E-04
	miR-223-5p	2.21E-05	PRDM14	2.72E-03	PRKDC	1.60E-03
	miR-6741-5p	6.73E-05	YBX1	6.24E-03	RAF1	4.58E-03
	miR-1277-5p	8.13E-05			ABL1	6.93E-03
	miR-590-3p	9.97E-05				

NK Cells	miR-21-5p	2.45E-07	PRDM14	7.06E-06	HDAC6	8.35E-04
	miR-8485	2.43E-06	AR	1.27E-05	EGFR	9.82E-04
	miR-5011-5p	5.00E-05	ETS1	1.69E-05	PTEN	2.33E-03
	miR-6883-3p	7.06E-05	TFAP2C	2.25E-03	LYN	3.88E-03
	miR-4762-3p	8.63E-05	FOXA1	2.99E-03	ADA	9.67E-03
Neutrophil Cells	miR-16-5p	6.61E-12	ETS1	1.04E-15	SRC	2.43E-03
	miR-15b-5p	1.02E-09	GATA1	1.25E-05	BIRC2	2.64E-03
	miR-19b-3p	1.55E-09	FOXP3	1.60E-05	GRM8	6.90E-03
	miR-21-5p	4.32E-09	AR	5.72E-05	ITPR1	7.63E-03
	miR-195-5p	5.06E-09	YBX1	2.20E-04	BIRC6	8.82E-03
Monocyte Cells	miR-4747-5p	3.61E-04	GATA2	7.80E-03		
	miR-5196-5p	3.61E-04				
	miR-6511a-3p	5.10E-04				
	miR-3149	5.19E-04				
	miR-6511b-3p	5.51E-04				

4.5. Metabolic signatures in RA

Reporter metabolites have been identified for each dataset through the integration of established DEGs with the genome-scale metabolic network. The top five reporter metabolites have been taken into consideration (Table 4.3). As a result of the reporter metabolite analysis, different and common metabolic signatures were observed in different tissues with RA (Supplementary Table 21-30). A common metabolic reporter could not be detected in studied all tissues.

Note that it was removed some metabolites from the reporter metabolite analysis, including proton, water, oxygen molecule, NADH, NAD⁺, NADPH, NADP⁺, ATP, ADP, carbon dioxide, carbon monoxide, phosphate, ammonia, hydrogen peroxide, oxidized electron acceptor, and reduced electron acceptor etc. Their role in many reactions bias metabolite measurements (Kim et al., 2015).

Pyruvate were also reported in T- group cells member: CD8⁺ T cells, NKT cells, and NK cells. Pyruvate undergoes a series of oxidizing reactions, thereby generating ATP (Sanchez-Lopez et al., 2019). Pyruvate kinase is the enzyme responsible for the final rate-limiting step of glycolysis, catalyzing phosphoenolpyruvic acid, and ADP to pyruvate and ATP (Alves-Filho & Pålsson-McDermott, 2016). On the other hand, ethyl pyruvate the ethyl ester of pyruvate and has antioxidant and anti-inflammatory effects. Ethyl pyruvate had attenuated synovial inflammation and bone resorption in the experimental arthritis model through suppression of IL-17 and HMGB-1 (Jung et al., 2017).

On the other side, the de-Fuc form of PA6, keratan sulfate I, and hypoxanthine, were chased as reporter metabolites in synovial tissue and macrophage cells. Moreover, succinate, pyruvate, succinate semialdehyde, (11Z)-docos enoyl-CoA, (13Z,16Z)-docosadi enoyl-CoA, (8Z,11Z)-eicosadi enoyl-CoA, 10,13,16-docosatri enoyl-CoA, 13,16,19-docosatri enoyl-CoA, NAD⁺ and L-lactate were common reporter metabolites in macrophage cells and neutrophils. Furthermore, (13Z)-octadec enoyl-CoA, (7Z)-octade cenoyl-CoA, (9E)-octadec enoyl-CoA and (9E)-tetradec enoyl-CoA were common metabolites in synovial tissue and neutrophils. Acetyl-CoA (acetyl coenzyme A) is a molecule that participates in several biochemical reactions in protein, carbohydrate, and lipid metabolism. Its main task is to bring the acetyl group to citric transformation (Krebs cycle) to be oxidized for energy production. The citric acid cycle is the main metabolic pathway for all aerobic processes. The cycle has enabled acetyl-CoA derived from fats, carbohydrates, and amino acids to fully oxidize to carbon dioxide and capture the released energy as reducing power in the form of NADH and FADH₂ in patients with RA (Yang et al., 2015).

Results of enrichment analysis based on reporter metabolites indicated RA -related metabolic pathways such as metabolic pathways, metabolism (pyrimidine metabolism, propanoate metabolism, nicotinate, and nicotinamide metabolism, propanoate metabolism, vitamin B6 metabolism), oxidative phosphorylation, biosynthesis of secondary metabolites, mTOR signaling pathway, neuroactive ligand-receptor interaction, calcium signaling pathway, lysosome, endocytosis, and also diseases such as Parkinson's disease and Type II diabetes mellitus (Table 4.4). This finding is not surprising in light of the fact that metabolic pathways were affected in almost all tissues (except T cells) of RA patients (Supplementary Table 31).

A fundamental abnormality of RA is the improper growth of immune cells and synovial cells, and its high metabolic demands to produce energy and biosynthetic precursors have reinforced different and common metabolic signatures in different tissues with RA. In RA, distinct cells undergo metabolic adaptations to generate biomass (Weyand and Goronzy, 2017) and our results have shown that each tissue or cells with RA has a different metabolic environment (Supplementary Table 31).

Table 4.3 The top five reporter metabolites of each data set

Synovial Tissues	GSE1919	3,4-dihydroxymandelaldehyde, 3,4-dihydroxyphenylacetaldehyde, 3-hydroxykynurenamine 3-methoxy-4-hydroxyphenylacetaldehyde, 3-methoxy-4-hydroxyphenylglycolaldehyde
	GSE55457	de-Fuc form of PA6 (wo peptide linkage), de-Fuc form of PA6, keratan sulfate I, degradation product 1, n2m2nm, n2m2nmasn
	GSE77298	2-deoxy-D-ribose-1-phosphate, hypoxanthine
Blood Cells	GSE93272	UTP, ubiquinol, ubiquinone, ferricytochrome C, ferrocyclochrome C
Macrophage Cells	GSE10500	beta-1,4-mannose-N-acetyl glucosamine, mannose, (5S,6S)-epoxy-(15R)-hydroxy-ETE, 11,12-DHET, 15-epi-lipoxin B5
	GSE97779	6-deoxy-L-galactose, de-Fuc form of PA6, keratan sulfate I, (5S,6S)-epoxy-(15R)-hydroxy-ETE, 1,2-dihydronaphthalene-1,2-diol
T Cells	GSE65010 Naïve	1-(1-alkenyl)-sn-glycero-3-phosphate, 1-(1-alkenyl)-sn-glycero-3-phosphoethanolamine, ethanolamine
CD4 ⁺ T Cells	GSE93776 Naïve	1D-myo-inositol-1,3,4,5-tetrakisphosphate, 1D-myo-inositol-1,3,4-trisphosphate, 13,14-dihydro-15-oxo-lipoxin A4, 15-oxo-lipoxin A4, 3alpha,7alpha,12alpha,25-tetrahydroxy-5beta-cholestane-24-one
	GSE56649	O-phosphoprotamine, protamine, carnosine,
CD8 ⁺ T Cells	GSE93776 Naïve	Pi, apppA, pyridoxamine, pyridoxamine-phosphate, succinate
NKT Cells	GSE93776	PEP, pyruvate, farnesy-l cysteine,

		PAPS, 2-trans,6-trans-farnesals
NK Cells	GSE93776	PEP, pyruvate, farnesy-l cysteine, PAPS, 2-trans,6-trans-farnesal
Neutrophil Cells	GSE93776	succinate, cholesterol, 1,2-diacylglycerol-LD-TAG pool, (11Z)-docosenoyl-CoA, (11Z,14Z)-eicosadienoyl-CoA
Monocyte Cells	GSE93776	1,2-diacylglycerol-LD-PE pool, 1,2-diacylglycerol-LD-PS pool, 1-alkenyl-2-acylglycerol, 1-alkyl-2-acylglycerol, 1-alkyl-2-acyl-glycerophosphoethanolamine

Table 4.4 The top five KEGG metabolic pathway of each data set

Synovial Tissues	GSE55457	Purine metabolism, Metabolic pathways, Biosynthesis of secondary metabolites, mTOR signaling pathway, Parkinson's disease
Blood Cells	GSE93272	Pyrimidine metabolism, Metabolic pathways, Neuroactive ligand-receptor interaction
Macrophage Cells	GSE10500	Pyrimidine metabolism, Metabolic pathways, Vitamin B6 metabolism
	GSE97779	Pyrimidine metabolism, Metabolic pathways, Vitamin B6 metabolism
CD4 ⁺ T Cells	GSE56649	Oxidative phosphorylation, Purine metabolism, Metabolic pathways, Biosynthesis of secondary metabolites, Calcium signaling pathway
CD8 ⁺ T Cells	GSE93776 naïve	Oxidative phosphorylation, Metabolic pathways, ABC transporters, Parkinson's disease, Purine metabolism
NKT Cells	GSE93776	Propanoate metabolism, Nicotinate and nicotinamide metabolism, Metabolic pathways, Oxidative phosphorylation, Purine metabolism
NK Cells	GSE93776	Propanoate metabolism, Nicotinate and nicotinamide metabolism, Metabolic pathways, Oxidative phosphorylation, Purine metabolism
Neutrophils Cells	GSE93776	Riboflavin metabolism, Metabolic pathways
Monocytes Cells	GSE93776	Purine metabolism, MAPK signaling pathway, Calcium signaling pathway, Chemokine signaling pathway, Oocyte meiosis

5. CONCLUSIONS

Diagnosing and developing effective treatment strategies for RA requires an understanding of its formation and progression mechanisms. Analyzes at the transcriptome level serve to understand the mechanisms behind disease pathogenesis, identify new biomarkers and therapeutic targets, and generate new information that can help discover novel drugs. Gene expression datasets have been used to elucidate the mechanisms of disease mechanism and miRNAs, TFs, receptors and hub proteins related to the tissue-specific progression of RA have been identified via holistic and comparative systems biology perspective.

Rapid advances in omics technologies have allowed massive functional genomic datasets associated with diseases. The network medicine perspective represents a holistic view of the underlying disease mechanism and providing better and effective treatment strategies by using disease-associated high-throughput datasets. To identify tissue-specific molecular signatures of RA will be useful for understanding the biological mechanisms of RA and these molecular signatures might give important candidate drug targets.

Biological insight of reporter biomolecules and DEGs provides valuable insight into RA pathogenesis. According to enrichment analysis results, interferon-gamma signaling was enriched in all tissues except T cells and CD8⁺ T cells. Furthermore, cytokine signaling in the immune system has come into the prominent pathway in almost all tissues.

It was analyzed synovial tissues, blood cells, macrophage cells, T cells, CD4⁺ T cells, CD8⁺ T cells, NKT cells, NK cells, neutrophil cells, and monocyte cells specific transcriptome data with the biological network as PPI network. It was concluded several common hub proteins identified two or more tissue types. CDKN1A was the hub protein in synovial tissue, macrophage cells, and NK cells. LMNA came into prominence in NKT cells, macrophages, and monocytes. HDAC family members HDAC2, HDAC4, and HDAC9 were identified as the hub proteins in NK, NKT cells, and monocyte, respectively. Ras family of protein members KRAS and HRAS were hub protein observed in macrophages, besides NRAS observed in the blood cells. SOCS family members SOCS1 and SOCS2 were seen in mutually CD4⁺ T cells and synovial tissues. SOCS2 Cullin family members CUL1 and CUL3 were hub protein observed in macrophages, CD4⁺ T cells.

The valuable information was obtained from the identification of reporter biomolecules analysis. AR was identified as reporter TF in all T group cells (T cells, CD4⁺ T cells, CD8⁺ T cells, NKT cells, NK cells) as well as blood cells, macrophage cells, and neutrophils cells. FOXP3 was also highlighted in all tissues except NKT and monocyte cells. Besides, it was found that GATA2 was a common TF in all tissues except T-group cells. Results of reporter miRNA analysis were represented miR-155-5p is common miRNAs in all tissues. Besides, miR-192-5p, miR-30a-5p, miR-155-5p, and miR-218-5p was identified in all T group cell tissues. Besides, miR-3160-3p and miR-142-3p were common miRNAs in synovial tissues, blood cells, macrophage cells, and neutrophil cells. Furthermore, there were not found common receptors in all tissues with RA. This finding is not surprising in light of the fact that differences in tissue or cell type.

According to reporter metabolite analysis results, pyruvate were reported in T- group cells member: CD8⁺ T cells, NKT cells, and NK cells. However, we chased some common reporters in each tissue. Pyruvate, and Acetyl-CoA members were shared in several cells/tissue levels. Distinct signatures were observed at the metabolome level, and different groups of metabolites were significantly enriched in each tissue. Overall, this study has resulted in discoveries of the utmost importance concerning relations between RA and specific metabolic pathways, diseases, oxidative phosphorylation, mTOR signaling pathway, neuroactive ligand-receptor interaction, calcium signaling pathway, lysosome, endocytosis.

Tissue-specific RA signatures were screened during the current study from different omics level reporter biomolecules. There was no opportunity to express specific reporters in each tissue because the number of gene or metabolites were abounding. In addition, these individual efforts showed that various signaling pathways and biological processes are associated with RA for each tissue or immunologic cell. Additionally, the overlap in the transcriptomic, proteomic, and metabolic results of the different experimental studies highlighted the important role of transcriptional and posttranscriptional control mechanisms of the RA. Consequently, miR-155-5p, common in all RA-specific tissues, demonstrates the importance of other biomolecules found (Su et al., 2017).

In summary, our systems biology approaches provide insight into genes/proteins, reporter TF, miRNAs, metabolites, hub proteins in PPI, and molecular pathways that mediate RA development and provide potentially valuable information for the diagnosis and treatment for this disease. All these findings provided the significance of integrative approaches within the concept of systems biology in future RA research. It was suggested that the molecular signatures for each tissue or cells may represent tissue-specific potential effective biomarkers and a pharmacologically tractable therapeutic target.



6. RECOMMENDATIONS

The pathogenesis of RA is not entirely understood. Early diagnosis and effective treatment are very important to prevent joint deterioration, functional disability, and negative disease consequences. RA is a heterogeneous disease with varying clinical manifestations and pathogenetic mechanisms located between individuals with the same formal diagnosis or at different disease stages (Smolen et al., 2018).

The results of the present study may have an important resource for understanding the molecular mechanism of RA. Future research investments could be considered as drug targets and the development of new diagnostic strategies. Common molecular signatures should be detailed investigated for future computational and experimental studies. Especially synovial tissue and blood samples from RA patients should be obtained to achieve the experimental studies such as real-time PCR for gene expression and western blotting for protein expression.

REFERENCES

- Afroz, S., Giddaluru, J., Vishwakarma, S., Naz, S., Khan, A. A., & Khan, N. (2017). A comprehensive gene expression meta-analysis identifies novel immune signatures in rheumatoid arthritis patients. *Frontiers in Immunology*, 8(FEB), 1–12.
<https://doi.org/10.3389/fimmu.2017.00074>
- Agren, R., Liu, L., Shoaie, S., Vongsangnak, W., Nookaew, I., & Nielsen, J. (2013). The RAVEN Toolbox and Its Use for Generating a Genome-scale Metabolic Model for *Penicillium chrysogenum*. *PLoS Computational Biology*, 9(3).
<https://doi.org/10.1371/journal.pcbi.1002980>
- Ahn, J. K., Kim, S., Hwang, J., Kim, J., Kim, K. H., & Cha, H. S. (2016). GC/TOF-MS-based metabolomic profiling in cultured fibroblast-like synoviocytes from rheumatoid arthritis. *Joint Bone Spine*, 83(6), 707–713. <https://doi.org/10.1016/j.jbspin.2015.11.009>
- Alsaleh, G., François, A., Philippe, L., Gong, Y. Z., Bahram, S., Cetin, S., Pfeffer, S., Gottenberg, J. E., Wachsmann, D., Georgel, P., & Sibilia, J. (2014). MiR-30a-3p negatively regulates BAFF synthesis in systemic sclerosis and rheumatoid arthritis fibroblasts. *PLoS ONE*, 9(10). <https://doi.org/10.1371/journal.pone.0111266>
- Alves-Filho, J. C., & Pålsson-McDermott, E. M. (2016). Pyruvate kinase M2: A potential target for regulating inflammation. *Frontiers in Immunology*, 7(APR), 1–7.
<https://doi.org/10.3389/fimmu.2016.00145>
- Amarnani, A. A., Poladian, K. R., Marciano, B. E., Daub, J. R., Williams, S. G., Livinski, A. A., Hsu, A. P., Palmer, C. L., Kenney, C. M., Avila, D. N., Holland, S. M., & Katz, J. D. (2020). A Panoply of Rheumatological Manifestations in Patients with GATA2 Deficiency. *Scientific Reports*, 10(1), 1–9. <https://doi.org/10.1038/s41598-020-64852-1>
- Article, R. (2019). The roles of anti-citrullinated protein antibodies in the immunopathogenesis of rheumatoid arthritis. *Tzu-Chi Medical Journal*, 31(1), 5–10.
<https://doi.org/10.4103/tcmj.tcmj>
- Azizieh, F. Y., Al Jarallah, K., Shehab, D., Gupta, R., Dingle, K., & Raghupathy, R. (2017). Patterns of circulatory and peripheral blood mononuclear cytokines in rheumatoid arthritis. *Rheumatology International*, 37(10), 1727–1734.
<https://doi.org/10.1007/s00296-017-3774-6>
- Barabási, A., Gulbahce, N., & Loscalzo, J. (2011). Network medicine : a network-based

- approach to human disease. *Nature Publishing Group*, 12(jANuARy).
<https://doi.org/10.1038/nrg2918>
- Barrett, T., Wilhite, S. E., Ledoux, P., Evangelista, C., Kim, I. F., Tomashevsky, M., Marshall, K. A., Phillippy, K. H., Sherman, P. M., Holko, M., Yefanov, A., Lee, H., Zhang, N., Robertson, C. L., Serova, N., Davis, S., & Soboleva, A. (2013). NCBI GEO: Archive for functional genomics data sets - Update. *Nucleic Acids Research*, 41(D1), 991–995. <https://doi.org/10.1093/nar/gks1193>
- Bartel, D. P. (2004). MicroRNAs: Genomics, Biogenesis, Mechanism, and Function. *Cell*, 116(2), 281–297. [https://doi.org/10.1016/S0092-8674\(04\)00045-5](https://doi.org/10.1016/S0092-8674(04)00045-5)
- Berzins, S. P., Smyth, M. J., & Baxter, A. G. (2011). Presumed guilty: Natural killer T cell defects and human disease. *Nature Reviews Immunology*, 11(2), 131–142.
<https://doi.org/10.1038/nri2904>
- Blake, J. A., Christie, K. R., Dolan, M. E., Drabkin, H. J., Hill, D. P., Ni, L., Sitnikov, D., Burgess, S., Buza, T., Gresham, C., McCarthy, F., Pillai, L., Wang, H., Carbon, S., Dietze, H., Lewis, S. E., Mungall, C. J., Munoz-Torres, M. C., Feuermann, M., ... Westerfeld, M. (2015). Gene ontology consortium: Going forward. *Nucleic Acids Research*, 43(D1), D1049–D1056. <https://doi.org/10.1093/nar/gku1179>
- Bovolenta, L. A., Acencio, M. L., & Lemke, N. (2012). HTRIdb: an open-access database for experimentally verified human transcriptional regulation interactions. *BMC Genomics*, 13(1), 405. <https://doi.org/10.1186/1471-2164-13-405>
- Broeren, M. G., de Vries, M., Bennink, M. B., Arntz, O. J., Blom, A. B., Koenders, M. I., ... & van de Loo, F. A. (2016). Disease-regulated gene therapy with anti-inflammatory interleukin-10 under the control of the CXCL10 promoter for the treatment of rheumatoid arthritis. 27(3), 244–254. <https://doi.org/10.2174/138161211796197016>
- Calimlioglu, B., Karagoz, K., Sevimoglu, T., Kilic, E., Gov, E., & Arga, K. Y. (2015). Tissue-Specific Molecular Biomarker Signatures of Type 2 Diabetes: An Integrative Analysis of Transcriptomics and Protein-Protein Interaction Data. *OMICS A Journal of Integrative Biology*, 19(9), 563–573. <https://doi.org/10.1089/omi.2015.0088>
- Carlson, A. K., Rawle, R. A., Wallace, C. W., Adams, E., Greenwood, M. C., Bothner, B., & June, R. K. (2019). Global metabolomic profiling of human synovial fluid for rheumatoid arthritis biomarkers. *Clinical and Experimental Rheumatology*, 37(3), 393–399.
- Carmona-Saez, P., Chagoyen, M., Tirado, F., Carazo, J. M., & Pascual-Montano, A. (2007).

- GENECODIS: A web-based tool for finding significant concurrent annotations in gene lists. *Genome Biology*, 8(1), 1–8. <https://doi.org/10.1186/gb-2007-8-1-r3>
- Chatr-Aryamontri, A., Oughtred, R., Boucher, L., Rust, J., Chang, C., Kolas, N. K., O'Donnell, L., Oster, S., Theesfeld, C., Sellam, A., Stark, C., Breitkreutz, B. J., Dolinski, K., & Tyers, M. (2017). The BioGRID interaction database: 2017 update. *Nucleic Acids Research*, 45(D1), D369–D379. <https://doi.org/10.1093/nar/gkw1102>
- Chen, C., Fuh, L., Huang, C., Hsu, C., & Su, C. (2017). Enhancement of CCL2 expression and monocyte migration by CCN1 in osteoblasts through inhibiting miR-518a-5p : implication of rheumatoid arthritis therapy. *Scientific Reports, February*, 1–11. <https://doi.org/10.1038/s41598-017-00513-0>
- Chen, J., Yang, J., Qiao, Y., & Li, X. (2016). *Understanding the Regulatory Roles of Natural Killer T Cells in Rheumatoid Arthritis : T Helper Cell Differentiation Dependent or Independent ?* 197–203. <https://doi.org/10.1111/sji.12460>
- Choi, S., You, S., Kim, D., Choi, S. Y., Kwon, H. M., Kim, H. S., Hwang, D., Park, Y. J., Cho, C. S., & Kim, W. U. (2017). Transcription factor NFAT5 promotes macrophage survival in rheumatoid arthritis. *Journal of Clinical Investigation*, 127(3), 954–969. <https://doi.org/10.1172/JCI87880>
- Chou, C. H., Chang, N. W., Shrestha, S., Hsu, S. Da, Lin, Y. L., Lee, W. H., Yang, C. D., Hong, H. C., Wei, T. Y., Tu, S. J., Tsai, T. R., Ho, S. Y., Jian, T. Y., Wu, H. Y., Chen, P. R., Lin, N. C., Huang, H. T., Yang, T. L., Pai, C. Y., ... Huang, H. Da. (2016). miRTarBase 2016: Updates to the experimentally validated miRNA-target interactions database. *Nucleic Acids Research*, 44(D1), D239–D247. <https://doi.org/10.1093/nar/gkv1258>
- Ciccacci, C., Latini, A., Perricone, C., Conigliaro, P., Colafrancesco, S., Ceccarelli, F., Priori, R., Conti, F., Perricone, R., Novelli, G., & Borgiani, P. (2019). TNFAIP3 gene polymorphisms in three common autoimmune diseases: Systemic lupus erythematosus, rheumatoid arthritis, and primary sjogren syndrome - association with disease susceptibility and clinical phenotypes in Italian patients. *Journal of Immunology Research*, 2019. <https://doi.org/10.1155/2019/6728694>
- Comertpay, B., & Gov, E. (2020). Identification of key biomolecules in rheumatoid arthritis through the reconstruction of comprehensive disease-specific biological networks. *Autoimmunity*, 0(0), 1–11. <https://doi.org/10.1080/08916934.2020.1722107>
- Croft, D., O'Kelly, G., Wu, G., Haw, R., Gillespie, M., Matthews, L., Caudy, M., Garapati,

- P., Gopinath, G., Jassal, B., Jupe, S., Kalatskaya, I., MayMahajan, S., May, B., Ndegwa, N., Schmidt, E., Shamovsky, V., Yung, C., Birney, E., ... Stein, L. (2011). Reactome: A database of reactions, pathways and biological processes. *Nucleic Acids Research*, 39(SUPPL. 1), 691–697. <https://doi.org/10.1093/nar/gkq1018>
- Dakin, S. G., Coles, M., Sherlock, J. P., Powrie, F., Carr, A. J., & Buckley, C. D. (2018). Pathogenic stromal cells as therapeutic targets in joint inflammation. *Nature Reviews Rheumatology*, 14(12), 714–726. <https://doi.org/10.1038/s41584-018-0112-7>
- Deng, H., Li, F., Li, H., Deng, Y., Liu, J., Wang, D., Han, G., Wang, X., & Zhang, Q. (2014). CtBP1 Overexpression in Keratinocytes Perturbs Skin Homeostasis. *Journal of Investigative Dermatology*, 134(5), 1323–1331. <https://doi.org/10.1038/jid.2013.504>
- Deodhar, A. A., & Woolf, A. D. (1996). Bone mass measurement and bone metabolism in rheumatoid arthritis: A review. *Revmatologiia*, 35(4), 309–322. <https://doi.org/10.1093/rheumatology/35.4.309>
- Ekwall, A. H., Whitaker, J. W., Hammaker, D., Bugbee, W. D., Wang, W., & Firestein, G. S. (2015). The Rheumatoid Arthritis Risk Gene LBH Regulates Growth in Fibroblast-like Synoviocytes. *Arthritis & Rheumatology*, 67(5), 1193–1202. <https://doi.org/10.1002/art.39060>
- Fu, J., Schoeman, J. C., Harms, A. C., van Wietmarschen, H. A., Vreeken, R. J., Berger, R., Cuppen, B. V. J., Lafeber, F. P. J. G., van der Greef, J., & Hankemeier, T. (2016). Metabolomics profiling of the free and total oxidised lipids in urine by LC-MS/MS: application in patients with rheumatoid arthritis. *Analytical and Bioanalytical Chemistry*, 408(23), 6307–6319. <https://doi.org/10.1007/s00216-016-9742-2>
- Galarza-Delgado, D. A., Villegas Gonzalez, M. J., Riega Torres, J., Soto-Galindo, G. A., Mendoza Flores, L., & Treviño González, J. L. (2018). Early hearing loss detection in rheumatoid arthritis and primary Sjögren syndrome using extended high frequency audiometry. *Clinical Rheumatology*, 37(2), 367–373. <https://doi.org/10.1007/s10067-017-3959-0>
- Gang, X., Xu, H., Si, L., Zhu, X., Yu, T., Jiang, Z., & Wang, Y. (2018). Treatment effect of CDKN1A on rheumatoid arthritis by mediating proliferation and invasion of fibroblast-like synoviocytes cells. 194(2), 220–230. <https://doi.org/10.1111/cei.13161>
- Gov, E., Kori, M., & Arga, K. Y. (2017). RNA-based ovarian cancer research from ‘a gene to systems biomedicine’ perspective. *Systems Biology in Reproductive Medicine*, 63(4), 219–238. <https://doi.org/10.1080/19396368.2017.1330368>

- Guo, Y., Walsh, A. M., Canavan, M., Wechalekar, M. D., Cole, S., Yin, X., Scott, B., Loza, M., Orr, C., McGarry, T., Bombardieri, M., Humby, F., Proudman, S. M., Pitzalis, C., Smith, M. D., Friedman, J. R., Anderson, I., Madakamutil, L., Veale, D. J., Nagpal, S. (2018). Immune checkpoint inhibitor PD-1 pathway is down-regulated in synovium at various stages of rheumatoid arthritis disease progression. *PLoS ONE*, 13(2), 1–17. <https://doi.org/10.1371/journal.pone.0192704>
- Hannemann, N., Jordan, J., Paul, S., Baenkler, H., Sonnewald, S., Vera, J., Schett, G., & Bozec, A. (2017). The AP-1 Transcription Factor c-Jun Promotes Arthritis by Regulating Cyclooxygenase-2 and Arginase-1 Expression in Macrophages. *The Journal of Immunology*, 198(9), 3605–3614. <https://doi.org/10.4049/jimmunol.1601330>
- Harshan, S., Dey, P., & Ragunathan, S. (2018). Effects of rheumatoid arthritis associated transcriptional changes on osteoclast differentiation network in the synovium. *PeerJ*, 2018(10), 1–33. <https://doi.org/10.7717/peerj.5743>
- Hasegawa, T., Kikuta, J., Sudo, T., Matsuura, Y., Matsui, T., Simmons, S., Ebina, K., Hirao, M., Okuzaki, D., Yoshida, Y., Hirao, A., Kalinichenko, V. V., Yamaoka, K., Takeuchi, T., & Ishii, M. (2019). Identification of a novel arthritis-associated osteoclast precursor macrophage regulated by FoxM1. *Nature Immunology*, 20(12), 1631–1643. <https://doi.org/10.1038/s41590-019-0526-7>
- Hashemi, V., Farrokhi, A. S., Tanomand, A., Babaloo, Z., Hojjat-Farsangi, M., Anvari, E., Tahoori, M. T., Ezzeddini, R., Hosseini, A., Gharibi, T., Ghalamfarsa, G., & Jadidi-Niaragh, F. (2018). Polymorphism of Foxp3 gene affects the frequency of regulatory T cells and disease activity in patients with rheumatoid arthritis in Iranian population. *Immunology Letters*, 204(September), 16–22. <https://doi.org/10.1016/j.imlet.2018.10.001>
- Hayashi, J., Kihara, M., Kato, H., & Nishimura, T. (2015). A proteomic profile of synoviocyte lesions microdissected from formalin-fixed paraffin-embedded synovial tissues of rheumatoid arthritis. *Clinical Proteomics*, 12(1), 4–13. <https://doi.org/10.1186/s12014-015-9091-8>
- Hernández-Walias, F., Ruiz-de-León, M. J., Rosado-Sánchez, I., Vázquez, E., Leal, M., Moreno, S., Vidal, F., Blanco, J., Pacheco, Y. M., & Vallejo, A. (2020). New signatures of poor CD4 cell recovery after suppressive antiretroviral therapy in HIV-1-infected individuals: involvement of miR-192, IL-6, sCD14 and miR-144. *Scientific Reports*, 10(1), 1–11. <https://doi.org/10.1038/s41598-020-60073-8>
- Hong, B. K., You, S., Yoo, S. A., Park, D., Hwang, D., Cho, C. S., & Kim, W. U. (2017).

- MicroRNA-143 and-145 modulate the phenotype of synovial fibroblasts in rheumatoid arthritis. *Experimental and Molecular Medicine*, 49(8).
<https://doi.org/10.1038/emm.2017.108>
- Hoodless, L. J., Lucas, C. D., Duffin, R., Denvir, M. A., Haslett, C., Tucker, C. S., & Rossi, A. G. (2016). Genetic and pharmacological inhibition of CDK9 drives neutrophil apoptosis to resolve inflammation in zebrafish in vivo. *Science Signaling*, 6(36980).
<https://doi.org/10.1038/srep36980>
- Huang, D. W., Sherman, B. T., Tan, Q., Collins, J. R., Alvord, W. G., Roayaei, J., Stephens, R., Baseler, M. W., Lane, H. C., & Lempicki, R. A. (2007). The DAVID Gene Functional Classification Tool: A novel biological module-centric algorithm to functionally analyze large gene lists. *Genome Biology*, 8(9). <https://doi.org/10.1186/gb-2007-8-9-r183>
- Huang, Y., Shen, X. J., Zou, Q., Wang, S. P., Tang, S. M., & Zhang, G. Z. (2011). Biological functions of microRNAs: A review. *Journal of Physiology and Biochemistry*, 67(1), 129–139. <https://doi.org/10.1007/s13105-010-0050-6>
- Hughes, G. C., & Choubey, D. (2014). Modulation of autoimmune rheumatic diseases by oestrogen and progesterone. *Nature Reviews Rheumatology*, 10(12), 740–751.
<https://doi.org/10.1038/nrrheum.2014.144>
- Hwang, H. W., & Mendell, J. T. (2006). MicroRNAs in cell proliferation, cell death, and tumorigenesis. *British Journal of Cancer*, 94(6), 776–780.
<https://doi.org/10.1038/sj.bjc.6603023>
- Iijima, N., Linehan, M. M., Zamora, M., Butkus, D., Dunn, R., Kehry, M. R., Laufer, T. M., & Iwasaki, A. (2008). Dendritic cells and B cells maximize mucosal Th1 memory response to herpes simplex virus. *Journal of Experimental Medicine*, 205(13), 3041–3052. <https://doi.org/10.1084/jem.20082039>
- Irizarry, R. A., Hobbs, B., Collin, F., Beazer-Barclay, Y. D., Antonellis, K. J., Scherf, U., & Speed, T. P. (2003). Exploration, normalization, and summaries of high density oligonucleotide array probe level data. *Biostatistics*, 4(2), 249–264.
https://doi.org/10.1007/978-1-4614-1347-9_15
- Ishigaki, K., Shoda, H., Kochi, Y., Yasui, T., Kadono, Y., Tanaka, S., Fujio, K., & Yamamoto, K. (2015). Quantitative and qualitative characterization of expanded CD4 + T cell clones in rheumatoid arthritis patients. *Scientific Reports*, 5(August), 1–9.
<https://doi.org/10.1038/srep12937>

- Jakubzick, C. V., Randolph, G. J., & Henson, P. M. (2017). Monocyte differentiation and antigen-presenting functions. *Nature Reviews Immunology*, 17(6), 349–362.
<https://doi.org/10.1038/nri.2017.28>
- Jin, H., Pi, J., Yang, F., Jiang, J., Wang, X., Bai, H., Shao, M., Huang, L., Zhu, H., Yang, P., Li, L., Li, T., Cai, J., & Chen, Z. W. (2016). Folate-Chitosan Nanoparticles Loaded with Ursolic Acid Confer Anti-Breast Cancer Activities in vitro and in vivo. *Scientific Reports*, 6(July), 1–11. <https://doi.org/10.1038/srep30782>
- Joost, I., Kaasch, A., Pausch, C., Peyerl-Hoffmann, G., Schneider, C., Voll, R. E., Seifert, H., Kern, W. V., & Rieg, S. (2017). Staphylococcus aureus bacteremia in patients with rheumatoid arthritis – Data from the prospective INSTINCT cohort. *Journal of Infection*, 74(6), 575–584. <https://doi.org/10.1016/j.jinf.2017.03.003>
- Jung, S. M., Lee, J., Baek, S. Y., Lee, J., Jang, S. G., Hong, S. M., Park, J. S., Cho, M. La, Park, S. H., & Kwok, S. K. (2017). Ethyl pyruvate ameliorates inflammatory arthritis in mice. *International Immunopharmacology*, 52(August), 333–341.
<https://doi.org/10.1016/j.intimp.2017.09.027>
- Kamburov, A., Wierling, C., Lehrach, H., & Herwig, R. (2009). ConsensusPathDB - A database for integrating human functional interaction networks. *Nucleic Acids Research*, 37(SUPPL. 1), 623–628. <https://doi.org/10.1093/nar/gkn698>
- Kanehisa, M., Goto, S., Sato, Y., Kawashima, M., Furumichi, M., & Tanabe, M. (2014). Data, information, knowledge and principle: Back to metabolism in KEGG. *Nucleic Acids Research*, 42(D1), 199–205. <https://doi.org/10.1093/nar/gkt1076>
- Kang, K., Park, S. H., Chen, J., Qiao, Y., Giannopoulou, E., Berg, K., ... & Park-Min, K. H. (2017). Interferon- γ represses M2 gene expression in human macrophages by disassembling enhancers bound by the transcription factor MAF. *Immunity*, 47(2), 235–250. <https://doi.org/10.1016/j.immuni.2017.07.017>
- Kawaida, R., Yamada, R., Kobayashi, K., Tokuhira, S., Suzuki, A., Kochi, Y., Chang, X., & Sekine, A. (2005). *CUL1*, a component of E3 ubiquitin ligase, alters lymphocyte signal transduction with possible effect on rheumatoid arthritis. 6, 194–202.
<https://doi.org/10.1038/sj.gene.6364177>
- Kim, D., Zeng, M. Y., & Núñez, G. (2017). *The interplay between host immune cells and gut microbiota in chronic inflammatory diseases*. January.
<https://doi.org/10.1038/emm.2017.24>
- Kim, S. jae, Chang, H. J., Volin, M. V., Umar, S., Van Raemdonck, K., Chevalier, A.,

- Palasiewicz, K., Christman, J. W., Volkov, S., Arami, S., Maz, M., Mehta, A., Zomorodi, R. K., Fox, D. A., Sweiss, N., & Shahrara, S. (2019). Macrophages are the primary effector cells in IL-7-induced arthritis. *Cellular and Molecular Immunology*, November 2018. <https://doi.org/10.1038/s41423-019-0235-z>
- Kim, T., Dreher, K., Nilo-Poyanco, R., Lee, I., Fiehn, O., Lange, B. M., et al. (2015). Patterns of metabolite changes identified from large-scale gene perturbations in Arabidopsis using a genome-scale metabolic network. *Plant Physiology*, 167, 1685–1698. doi: 10.1104/pp.114.252361
- Kolarz, B., Ciesla, M., Dryglewska, M., Rosenthal, A. K., & Majdan, M. (2020). Hypermethylation of the miR-155 gene in the whole blood and decreased plasma level of miR-155 in rheumatoid arthritis. *PLoS ONE*, 15(6), 1–12. <https://doi.org/10.1371/journal.pone.0233897>
- Kurkó, J., Besenyei, T., Laki, J., Glant, T. T., Mikecz, K., & Szekanecz, Z. (2013). Genetics of rheumatoid arthritis - A comprehensive review. *Clinical Reviews in Allergy and Immunology*, 45(2), 170–179. <https://doi.org/10.1007/s12016-012-8346-7>
- Lamana, A., Villares, R., Seoane, I. V., Andres, N., Lucas, P., Emery, P., Vital, E. M., Triguero-martínez, A., Marquez, A., Ortiz, A. M., Ponchel, F., González-álvaro, I., & Mellado, M. (2020). Identification of a Human SOCS1 Polymorphism That Predicts Rheumatoid Arthritis Severity. *Frontiers in Immunology*, 11(1336). <https://doi.org/10.3389/fimmu.2020.01336>
- Li, Li, Li, L., Xiao, L., & Shangguan, J. (2018). Progranulin ameliorates coxsackievirus-B3-induced viral myocarditis by downregulating Th1 and Th17 cells. *Experimental Cell Research*, 367(2), 241–250. <https://doi.org/10.1016/j.yexcr.2018.04.001>
- Li, Liya, Liu, W., Wang, H., Yang, Q., Zhang, L., Jin, F., & Jin, Y. (2018). Mutual inhibition between HDAC9 and miR-17 regulates osteogenesis of human periodontal ligament stem cells in inflammatory conditions. *Cell Death and Disease*, 9(5). <https://doi.org/10.1038/s41419-018-0480-6>
- Li, S., Yin, H., Zhang, K., Wang, T., Yang, Y., Liu, X., Chang, X., Zhang, M., Yan, X., Ren, Y., Pan, W., & Zhang, L. (2017). Effector T helper cell populations are elevated in the bone marrow of rheumatoid arthritis patients and correlate with disease severity. *Scientific Reports*, 7(1), 1–11. <https://doi.org/10.1038/s41598-017-05014-8>
- Li, Y., Zheng, J. Y., Liu, J. Q., Yang, J., Liu, Y., Wang, C., Ma, X. N., Liu, B. L., Xin, G. Z., & Liu, L. F. (2016). Succinate/NLRP3 inflammasome induces synovial fibroblast

- activation: Therapeutical effects of clematichinenoside AR on arthritis. *Frontiers in Immunology*, 7(DEC), 1–11. <https://doi.org/10.3389/fimmu.2016.00532>
- Lin, J., He, Y., Chen, J., Zeng, Z., Yang, B., & Ou, Q. (2017). A critical role of transcription factor YY1 in rheumatoid arthritis by regulation of interleukin-6. *Journal of Autoimmunity*, 77, 67–75. <https://doi.org/10.1016/j.jaut.2016.10.008>
- López-Ibáñez, J., Pazos, F., & Chagoyen, M. (2016). MBROLE 2.0-functional enrichment of chemical compounds. *Nucleic Acids Research*, 44(W1), W201–W204. <https://doi.org/10.1093/nar/gkw253>
- Loscalzo, J., Barabási, A.-L., & Silverman, E. K. (2017). *Network Medicine: Complex Systems in Human Disease and Therapeutics*.
- Lund, F. E., & Randall, T. D. (2010). Effector and regulatory B cells: Modulators of CD4+ T cell immunity. *Nature Reviews Immunology*, 10(4), 236–247. <https://doi.org/10.1038/nri2729>
- Ma, C., Lv, Q., Teng, S., Yu, Y., Niu, K., & Yi, C. (2017). Identifying key genes in rheumatoid arthritis by weighted gene co-expression network analysis. *International Journal of Rheumatic Diseases*, 20(8), 971–979. <https://doi.org/10.1111/1756-185X.13063>
- Maeda, Y., & Takeda, K. (2019). Host–microbiota interactions in rheumatoid arthritis. *Experimental and Molecular Medicine*, 51(12). <https://doi.org/10.1038/s12276-019-0283-6>
- Malavia, T. A., Chaparala, S., Wood, J., Chowdari, K., Prasad, K. M., McClain, L., Jegga, A. G., Ganapathiraju, M. K., & Nimgaonkar, V. L. (2017). Generating testable hypotheses for schizophrenia and rheumatoid arthritis pathogenesis by integrating epidemiological, genomic, and protein interaction data. *Npj Schizophrenia*, 3(1), 1–9. <https://doi.org/10.1038/s41537-017-0010-z>
- Mardinoglu, A., Agren, R., Kampf, C., Asplund, A., Uhlen, M., & Nielsen, J. (2014). Genome-scale metabolic modelling of hepatocytes reveals serine deficiency in patients with non-alcoholic fatty liver disease. *Nature Communications*, 5(May 2013), 1–11. <https://doi.org/10.1038/ncomms4083>
- Mertens, M., & Singh, J. A. (2009). Anakinra for rheumatoid arthritis: A systematic review. *Journal of Rheumatology*, 36(6), 1118–1125. <https://doi.org/10.3899/jrheum.090074>
- Messina, S. (2018). Small GTPase RAS in multiple sclerosis - exploring the role of RAS GTPase in the etiology of multiple sclerosis Small GTPase RAS in multiple sclerosis -

- exploring the role of RAS GTPase in the etiology of multiple sclerosis. *Small GTPases*, 00(00), 1–8. <https://doi.org/10.1080/21541248.2018.1502591>
- Migita, K., Iwanaga, N., Izumi, Y., Kawahara, C., Kumagai, K., Nakamura, T., Koga, T., & Kawakami, A. (2017). TNF- α -induced miR-155 regulates IL-6 signaling in rheumatoid synovial fibroblasts. *BMC Research Notes*, 10(1), 403. <https://doi.org/10.1186/s13104-017-2715-5>
- Moschovakis, G. L., Bubke, A., Friedrichsen, M., Falk, C. S., & Förster, R. (2017). *OPEN T cell specific Cxcr5 deficiency prevents rheumatoid arthritis*. 1–13. <https://doi.org/10.1038/s41598-017-08935-6>
- Mu, N., Gu, J., Huang, T., Zhang, C., Shu, Z., Li, M., Hao, Q., Li, W., Zhang, W., Zhao, J., Zhang, Y., Huang, L., Wang, S., Jin, X., Xue, X., Zhang, W., & Zhang, Y. (2016). A novel NF- κ B/YY1/microRNA-10a regulatory circuit in fibroblast-like synoviocytes regulates inflammation in rheumatoid arthritis. *Scientific Reports*, 6(December 2015), 1–14. <https://doi.org/10.1038/srep20059>
- Nagafuchi, Y., Shoda, H., Sumitomo, S., Nakachi, S., Kato, R., Tsuchida, Y., Tsuchiya, H., Sakurai, K., Hanata, N., Tateishi, S., Kanda, H., Ishigaki, K., Okada, Y., Suzuki, A., Kochi, Y., Fujio, K., & Yamamoto, K. (2016). Immunophenotyping of rheumatoid arthritis reveals a linkage between HLA-DRB1 genotype, CXCR4 expression on memory CD4⁺ T cells, and disease activity. *Scientific Reports*, 6(June), 1–11. <https://doi.org/10.1038/srep29338>
- Nehmar, R., Mariotte, A., Cauwer, A. De, Sibilia, J., Bahram, S., & Georgel, P. (2018). Therapeutic Perspectives for Interferons and Plasmacytoid Dendritic Cells in Rheumatoid Arthritis. *Trends in Molecular Medicine*, 24(4), 338–347. <https://doi.org/10.1016/j.molmed.2018.02.001>
- Németh, T., Sperandio, M., & Mócsai, A. (2020). Neutrophils as emerging therapeutic targets. In *Nature Reviews Drug Discovery* (Vol. 19, Issue 4, pp. 1–23). <https://doi.org/10.1038/s41573-019-0054-z>
- Nocturne, G., Boudaoud, S., Ly, B., Pascaud, J., Paoletti, A., & Mariette, X. (2017). Impact of anti-TNF therapy on NK cells function and on immunosurveillance against B-cell lymphomas. *Journal of Autoimmunity*, 1–9. <https://doi.org/10.1016/j.jaut.2017.02.001>
- Nygaard, G., & Firestein, G. S. (2020). Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes. *Nature Reviews Rheumatology*, 16(6), 316–333. <https://doi.org/10.1038/s41584-020-0413-5>

- Orr, C., Sousa, E., Boyle, D. L., Buch, M. H., Buckley, C. D., Cañete, J. D., Catrina, A. I., Choy, E. H. S., Emery, P., Fearon, U., Filer, A., Gerlag, D., Humby, F., Isaacs, J. D., Just, S. A., Lauwerys, B. R., Le Goff, B., Manzo, A., McGarry, T., Veale, D. J. (2017). Synovial tissue research: A state-of-the-art review. *Nature Reviews Rheumatology*, 13(8), 463–475. <https://doi.org/10.1038/nrrheum.2017.115>
- Ouyang, Q., Wu, J., Jiang, Z., Zhao, J., Wang, R., Lou, A., Zhu, D., Shi, G. P., & Yang, M. (2017). Microarray Expression Profile of Circular RNAs in Peripheral Blood Mononuclear Cells from Rheumatoid Arthritis Patients. *Cellular Physiology and Biochemistry*, 42(2), 651–659. <https://doi.org/10.1159/000477883>
- Pandya, J. M., Lundell, A. C., Andersson, K., Nordström, I., Theander, E., & Rudin, A. (2017). Blood chemokine profile in untreated early rheumatoid arthritis: CXCL10 as a disease activity marker. *Arthritis Research and Therapy*, 19(1), 1–12. <https://doi.org/10.1186/s13075-017-1224-1>
- Panga, V., Kallor, A. A., Nair, A., Harshan, S., & Id, S. R. (2019). *Mitochondrial dysfunction in rheumatoid arthritis : A comprehensive analysis by integrating gene expression , protein-protein interactions and gene ontology data*. 1–28. <https://doi.org/10.1371/journal.pone.0224632>
- Shannon, P., Markiel, A., Ozier, O., Baliga, N. S., Wang, J. T., Ramage, D., Amin, N., Schwikowski, B., Ideker, T. (2003). Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome research*, 13(11), 2498-2504. <https://doi.org/10.1101/gr.1239303.metabolite>
- Paust, S., & Andrian, U. H. Von. (2011). Natural killer cell memory. *Nature Publishing Group*, 131(6), 500–508. <https://doi.org/10.1038/ni.2032>
- Petrelli, A., & Van Wijk, F. (2016). CD8+ T cells in human autoimmune arthritis: The unusual suspects. *Nature Reviews Rheumatology*, 12(7), 421–428. <https://doi.org/10.1038/nrrheum.2016.74>
- Pörings, A. S., Lowin, T., Dufner, B., Grifka, J., & Straub, R. H. (2019). A thyroid hormone network exists in synovial fibroblasts of rheumatoid arthritis and osteoarthritis patients. *Scientific Reports*, 9(1), 1–14. <https://doi.org/10.1038/s41598-019-49743-4>
- Puccetti, A., Pelosi, A., Fiore, P. F., Patuzzo, G., Lunardi, C., & Dolcino, M. (2018). MicroRNA expression profiling in behçet's disease. *Journal of Immunology Research*, 2018. <https://doi.org/10.1155/2018/2405150>
- Rajasekhar, M., Olsson, A. M., Steel, K. J. A., Georgouli, M., Ranasinghe, U., Brender Read,

- C., Frederiksen, K. S., & Taams, L. S. (2017). MicroRNA-155 contributes to enhanced resistance to apoptosis in monocytes from patients with rheumatoid arthritis. *Journal of Autoimmunity*, 79, 53–62. <https://doi.org/10.1016/j.jaut.2017.01.002>
- Rolland, T., Taşan, M., Charlotiaux, B., Pevzner, S. J., Zhong, Q., Sahni, N., Yi, S., Lemmens, I., Fontanillo, C., Mosca, R., Kamburov, A., Ghiassian, S. D., Yang, X., Ghamsari, L., Balcha, D., Begg, B. E., Braun, P., Brehme, M., Broly, M. P., ... Vidal, M. (2014). A proteome-scale map of the human interactome network. *Cell*, 159(5), 1212–1226. <https://doi.org/10.1016/j.cell.2014.10.050>
- Safari-alighiarloo, N., Taghizadeh, M., Seyyed, M. T., Namaki, S., & Rezaei, M. T. (2020). Identification of common key genes and pathways between type 1 diabetes and multiple sclerosis using transcriptome and interactome analysis. *Endocrine*, 1–12. <https://doi.org/10.1007/s12020-019-02181-8>
- Safran, M., Dalah, I., Alexander, J., Rosen, N., Iny Stein, T., Shmoish, M., Nativ, N., Bahir, I., Doniger, T., Krug, H., Sirota-Madi, A., Olender, T., Golan, Y., Stelzer, G., Harel, A., & Lancet, D. (2010). GeneCards Version 3: the human gene integrator. *Database : The Journal of Biological Databases and Curation*, 2010, 1–16. <https://doi.org/10.1093/database/baq020>
- Sanchez-Lopez, E., Cheng, A., & Guma, M. (2019). Can Metabolic Pathways Be Therapeutic Targets in Rheumatoid Arthritis? *Journal of Clinical Medicine*, 8(5), 753. <https://doi.org/10.3390/jcm8050753>
- Savola, P., Kelkka, T., Rajala, H. L., Kuuliala, A., Kuuliala, K., Eldfors, S., Ellonen, P., Lagström, S., Lepistö, M., Hannunen, T., Andersson, E. I., Khajuria, R. K., Jaatinen, T., Koivuniemi, R., Repo, H., Saarela, J., Porkka, K., Leirisalo-Repo, M., & Mustjoki, S. (2017). Somatic mutations in clonally expanded cytotoxic T lymphocytes in patients with newly diagnosed rheumatoid arthritis. *Nature Communications*, 8(May). <https://doi.org/10.1038/ncomms15869>
- Sebastiani, M., Milazzo, L., Atzeni, F., Vacchi, C., Manfredi, A., Quartuccio, L., Scirè, C., Gaeta, G. B., Lapadula, G., Armignacco, O., Tavio, M., D'Angelo, S., Meroni, P., Bazzichi, L., Grassi, W., Mathieu, A., Mastroianni, C., Sagnelli, E., Santantonio, T., ... Galli, M. (2019). Italian consensus recommendations for the management of hepatitis C infection in patients with rheumatoid arthritis. *Modern Rheumatology*, 29(6), 895–902. <https://doi.org/10.1080/14397595.2018.1558918>
- Shao, L., & Hou, C. (2019). miR-138 activates NF-κB signaling and PGRN to promote

- rheumatoid arthritis via regulating HDAC4. *Biochemical and Biophysical Research Communications*, 519(1), 166–171. <https://doi.org/10.1016/j.bbrc.2019.08.092>
- Sharma, A. R., Sharma, G., Lee, S., & Chakraborty, C. (2016). miRNA-Regulated Key Components of Cytokine Signaling Pathways and Inflammation in Rheumatoid Arthritis. *Medicinal Research Reviews*, 36(3), 425–439. <https://doi.org/10.1002/med>
- Shchetynsky, K., Diaz-Gallo, L. M., Folkersen, L., Hensvold, A. H., Catrina, A. I., Berg, L., Klareskog, L., & Padyukov, L. (2017). Discovery of new candidate genes for rheumatoid arthritis through integration of genetic association data with expression pathway analysis. *Arthritis Research and Therapy*, 19(1), 1–9. <https://doi.org/10.1186/s13075-017-1220-5>
- Shi, C., & Pamer, E. G. (2011). Monocyte recruitment during infection and inflammation. *Nature Reviews Immunology*, 11(11), 762–774. <https://doi.org/10.1038/nri3070>
- Smolen, J. S., Aletaha, D., Barton, A., Burmester, G. R., Emery, P., Firestein, G. S., Kavanaugh, A., McInnes, I. B., Solomon, D. H., Strand, V., & Yamamoto, K. (2018). Rheumatoid arthritis. *Nature Reviews Disease Primers*, 4, 1–23. <https://doi.org/10.1038/nrdp.2018.1>
- Smyth, G. K. (2005). Limma: linear models for microarray data BT - Bioinformatics and Computational Biology Solutions Using R and Bioconductor. *Bioinformatics and Computational Biology Solutions Using R and Bioconductor*, 397–420. http://link.springer.com/chapter/10.1007/0-387-29362-0_23%5Cnpapers3://publication/uuid/7617F4B3-24B5-4568-9C76-1C22000E7796
- Tanaka, Y., Takada, S., Iizasa, H., Hatzigeorgiou, A., Miyazawa, S.-I., Furumatsu, T., Nishida, K., & Asahara, H. (2016). THU0028 Microrna-381 Ameliorates Arthritis by Controlling Functions of Fibroblast-like Synoviocytes, Which Are Affected by A To I RNA Editing. *Annals of the Rheumatic Diseases*, 75(Suppl 2), 187 LP – 187. <https://doi.org/10.1136/annrheumdis-2016-eular.2299>
- Tang, M., Tian, L., Luo, G., & Yu, X. (2018). Interferon-Gamma-Mediated Osteoimmunology. *Frontiers in Immunology*, 9, 1508. <https://doi.org/10.3389/fimmu.2018.01508>
- Tasaki, S., Suzuki, K., Kassai, Y., Takeshita, M., Murota, A., Kondo, Y., Ando, T., Nakayama, Y., Okuzono, Y., Takiguchi, M., Kurisu, R., Miyazaki, T., Yoshimoto, K., Yasuoka, H., Yamaoka, K., Morita, R., Yoshimura, A., Toyoshiba, H., & Takeuchi, T. (2018). Multi-omics monitoring of drug response in rheumatoid arthritis in pursuit of

- molecular remission. *Nature Communications*, 9(1). <https://doi.org/10.1038/s41467-018-05044-4>
- Tesovnik, T., Kovač, J., Pohar, K., Hudoklin, S., Dovč, K., Bratina, N., Trebušak Podkrajšek, K., Debeljak, M., Veranič, P., Bosi, E., Piemonti, L., Ihan, A., & Battelino, T. (2020). Extracellular Vesicles Derived Human-miRNAs Modulate the Immune System in Type 1 Diabetes. *Frontiers in Cell and Developmental Biology*, 8(March), 1–24. <https://doi.org/10.3389/fcell.2020.00202>
- Thomas, P. D., Kejariwal, A., Campbell, M. J., Mi, H., Diemer, K., Guo, N., Ladunga, I., Ulitsky-Lazareva, B., Muruganujan, A., Rabkin, S., Vandergriff, J. A., & Doremeieux, O. (2003). PANTHER: A browsable database of gene products organized by biological function, using curated protein family and subfamily classification. *Nucleic Acids Research*, 31(1), 334–341. <https://doi.org/10.1093/nar/gkg115>
- Tracy, A., Buckley, C. D., & Raza, K. (2017). *Pre-symptomatic autoimmunity in rheumatoid arthritis : when does the disease start ?* 423–435. <https://doi.org/10.1007/s00281-017-0620-6>
- Traylor, M., Knevel, R., Cui, J., Taylor, J., Harm-Jan, W., Conaghan, P. G., Cope, A. P., Curtis, C., Emery, P., Newhouse, S., Patel, H., Steer, S., Gregersen, P., Shadick, N. A., Weinblatt, M. E., van der Helm-Van Mil, A., Barrett, J. H., Morgan, A. W., Lewis, C. M., & Scott, I. C. (2019). Genetic associations with radiological damage in rheumatoid arthritis: Meta-analysis of seven genome-wide association studies of 2,775 cases. *PLoS ONE*, 14(10), 1–12. <https://doi.org/10.1371/journal.pone.0223246>
- Tripathy, A., Khanna, S., Padhan, P., Smita, S., Raghav, S., & Gupta, B. (2017). Direct recognition of LPS drive TLR4 expressing CD8+ T cell activation in patients with rheumatoid arthritis. *Scientific Reports*, 7(1), 1–10. <https://doi.org/10.1038/s41598-017-01033-7>
- Twohig, J. P., Cardus Figueras, A., Andrews, R., Wiede, F., Cossins, B. C., Derrac Soria, A., Lewis, M. J., Townsend, M. J., Millrine, D., Li, J., Hill, D. G., Uceda Fernandez, J., Liu, X., Szomolay, B., Pepper, C. J., Taylor, P. R., Pitzalis, C., Tiganis, T., Williams, N. M., ... Jones, S. A. (2019). Activation of naïve CD4 + T cells re-tunes STAT1 signaling to deliver unique cytokine responses in memory CD4 + T cells. *Nature Immunology*, 20(4), 458–470. <https://doi.org/10.1038/s41590-019-0350-0>
- Udalova, I. A., Mantovani, A., & Feldmann, M. (2016). Macrophage heterogeneity in the context of rheumatoid arthritis. *Nature Reviews Rheumatology*, 12(8), 472–485.

- <https://doi.org/10.1038/nrrheum.2016.91>
- Uguccioni, M. (2018). *Redox-Mediated Mechanisms Fuel Monocyte Responses to CXCL12 / HMGB1 in Active Rheumatoid Arthritis*. 9(September), 1–12.
<https://doi.org/10.3389/fimmu.2018.02118>
- Ungethuem, U., Haeupl, T., Witt, H., Koczan, D., Krenn, V., Huber, H., Von Helversen, T. M., Drungowski, M., Seyfert, C., Zacher, J., Pruss, A., Neidel, J., Lehrach, H., Thiesen, H. J., Ruiz, P., & Bläß, S. (2010). Molecular signatures and new candidates to target the pathogenesis of rheumatoid arthritis. *Physiological Genomics*, 42 A(4), 267–282.
<https://doi.org/10.1152/physiolgenomics.00004.2010>
- Venrooij, W. J. Van, Beers, J. J. B. C. Van, & Pruijn, G. J. M. (2008). *Anti-CCP Antibody , a Marker for the Early Detection of Rheumatoid Arthritis*. 285, 268–285.
<https://doi.org/10.1196/annals.1443.013>
- Walter, G. J., Fleskens, V., Frederiksen, K. S., Rajasekhar, M., Menon, B., Gerwien, J. G., Evans, H. G., & Taams, L. S. (2016). Phenotypic, Functional, and Gene Expression Profiling of Peripheral CD45RA⁺ and CD45RO⁺ CD4⁺CD25⁺CD127^{low} Treg Cells in Patients with Chronic Rheumatoid Arthritis. *Arthritis and Rheumatology*, 68(1), 103–116. <https://doi.org/10.1002/art.39408>
- Wehrens, E. J., Prakken, B. J., & Van Wijk, F. (2013). T cells out of control-impaired immune regulation in the inflamed joint. *Nature Reviews Rheumatology*, 9(1), 34–42.
<https://doi.org/10.1038/nrrheum.2012.149>
- Wei, K., Korsunsky, I., Marshall, J. L., Gao, A., M Watts, G. F., Major, T., Croft, A. P., Watts, J., Blazar, P. E., Lange, J. K., Thornhill, T. S., Filer, A., Raza, K., Donlin, L. T., Siebel, C. W., Buckley, C. D., Raychaudhuri, S., & Brenner, M. B. (2020). Notch signalling drives synovial fibroblast identity and arthritis pathology Accelerating Medicines Partnership Rheumatoid Arthritis & Systemic Lupus Erythematosus (AMP RA/SLE). *Nature*, February 2019, 1–6. <https://doi.org/10.1038/s41586-020-2222-z>
- Weyand, C. M., & Goronzy, J. J. (2006). T-cell-targeted therapies in rheumatoid arthritis. *Nature Clinical Practice Rheumatology*, 2(4), 201–210.
<https://doi.org/10.1038/ncprheum0142>
- Whitaker, J. W., Boyle, D. L., Bartok, B., Ball, S. T., Gay, S., Wang, W., & Firestein, G. S. (2015). Integrative omics analysis of rheumatoid arthritis identifies non-obvious therapeutic targets. *PLoS ONE*, 10(4), 1–14.
<https://doi.org/10.1371/journal.pone.0124254>

- Woetzel, D., Huber, R., Kupfer, P., Pohlers, D., Pfaff, M., Driesch, D., Häupl, T., Koczan, D., Stiehl, P., Guthke, R., & Kinne, R. W. (2014). Identification of rheumatoid arthritis and osteoarthritis patients by transcriptome-based rule set generation. *Arthritis Research and Therapy*, 16(2). <https://doi.org/10.1186/ar4526>
- Wright, H. L., Moots, R. J., & Edwards, S. W. (2014). The multifactorial role of neutrophils in rheumatoid arthritis. *Nature Publishing Group*, 10(October), 593–601. <https://doi.org/10.1038/nrrheum.2014.80>
- Xu, K., Xu, P., Yao, J. F., Zhang, Y. G., Hou, W. K., & Lu, S. M. (2013). Reduced apoptosis correlates with enhanced autophagy in synovial tissues of rheumatoid arthritis. *Inflammation Research*, 62(2), 229–237. <https://doi.org/10.1007/s00011-012-0572-1>
- Yamin, R., Berhani, O., Peleg, H., Aamar, S., Stein, N., Gamliel, M., Hindi, I., Scheiman-Elazary, A., & Gur, C. (2019). High percentages and activity of synovial fluid NK cells present in patients with advanced stage active Rheumatoid Arthritis. *Scientific Reports*, 9(1), 1–12. <https://doi.org/10.1038/s41598-018-37448-z>
- Yang, X. Y., Zheng, K. Di, Lin, K., Zheng, G., Zou, H., Wang, J. M., Lin, Y. Y., Chuka, C. M., Ge, R. S., Zhai, W., & Wang, J. G. (2015). Energy metabolism disorder as a contributing factor of rheumatoid arthritis: A comparative proteomic and metabolomic study. *PLoS ONE*, 10(7), 1–15. <https://doi.org/10.1371/journal.pone.0132695>
- Yates, L. A., Norbury, C. J., & Gilbert, R. J. C. (2013). The long and short of microRNA. *Cell*, 153(3), 516–519. <https://doi.org/10.1016/j.cell.2013.04.003>
- Ye, H., Zhang, J., Wang, J., Gao, Y., Du, Y., Li, C., Deng, M., Guo, J., & Li, Z. (2015). CD4 T-cell transcriptome analysis reveals aberrant regulation of STAT3 and Wnt signaling pathways in rheumatoid arthritis: Evidence from a case-control study. *Arthritis Research and Therapy*, 17(1), 1–10. <https://doi.org/10.1186/s13075-015-0590-9>
- Zhang, L., Luo, J., Wen, H., Zhang, T., Zuo, X., & Li, X. (2016). International Immunopharmacology MDM2 promotes rheumatoid arthritis via activation of MAPK and NF- κ B. *International Immunopharmacology*, 30, 69–73. <https://doi.org/10.1016/j.intimp.2015.11.030>
- Zhao, M., Svensson, M. N. D., Venken, K., Chawla, A., Liang, S., Engel, I., Mydel, P., Day, J., Elewaut, D., Bottini, N., & Kronenberg, M. (n.d.). Altered thymic differentiation and modulation of arthritis by invariant NKT cells expressing mutant ZAP70. *Nature Communications*, 2018. <https://doi.org/10.1038/s41467-018-05095-7>
- Zhao, Y., Chen, B., Li, S., Yang, L., Zhu, D., Wang, Y., Wang, H., Wang, T., Shi, B., Gai, Z.,

Yang, J., Heng, X., Yang, J., & Zhang, L. (2018). Detection and characterization of bacterial nucleic acids in culture-negative synovial tissue and fluid samples from rheumatoid arthritis or osteoarthritis patients. *Scientific Reports*, 8(1), 1–12.

<https://doi.org/10.1038/s41598-018-32675-w>

Zheng, J., Zhu, L., Iok In, I., Chen, Y., Jia, N., & Zhu, W. (2020). Bone marrow-derived mesenchymal stem cells-secreted exosomal microRNA-192-5p delays inflammatory response in rheumatoid arthritis. *International Immunopharmacology*, 78(October 2019), 105985. <https://doi.org/10.1016/j.intimp.2019.105985>



APPENDICES

Supplementary Table 1 Enriched pathways of common DEGs in synovial tissues

Synovial tissue enriched pathway-based sets		
Pathway	Source	p-value
Immune System	Reactome	1.04E-19
Cytokine Signaling in Immune system	Reactome	8.38E-15
Adaptive Immune System	Reactome	2.26E-14
Epstein Barr virus infection	KEGG	5.43E-11
Leishmaniasis	KEGG	8.93E-11
Interferon Signaling	Reactome	1.16E-10
Interferon gamma signaling	Reactome	1.36E-10
Rheumatoid arthritis	KEGG	9.71E-10
Influenza A	KEGG	3.38E-09
Intestinal immune network for IgA production	KEGG	5.29E-09
Chemokine signaling pathway	KEGG	1.33E-08
Hematopoietic cell lineage	KEGG	2.85E-08
Viral myocarditis	KEGG	3.68E-08
Osteoclast differentiation	KEGG	5.85E-08
Signaling by Interleukins	Reactome	1.11E-07
Fc gamma R mediated phagocytosis	KEGG	1.67E-07
Chemokine receptors bind chemokines	Reactome	1.69E-07
Cell adhesion molecules (CAMs)	KEGG	2.18E-07
Allograft rejection	KEGG	3.09E-07
Staphylococcus aureus infection	KEGG	3.64E-07
Cell surface interactions at the vascular wall	Reactome	5.71E-07
Human T cell leukemia virus 1 infection	KEGG	6.03E-07
Graft versus host disease	KEGG	6.48E-07
Cytokine cytokine receptor interaction	KEGG	8.06E-07
JAK STAT signaling pathway	KEGG	8.40E-07
Th17 cell differentiation	KEGG	8.55E-07
Type I diabetes mellitus	KEGG	9.09E-07
Inflammatory bowel disease (IBD)	KEGG	1.36E-06
Toxoplasmosis	KEGG	1.42E-06
Phosphorylation of CD3 and TCR zeta chains	Reactome	1.59E-06
PD 1 signaling	Reactome	1.95E-06
Th1 and Th2 cell differentiation	KEGG	2.09E-06
B cell receptor signaling pathway	KEGG	2.41E-06
Phagosome	KEGG	2.88E-06
TCR signaling	Reactome	2.99E-06
Downstream TCR signaling	Reactome	3.00E-06
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	Reactome	3.35E-06
Herpes simplex infection	KEGG	3.41E-06

Autoimmune thyroid disease	KEGG	3.44E-06
Signaling by the B Cell Receptor (BCR)	Reactome	4.11E-06
Primary immunodeficiency	KEGG	4.89E-06
Antigen processing and presentation	KEGG	4.98E-06
Costimulation by the CD28 family	Reactome	4.98E-06
Natural killer cell-mediated cytotoxicity	KEGG	5.07E-06
Innate Immune System	Reactome	6.72E-06
Interleukin 2 family signaling	Reactome	6.80E-06
MHC class II antigen presentation	Reactome	8.14E-06
Pathways in cancer	KEGG	8.65E-06
Tuberculosis	KEGG	1.40E-05
Interleukin 3, 5 and GM CSF signaling	Reactome	1.63E-05
Translocation of ZAP 70 to Immunological synapse	Reactome	1.83E-05
RUNX3 regulates CDKN1A transcription	Reactome	1.87E-05
Interferon-alpha/beta signaling	Reactome	2.55E-05
Hemostasis	Reactome	2.76E-05
Antigen activates B Cell Receptor (BCR) leading to generation of second messengers	Reactome	2.77E-05
Asthma	KEGG	3.14E-05
AGE-RAGE signaling pathway in diabetic complications	KEGG	3.21E-05
Pancreatic cancer	KEGG	4.01E-05
Toll-like receptor signaling pathway	KEGG	4.59E-05
Growth hormone receptor signaling	Reactome	7.80E-05
Colorectal cancer	KEGG	9.68E-05
Human cytomegalovirus infection	KEGG	1.19E-04
Generation of second messenger molecules	Reactome	1.48E-04
Crosslinking of collagen fibrils	Reactome	2.14E-04
Relaxin signaling pathway	KEGG	2.20E-04
FoxO signaling pathway	KEGG	2.32E-04
Systemic lupus erythematosus	KEGG	2.44E-04
T cell receptor signaling pathway	KEGG	2.65E-04
Apoptosis	KEGG	3.00E-04
Interleukin receptor SHC signaling	Reactome	3.27E-04
TNF signaling pathway	KEGG	4.47E-04
Biosynthesis of aspirin-triggered D series resolvins	Reactome	4.60E-04
The AIM2 inflammasome	Reactome	4.60E-04
Leukocyte transendothelial migration	KEGG	4.98E-04
Regulation of IFNG signaling	Reactome	6.26E-04
GPVI mediated activation cascade	Reactome	7.19E-04
Platelet activation	KEGG	8.71E-04
Biosynthesis of D series resolvins	Reactome	9.12E-04
Biosynthesis of E series 18(R) resolvins	Reactome	9.12E-04
Collagen formation	Reactome	1.01E-03
Neutrophil degranulation	Reactome	1.09E-03
Extracellular matrix organization	Reactome	1.15E-03
Amoebiasis	KEGG	1.19E-03

Regulation of signaling by CBL	Reactome	1.35E-03
Human immunodeficiency virus 1 infection	KEGG	1.36E-03
Non-small cell lung cancer	KEGG	1.37E-03
Fc epsilon RI signaling pathway	KEGG	1.47E-03
Cross presentation of soluble exogenous antigens (endosomes)	Reactome	1.51E-03
Biosynthesis of E series 18(S) resolvins	Reactome	1.51E-03
RUNX3 regulates BCL2L1 (BIM) transcription	Reactome	1.51E-03
Binding and entry of HIV virion	Reactome	1.51E-03
Bladder cancer	KEGG	1.65E-03
Glioma	KEGG	1.90E-03
CD22 mediated BCR regulation	Reactome	1.90E-03
Hepatitis B	KEGG	2.17E-03
Transcriptional misregulation in cancer	KEGG	2.23E-03
Biosynthesis of EPA derived SPMs	Reactome	2.24E-03
Role of phospholipids in phagocytosis	Reactome	2.30E-03
Kaposi sarcoma-associated herpesvirus infection	KEGG	2.30E-03
Pertussis	KEGG	2.57E-03
Fc epsilon receptor (FCERI) signaling	Reactome	2.73E-03
Assembly of collagen fibrils and other multimeric structures	Reactome	2.96E-03
Peptide ligand-binding receptors	Reactome	2.99E-03
Antigen processing Cross presentation	Reactome	3.19E-03
Hepatitis C	KEGG	3.28E-03
Focal adhesion	KEGG	3.49E-03
Fc gamma receptor (FCGR) dependent phagocytosis	Reactome	3.77E-03
Regulation of IFNA signaling	Reactome	4.01E-03
ErbB signaling pathway	KEGG	4.17E-03
Hepatocellular carcinoma	KEGG	5.09E-03
NOD-like receptor signaling pathway	KEGG	5.09E-03
FCGR activation	Reactome	5.31E-03
Platelet activation, signaling, and aggregation	Reactome	5.32E-03
Endometrial cancer	KEGG	5.86E-03
GnRH signaling pathway	KEGG	6.10E-03
Role of LAT2/NTAL/LAB on calcium mobilization	Reactome	6.10E-03
EGFR Transactivation by Gastrin	Reactome	6.51E-03
Interleukin 27 signaling	Reactome	6.51E-03
Cytosolic DNA sensing pathway	KEGG	7.84E-03
Pyrimidine salvage	Reactome	7.89E-03
GAB1 signalosome	Reactome	7.89E-03
Interleukin 6 signaling	Reactome	7.89E-03
Choline metabolism in cancer	KEGG	7.91E-03
Cargo recognition for clathrin-mediated endocytosis	Reactome	7.91E-03
HIF 1 signaling pathway	KEGG	8.24E-03
Semaphorin interactions	Reactome	8.28E-03
Regulation of actin dynamics for phagocytic cup formation	Reactome	8.44E-03
Chagas disease (American trypanosomiasis)	KEGG	8.94E-03
Prion diseases	KEGG	9.30E-03

PECAM1 interactions	Reactome	9.39E-03
C type lectin receptor signaling pathway	KEGG	9.68E-03

Supplementary Table 2 Enriched pathways of common DEGs in Blood cells

Blood cells enriched pathway-based sets		
Pathway	Source	p-value
Ribosome	KEGG	5.56E-12
Interleukin-7 signaling	Reactome	6.35E-12
Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex	Reactome	1.06E-11
Nonsense-Mediated Decay (NMD)	Reactome	1.06E-11
Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex	Reactome	4.18E-11
Peptide chain elongation	Reactome	1.02E-10
Eukaryotic Translation Termination	Reactome	1.88E-10
Selenocysteine synthesis	Reactome	1.88E-10
SRP-dependent cotranslational protein targeting to membrane	Reactome	2.05E-10
Eukaryotic Translation Elongation	Reactome	2.78E-10
Selenoamino acid metabolism	Reactome	5.74E-10
Metabolism of proteins	Reactome	7.22E-10
L13a-mediated translational silencing of Ceruloplasmin expression	Reactome	1.18E-09
Formation of a pool of free 40S subunits	Reactome	1.23E-09
GTP hydrolysis and joining of the 60S ribosomal subunit	Reactome	1.40E-09
Translation	Reactome	1.70E-09
Cap-dependent Translation Initiation	Reactome	4.26E-09
Eukaryotic Translation Initiation	Reactome	4.26E-09
Cytokine Signaling in Immune system	Reactome	7.61E-08
Immune System	Reactome	2.44E-07
Interferon Signaling	Reactome	6.50E-07
HDMs demethylate histones	Reactome	8.80E-07
Metabolism of RNA	Reactome	2.30E-06
Transcriptional misregulation in cancer	KEGG	2.71E-06
RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function	Reactome	5.58E-06
RHO GTPases activate PKNs	Reactome	8.37E-06
PKMTs methylate histone lysines	Reactome	8.68E-06
RMTs methylate histone arginines	Reactome	1.01E-05
RNA Polymerase I Promoter Opening	Reactome	1.11E-05
Meiotic recombination	Reactome	1.11E-05
RUNX1 regulates transcription of genes involved in differentiation of HSCs	Reactome	1.16E-05
Neutrophil degranulation	Reactome	1.33E-05
DNA methylation	Reactome	1.54E-05
Respiratory electron transport	Reactome	1.59E-05

Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3	Reactome	2.11E-05
RNA Polymerase I Chain Elongation	Reactome	2.26E-05
SIRT1 negatively regulates rRNA expression	Reactome	2.46E-05
Amyloid fiber formation	Reactome	2.78E-05
Interferon-alpha/beta signaling	Reactome	2.86E-05
B-WICH complex positively regulates rRNA expression	Reactome	2.91E-05
Factors involved in megakaryocyte development and platelet production	Reactome	3.09E-05
Transcriptional regulation by small RNAs	Reactome	3.22E-05
HDACs deacetylate histones	Reactome	3.29E-05
NoRC negatively regulates rRNA expression	Reactome	3.61E-05
Oxidative phosphorylation	KEGG	3.76E-05
Non-alcoholic fatty liver disease (NAFLD)	KEGG	4.81E-05
Negative epigenetic regulation of rRNA expression	Reactome	5.01E-05
PRC2 methylates histones and DNA	Reactome	5.07E-05
Senescence-Associated Secretory Phenotype (SASP)	Reactome	5.58E-05
Condensation of Prophase Chromosomes	Reactome	6.65E-05
Meiosis	Reactome	7.58E-05
Translation initiation complex formation	Reactome	8.03E-05
Ribosomal scanning and start codon recognition	Reactome	8.03E-05
ERCC6 (CSB) and EHMT2 (G9a) positively regulate rRNA expression	Reactome	8.63E-05
Parkinson disease	KEGG	8.69E-05
Activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to 43S	Reactome	9.25E-05
Mitotic Prophase	Reactome	9.49E-05
Gene Silencing by RNA	Reactome	1.31E-04
Formation of the ternary complex, and subsequently, the 43S complex	Reactome	1.46E-04
Positive epigenetic regulation of rRNA expression	Reactome	1.54E-04
Epigenetic regulation of gene expression	Reactome	1.71E-04
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.	Reactome	1.82E-04
ISG15 antiviral mechanism	Reactome	1.86E-04
Antiviral mechanism by IFN-stimulated genes	Reactome	1.86E-04
Metabolism of amino acids and derivatives	Reactome	2.01E-04
RNA Polymerase I Promoter Clearance	Reactome	2.07E-04
NOD-like receptor signaling pathway	KEGG	2.27E-04
RNA Polymerase I Transcription	Reactome	2.50E-04
Mitochondrial translation termination	Reactome	2.80E-04
Mitochondrial translation elongation	Reactome	2.80E-04
Mitochondrial translation initiation	Reactome	2.80E-04
Negative regulators of DDX58/IFIH1 signaling	Reactome	2.82E-04
Mitophagy - animal	KEGG	3.32E-04

Signaling by Interleukins	Reactome	4.05E-04
Processing of Capped Intron-Containing Pre-mRNA	Reactome	4.55E-04
mRNA Splicing - Major Pathway	Reactome	4.63E-04
Formation of the beta-catenin: TCF transactivating complex	Reactome	4.69E-04
Mitochondrial translation	Reactome	5.18E-04
mRNA Splicing	Reactome	7.80E-04
Alzheimer disease	KEGG	8.00E-04
HATs acetylate histones	Reactome	8.58E-04
Cellular Senescence	Reactome	8.84E-04
Reproduction	Reactome	1.18E-03
Huntington disease	KEGG	1.20E-03
Systemic lupus erythematosus	KEGG	1.21E-03
Transcriptional regulation by RUNX1	Reactome	1.43E-03
Thermogenesis	KEGG	1.47E-03
Metabolism	Reactome	1.65E-03
Interferon-gamma signaling	Reactome	1.81E-03
Cell Cycle, Mitotic	Reactome	1.81E-03
DDX58/IFIH1-mediated induction of interferon-alpha/beta	Reactome	2.11E-03
Oxidative Stress-Induced Senescence	Reactome	2.14E-03
The citric acid (TCA) cycle and respiratory electron transport	Reactome	2.39E-03
Inflammasomes	Reactome	2.83E-03
mRNA decay by 5, to 3, exoribonuclease	Reactome	2.83E-03
Interleukin-15 signaling	Reactome	3.45E-03
Alcoholism	KEGG	3.56E-03
ESR-mediated signaling	Reactome	3.56E-03
Regulation of TLR by endogenous ligand	Reactome	3.65E-03
Spliceosome	KEGG	3.94E-03
Cellular responses to external stimuli	Reactome	4.32E-03
Innate Immune System	Reactome	4.41E-03
Chromatin modifying enzymes	Reactome	4.99E-03
Chromatin organization	Reactome	4.99E-03
MAPK1 (ERK2) activation	Reactome	5.02E-03
Cellular responses to stress	Reactome	5.06E-03
The AIM2 inflammasome	Reactome	5.07E-03
Influenza A	KEGG	5.29E-03
IL-17 signaling pathway	KEGG	5.31E-03
Estrogen-dependent gene expression	Reactome	5.70E-03
Signaling by Nuclear Receptors	Reactome	6.95E-03
The NLRP3 inflammasome	Reactome	6.95E-03
MAPK3 (ERK1) activation	Reactome	6.95E-03
Interleukin-27 signaling	Reactome	6.95E-03
Pantothenate and CoA biosynthesis	KEGG	7.04E-03
Complex I biogenesis	Reactome	7.56E-03
Hemostasis	Reactome	8.21E-03
Mucin type O-glycan biosynthesis	KEGG	8.57E-03
Measles	KEGG	8.60E-03

Interleukin-6 signaling	Reactome	9.27E-03
Ubiquinone and other terpenoid-quinone biosynthesis	KEGG	9.27E-03
TP53 Regulates Transcription of Cell Death Genes	Reactome	9.40E-03
TP53 Regulates Metabolic Genes	Reactome	9.49E-03
Biosynthesis of DPAn-3 SPMs	Reactome	9.85E-03
Biosynthesis of DPA-derived SPMs	Reactome	9.85E-03
Kaposi sarcoma-associated herpesvirus infection	KEGG	1.12E-02
Cell Cycle	Reactome	1.19E-02
Pink/Parkin Mediated Mitophagy	Reactome	1.20E-02
COPI-independent Golgi-to-ER retrograde traffic	Reactome	1.27E-02
Interconversion of nucleotide di- and triphosphates	Reactome	1.27E-02
Hepatitis C	KEGG	1.29E-02
Disease	Reactome	1.33E-02
Regulation of RAS by GAPs	Reactome	1.41E-02
Protein export	KEGG	1.41E-02
Advanced glycosylation endproduct receptor signaling	Reactome	1.51E-02
M Phase	Reactome	1.51E-02
Cardiac muscle contraction	KEGG	1.58E-02
Biosynthesis of the N-glycan precursor (dolichol lipid-linked oligosaccharide, LLO) and transfer to a nascent protein	Reactome	1.58E-02
Cross-presentation of soluble exogenous antigens (endosomes)	Reactome	1.60E-02
MET activates PTPN11	Reactome	1.60E-02
Nicotinate metabolism	Reactome	1.64E-02
Vitamin B5 (pantothenate) metabolism	Reactome	1.86E-02
Neddylation	Reactome	1.88E-02
Epstein-Barr virus infection	KEGG	2.04E-02
Caspase activation via extrinsic apoptotic signalling pathway	Reactome	2.16E-02
Transcriptional Regulation by TP53	Reactome	2.23E-02
IL-6-type cytokine receptor-ligand interactions	Reactome	2.26E-02
MET activates PI3K/AKT signaling	Reactome	2.33E-02
Metal sequestration by antimicrobial proteins	Reactome	2.33E-02
Protein repair	Reactome	2.33E-02
Phagosome	KEGG	2.42E-02
Post-translational protein modification	Reactome	2.55E-02
Apoptosis	Reactome	2.56E-02
TCF dependent signaling in response to WNT	Reactome	2.59E-02
RIG-I-like receptor signaling pathway	KEGG	2.63E-02
RHO GTPase Effectors	Reactome	2.65E-02
RIPK1-mediated regulated necrosis	Reactome	2.70E-02
Regulated Necrosis	Reactome	2.70E-02
Ligand-dependent caspase activation	Reactome	2.70E-02
Synthesis of Prostaglandins (PG) and Thromboxanes (TX)	Reactome	2.70E-02
Prefoldin mediated transfer of substrate to CCT/TriC	Reactome	2.77E-02
Programmed Cell Death	Reactome	2.98E-02
Late Phase of HIV Life Cycle	Reactome	3.38E-02

Mitophagy	Reactome	3.47E-02
RNA Polymerase II Transcription	Reactome	3.58E-02
Transcription of the HIV genome	Reactome	3.65E-02
Proteasome	KEGG	3.84E-02
Gene expression (Transcription)	Reactome	3.84E-02
Arachidonic acid metabolism	Reactome	4.10E-02
Cross-presentation of particulate exogenous antigens (phagosomes)	Reactome	4.12E-02
Ubiquinol biosynthesis	Reactome	4.12E-02
Proteoglycans in cancer	KEGG	4.21E-02
Ub-specific processing proteases	Reactome	4.25E-02
Interleukin-12 family signaling	Reactome	4.25E-02
MAPK1/MAPK3 signaling	Reactome	4.36E-02
RNA Polymerase II Transcription Pre-Initiation And Promoter Opening	Reactome	4.51E-02
RNA Polymerase II Transcription Initiation	Reactome	4.51E-02
RNA Polymerase II Transcription Initiation And Promoter Clearance	Reactome	4.51E-02
HIV Transcription Initiation	Reactome	4.51E-02
RNA Polymerase II HIV Promoter Escape	Reactome	4.51E-02
Nucleotide-binding domain, leucine-rich repeat containing receptor (NLR) signaling pathways	Reactome	4.51E-02
Retrograde endocannabinoid signaling	KEGG	4.55E-02
Cytosolic DNA-sensing pathway	KEGG	4.69E-02
Cooperation of Prefoldin and TriC/CCT in actin and tubulin folding	Reactome	4.71E-02
TP53 Regulates Transcription of Genes Involved in Cytochrome C Release	Reactome	4.85E-02
Syndecan interactions	Reactome	4.85E-02
G beta: gamma signalling through PI3Kgamma	Reactome	4.87E-02

Supplementary Table 3 Enriched pathways of common DEGs in Macrophage cells

Macrophage cells enriched pathway-based sets		
Pathway	Source	p-value
Immune System	Reactome	9.98E-25
Innate Immune System	Reactome	1.96E-18
Neutrophil degranulation	Reactome	6.38E-17
Pathways in cancer	KEGG	1.56E-12
Lysosome	KEGG	8.16E-12
Cytokine Signaling in Immune system	Reactome	2.03E-11
Transcriptional misregulation in cancer	KEGG	1.25E-10
MAPK signaling pathway	KEGG	1.39E-10
Apoptosis	KEGG	2.72E-09
Focal adhesion	KEGG	3.95E-09
Proteoglycans in cancer	KEGG	5.21E-09

Osteoclast differentiation	KEGG	1.03E-08
Acute myeloid leukemia	KEGG	5.33E-08
Hepatitis C	KEGG	6.01E-08
Prostate cancer	KEGG	7.01E-08
Signaling by Receptor Tyrosine Kinases	Reactome	9.18E-08
Interferon Signaling	Reactome	9.30E-08
Human cytomegalovirus infection	KEGG	1.07E-07
Human T-cell leukemia virus 1 infection	KEGG	1.65E-07
TNF signaling pathway	KEGG	1.74E-07
Glioma	KEGG	1.81E-07
Platelet activation, signaling, and aggregation	Reactome	1.85E-07
Measles	KEGG	3.30E-07
Rap1 signaling pathway	KEGG	3.52E-07
Bladder cancer	KEGG	5.67E-07
T cell receptor signaling pathway	KEGG	6.57E-07
Metabolism of carbohydrates	Reactome	6.96E-07
Human papillomavirus infection	KEGG	7.77E-07
Kaposi sarcoma-associated herpesvirus infection	KEGG	1.03E-06
Melanoma	KEGG	1.18E-06
FoxO signaling pathway	KEGG	1.22E-06
Rheumatoid arthritis	KEGG	1.46E-06
Adaptive Immune System	Reactome	1.58E-06
Epstein-Barr virus infection	KEGG	1.64E-06
Hemostasis	Reactome	1.68E-06
Hepatitis B	KEGG	2.07E-06
PI3K-Akt signaling pathway	KEGG	2.38E-06
Renal cell carcinoma	KEGG	3.12E-06
Legionellosis	KEGG	3.98E-06
Cellular senescence	KEGG	4.65E-06
Toll-Like Receptors Cascades	Reactome	7.18E-06
AGE-RAGE signaling pathway in diabetic complications	KEGG	7.72E-06
Gastrin-CREB signalling pathway via PKC and MAPK	Reactome	8.05E-06
Estrogen signaling pathway	KEGG	8.27E-06
Pancreatic cancer	KEGG	9.87E-06
Ras signaling pathway	KEGG	1.39E-05
Metabolism of ingested H ₂ SeO ₄ and H ₂ SeO ₃ into H ₂ Se	Reactome	1.41E-05
Signaling by Interleukins	Reactome	1.45E-05
Colorectal cancer	KEGG	1.53E-05
Influenza A	KEGG	1.59E-05
C-type lectin receptor signaling pathway	KEGG	1.62E-05
Interferon-alpha/beta signaling	Reactome	1.76E-05
MET activates RAS signaling	Reactome	1.86E-05
MAPK family signaling cascades	Reactome	1.98E-05
Diseases of signal transduction	Reactome	2.18E-05
RAF/MAP kinase cascade	Reactome	2.48E-05
Chemokine signaling pathway	KEGG	3.45E-05

Neurotrophin signaling pathway	KEGG	3.48E-05
Signaling by BRAF and RAF fusions	Reactome	3.84E-05
Metabolism	Reactome	3.85E-05
MAPK1/MAPK3 signaling	Reactome	4.32E-05
Phagosome	KEGG	4.70E-05
Costimulation by the CD28 family	Reactome	5.75E-05
Oncogenic MAPK signaling	Reactome	6.73E-05
Longevity regulating pathway - multiple species	KEGG	8.05E-05
Th17 cell differentiation	KEGG	8.35E-05
CD209 (DC-SIGN) signaling	Reactome	8.42E-05
Tuberculosis	KEGG	8.81E-05
SHC-related events triggered by IGF1R	Reactome	8.84E-05
Toll-Like Receptor 4 (TLR4) Cascade	Reactome	8.98E-05
Hepatocellular carcinoma	KEGG	9.25E-05
Viral carcinogenesis	KEGG	1.02E-04
Human immunodeficiency virus 1 infection	KEGG	1.02E-04
p53 signaling pathway	KEGG	1.03E-04
Regulation of actin cytoskeleton	KEGG	1.11E-04
Fluid shear stress and atherosclerosis	KEGG	1.12E-04
Platelet degranulation	Reactome	1.12E-04
Negative regulation of MAPK pathway	Reactome	1.13E-04
Signaling by VEGF	Reactome	1.14E-04
HIF-1 signaling pathway	KEGG	1.14E-04
Rho GTPase cycle	Reactome	1.24E-04
Relaxin signaling pathway	KEGG	1.25E-04
Natural killer cell-mediated cytotoxicity	KEGG	1.25E-04
Central carbon metabolism in cancer	KEGG	1.34E-04
Programmed Cell Death	Reactome	1.39E-04
Leukocyte transendothelial migration	KEGG	1.53E-04
Signaling by high-kinase activity BRAF mutants	Reactome	1.55E-04
Non-small cell lung cancer	KEGG	1.58E-04
EGFR Transactivation by Gastrin	Reactome	1.68E-04
Viral myocarditis	KEGG	1.72E-04
Chronic myeloid leukemia	KEGG	1.89E-04
Response to elevated platelet cytosolic Ca ²⁺	Reactome	1.91E-04
Hematopoietic cell lineage	KEGG	2.28E-04
Signaling by RAS mutants	Reactome	2.49E-04
Toll-Like Receptor 3 (TLR3) Cascade	Reactome	2.58E-04
Prolactin signaling pathway	KEGG	2.92E-04
RHO GTPases activate IQGAPs	Reactome	2.92E-04
Autophagy - animal	KEGG	2.94E-04
Apoptosis	Reactome	2.99E-04
ISG15 antiviral mechanism	Reactome	3.41E-04
Antiviral mechanism by IFN-stimulated genes	Reactome	3.41E-04
Phosphorylation of CD3 and TCR zeta chains	Reactome	3.41E-04
JAK-STAT signaling pathway	KEGG	3.71E-04

Signaling by moderate kinase activity BRAF mutants	Reactome	3.85E-04
Paradoxical activation of RAF signaling by kinase inactive BRAF	Reactome	3.85E-04
MAP2K and MAPK activation	Reactome	3.85E-04
Glycosphingolipid metabolism	Reactome	3.89E-04
TRIF(TICAM1)-mediated TLR4 signaling	Reactome	4.13E-04
MyD88-independent TLR4 cascade	Reactome	4.13E-04
Pathogenic Escherichia coli infection	KEGG	4.34E-04
VEGFA-VEGFR2 Pathway	Reactome	4.52E-04
Nucleotide-binding domain, leucine-rich repeat containing receptor (NLR) signaling pathways	Reactome	4.68E-04
CD28 dependent Vav1 pathway	Reactome	4.75E-04
GnRH signaling pathway	KEGG	5.09E-04
NF-kappa B signaling pathway	KEGG	5.73E-04
Interferon-gamma signaling	Reactome	5.73E-04
Extracellular matrix organization	Reactome	5.76E-04
Nuclear Events (kinase and transcription factor activation)	Reactome	5.81E-04
Cellular responses to stress	Reactome	6.24E-04
Breast cancer	KEGG	6.58E-04
Malaria	KEGG	6.64E-04
Fc epsilon RI signaling pathway	KEGG	6.96E-04
Long-term potentiation	KEGG	6.96E-04
Endometrial cancer	KEGG	6.99E-04
Thyroid hormone signaling pathway	KEGG	6.99E-04
Aldosterone synthesis and secretion	KEGG	7.19E-04
Basigin interactions	Reactome	7.54E-04
G alpha (12/13) signalling events	Reactome	7.93E-04
MyD88 cascade initiated on plasma membrane	Reactome	7.93E-04
Toll-Like Receptor 10 (TLR10) Cascade	Reactome	7.93E-04
Toll-Like Receptor 5 (TLR5) Cascade	Reactome	7.93E-04
Nef and signal transduction	Reactome	8.10E-04
VEGF signaling pathway	KEGG	8.12E-04
mTOR signaling pathway	KEGG	8.53E-04
Cellular responses to external stimuli	Reactome	8.75E-04
Glycosaminoglycan metabolism	Reactome	9.38E-04
CREB phosphorylation through the activation of Ras	Reactome	9.64E-04
Translocation of ZAP-70 to Immunological synapse	Reactome	9.64E-04
Inflammatory mediator regulation of TRP channels	KEGG	9.97E-04
Longevity regulating pathway	KEGG	9.99E-04
Post NMDA receptor activation events	Reactome	1.04E-03
Detoxification of Reactive Oxygen Species	Reactome	1.27E-03
Signal Transduction	Reactome	1.30E-03
TCR signaling	Reactome	1.35E-03
Platelet activation	KEGG	1.36E-03
Th1 and Th2 cell differentiation	KEGG	1.39E-03
Signaling by PTK6	Reactome	1.46E-03

Signaling by Non-Receptor Tyrosine Kinases	Reactome	1.46E-03
Cyclin E associated events during G1/S transition	Reactome	1.52E-03
Cyclin A: Cdk2-associated events at S phase entry	Reactome	1.52E-03
The role of Nef in HIV-1 replication and disease pathogenesis	Reactome	1.52E-03
Thyroid cancer	KEGG	1.53E-03
Small cell lung cancer	KEGG	1.55E-03
IL-17 signaling pathway	KEGG	1.55E-03
Semaphorin interactions	Reactome	1.63E-03
CD28 dependent PI3K/Akt signaling	Reactome	1.68E-03
ERK/MAPK targets	Reactome	1.68E-03
Bacterial invasion of epithelial cells	KEGG	1.72E-03
Apoptotic cleavage of cellular proteins	Reactome	1.84E-03
Cell surface interactions at the vascular wall	Reactome	1.90E-03
Activation of caspases through apoptosome-mediated cleavage	Reactome	2.10E-03
Cytochrome c-mediated apoptotic response	Reactome	2.10E-03
Activation of RAS in B cells	Reactome	2.10E-03
Nucleotide-like (purinergic) receptors	Reactome	2.13E-03
Branched-chain amino acid catabolism	Reactome	2.16E-03
Signaling by NTRK1 (TRKA)	Reactome	2.17E-03
Activation of NMDA receptor and postsynaptic events	Reactome	2.19E-03
RUNX3 regulates p14-ARF	Reactome	2.20E-03
Sphingolipid signaling pathway	KEGG	2.28E-03
Valine, leucine and isoleucine degradation	KEGG	2.29E-03
MAPK targets/ Nuclear events mediated by MAP kinases	Reactome	2.30E-03
PD-1 signaling	Reactome	2.30E-03
MyD88: Mal cascade initiated on plasma membrane	Reactome	2.33E-03
Toll-Like Receptor TLR1: TLR2 Cascade	Reactome	2.33E-03
Toll-Like Receptor TLR6: TLR2 Cascade	Reactome	2.33E-03
Toll-Like Receptor 2 (TLR2) Cascade	Reactome	2.33E-03
Integrin cell surface interactions	Reactome	2.38E-03
TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	Reactome	2.67E-03
Glycolysis / Gluconeogenesis	KEGG	2.69E-03
Epithelial cell signaling in Helicobacter pylori infection	KEGG	2.69E-03
Sema4D in semaphorin signaling	Reactome	2.73E-03
Translocation of GLUT4 to the plasma membrane	Reactome	2.79E-03
Progesterone-mediated oocyte maturation	KEGG	2.82E-03
G alpha (q) signalling events	Reactome	2.93E-03
Signaling by NTRKs	Reactome	2.95E-03
Generation of second messenger molecules	Reactome	3.05E-03
Signaling by ERBB2	Reactome	3.06E-03
Disease	Reactome	3.15E-03
MyD88 dependent cascade initiated on endosome	Reactome	3.26E-03
Toll-Like Receptor 7/8 (TLR7/8) Cascade	Reactome	3.26E-03
Interleukin-1 signaling	Reactome	3.31E-03
CD28 co-stimulation	Reactome	3.36E-03

Cargo concentration in the ER	Reactome	3.36E-03
NOD-like receptor signaling pathway	KEGG	3.38E-03
Transcriptional regulation by RUNX3	Reactome	3.52E-03
Sphingolipid metabolism	Reactome	3.60E-03
Fructose biosynthesis	Reactome	3.77E-03
Hyaluronan biosynthesis and export	Reactome	3.77E-03
Cell cycle	KEGG	3.77E-03
SCF(Skp2)-mediated degradation of p27/p21	Reactome	3.78E-03
Toxoplasmosis	KEGG	3.78E-03
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	Reactome	3.95E-03
Intrinsic Pathway for Apoptosis	Reactome	4.16E-03
Signaling by SCF-KIT	Reactome	4.16E-03
Signaling by EGFR	Reactome	4.16E-03
Apelin signaling pathway	KEGG	4.33E-03
Gastric cancer	KEGG	4.51E-03
C-type lectin receptors (CLRs)	Reactome	4.58E-03
Death Receptor Signalling	Reactome	4.66E-03
Hyaluronan metabolism	Reactome	4.70E-03
NOTCH2 intracellular domain regulates transcription	Reactome	4.70E-03
Smooth Muscle Contraction	Reactome	4.76E-03
EPHB-mediated forward signaling	Reactome	4.76E-03
Toll-Like Receptor 9 (TLR9) Cascade	Reactome	4.77E-03
Interleukin-3, 5 and GM-CSF signaling	Reactome	4.82E-03
Cyclin D associated events in G1	Reactome	4.82E-03
G1 Phase	Reactome	4.82E-03
Degradation of the extracellular matrix	Reactome	4.86E-03
Glycosaminoglycan degradation	KEGG	4.87E-03
HSP90 chaperone cycle for steroid hormone receptors (SHR)	Reactome	4.87E-03
VEGFR2 mediated cell proliferation	Reactome	4.87E-03
Integrin alphaIIb beta3 signaling	Reactome	5.12E-03
Integrin signaling	Reactome	5.12E-03
MicroRNAs in cancer	KEGG	5.49E-03
Signaling by Rho GTPases	Reactome	5.65E-03
MAP kinase activation	Reactome	5.97E-03
Interleukin-17 signaling	Reactome	5.97E-03
One carbon pool by folate	KEGG	6.17E-03
NOTCH3 Intracellular Domain Regulates Transcription	Reactome	6.17E-03
Recycling pathway of L1	Reactome	6.19E-03
Pertussis	KEGG	6.45E-03
Metabolism of vitamins and cofactors	Reactome	6.47E-03
Glutathione metabolism	KEGG	6.67E-03
Fructose metabolism	Reactome	6.70E-03
GRB2 events in EGFR signaling	Reactome	6.70E-03
SOS-mediated signalling	Reactome	6.70E-03
CREB phosphorylation	Reactome	6.70E-03

Apoptotic factor-mediated response	Reactome	6.70E-03
Adrenergic signaling in cardiomyocytes	KEGG	7.15E-03
Axon guidance	Reactome	7.24E-03
Interleukin-2 family signaling	Reactome	7.61E-03
CTLA4 inhibitory signaling	Reactome	7.70E-03
HS-GAG degradation	Reactome	7.70E-03
Endocytosis	KEGG	8.26E-03
Iron uptake and transport	Reactome	8.40E-03
Fc gamma R-mediated phagocytosis	KEGG	8.77E-03
Downstream signaling events of B Cell Receptor (BCR)	Reactome	8.79E-03
DAP12 signaling	Reactome	8.79E-03
Downstream signal transduction	Reactome	8.79E-03
COPII-mediated vesicle transport	Reactome	9.10E-03
MHC class II antigen presentation	Reactome	9.39E-03
B cell receptor signaling pathway	KEGG	1.00E-02
Tryptophan metabolism	KEGG	1.01E-02
Cross-presentation of particulate exogenous antigens (phagosomes)	Reactome	1.02E-02
Interleukin-15 signaling	Reactome	1.02E-02
SHC1 events in EGFR signaling	Reactome	1.02E-02
Sema4D mediated inhibition of cell attachment and migration	Reactome	1.02E-02
VEGF binds to VEGFR leading to receptor dimerization	Reactome	1.02E-02
VEGF ligand-receptor interactions	Reactome	1.02E-02
Dectin-1 mediated noncanonical NF-kB signaling	Reactome	1.02E-02
NIK-->noncanonical NF-kB signaling	Reactome	1.02E-02
Regulation of cytoskeletal remodeling and cell spreading by IPP complex components	Reactome	1.02E-02
HSF1 activation	Reactome	1.03E-02
Transferrin endocytosis and recycling	Reactome	1.03E-02
Chemokine receptors bind chemokines	Reactome	1.06E-02
cAMP signaling pathway	KEGG	1.07E-02
CaMK IV-mediated phosphorylation of CREB	Reactome	1.08E-02
MET activates STAT3	Reactome	1.08E-02
Mitotic G1-G1/S phases	Reactome	1.11E-02
Toll-like receptor signaling pathway	KEGG	1.11E-02
GRB2: SOS provides linkage to MAPK signaling for Integrins	Reactome	1.12E-02
Interleukin-4 and 13 signaling	Reactome	1.12E-02
Inflammasomes	Reactome	1.12E-02
RAF-independent MAPK1/3 activation	Reactome	1.15E-02
Binding and Uptake of Ligands by Scavenger Receptors	Reactome	1.16E-02
Downstream TCR signaling	Reactome	1.19E-02
PI3K/AKT Signaling in Cancer	Reactome	1.22E-02
Parathyroid hormone synthesis, secretion, and action	KEGG	1.29E-02
Apoptotic execution phase	Reactome	1.33E-02
Leishmaniasis	KEGG	1.34E-02
GPVI-mediated activation cascade	Reactome	1.40E-02

NOD1/2 Signaling Pathway	Reactome	1.40E-02
RIPK1-mediated regulated necrosis	Reactome	1.42E-02
Regulated Necrosis	Reactome	1.42E-02
Rap1 signalling	Reactome	1.42E-02
Cell-extracellular matrix interactions	Reactome	1.42E-02
Signaling by NOTCH	Reactome	1.43E-02
Thyroid hormone synthesis	KEGG	1.46E-02
PPAR signaling pathway	KEGG	1.46E-02
AKT phosphorylates targets in the nucleus	Reactome	1.47E-02
Activated NTRK2 signals through RAS	Reactome	1.47E-02
MET activates RAP1 and RAC1	Reactome	1.47E-02
Sulfur metabolism	KEGG	1.47E-02
Alcoholism	KEGG	1.47E-02
Type I diabetes mellitus	KEGG	1.49E-02
AMPK signaling pathway	KEGG	1.53E-02
Intracellular signaling by second messengers	Reactome	1.59E-02
Transcriptional regulation by RUNX2	Reactome	1.60E-02
Gastric acid secretion	KEGG	1.60E-02
Gluconeogenesis	Reactome	1.62E-02
RAF activation	Reactome	1.64E-02
Inhibition of voltage-gated Ca ²⁺ channels via G beta/gamma subunits	Reactome	1.64E-02
Activation of G protein gated Potassium channels	Reactome	1.64E-02
G protein gated Potassium channels	Reactome	1.64E-02
Heparan sulfate/heparin (HS-GAG) metabolism	Reactome	1.65E-02
Signaling by PDGF	Reactome	1.65E-02
Vasopressin-regulated water reabsorption	KEGG	1.68E-02
Signaling by NOTCH3	Reactome	1.68E-02
Shigellosis	KEGG	1.73E-02
Mitophagy - animal	KEGG	1.73E-02
G1/S Transition	Reactome	1.74E-02
Regulation of RUNX1 Expression and Activity	Reactome	1.77E-02
Selenocompound metabolism	KEGG	1.77E-02
Metabolism of folate and pterines	Reactome	1.77E-02
Staphylococcus aureus infection	KEGG	1.83E-02
Collagen degradation	Reactome	1.85E-02
Interleukin-1 family signaling	Reactome	1.90E-02
Antigen processing and presentation	KEGG	1.90E-02
Caspase activation via extrinsic apoptotic signalling pathway	Reactome	1.93E-02
Calmodulin induced events	Reactome	1.93E-02
CaM pathway	Reactome	1.93E-02
Signaling by FGFR3 fusions in cancer	Reactome	2.00E-02
The NLRP3 inflammasome	Reactome	2.00E-02
Melanogenesis	KEGG	2.07E-02
Adenosine P1 receptors	Reactome	2.08E-02
Regulation of gene expression by Hypoxia-inducible Factor	Reactome	2.08E-02

CREB phosphorylation through the activation of CaMKK	Reactome	2.08E-02
Carnitine synthesis	Reactome	2.08E-02
Insulin signaling pathway	KEGG	2.10E-02
Oocyte meiosis	KEGG	2.11E-02
Primary immunodeficiency	KEGG	2.11E-02
Glucose metabolism	Reactome	2.16E-02
Salivary secretion	KEGG	2.16E-02
PKA-mediated phosphorylation of CREB	Reactome	2.16E-02
Other glycan degradation	KEGG	2.16E-02
Signalling to RAS	Reactome	2.16E-02
Tie2 Signaling	Reactome	2.16E-02
Regulation of signaling by CBL	Reactome	2.16E-02
Cellular Senescence	Reactome	2.23E-02
Complement and coagulation cascades	KEGG	2.23E-02
Transcriptional activation of mitochondrial biogenesis	Reactome	2.25E-02
Interleukin receptor SHC signaling	Reactome	2.25E-02
Biosynthesis of unsaturated fatty acids	KEGG	2.25E-02
Sphingolipid metabolism	KEGG	2.36E-02
Glucagon signaling pathway	KEGG	2.38E-02
Allograft rejection	KEGG	2.39E-02
Platelet Aggregation (Plug Formation)	Reactome	2.39E-02
Negative regulation of the PI3K/AKT network	Reactome	2.55E-02
Attenuation phase	Reactome	2.61E-02
Ca-dependent events	Reactome	2.61E-02
G beta: gamma signalling through PI3Kgamma	Reactome	2.62E-02
Dimerization of procaspase-8	Reactome	2.63E-02
Regulation by c-FLIP	Reactome	2.63E-02
CASP8 activity is inhibited	Reactome	2.63E-02
Regulation of necroptotic cell death	Reactome	2.63E-02
p38MAPK events	Reactome	2.63E-02
Signaling by FGFR4 in disease	Reactome	2.63E-02
Glycolysis	Reactome	2.68E-02
Ovarian steroidogenesis	KEGG	2.90E-02
Antigen processing-Cross presentation	Reactome	2.90E-02
Long-term depression	KEGG	2.95E-02
Disassembly of the destruction complex and recruitment of AXIN to the membrane	Reactome	3.00E-02
Signalling to ERKs	Reactome	3.00E-02
Dopaminergic synapse	KEGG	3.02E-02
Activation of GABAB receptors	Reactome	3.03E-02
GABA B receptor activation	Reactome	3.03E-02
Signaling by NTRK2 (TRKB)	Reactome	3.11E-02
Syndecan interactions	Reactome	3.11E-02
TNFR2 non-canonical NF-kB pathway	Reactome	3.20E-02
Cholesterol metabolism	KEGG	3.20E-02
Vibrio cholerae infection	KEGG	3.20E-02

Signaling by MET	Reactome	3.22E-02
Phospholipase D signaling pathway	KEGG	3.28E-02
p75 NTR receptor-mediated signalling	Reactome	3.30E-02
SMAC binds to IAPs	Reactome	3.33E-02
SMAC-mediated dissociation of IAP: caspase complexes	Reactome	3.33E-02
SMAC-mediated apoptotic response	Reactome	3.33E-02
Cross-presentation of soluble exogenous antigens (endosomes)	Reactome	3.33E-02
Keratan sulfate degradation	Reactome	3.33E-02
PTK6 Expression	Reactome	3.33E-02
MET activates PTPN11	Reactome	3.33E-02
MET interacts with TNS proteins	Reactome	3.33E-02
Propionyl-CoA catabolism	Reactome	3.33E-02
Catabolism of glucuronate to xylulose-5-phosphate	Reactome	3.33E-02
LRR FLII-interacting protein 1 (LRRFIP1) activates type I IFN production	Reactome	3.33E-02
Interleukin-2 signaling	Reactome	3.35E-02
Caspase-mediated cleavage of cytoskeletal proteins	Reactome	3.35E-02
P2Y receptors	Reactome	3.35E-02
Ferroptosis	KEGG	3.39E-02
Glyoxylate and dicarboxylate metabolism	KEGG	3.42E-02
ErbB signaling pathway	KEGG	3.50E-02
G-protein beta: gamma signalling	Reactome	3.52E-02
Herpes simplex infection	KEGG	3.56E-02
Metabolism of lipids	Reactome	3.67E-02
Salmonella infection	KEGG	3.75E-02
TP53 Regulates Metabolic Genes	Reactome	3.75E-02
Graft-versus-host disease	KEGG	3.77E-02
beta-Alanine metabolism	KEGG	3.88E-02
Galactose metabolism	KEGG	3.88E-02
Inwardly rectifying K ⁺ channels	Reactome	3.88E-02
Activation of Matrix Metalloproteinases	Reactome	3.88E-02
Cytokine-cytokine receptor interaction	KEGG	3.90E-02
Metabolism of water-soluble vitamins and cofactors	Reactome	3.96E-02
Signaling by Insulin receptor	Reactome	3.96E-02
PIP3 activates AKT signaling	Reactome	4.01E-02
Necroptosis	KEGG	4.07E-02
DEX/H-box helicases activate type I IFN and inflammatory cytokines production	Reactome	4.16E-02
Constitutive Signaling by EGFRvIII	Reactome	4.16E-02
Signaling by EGFRvIII in Cancer	Reactome	4.16E-02
ERKs are inactivated	Reactome	4.16E-02
alpha-linolenic acid (ALA) metabolism	Reactome	4.16E-02
alpha-linolenic (omega3) and linoleic (omega6) acid metabolism	Reactome	4.16E-02
Cholinergic synapse	KEGG	4.20E-02
Cell death signalling via NRAGE, NRIF, and NADE	Reactome	4.26E-02

SHC1 events in ERBB2 signaling	Reactome	4.26E-02
Nef-mediates down modulation of cell surface receptors by recruiting them to clathrin adapters	Reactome	4.26E-02
cGMP-PKG signaling pathway	KEGG	4.27E-02
Propanoate metabolism	KEGG	4.38E-02
DAG and IP3 signaling	Reactome	4.38E-02
Amino acid transport across the plasma membrane	Reactome	4.38E-02
Dilated cardiomyopathy (DCM)	KEGG	4.58E-02
Hedgehog, off, state	Reactome	4.61E-02
Signaling pathways regulating pluripotency of stem cells	KEGG	4.64E-02
Oxytocin signaling pathway	KEGG	4.67E-02
Scavenging by Class B Receptors	Reactome	4.79E-02
PTK6 Regulates Cell Cycle	Reactome	4.79E-02
MET activates PI3K/AKT signaling	Reactome	4.79E-02
MET Receptor Activation	Reactome	4.79E-02
RSK activation	Reactome	4.79E-02
Metal sequestration by antimicrobial proteins	Reactome	4.79E-02
Transport and synthesis of PAPS	Reactome	4.79E-02
Chagas disease (American trypanosomiasis)	KEGG	4.81E-02
Apoptosis - multiple species	KEGG	4.91E-02
Fructose and mannose metabolism	KEGG	4.91E-02
Signaling by NOTCH2	Reactome	4.91E-02

Supplementary Table 4 Enriched pathways of common DEGs in T cells

T cells enriched pathway-based sets		
Pathway	Source	p-value
Growth hormone receptor signaling	Reactome	3.30E-05
Cytokine Signaling in Immune system	Reactome	1.95E-04
Eicosanoid ligand-binding receptors	Reactome	4.08E-04
Immune System	Reactome	8.98E-04
Signaling by Interleukins	Reactome	1.02E-03
Signaling by the B Cell Receptor (BCR)	Reactome	1.72E-03
Legionellosis	KEGG	2.20E-03
Transcriptional regulation of pluripotent stem cells	Reactome	2.67E-03
Cytokine-cytokine receptor interaction	KEGG	2.78E-03
MAPK signaling pathway	KEGG	2.84E-03
Antigen activates BCR leading to generation of second messengers	Reactome	2.87E-03
Prostanoid ligand receptors	Reactome	3.42E-03
Platelet activation, signaling, and aggregation	Reactome	4.60E-03
POU5F1, SOX2, NANOG repress genes related to differentiation	Reactome	5.15E-03
G alpha (q) signalling events	Reactome	5.57E-03
Signal regulatory protein family interactions	Reactome	7.21E-03
Interleukin-1 family signaling	Reactome	7.38E-03

Toll-Like Receptor 4 (TLR4) Cascade	Reactome	8.93E-03
Osteoclast differentiation	KEGG	8.93E-03
MicroRNAs in cancer	KEGG	1.03E-02
Regulation of KIT signaling	Reactome	1.09E-02
Regulation of signaling by CBL	Reactome	1.37E-02
Adaptive Immune System	Reactome	1.41E-02
Role of LAT2/NTAL/LAB on calcium mobilization	Reactome	1.41E-02
HSP90 chaperone cycle for steroid hormone receptors	Reactome	1.52E-02
Other semaphorin interactions	Reactome	1.52E-02
Hematopoietic cell lineage	KEGG	1.57E-02
MyD88: Mal cascade initiated on plasma membrane	Reactome	1.62E-02
Toll-Like Receptor TLR1: TLR2 Cascade	Reactome	1.62E-02
Toll-Like Receptor TLR6: TLR2 Cascade	Reactome	1.62E-02
Toll-Like Receptor 2 (TLR2) Cascade	Reactome	1.62E-02
Signaling by Hippo	Reactome	1.68E-02
Fc epsilon receptor (FCERI) signaling	Reactome	1.74E-02
Innate Immune System	Reactome	1.92E-02
Toll-Like Receptors Cascades	Reactome	1.92E-02
C-type lectin receptor signaling pathway	KEGG	2.04E-02
Interleukin-1 signaling	Reactome	2.21E-02
FCERI mediated Ca ²⁺ mobilization	Reactome	2.31E-02
TNF signaling pathway	KEGG	2.45E-02
Semaphorin interactions	Reactome	2.62E-02
Toxoplasmosis	KEGG	2.67E-02
Signaling by BMP	Reactome	2.76E-02
Fc epsilon RI signaling pathway	KEGG	2.95E-02
CREB phosphorylation through the activation of Ras	Reactome	2.96E-02
Integrin alphaIIb beta3 signaling	Reactome	2.96E-02
Integrin signaling	Reactome	2.96E-02
Attenuation phase	Reactome	3.17E-02
Prolactin signaling pathway	KEGG	3.30E-02
B cell receptor signaling pathway	KEGG	3.30E-02
Dectin-2 family	Reactome	3.38E-02
TNFs bind their physiological receptors	Reactome	3.38E-02
CD22 mediated BCR regulation	Reactome	3.42E-02
Platelet activation	KEGG	3.49E-02
Hemostasis	Reactome	3.50E-02
Clathrin derived vesicle budding	Reactome	3.54E-02
trans-Golgi Network Vesicle Budding	Reactome	3.54E-02
Circadian rhythm	KEGG	3.60E-02
DAP12 signaling	Reactome	3.60E-02
HSF1 activation	Reactome	3.82E-02
Signal Transduction	Reactome	4.02E-02
Natural killer cell-mediated cytotoxicity	KEGG	4.15E-02
Measles	KEGG	4.25E-02
Cargo concentration in the ER	Reactome	4.29E-02

CD28 co-stimulation	Reactome	4.29E-02
GPVI-mediated activation cascade	Reactome	4.29E-02
Developmental Biology	Reactome	4.60E-02
Transcriptional regulation by RUNX1	Reactome	4.70E-02
EPHB-mediated forward signaling	Reactome	4.77E-02
Post NMDA receptor activation events	Reactome	4.77E-02

Supplementary Table 5 Enriched pathways of common DEGs in CD4⁺ T cells

CD4 ⁺ T cells enriched pathway-based sets		
Pathway	Source	p-value
Antigen processing: Ubiquitination & Proteasome degradation	Reactome	1.72E-05
Class I MHC mediated antigen processing & presentation	Reactome	2.19E-04
Epstein-Barr virus infection	KEGG	5.91E-04
Measles	KEGG	1.11E-03
Interleukin-7 signaling	Reactome	1.54E-03
Interleukin receptor SHC signaling	Reactome	1.78E-03
Immune System	Reactome	1.94E-03
TET1,2,3 and TDG demethylate DNA	Reactome	2.24E-03
Adaptive Immune System	Reactome	2.30E-03
Repression of WNT target genes	Reactome	2.32E-03
Lysosome	KEGG	2.92E-03
Choline metabolism in cancer	KEGG	3.32E-03
Hepatitis C	KEGG	3.51E-03
Interleukin-9 signaling	Reactome	3.69E-03
Trafficking of myristoylated proteins to the cilium	Reactome	3.69E-03
Signaling by BRAF and RAF fusions	Reactome	5.50E-03
MAPK signaling pathway	KEGG	5.57E-03
HSP90 chaperone cycle for steroid hormone receptors (SHR)	Reactome	5.74E-03
Thyroid cancer	KEGG	5.75E-03
Interleukin-2 family signaling	Reactome	6.33E-03
Neddylation	Reactome	6.55E-03
Influenza A	KEGG	6.64E-03
Oncogenic MAPK signaling	Reactome	6.81E-03
Colorectal cancer	KEGG	6.85E-03
Non-small cell lung cancer	KEGG	9.46E-03
Diseases of signal transduction	Reactome	9.92E-03
Interleukin-15 signaling	Reactome	9.94E-03
Competing endogenous RNAs (ceRNAs) regulate PTEN translation	Reactome	9.94E-03
Regulation of PTEN mRNA translation	Reactome	9.94E-03
Phospholipid metabolism	Reactome	1.03E-02
Interferon-gamma signaling	Reactome	1.04E-02
Interleukin-3, 5 and GM-CSF signaling	Reactome	1.06E-02
Renal cell carcinoma	KEGG	1.13E-02

Disease	Reactome	1.14E-02
Cilium Assembly	Reactome	1.16E-02
B cell receptor signaling pathway	KEGG	1.20E-02
Autophagy - animal	KEGG	1.31E-02
Notch signaling pathway	KEGG	1.43E-02
FoxO signaling pathway	KEGG	1.47E-02
Neutrophil degranulation	Reactome	1.52E-02
Retrograde transport at the Trans-Golgi-Network	Reactome	1.54E-02
Signaling by FGFR3 fusions in cancer	Reactome	1.56E-02
Chronic myeloid leukemia	KEGG	1.67E-02
Transcriptional regulation by RUNX3	Reactome	1.76E-02
Cargo trafficking to the periciliary membrane	Reactome	1.76E-02
Apoptosis	KEGG	1.78E-02
NOD-like receptor signaling pathway	KEGG	1.78E-02
Insulin signaling pathway	KEGG	1.84E-02
Interleukin-6 signaling	Reactome	1.88E-02
Signaling by FGFR4 in disease	Reactome	1.88E-02
Synthesis of PIPs at the plasma membrane	Reactome	2.00E-02
Pre-NOTCH Transcription and Translation	Reactome	2.05E-02
Interleukin-2 signaling	Reactome	2.22E-02
Export of Viral Ribonucleoproteins from Nucleus	Reactome	2.24E-02
Oncogene Induced Senescence	Reactome	2.44E-02
ErbB signaling pathway	KEGG	2.58E-02
Constitutive Signaling by EGFRvIII	Reactome	2.60E-02
Signaling by EGFRvIII in Cancer	Reactome	2.60E-02
BMAL1: CLOCK, NPAS2 activates circadian gene expression	Reactome	2.60E-02
Mitochondrial iron-sulfur cluster biogenesis	Reactome	2.60E-02
Transport of the SLBP independent Mature mRNA	Reactome	2.64E-02
Endometrial cancer	KEGG	2.69E-02
Signaling by high-kinase activity BRAF mutants	Reactome	2.86E-02
Transport of the SLBP Dependant Mature mRNA	Reactome	2.86E-02
COPI-independent Golgi-to-ER retrograde traffic	Reactome	2.86E-02
Herpes simplex infection	KEGG	2.96E-02
Signaling by NOTCH	Reactome	2.98E-02
Regulation of IFNG signaling	Reactome	2.99E-02
SEMA3A-Plexin repulsion signaling by inhibiting Integrin adhesion	Reactome	2.99E-02
Synthesis of PE	Reactome	2.99E-02
Intra-Golgi and retrograde Golgi-to-ER traffic	Reactome	3.05E-02
Circadian Clock	Reactome	3.08E-02
Signaling by RAS mutants	Reactome	3.31E-02
Longevity regulating pathway - multiple species	KEGG	3.33E-02
Interleukin-4 and 13 signaling	Reactome	3.40E-02
Constitutive Signaling by Ligand-Responsive EGFR Cancer Variants	Reactome	3.40E-02
Signaling by Ligand-Responsive EGFR Variants in Cancer	Reactome	3.40E-02

Signaling by EGFR in Cancer	Reactome	3.40E-02
Interferon Signaling	Reactome	3.63E-02
MAP2K and MAPK activation	Reactome	3.81E-02
Signaling by moderate kinase activity BRAF mutants	Reactome	3.81E-02
Paradoxical activation of RAF signaling by kinase inactive BRAF	Reactome	3.81E-02
Signaling by FGFR1 in disease	Reactome	3.81E-02
Hedgehog ,on, state	Reactome	3.81E-02
TGF-beta receptor signaling in EMT (epithelial to mesenchymal transition)	Reactome	3.84E-02
Mitophagy - animal	KEGG	3.86E-02
Acute myeloid leukemia	KEGG	4.05E-02
Degradation of beta-catenin by the destruction complex	Reactome	4.07E-02
Glycerophospholipid metabolism	KEGG	4.21E-02
Fc epsilon RI signaling pathway	KEGG	4.25E-02
Regulation of RUNX1 Expression and Activity	Reactome	4.30E-02
Natural killer cell mediated cytotoxicity	KEGG	4.30E-02
Signaling by FGFR3	Reactome	4.33E-02
Transport of Mature mRNA Derived from an Intronless Transcript	Reactome	4.33E-02
Viral carcinogenesis	KEGG	4.49E-02
Signaling by FGFR4	Reactome	4.61E-02
Graft-versus-host disease	KEGG	4.61E-02
Transport of Mature mRNAs Derived from Intronless Transcripts	Reactome	4.61E-02
Glycerophospholipid biosynthesis	Reactome	4.71E-02
Organelle biogenesis and maintenance	Reactome	4.74E-02
Tie2 Signaling	Reactome	4.78E-02
Signaling by cytosolic FGFR1 fusion mutants	Reactome	4.78E-02
Spliceosome	KEGG	4.86E-02
T cell receptor signaling pathway	KEGG	4.86E-02
Pre-NOTCH Expression and Processing	Reactome	4.90E-02

Supplementary Table 6 Enriched pathways of common DEGs in CD8⁺ T cells

CD8 ⁺ T cells enriched pathway-based sets		
Pathway	Source	p-value
RNA Polymerase II Transcription	Reactome	6.59E-08
Gene expression (Transcription)	Reactome	6.89E-08
Transcriptional regulation by RUNX1	Reactome	6.74E-07
Generic Transcription Pathway	Reactome	8.20E-07
Chromatin modifying enzymes	Reactome	4.38E-06
Chromatin organization	Reactome	4.38E-06
Estrogen-dependent gene expression	Reactome	5.13E-06
Epigenetic regulation of gene expression	Reactome	5.88E-06
NoRC negatively regulates rRNA expression	Reactome	6.32E-06

Cellular Senescence	Reactome	6.61E-06
Negative epigenetic regulation of rRNA expression	Reactome	9.93E-06
HDACs deacetylate histones	Reactome	1.11E-05
ESR-mediated signaling	Reactome	1.41E-05
Oxidative Stress-Induced Senescence	Reactome	2.36E-05
Signaling by TGF-beta Receptor Complex	Reactome	2.61E-05
RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function	Reactome	2.99E-05
RNA Polymerase I Promoter Clearance	Reactome	3.87E-05
RUNX1 regulates transcription of genes involved in differentiation of HSCs	Reactome	4.30E-05
RNA Polymerase I Transcription	Reactome	5.04E-05
Signaling by TGF-beta family members	Reactome	5.41E-05
ERCC6 (CSB) and EHMT2 (G9a) positively regulate rRNA expression	Reactome	1.66E-04
TGF-beta receptor signaling activates SMADs	Reactome	1.71E-04
Signaling by Nuclear Receptors	Reactome	1.92E-04
Downregulation of TGF-beta receptor signaling	Reactome	1.98E-04
Cellular responses to stress	Reactome	1.98E-04
RNA Polymerase I Promoter Opening	Reactome	2.53E-04
Amyloid fiber formation	Reactome	2.56E-04
Downregulation of SMAD2/3: SMAD4 transcriptional activity	Reactome	2.88E-04
RNA Polymerase I Chain Elongation	Reactome	3.00E-04
PRC2 methylates histones and DNA	Reactome	3.24E-04
Lysine degradation - Homo sapiens (human)	KEGG	4.28E-04
RHO GTPases activate PKNs	Reactome	4.96E-04
Signaling by TGF-beta Receptor Complex in Cancer	Reactome	5.80E-04
Packaging Of Telomere Ends	Reactome	6.15E-04
Deubiquitination	Reactome	6.56E-04
Transcriptional activity of SMAD2/SMAD3: SMAD4 heterotrimer	Reactome	6.94E-04
Ub-specific processing proteases	Reactome	7.08E-04
Cellular responses to external stimuli	Reactome	7.29E-04
Positive epigenetic regulation of rRNA expression	Reactome	7.50E-04
Signaling by WNT	Reactome	7.62E-04
Apoptosis	Reactome	7.79E-04
Meiotic recombination	Reactome	9.24E-04
Programmed Cell Death	Reactome	1.05E-03
Formation of the beta-catenin: TCF transactivating complex	Reactome	1.17E-03
DNA methylation	Reactome	1.23E-03
Gene Silencing by RNA	Reactome	1.27E-03
Regulation of lipid metabolism by Peroxisome proliferator-activated receptor alpha	Reactome	1.48E-03
Meiosis	Reactome	1.59E-03
Activated PKN1 stimulates transcription of AR regulated genes KLK2 and KLK3	Reactome	1.60E-03

Transcriptional regulation by small RNAs	Reactome	1.67E-03
SIRT1 negatively regulates rRNA expression	Reactome	1.83E-03
Diseases of signal transduction	Reactome	2.17E-03
mRNA decay by 5, to 3, exoribonuclease	Reactome	2.21E-03
Cell Cycle, Mitotic	Reactome	3.00E-03
Telomere Maintenance	Reactome	3.17E-03
B-WICH complex positively regulates rRNA expression	Reactome	3.26E-03
Transcriptional regulation of white adipocyte differentiation	Reactome	3.39E-03
TCF dependent signaling in response to WNT	Reactome	3.40E-03
M Phase	Reactome	3.66E-03
Formation of Senescence-Associated Heterochromatin Foci (SAHF)	Reactome	4.08E-03
Cell Cycle	Reactome	4.13E-03
Condensation of Prophase Chromosomes	Reactome	4.20E-03
PTEN Regulation	Reactome	4.37E-03
Death Receptor Signalling	Reactome	4.60E-03
Autophagy - animal - Homo sapiens (human)	KEGG	4.82E-03
SMAD2/3 Phosphorylation Motif Mutants in Cancer	Reactome	5.05E-03
SMAD2/3 MH2 Domain Mutants in Cancer	Reactome	5.05E-03
Loss of Function of SMAD2/3 in Cancer	Reactome	5.05E-03
Antigen processing: Ubiquitination & Proteasome degradation	Reactome	5.10E-03
Signaling by NOTCH	Reactome	5.45E-03
RHO GTPase Effectors	Reactome	5.55E-03
Nonhomologous End-Joining (NHEJ)	Reactome	5.57E-03
RNA degradation - Homo sapiens (human)	KEGG	5.78E-03
Pre-NOTCH Expression and Processing	Reactome	5.82E-03
tRNA modification in the nucleus and cytosol	Reactome	5.82E-03
HATs acetylate histones	Reactome	6.21E-03
Protein ubiquitination	Reactome	6.40E-03
Senescence-Associated Secretory Phenotype (SASP)	Reactome	6.68E-03
Mitotic Prophase	Reactome	6.68E-03
Apoptotic execution phase	Reactome	6.80E-03
VEGFA-VEGFR2 Pathway	Reactome	7.71E-03
tRNA processing	Reactome	8.19E-03
Reproduction	Reactome	8.19E-03
Post-transcriptional silencing by small RNAs	Reactome	8.40E-03
Alcoholism - Homo sapiens (human)	KEGG	8.53E-03
Activation of DNA fragmentation factor	Reactome	8.59E-03
Apoptosis induced DNA fragmentation	Reactome	8.59E-03
Regulation of TP53 Degradation	Reactome	8.62E-03
Metalloprotease DUBs	Reactome	8.62E-03
G-protein mediated events	Reactome	8.91E-03
DNA Damage/Telomere Stress Induced Senescence	Reactome	9.10E-03
RMTs methylate histone arginines	Reactome	9.45E-03

Supplementary Table 7 Enriched pathways of common DEGs in NKT cells

NKT cells enriched pathway-based sets		
Pathway	Source	p-value
Systemic lupus erythematosus	KEGG	2.83E-15
RNA Polymerase I Promoter Opening	Reactome	1.98E-13
Meiotic recombination	Reactome	2.25E-12
Amyloid fiber formation	Reactome	2.89E-12
DNA methylation	Reactome	4.15E-12
Activated PKN1 stimulates transcription of AR regulated genes KLK2 and KLK3	Reactome	7.47E-12
HDACs deacetylate histones	Reactome	8.11E-12
SIRT1 negatively regulates rRNA expression	Reactome	9.94E-12
NoRC negatively regulates rRNA expression	Reactome	1.78E-11
Negative epigenetic regulation of rRNA expression	Reactome	3.24E-11
RNA Polymerase I Chain Elongation	Reactome	3.25E-11
PRC2 methylates histones and DNA	Reactome	3.84E-11
Condensation of Prophase Chromosomes	Reactome	6.37E-11
Meiosis	Reactome	8.15E-11
ERCC6 and EHMT2 positively regulate rRNA expression	Reactome	1.04E-10
RNA Polymerase I Promoter Clearance	Reactome	2.62E-10
Formation of the beta-catenin: TCF transactivating complex	Reactome	3.72E-10
RNA Polymerase I Transcription	Reactome	3.76E-10
RHO GTPases activate PKNs	Reactome	5.57E-10
RUNX1 regulates transcription of genes involved in differentiation of HSCs	Reactome	6.31E-10
HATs acetylate histones	Reactome	1.24E-09
RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function	Reactome	2.12E-09
B-WICH complex positively regulates rRNA expression	Reactome	2.57E-09
Transcriptional regulation by small RNAs	Reactome	4.24E-09
Mitotic Prophase	Reactome	7.42E-09
Alcoholism	KEGG	8.10E-09
Gene Silencing by RNA	Reactome	9.26E-09
Reproduction	Reactome	1.53E-08
Epigenetic regulation of gene expression	Reactome	1.89E-08
Interleukin-7 signaling	Reactome	2.35E-08
Positive epigenetic regulation of rRNA expression	Reactome	3.42E-08
Senescence-Associated Secretory Phenotype (SASP)	Reactome	5.42E-08
Oxidative Stress-Induced Senescence	Reactome	7.79E-08
Allograft rejection	KEGG	1.01E-07
Asthma	KEGG	1.15E-07
Estrogen-dependent gene expression	Reactome	1.16E-07
Transcriptional regulation by RUNX1	Reactome	1.91E-07
ESR-mediated signaling	Reactome	3.05E-07
Graft-versus-host disease	KEGG	3.25E-07

TCF dependent signaling in response to WNT	Reactome	3.30E-07
Signaling by Rho GTPases	Reactome	3.38E-07
HDMs demethylate histones	Reactome	4.52E-07
Type I diabetes mellitus	KEGG	5.52E-07
Chromatin modifying enzymes	Reactome	9.64E-07
Chromatin organization	Reactome	9.64E-07
Signaling by WNT	Reactome	1.30E-06
Intestinal immune network for IgA production	KEGG	1.45E-06
Phagosome	KEGG	1.77E-06
Signaling by Nuclear Receptors	Reactome	1.96E-06
Viral myocarditis	KEGG	1.98E-06
E3 ubiquitin ligases ubiquitinate target proteins	Reactome	2.39E-06
Autoimmune thyroid disease	KEGG	4.21E-06
RMTs methylate histone arginines	Reactome	5.14E-06
RHO GTPase Effectors	Reactome	6.89E-06
Staphylococcus aureus infection	KEGG	7.49E-06
Influenza A	KEGG	1.21E-05
Interferon Signaling	Reactome	1.33E-05
Cellular Senescence	Reactome	1.50E-05
MHC class II antigen presentation	Reactome	1.52E-05
PD-1 signaling	Reactome	1.87E-05
Hematopoietic cell lineage	KEGG	2.09E-05
Leishmaniasis	KEGG	2.39E-05
Cytokine Signaling in Immune system	Reactome	2.43E-05
Inflammatory bowel disease (IBD)	KEGG	3.93E-05
Antigen processing and presentation	KEGG	4.14E-05
Costimulation by the CD28 family	Reactome	4.14E-05
Translocation of ZAP-70 to Immunological synapse	Reactome	6.09E-05
Protein ubiquitination	Reactome	6.10E-05
Interferon-gamma signaling	Reactome	7.24E-05
Herpes simplex infection	KEGG	1.19E-04
Viral carcinogenesis	KEGG	1.23E-04
Phosphorylation of CD3 and TCR zeta chains	Reactome	1.26E-04
Toxoplasmosis	KEGG	1.31E-04
Cell Cycle, Mitotic	Reactome	1.44E-04
MAPK family signaling cascades	Reactome	1.50E-04
Generation of second messenger molecules	Reactome	1.60E-04
M Phase	Reactome	1.64E-04
Rheumatoid arthritis	KEGG	1.75E-04
Packaging Of Telomere Ends	Reactome	1.93E-04
RAF-independent MAPK1/3 activation	Reactome	2.00E-04
Tuberculosis	KEGG	2.17E-04
Th1 and Th2 cell differentiation	KEGG	2.40E-04
Generic Transcription Pathway	Reactome	2.92E-04
Nonhomologous End-Joining (NHEJ)	Reactome	3.31E-04
Meiotic synapsis	Reactome	3.68E-04

Cell adhesion molecules (CAMs)	KEGG	4.84E-04
PKMTs methylate histone lysines	Reactome	5.26E-04
Gene expression (Transcription)	Reactome	5.90E-04
HDR through Homologous Recombination (HR) or Single Strand Annealing (SSA)	Reactome	7.14E-04
DNA Repair	Reactome	7.17E-04
Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double-strand breaks	Reactome	7.28E-04
Cell Cycle	Reactome	7.59E-04
G2/M Checkpoints	Reactome	7.72E-04
DNA Double-Strand Break Response	Reactome	8.08E-04
RNA Polymerase II Transcription	Reactome	8.25E-04
DNA Double-Strand Break Repair	Reactome	8.66E-04
Th17 cell differentiation	KEGG	9.65E-04
MAPK1/MAPK3 signaling	Reactome	9.93E-04
Homology Directed Repair	Reactome	1.10E-03
G2/M DNA damage checkpoint	Reactome	1.19E-03
PDE3B signalling	Reactome	1.53E-03
PKB-mediated events	Reactome	1.53E-03
Attachment of GPI anchor to uPAR	Reactome	1.86E-03
Factors involved in megakaryocyte development and platelet production	Reactome	1.88E-03
Downstream TCR signaling	Reactome	3.53E-03
Negative regulation of MAPK pathway	Reactome	4.34E-03
RAF/MAP kinase cascade	Reactome	4.46E-03
Cellular responses to stress	Reactome	4.56E-03
Fanconi anemia pathway	KEGG	4.88E-03
PI3K Cascade	Reactome	4.92E-03
Interaction between L1 and Ankyrins	Reactome	4.93E-03
Processing of DNA double-strand break ends	Reactome	4.98E-03
Telomere Maintenance	Reactome	5.07E-03
Epstein-Barr virus infection	KEGG	5.41E-03
Human T-cell leukemia virus 1 infection	KEGG	5.69E-03
Interferon-alpha/beta signaling	Reactome	5.87E-03
TCR signaling	Reactome	6.96E-03
IRS-mediated signalling	Reactome	7.81E-03
CTLA4 inhibitory signaling	Reactome	8.19E-03
Signaling by Insulin receptor	Reactome	8.86E-03
Cell Cycle Checkpoints	Reactome	9.25E-03
NOTCH1 Intracellular Domain Regulates Transcription	Reactome	9.64E-03
Negative regulation of FGFR2 signaling	Reactome	9.84E-03
NK cells enriched pathway-based sets		
Pathway	Source	p-value
Hematopoietic cell lineage	KEGG	1.70E-13
Antigen processing and presentation	KEGG	2.16E-10
Leishmaniasis	KEGG	4.03E-10

Immune System	Reactome	6.53E-10
Allograft rejection	KEGG	9.21E-10
Type I diabetes mellitus	KEGG	1.48E-09
PD-1 signaling	Reactome	5.26E-09
Generation of second messenger molecules	Reactome	5.65E-09
Graft-versus-host disease	KEGG	5.65E-09
Translocation of ZAP-70 to Immunological synapse	Reactome	7.06E-09
Costimulation by the CD28 family	Reactome	7.55E-09
Inflammatory bowel disease (IBD)	KEGG	8.88E-09
Asthma	KEGG	3.46E-08
Phosphorylation of CD3 and TCR zeta chains	Reactome	3.46E-08
MHC class II antigen presentation	Reactome	5.70E-08
Influenza A	KEGG	7.78E-08
Toxoplasmosis	KEGG	1.95E-07
Tuberculosis	KEGG	2.09E-07
Viral myocarditis	KEGG	2.55E-07
Intestinal immune network for IgA production	KEGG	3.78E-07
Rheumatoid arthritis	KEGG	5.94E-07
Th17 cell differentiation	KEGG	1.03E-06
Th1 and Th2 cell differentiation	KEGG	1.07E-06
Downstream TCR signaling	Reactome	1.23E-06
TCR signaling	Reactome	1.53E-06
Adaptive Immune System	Reactome	2.96E-06
Cell adhesion molecules (CAMs)	KEGG	5.82E-06
Osteoclast differentiation	KEGG	6.64E-06
Epstein-Barr virus infection	KEGG	8.69E-06
Autoimmune thyroid disease	KEGG	8.77E-06
Cytokine Signaling in Immune system	Reactome	2.80E-05
Phagosome	KEGG	4.58E-05
Regulation of TLR by endogenous ligand	Reactome	5.24E-05
Interferon-gamma signaling	Reactome	7.71E-05
Staphylococcus aureus infection	KEGG	8.13E-05
Herpes simplex infection	KEGG	8.60E-05
Amoebiasis	KEGG	8.90E-05
Human T-cell leukemia virus 1 infection	KEGG	1.32E-04
Neutrophil degranulation	Reactome	1.35E-04
Platelet activation, signaling, and aggregation	Reactome	1.39E-04
Signaling by Interleukins	Reactome	1.93E-04
Chagas disease (American trypanosomiasis)	KEGG	2.28E-04
JAK-STAT signaling pathway	KEGG	3.72E-04
Antigen processing-Cross presentation	Reactome	4.59E-04
HIF-1 signaling pathway	KEGG	5.30E-04
Pathways in cancer	KEGG	6.07E-04
Interferon Signaling	Reactome	6.28E-04
Primary immunodeficiency	KEGG	6.50E-04
Innate Immune System	Reactome	8.63E-04

ER-Phagosome pathway	Reactome	9.66E-04
Transcriptional misregulation in cancer	KEGG	1.13E-03
MAPK6/MAPK4 signaling	Reactome	1.21E-03
Cross-presentation of particulate exogenous antigens (phagosomes)	Reactome	1.33E-03
Cytokine-cytokine receptor interaction	KEGG	1.39E-03
Proteoglycans in cancer	KEGG	1.73E-03
Malaria	KEGG	1.80E-03
African trypanosomiasis	KEGG	1.97E-03
PI3K/AKT Signaling in Cancer	Reactome	2.13E-03
Platelet activation	KEGG	2.21E-03
Beta-oxidation of pristanoyl-CoA	Reactome	2.26E-03
Toll-Like Receptors Cascades	Reactome	2.43E-03
Response to elevated platelet cytosolic Ca ²⁺	Reactome	2.45E-03
Parathyroid hormone synthesis, secretion, and action	KEGG	2.76E-03
Constitutive Signaling by Aberrant PI3K in Cancer	Reactome	2.77E-03
Common Pathway of Fibrin Clot Formation	Reactome	3.26E-03
Fluid shear stress and atherosclerosis	KEGG	3.72E-03
Platelet degranulation	Reactome	3.75E-03
T cell receptor signaling pathway	KEGG	4.32E-03
Legionellosis	KEGG	4.37E-03
VEGFA-VEGFR2 Pathway	Reactome	4.59E-03
Signal amplification	Reactome	4.78E-03
Biosynthesis of electrophilic -3 PUFA oxo-derivatives	Reactome	4.89E-03
Formation of Fibrin Clot (Clotting Cascade)	Reactome	4.89E-03
Toll-like receptor signaling pathway	KEGG	5.70E-03
Ovarian steroidogenesis	KEGG	6.27E-03
Bladder cancer	KEGG	6.71E-03
CD28 co-stimulation	Reactome	6.87E-03
Signaling by Rho GTPases	Reactome	6.97E-03
CD28 dependent Vav1 pathway	Reactome	7.48E-03
Non-integrin membrane-ECM interactions	Reactome	7.80E-03
Caspase activation via extrinsic apoptotic signalling pathway	Reactome	7.91E-03
Hemostasis	Reactome	8.66E-03
AGE-RAGE signaling pathway in diabetic complications	KEGG	8.82E-03
Signaling by VEGF	Reactome	9.61E-03

Supplementary Table 8 Enriched pathways of common DEGs in NK cells

NK cells enriched pathway-based sets		
Pathway	Source	p-value
Hematopoietic cell lineage	KEGG	1.70E-13
Antigen processing and presentation	KEGG	2.16E-10
Leishmaniasis	KEGG	4.03E-10
Immune System	Reactome	6.53E-10

Allograft rejection	KEGG	9.21E-10
Type I diabetes mellitus	KEGG	1.48E-09
PD-1 signaling	Reactome	5.26E-09
Generation of second messenger molecules	Reactome	5.65E-09
Graft-versus-host disease	KEGG	5.65E-09
Translocation of ZAP-70 to Immunological synapse	Reactome	7.06E-09
Costimulation by the CD28 family	Reactome	7.55E-09
Inflammatory bowel disease (IBD)	KEGG	8.88E-09
Asthma	KEGG	3.46E-08
Phosphorylation of CD3 and TCR zeta chains	Reactome	3.46E-08
MHC class II antigen presentation	Reactome	5.70E-08
Influenza A	KEGG	7.78E-08
Toxoplasmosis	KEGG	1.95E-07
Tuberculosis	KEGG	2.09E-07
Viral myocarditis	KEGG	2.55E-07
Intestinal immune network for IgA production	KEGG	3.78E-07
Rheumatoid arthritis	KEGG	5.94E-07
Th17 cell differentiation	KEGG	1.03E-06
Th1 and Th2 cell differentiation	KEGG	1.07E-06
Downstream TCR signaling	Reactome	1.23E-06
TCR signaling	Reactome	1.53E-06
Adaptive Immune System	Reactome	2.96E-06
Cell adhesion molecules (CAMs)	KEGG	5.82E-06
Osteoclast differentiation	KEGG	6.64E-06
Epstein-Barr virus infection	KEGG	8.69E-06
Autoimmune thyroid disease	KEGG	8.77E-06
Cytokine Signaling in Immune system	Reactome	2.80E-05
Phagosome	KEGG	4.58E-05
Regulation of TLR by endogenous ligand	Reactome	5.24E-05
Interferon-gamma signaling	Reactome	7.71E-05
Staphylococcus aureus infection	KEGG	8.13E-05
Herpes simplex infection	KEGG	8.60E-05
Amoebiasis	KEGG	8.90E-05
Human T-cell leukemia virus 1 infection	KEGG	1.32E-04
Neutrophil degranulation	Reactome	1.35E-04
Platelet activation, signaling, and aggregation	Reactome	1.39E-04
Signaling by Interleukins	Reactome	1.93E-04
Chagas disease (American trypanosomiasis)	KEGG	2.28E-04
JAK-STAT signaling pathway	KEGG	3.72E-04
Antigen processing-Cross presentation	Reactome	4.59E-04
HIF-1 signaling pathway	KEGG	5.30E-04
Pathways in cancer	KEGG	6.07E-04
Interferon Signaling	Reactome	6.28E-04
Primary immunodeficiency	KEGG	6.50E-04
Innate Immune System	Reactome	8.63E-04
ER-Phagosome pathway	Reactome	9.66E-04

Transcriptional misregulation in cancer	KEGG	1.13E-03
MAPK6/MAPK4 signaling	Reactome	1.21E-03
Cross-presentation of particulate exogenous antigens (phagosomes)	Reactome	1.33E-03
Cytokine-cytokine receptor interaction	KEGG	1.39E-03
Proteoglycans in cancer	KEGG	1.73E-03
Malaria	KEGG	1.80E-03
African trypanosomiasis	KEGG	1.97E-03
PI3K/AKT Signaling in Cancer	Reactome	2.13E-03
Platelet activation	KEGG	2.21E-03
Beta-oxidation of pristanoyl-CoA	Reactome	2.26E-03
Toll-Like Receptors Cascades	Reactome	2.43E-03
Response to elevated platelet cytosolic Ca ²⁺	Reactome	2.45E-03
Parathyroid hormone synthesis, secretion, and action	KEGG	2.76E-03
Constitutive Signaling by Aberrant PI3K in Cancer	Reactome	2.77E-03
Common Pathway of Fibrin Clot Formation	Reactome	3.26E-03
Fluid shear stress and atherosclerosis	KEGG	3.72E-03
Platelet degranulation	Reactome	3.75E-03
T cell receptor signaling pathway	KEGG	4.32E-03
Legionellosis	KEGG	4.37E-03
VEGFA-VEGFR2 Pathway	Reactome	4.59E-03
Signal amplification	Reactome	4.78E-03
Biosynthesis of electrophilic -3 PUFA oxo-derivatives	Reactome	4.89E-03
Formation of Fibrin Clot (Clotting Cascade)	Reactome	4.89E-03
Toll-like receptor signaling pathway	KEGG	5.70E-03
Ovarian steroidogenesis	KEGG	6.27E-03
Bladder cancer	KEGG	6.71E-03
CD28 co-stimulation	Reactome	6.87E-03
Signaling by Rho GTPases	Reactome	6.97E-03
CD28 dependent Vav1 pathway	Reactome	7.48E-03
Non-integrin membrane-ECM interactions	Reactome	7.80E-03
Caspase activation via extrinsic apoptotic signalling pathway	Reactome	7.91E-03
Hemostasis	Reactome	8.66E-03
AGE-RAGE signaling pathway in diabetic complications	KEGG	8.82E-03
Signaling by VEGF	Reactome	9.61E-03

Supplementary Table 9 Enriched pathways of common DEGs in Neutrophil cellsNeutrophil cells enriched pathway-based sets

Pathway	Source	p-value
Synthesis of PIPs at the early endosome membrane	Reactome	8.97E-05
Estrogen-dependent gene expression	Reactome	9.10E-05
RNA Polymerase II Transcription	Reactome	1.01E-04
Gene expression (Transcription)	Reactome	1.12E-04
ESR-mediated signaling	Reactome	1.92E-04
Translocation of ZAP-70 to Immunological synapse	Reactome	3.19E-04

Antigen processing: Ubiquitination & Proteasome degradation	Reactome	4.39E-04
Generic Transcription Pathway	Reactome	4.54E-04
Phosphorylation of CD3 and TCR zeta chains	Reactome	6.40E-04
Chromatin modifying enzymes	Reactome	7.40E-04
Chromatin organization	Reactome	7.40E-04
PD-1 signaling	Reactome	7.91E-04
Generation of second messenger molecules	Reactome	9.51E-04
PI Metabolism	Reactome	1.10E-03
Class I MHC mediated antigen processing & presentation	Reactome	1.15E-03
Synthesis of PIPs at the late endosome membrane	Reactome	1.67E-03
Staphylococcus aureus infection	KEGG	1.73E-03
Signaling by Nuclear Receptors	Reactome	2.08E-03
Transcriptional regulation by RUNX1	Reactome	2.50E-03
Vesicle-mediated transport	Reactome	2.59E-03
RNA transport	KEGG	2.87E-03
G2/M Checkpoints	Reactome	2.98E-03
Degradation of beta-catenin by the destruction complex	Reactome	3.24E-03
Cellular Senescence	Reactome	3.52E-03
Membrane Trafficking	Reactome	3.57E-03
Asthma	KEGG	3.61E-03
Signaling by WNT	Reactome	3.97E-03
CS/DS degradation	Reactome	3.98E-03
APOBEC3G mediated resistance to HIV-1 infection	Reactome	3.98E-03
Downstream TCR signaling	Reactome	4.05E-03
Epigenetic regulation of gene expression	Reactome	4.21E-03
APC/C-mediated degradation of cell cycle proteins	Reactome	4.34E-03
Regulation of mitotic cell cycle	Reactome	4.34E-03
mRNA Splicing - Major Pathway	Reactome	4.41E-03
Repression of WNT target genes	Reactome	4.48E-03
Oxidative Stress-Induced Senescence	Reactome	4.66E-03
Cell Cycle	Reactome	5.40E-03
Costimulation by the CD28 family	Reactome	5.64E-03
Adaptive Immune System	Reactome	5.66E-03
RHO GTPase Effectors	Reactome	5.98E-03
Competing endogenous RNAs (ceRNAs) regulate PTEN translation	Reactome	6.13E-03
Regulation of PTEN mRNA translation	Reactome	6.13E-03
mRNA Splicing	Reactome	6.94E-03
Intra-Golgi and retrograde Golgi-to-ER traffic	Reactome	6.94E-03
Basal transcription factors	KEGG	7.35E-03
Signaling by Rho GTPases	Reactome	7.63E-03
Interferon-gamma signaling	Reactome	8.33E-03
E2F-enabled inhibition of pre-replication complex formation	Reactome	8.85E-03
Viral myocarditis	KEGG	8.91E-03
Signaling by BMP	Reactome	9.23E-03
Activation of gene expression by SREBF (SREBP)	Reactome	9.23E-03

Intestinal immune network for IgA production	KEGG	9.33E-03
Regulation of RUNX1 Expression and Activity	Reactome	9.44E-03
Signaling by TGF-beta family members	Reactome	9.71E-03
MHC class II antigen presentation	Reactome	9.86E-03

Supplementary Table 10 Enriched pathways of common DEGs in Monocyte cells

Monocyte cells enriched pathway-based sets		
Pathway	Source	p-value
Intestinal immune network for IgA production	KEGG	1.95E-08
Allograft rejection	KEGG	4.46E-08
Translocation of ZAP-70 to Immunological synapse	Reactome	8.26E-08
Type I diabetes mellitus	KEGG	1.56E-07
Asthma	KEGG	1.82E-07
Phosphorylation of CD3 and TCR zeta chains	Reactome	1.82E-07
PD-1 signaling	Reactome	2.33E-07
Inflammatory bowel disease (IBD)	KEGG	3.65E-07
Interferon-gamma signaling	Reactome	9.99E-07
Staphylococcus aureus infection	KEGG	1.13E-06
Graft-versus-host disease	KEGG	1.76E-06
Generation of second messenger molecules	Reactome	1.76E-06
Influenza A	KEGG	7.03E-06
Th1 and Th2 cell differentiation	KEGG	7.09E-06
Downstream TCR signaling	Reactome	8.03E-06
Autoimmune thyroid disease	KEGG	9.16E-06
Leishmaniasis	KEGG	9.97E-06
Herpes simplex infection	KEGG	1.56E-05
Viral myocarditis	KEGG	1.91E-05
MHC class II antigen presentation	Reactome	2.15E-05
Rheumatoid arthritis	KEGG	4.30E-05
Phagosome	KEGG	6.80E-05
Hematopoietic cell lineage	KEGG	7.41E-05
TCR signaling	Reactome	7.91E-05
Interferon Signaling	Reactome	9.94E-05
Costimulation by the CD28 family	Reactome	1.22E-04
Antigen processing and presentation	KEGG	1.22E-04
Toxoplasmosis	KEGG	2.32E-04
Tuberculosis	KEGG	2.64E-04
TP53 Regulates Transcription of Cell Death Genes	Reactome	4.13E-04
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	KEGG	6.00E-04
Th17 cell differentiation	KEGG	9.16E-04
Cell adhesion molecules (CAMs)	KEGG	1.12E-03
NRAGE signals death through JNK	Reactome	1.60E-03
Systemic lupus erythematosus	KEGG	3.06E-03
Rho GTPase cycle	Reactome	4.24E-03

Gastric acid secretion	KEGG	4.58E-03
Human T-cell leukemia virus 1 infection	KEGG	4.61E-03
Cell death signalling via NRAGE, NRIF, and NADE	Reactome	4.85E-03
HDMs demethylate histones	Reactome	6.24E-03
Ion homeostasis	Reactome	6.69E-03
Cytokine Signaling in Immune system	Reactome	6.78E-03
Interleukin-23 signaling	Reactome	7.01E-03
Immune System	Reactome	7.37E-03
Muscle contraction	Reactome	7.48E-03
G alpha (12/13) signalling events	Reactome	8.54E-03
Epstein-Barr virus infection	KEGG	8.66E-03
Interleukin-12 signaling	Reactome	8.68E-03
Dilated cardiomyopathy (DCM)	KEGG	9.37E-03
Synthesis of PIPs at the late endosome membrane	Reactome	1.05E-02
Cytokine-cytokine receptor interaction	KEGG	1.05E-02
Autophagy - other	KEGG	1.09E-02
Cardiac conduction	Reactome	1.19E-02
p75 NTR receptor-mediated signalling	Reactome	1.27E-02
RHO GTPases Activate NADPH Oxidases	Reactome	1.46E-02
Death Receptor Signalling	Reactome	1.51E-02
TP53 regulates transcription of several additional cell death genes whose specific roles in p53-dependent apoptosis remain uncertain	Reactome	1.69E-02
Apoptotic cleavage of cellular proteins	Reactome	1.73E-02
Calcium signaling pathway	KEGG	1.81E-02
Inflammasomes	Reactome	1.93E-02
Synthesis of PIPs at the early endosome membrane	Reactome	2.19E-02
Signaling by Rho GTPases	Reactome	2.26E-02
Regulation of RUNX1 Expression and Activity	Reactome	2.46E-02
cGMP effects	Reactome	2.74E-02
Synthesis of PIPs at the Golgi membrane	Reactome	2.74E-02
Apoptosis	Reactome	2.84E-02
Scavenging by Class A Receptors	Reactome	3.03E-02
Interleukin-12 family signaling	Reactome	3.03E-02
Programmed Cell Death	Reactome	3.11E-02
cGMP-PKG signaling pathway	KEGG	3.12E-02
Hypertrophic cardiomyopathy (HCM)	KEGG	3.22E-02
NOD-like receptor signaling pathway	KEGG	3.54E-02
RHO GTPases activate PAKs	Reactome	3.65E-02
Autophagy - animal	KEGG	3.83E-02
Apoptotic execution phase	Reactome	3.93E-02
Laminin interactions	Reactome	4.32E-02
Mismatch repair	KEGG	4.32E-02
VEGFA-VEGFR2 Pathway	Reactome	4.44E-02
Apoptosis	KEGG	4.76E-02
Apelin signaling pathway	KEGG	4.88E-02

Macroautophagy	Reactome	4.94E-02
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Supplementary Table 11 Reporter biomolecules in synovial tissues

Synovial miRNA	p-value	Synovial TF	Hypergeo	Synovial receptor	p-value
hsa-miR-146a-5p	1.18E-06	FOXP3	1.54E-10	LCK	9.4E-12
hsa-miR-335-5p	1.25E-06	ESR1	2.59E-07	JAK2	3.7E-05
hsa-miR-127-3p	3.32E-05	GATA3	6.58E-05	EPOR	0.000159
hsa-miR-124-3p	0.000372	FOXA1	0.000295	CCR5	0.000199
hsa-miR-558	0.000412	EGR1	0.000817	DPP4	0.000329
hsa-miR-22-3p	0.000723	SP1	0.001441	JAK1	0.000462
hsa-miR-299-5p	0.001201	GATA2	0.00235	CXCR5	0.001348
hsa-miR-3908	0.001278	MYC	0.002381	EPHB4	0.001348
hsa-miR-6886-3p	0.001358	VDR	0.004068	FYN	0.00187
hsa-miR-143-3p	0.001582	FBXL10	0.008199	CXCR4	0.002524
hsa-miR-155-5p	0.001669	MYF6	0.008199	CXCR3	0.002819
hsa-miR-6805-5p	0.001714	MYOD1	0.008199	LYN	0.00352
hsa-miR-4488	0.001913	MYOG	0.008199	GHR	0.00397
hsa-miR-4697-5p	0.001913	NR4A1	0.008199	KDM2A	0.004768
hsa-miR-1237-5p	0.002239	SP7	0.008199	EP300	0.004985
hsa-miR-3160-3p	0.002393	TCFL5	0.008199	CSK	0.00538
hsa-miR-15a-5p	0.002786	SP3	0.009334	CD22	0.005518
hsa-miR-9-5p	0.002818			KDM5C	0.006315
hsa-miR-7853-5p	0.004985			INSR	0.006683
hsa-miR-105-5p	0.006009			IL1B	0.007159
hsa-miR-511-5p	0.006229			PTK6	0.008048
hsa-miR-8078	0.006315			HDAC4	0.008165
hsa-miR-3074-5p	0.006453			ABCG4	0.008199
hsa-miR-6815-3p	0.006882			PANX3	0.008199
hsa-miR-5011-3p	0.007262			PTPRC	0.008896
hsa-miR-29b-3p	0.007573			CD2	0.00898
hsa-miR-532-5p	0.008056				
hsa-miR-1827	0.008631				
hsa-miR-142-3p	0.008789				
hsa-miR-646	0.009821				

Supplementary Table 12 Reporter biomolecules in blood cells

Blood miRNA	p-value	Blood TF	p-value	Blood receptor	p-value
hsa-miR-32-5p	2.42E-08	ETS1	6.57E-16	EP300	0.005723
hsa-miR-146a-5p	8.89E-08	FOXP3	7.41E-09		
hsa-miR-192-5p	1.71E-07	SPI1	0.000388		
hsa-miR-215-5p	5.54E-07	AR	0.001006		
hsa-miR-30a-5p	2.2E-06	CEBPA	0.001793		
hsa-miR-155-5p	4.64E-06	GATA2	0.002034		

hsa-miR-548l	1.03E-05	E2F4	0.003604
hsa-miR-92a-3p	1.55E-05		
hsa-miR-30b-5p	1.82E-05		
hsa-miR-26b-5p	2.27E-05		
hsa-miR-17-5p	2.27E-05		
hsa-miR-190a-3p	2.32E-05		
hsa-miR-4317	2.51E-05		
hsa-miR-410-3p	2.67E-05		
hsa-miR-548av-5p	3E-05		
hsa-miR-548k	3E-05		
hsa-miR-8054	3E-05		
hsa-let-7c*	3.15E-05		
hsa-miR-128-3p	3.55E-05		
hsa-miR-30c-5p	4.65E-05		
hsa-miR-32-3p	5.21E-05		
hsa-let-7b-5p	5.51E-05		
hsa-miR-6755-3p	7.21E-05		
hsa-miR-548ba	7.87E-05		
hsa-miR-30d-5p	8.03E-05		
hsa-miR-1277-5p	8.49E-05		
hsa-miR-548ai	8.93E-05		
hsa-miR-570-5p	8.93E-05		
hsa-miR-21-5p	9.13E-05		
hsa-miR-363-3p	9.84E-05		
hsa-miR-548ag	0.000101		
hsa-miR-33a-5p	0.000103		
hsa-miR-153-5p	0.000116		
hsa-miR-548n	0.000117		
hsa-miR-20a-5p	0.000128		
hsa-let-7a-5p	0.000153		
hsa-miR-30e-5p	0.000154		
hsa-miR-367-3p	0.00016		
hsa-miR-5011-5p	0.000177		
hsa-miR-4699-3p	0.000179		
hsa-miR-16-5p	0.000195		
hsa-miR-369-3p	0.000216		
hsa-miR-106b-5p	0.000219		
hsa-miR-142-3p	0.000228		
hsa-miR-5680	0.000231		
hsa-miR-519b-3p	0.000243		
hsa-miR-92b-3p	0.000264		
hsa-miR-519a-3p	0.000276		
hsa-miR-320a	0.000303		
hsa-miR-519c-3p	0.000313		
hsa-miR-4789-5p	0.000317		
hsa-miR-7852-3p	0.000383		
hsa-miR-5696	0.000419		

hsa-miR-93-5p	0.000453
hsa-miR-7849-3p	0.000475
hsa-miR-548az-5p	0.000484
hsa-miR-548t-5p	0.000484
hsa-miR-944	0.000568
hsa-miR-3977	0.000584
hsa-miR-590-3p	0.0006
hsa-miR-519d-3p	0.000666
hsa-miR-4643	0.000701
hsa-miR-135a-5p	0.000712
hsa-miR-568	0.000712
hsa-miR-889-5p	0.000757
hsa-miR-4766-3p	0.000782
hsa-miR-20b-5p	0.000806
hsa-miR-8076	0.000861
hsa-miR-26a-5p	0.000906
hsa-miR-5697	0.000914
hsa-miR-3187-5p	0.000923
hsa-miR-6860	0.000923
hsa-miR-25-3p	0.000924
hsa-miR-19a-3p	0.000945
hsa-miR-374a-5p	0.000965
hsa-miR-5189-5p	0.000973
hsa-let-7c-3p	0.000989
hsa-miR-612	0.001026
hsa-miR-548u	0.001071
hsa-miR-1285-3p	0.001138
hsa-miR-7161-5p	0.001159
hsa-miR-8063	0.001198
hsa-miR-5589-3p	0.001208
hsa-miR-376b-5p	0.001237
hsa-miR-376c-5p	0.001237
hsa-miR-1185-1-3p	0.001294
hsa-miR-520f-3p	0.00135
hsa-miR-3668	0.00136
hsa-miR-195-5p	0.001387
hsa-miR-96-5p	0.001392
hsa-let-7c-5p	0.001442
hsa-miR-5197-3p	0.001451
hsa-miR-6074	0.00146
hsa-miR-3653-3p	0.001481
hsa-miR-186-5p	0.00158
hsa-miR-1185-2-3p	0.001583
hsa-miR-661	0.001682
hsa-miR-577	0.001689
hsa-miR-375	0.001706
hsa-miR-3681-5p	0.001741

hsa-miR-6849-5p	0.001741
hsa-miR-548ah-3p	0.001754
hsa-miR-548am-3p	0.001754
hsa-miR-4770	0.001801
hsa-miR-6088	0.001801
hsa-miR-607	0.001824
hsa-miR-4477a	0.001841
hsa-miR-548f-5p	0.001843
hsa-miR-548g-3p	0.001861
hsa-miR-4252	0.001863
hsa-miR-548j-3p	0.001891
hsa-miR-548aj-5p	0.001917
hsa-miR-548g-5p	0.001917
hsa-miR-548x-5p	0.001917
hsa-miR-3160-3p	0.001919
hsa-miR-548ae-3p	0.001963
hsa-miR-548aj-3p	0.001963

Supplementary Table 13 Reporter biomolecules in macrophage cells

Macrophage miRNA	p-value	Macrophage TF	p-value	Macrophage receptor	p-value
hsa-miR-26b-5p	3.82E-20	ETS1	1.07E-34	SRC	2.37E-05
hsa-miR-155-5p	1.81E-15	GATA2	2.81E-32	ERBB2	0.000115
hsa-miR-17-5p	1.33E-13	FOXP3	3.29E-30	HIPK3	0.0002
hsa-miR-106a-5p	9.17E-13	ESR1	1.28E-26	CDK2	0.000276
hsa-miR-16-5p	1.15E-12	AR	1.32E-24	IL1B	0.000278
hsa-miR-1-3p	2.46E-11	GATA3	1.9E-16	HDAC1	0.000328
hsa-miR-93-5p	3.41E-11	GATA1	4.47E-16	LCK	0.00033
hsa-miR-20a-5p	9.83E-11	FOXA1	1.19E-11	SP100	0.000739
hsa-miR-19b-3p	1.43E-10	MYC	1.95E-11	JAK1	0.000945
hsa-miR-21-5p	5.75E-10	HIF1A	1.27E-08	CDK6	0.001185
hsa-miR-526b-3p	1.19E-09	RELA	9.95E-08	CCR6	0.001587
hsa-miR-98-5p	1.26E-09	JUN	3.85E-07	PAK2	0.002141
hsa-miR-124-3p	1.43E-09	EGR1	1.65E-06	ITK	0.002284
hsa-miR-20b-5p	1.85E-09	SP1	2.53E-06	MMP7	0.002885
hsa-miR-519d-3p	2.75E-09	JUND	5.1E-06	HDAC2	0.003198
hsa-miR-19a-3p	4.64E-09	CEBPD	1.2E-05	JAK2	0.003631
hsa-miR-106b-5p	6.64E-09	PRDM14	2.59E-05	PLD1	0.003855
hsa-miR-145-5p	2.29E-08	FOXO3	3.61E-05	PLD2	0.003855
hsa-miR-30a-5p	3.13E-08	YBX1	4.6E-05	EP300	0.003887
hsa-miR-3609	3.8E-08	ATF4	6.31E-05	CD2	0.004351
hsa-miR-4796-3p	4.03E-08	MYB	0.000149	PTPRO	0.004351
hsa-miR-34a-5p	7.57E-08	TP63	0.000166	LYN	0.004469
hsa-miR-548ah-5p	1.1E-07	TFAP2C	0.000211	CASP3	0.004884
hsa-miR-122-5p	1.73E-07	ATF2	0.000242	ERBB3	0.005166
hsa-miR-340-5p	1.99E-07	TP53	0.000274	EGFR	0.00526

hsa-miR-373-5p	2.13E-07	CEBPA	0.000278	CTLA4	0.005701
hsa-miR-371b-5p	2.29E-07	FOSL1	0.000582	RGS16	0.005701
hsa-miR-218-5p	2.38E-07	E2F4	0.000691	TXK	0.005701
hsa-miR-616-5p	2.63E-07	PPARG	0.001118	BIRC2	0.005759
hsa-miR-375	3.38E-07	STAT2	0.001587	PAK3	0.009638
hsa-miR-92a-3p	5.1E-07	USF2	0.001674	BIRC3	0.009693
hsa-miR-215-5p	1.11E-06	CEBPB	0.00196	AKT1	0.009812
hsa-miR-181b-5p	1.19E-06	TFAP2A	0.004351		
hsa-miR-101-3p	1.34E-06	RXRΒ	0.004571		
hsa-miR-4662a-3p	1.43E-06	NFKB1	0.005902		
hsa-miR-497-5p	1.51E-06	FOSL2	0.008778		
hsa-miR-181a-5p	1.64E-06	KLF4	0.008778		
hsa-miR-128-3p	1.75E-06	RARB	0.008778		
hsa-miR-15a-5p	1.85E-06	SREBF1	0.008778		
hsa-miR-92b-3p	2.1E-06				
hsa-miR-146a-5p	2.65E-06				
hsa-miR-548aw	2.96E-06				
hsa-let-7b-5p	3.52E-06				
hsa-miR-9-5p	3.53E-06				
hsa-miR-181d-5p	3.58E-06				
hsa-let-7a-5p	3.76E-06				
hsa-miR-32-5p	3.85E-06				
hsa-miR-9500	3.89E-06				
hsa-miR-27a-3p	3.99E-06				
hsa-miR-498	5.28E-06				
hsa-miR-137	5.37E-06				
hsa-miR-30c-5p	5.61E-06				
hsa-miR-30b-5p	6.13E-06				
hsa-miR-29b-3p	6.15E-06				
hsa-miR-181c-5p	6.32E-06				
hsa-miR-505-3p	6.53E-06				
hsa-miR-421	6.63E-06				
hsa-miR-195-5p	6.75E-06				
hsa-miR-3185	6.95E-06				
hsa-miR-24-3p	7.23E-06				
hsa-miR-15b-5p	7.5E-06				
hsa-miR-335-5p	8.62E-06				
hsa-miR-185-5p	8.88E-06				
hsa-miR-548az-5p	9.12E-06				
hsa-miR-548t-5p	9.12E-06				
hsa-miR-205-5p	9.21E-06				
hsa-miR-324-5p	9.44E-06				
hsa-miR-7159-5p	9.55E-06				
hsa-miR-224-5p	1.01E-05				
hsa-miR-192-5p	1.03E-05				
hsa-miR-1468-3p	1.11E-05				
hsa-miR-29a-3p	1.48E-05				

hsa-miR-18a-5p	1.5E-05
hsa-miR-545-3p	1.7E-05
hsa-miR-503-5p	1.9E-05
hsa-miR-548e-5p	1.99E-05
hsa-miR-372-5p	2.08E-05
hsa-miR-410-3p	2.17E-05
hsa-miR-23b-3p	2.43E-05
hsa-miR-374a-5p	2.5E-05
hsa-miR-519c-3p	2.92E-05
hsa-miR-302a-3p	3.07E-05
hsa-miR-372-3p	3.07E-05
hsa-miR-5683	3.09E-05
hsa-miR-200a-3p	3.1E-05
hsa-miR-96-5p	3.33E-05
hsa-miR-3163	3.43E-05
hsa-miR-4282	3.56E-05
hsa-miR-141-3p	3.74E-05
hsa-miR-5586-3p	3.74E-05
hsa-miR-26a-5p	3.77E-05
hsa-miR-6838-5p	3.86E-05
hsa-miR-4668-5p	4.01E-05
hsa-miR-548f-5p	4.09E-05
hsa-miR-144-3p	4.15E-05
hsa-miR-484	4.31E-05
hsa-miR-548aj-5p	4.35E-05
hsa-miR-548g-5p	4.35E-05
hsa-miR-548x-5p	4.35E-05
hsa-miR-95-5p	4.36E-05
hsa-miR-30d-5p	4.89E-05
hsa-miR-27b-3p	4.97E-05
hsa-miR-5590-3p	5.03E-05
hsa-miR-519b-3p	5.16E-05
hsa-miR-423-5p	5.59E-05
hsa-miR-373-3p	5.6E-05
hsa-miR-603	5.6E-05
hsa-miR-519a-3p	6.02E-05
hsa-miR-199a-3p	6.15E-05
hsa-miR-206	6.15E-05
hsa-miR-142-5p	6.56E-05
hsa-miR-7-5p	6.83E-05
hsa-miR-186-5p	6.85E-05
hsa-miR-362-3p	7.51E-05
hsa-miR-6734-5p	8.47E-05
hsa-miR-424-5p	9.33E-05
hsa-miR-548n	9.48E-05
hsa-miR-25-3p	9.72E-05
hsa-miR-583	9.76E-05

hsa-miR-3121-5p	0.000109
hsa-miR-520b	0.00011
hsa-miR-371a-5p	0.000111
hsa-miR-130b-3p	0.000112
hsa-let-7e-5p	0.000114
hsa-miR-130b-5p	0.000119
hsa-miR-302d-3p	0.00012
hsa-miR-493-3p	0.000126
hsa-miR-539-5p	0.000129
hsa-miR-33b-5p	0.00013
hsa-miR-302c-3p	0.000143
hsa-miR-512-3p	0.000143
hsa-miR-7845-5p	0.000146
hsa-miR-329-3p	0.000148
hsa-miR-142-3p	0.000154
hsa-miR-103a-3p	0.000159
hsa-miR-152-3p	0.000165
hsa-miR-3190-3p	0.000165
hsa-miR-5692a	0.000166
hsa-miR-590-3p	0.000174
hsa-miR-4753-3p	0.000181
hsa-miR-520a-3p	0.000188
hsa-miR-520d-3p	0.000188
hsa-miR-10b-5p	0.000192
hsa-miR-561-3p	0.000194
hsa-miR-520e	0.000203
hsa-miR-22-3p	0.00021
hsa-miR-6513-3p	0.000211
hsa-miR-100-5p	0.000213
hsa-miR-363-3p	0.000215
hsa-miR-302b-3p	0.000228
hsa-miR-520c-3p	0.000228
hsa-miR-4435	0.000233
hsa-miR-5692b	0.000238
hsa-miR-5692c	0.000238
hsa-miR-877-3p	0.000251
hsa-miR-4465	0.000254
hsa-miR-548at-5p	0.000259
hsa-miR-216a-3p	0.000268
hsa-miR-3681-3p	0.000268
hsa-miR-8485	0.000269
hsa-miR-455-3p	0.00027
hsa-miR-1277-5p	0.000271
hsa-miR-1297	0.000272
hsa-miR-548a-5p	0.000275
hsa-miR-548ab	0.000275
hsa-miR-548ad-5p	0.000275

hsa-miR-548ae-5p	0.000275
hsa-miR-548ak	0.000275
hsa-miR-548am-5p	0.000275
hsa-miR-548ap-5p	0.000275
hsa-miR-548aq-5p	0.000275
hsa-miR-548ar-5p	0.000275
hsa-miR-548as-5p	0.000275
hsa-miR-548au-5p	0.000275
hsa-miR-548ay-5p	0.000275
hsa-miR-548b-5p	0.000275
hsa-miR-548bb-5p	0.000275
hsa-miR-548c-5p	0.000275
hsa-miR-548h-5p	0.000275
hsa-miR-548i	0.000275
hsa-miR-548j-5p	0.000275
hsa-miR-548o-5p	0.000275
hsa-miR-548w	0.000275
hsa-miR-548y	0.000275
hsa-miR-6843-3p	0.000284
hsa-miR-6848-3p	0.000284
hsa-let-7d-5p	0.000289
hsa-let-7g-5p	0.000294
hsa-miR-646	0.000306
hsa-miR-222-3p	0.000312
hsa-miR-6873-3p	0.000312
hsa-miR-133a-3p	0.000317
hsa-miR-4653-3p	0.000317
hsa-miR-4752	0.000317
hsa-miR-548d-5p	0.000331
hsa-miR-4670-3p	0.000338
hsa-miR-4757-5p	0.000345
hsa-miR-6744-3p	0.000345
hsa-miR-4654	0.000361
hsa-miR-342-3p	0.000363
hsa-miR-302e	0.000367
hsa-miR-559	0.000373
hsa-miR-140-5p	0.000374
hsa-miR-6833-5p	0.000374
hsa-miR-548av-5p	0.000381
hsa-miR-548k	0.000381
hsa-miR-8054	0.000381
hsa-miR-615-3p	0.000385
hsa-miR-320a	0.000391
hsa-miR-4524b-3p	0.000399
hsa-miR-30e-5p	0.000405
hsa-miR-548an	0.000407
hsa-miR-216a-5p	0.000409

hsa-miR-3941	0.000425
hsa-miR-4433b-5p	0.000425
hsa-miR-568	0.000425
hsa-miR-1249-5p	0.000445
hsa-miR-548l	0.00045
hsa-miR-4769-5p	0.000462
hsa-miR-34b-3p	0.000469
hsa-miR-5696	0.000469
hsa-miR-877-5p	0.000487
hsa-miR-107	0.00049
hsa-miR-6797-5p	0.000499
hsa-miR-376c-3p	0.000526
hsa-miR-4701-5p	0.00054
hsa-miR-3611	0.000548
hsa-miR-6077	0.000568
hsa-miR-5010-3p	0.000595
hsa-miR-339-5p	0.000598
hsa-let-7c*	0.000634
hsa-miR-6836-3p	0.000644
hsa-miR-3613-3p	0.000647
hsa-miR-124-5p	0.000655
hsa-miR-331-3p	0.000692
hsa-miR-3659	0.000694
hsa-miR-5096	0.0007
hsa-miR-455-5p	0.000718
hsa-miR-8066	0.000718
hsa-miR-4789-3p	0.000731
hsa-miR-4515	0.000739
hsa-miR-367-3p	0.000748
hsa-miR-3688-3p	0.000751
hsa-miR-643	0.000768
hsa-miR-29c-3p	0.000774
hsa-miR-6862-5p	0.000788
hsa-miR-941	0.000788
hsa-miR-6794-3p	0.000812
hsa-miR-520h	0.000814
hsa-miR-654-3p	0.000816
hsa-miR-6778-3p	0.000822
hsa-miR-660-3p	0.000833
hsa-miR-6878-3p	0.000844
hsa-miR-383-5p	0.000853
hsa-miR-328-3p	0.000869
hsa-miR-130a-3p	0.000876
hsa-miR-7702	0.000888
hsa-miR-711	0.000889
hsa-miR-4253	0.000891
hsa-miR-182-5p	0.000897

hsa-miR-3187-3p	0.000898
hsa-miR-4760-3p	0.001007
hsa-miR-3691-3p	0.001008
hsa-miR-3617-3p	0.001025
hsa-miR-1270	0.001036
hsa-miR-588	0.001055
hsa-miR-33a-5p	0.001075
hsa-miR-197-3p	0.001086
hsa-miR-1251-3p	0.001129
hsa-miR-620	0.001133
hsa-miR-3184-5p	0.001146
hsa-miR-6778-5p	0.001146
hsa-miR-1224-3p	0.001161
hsa-miR-4666a-3p	0.001185
hsa-miR-4311	0.001208
hsa-miR-570-3p	0.001208
hsa-miR-5003-3p	0.001225
hsa-miR-30e-3p	0.00128
hsa-miR-6865-3p	0.001282
hsa-miR-3667-3p	0.001284
hsa-miR-4524a-5p	0.001302
hsa-miR-4524b-5p	0.001302
hsa-miR-664b-3p	0.001308
hsa-miR-1233-5p	0.001308
hsa-miR-520g-3p	0.001337
hsa-miR-1284	0.001343
hsa-miR-223-3p	0.001349
hsa-miR-6835-3p	0.001396
hsa-miR-8071	0.001413
hsa-miR-149-5p	0.001477
hsa-miR-4688	0.001492
hsa-miR-193b-3p	0.001508
hsa-miR-548j-3p	0.001563
hsa-miR-4667-3p	0.001572
hsa-miR-34a-3p	0.001574
hsa-miR-3653-5p	0.001588
hsa-miR-7-1-3p	0.001601
hsa-miR-135a-5p	0.001638
hsa-miR-2054	0.001638
hsa-miR-3160-5p	0.001638
hsa-miR-4511	0.001638
hsa-miR-3160-3p	0.001678
hsa-miR-656-3p	0.001678
hsa-miR-6739-5p	0.00169
hsa-miR-23a-3p	0.001702
hsa-miR-4699-3p	0.001732
hsa-miR-6515-5p	0.001732

hsa-miR-664a-3p	0.001732
hsa-miR-3908	0.001749
hsa-miR-4755-3p	0.001785
hsa-miR-183-5p	0.001828
hsa-miR-4476	0.00186
hsa-miR-6876-5p	0.00186
hsa-miR-3148	0.001864
hsa-miR-3692-3p	0.001917
hsa-miR-582-5p	0.001917
hsa-miR-4641	0.001952
hsa-miR-635	0.001952
hsa-miR-744-5p	0.002006
hsa-miR-4799-5p	0.00203
hsa-miR-558	0.002046
hsa-miR-148a-3p	0.002064
hsa-miR-4306	0.002064
hsa-miR-378a-3p	0.00208
hsa-miR-125b-5p	0.002105
hsa-miR-3175	0.002111
hsa-miR-3976	0.002141
hsa-miR-6760-3p	0.002142
hsa-miR-4496	0.002149
hsa-miR-663a	0.002149
hsa-miR-6877-3p	0.002149
hsa-miR-3134	0.002195
hsa-miR-378a-5p	0.002276
hsa-miR-300	0.002303
hsa-miR-7152-5p	0.002303
hsa-miR-200b-3p	0.002321
hsa-miR-1910-3p	0.002331
hsa-let-7c-5p	0.002347
hsa-miR-24-2-5p	0.002353
hsa-miR-4423-3p	0.002362
hsa-miR-221-3p	0.002381
hsa-miR-6811-3p	0.002434
hsa-miR-5688	0.002449
hsa-miR-7-2-3p	0.002449
hsa-miR-6819-3p	0.002466
hsa-miR-203a-3p	0.00249
hsa-miR-6511a-5p	0.002504
hsa-miR-202-5p	0.002536
hsa-miR-28-5p	0.002536
hsa-miR-708-5p	0.002536
hsa-miR-640	0.00262
hsa-miR-4495	0.002629
hsa-miR-6768-5p	0.002629
hsa-miR-1276	0.002708

hsa-miR-5195-3p	0.002754
hsa-miR-2392	0.002817
hsa-miR-30a-3p	0.002822
hsa-miR-1253	0.002866
hsa-miR-548s	0.00288
hsa-miR-186-3p	0.002939
hsa-miR-3074-5p	0.00295
hsa-miR-338-5p	0.00295
hsa-miR-513a-3p	0.002962
hsa-miR-548ah-3p	0.002971
hsa-miR-548am-3p	0.002971
hsa-miR-4443	0.002985
hsa-miR-3672	0.00301
hsa-miR-6864-3p	0.00301
hsa-miR-579-3p	0.003025
hsa-miR-486-5p	0.003057
hsa-miR-133b	0.003124
hsa-miR-7111-3p	0.003141
hsa-miR-1260b	0.003198
hsa-miR-4747-5p	0.003276
hsa-miR-5196-5p	0.003276
hsa-miR-6817-3p	0.0033
hsa-miR-7977	0.0033
hsa-miR-548ae-3p	0.003317
hsa-miR-548aj-3p	0.003317
hsa-miR-548aq-3p	0.003317
hsa-miR-548x-3p	0.003317
hsa-miR-6124	0.003337
hsa-miR-3065-5p	0.003413
hsa-miR-769-5p	0.003435
hsa-miR-548bb-3p	0.003693
hsa-miR-548h-3p	0.003693
hsa-miR-548z	0.003693
hsa-miR-4802-3p	0.003723
hsa-miR-6847-3p	0.003743
hsa-miR-219a-1-3p	0.003753
hsa-miR-566	0.003753
hsa-miR-6774-5p	0.003753
hsa-miR-938	0.003753
hsa-miR-4458	0.003826
hsa-miR-4500	0.003826
hsa-miR-548ac	0.003826
hsa-miR-4284	0.003844
hsa-miR-4305	0.003855
hsa-miR-302a-5p	0.00386
hsa-miR-4423-5p	0.003864
hsa-miR-495-3p	0.003864

hsa-let-7i-5p	0.003936
hsa-miR-2113	0.003949
hsa-miR-665	0.003996
hsa-miR-190a-3p	0.003999
hsa-miR-548c-3p	0.004038
hsa-miR-6884-3p	0.004052
hsa-miR-744-3p	0.004093
hsa-miR-577	0.0041
hsa-miR-548d-3p	0.004102
hsa-miR-4454	0.004142
hsa-miR-571	0.004142
hsa-miR-1228-3p	0.004182
hsa-miR-3663-5p	0.004251
hsa-miR-6802-5p	0.004307
hsa-miR-212-5p	0.004361
hsa-miR-1294	0.004362
hsa-miR-20b-3p	0.004362
hsa-miR-3620-3p	0.004362
hsa-miR-6791-3p	0.004393
hsa-miR-6829-3p	0.004393
hsa-miR-502-5p	0.004402
hsa-miR-135a-3p	0.004473
hsa-miR-6772-5p	0.004473
hsa-miR-6790-5p	0.004557
hsa-miR-1469	0.004571
hsa-miR-939-5p	0.004647
hsa-let-7f-5p	0.004752
hsa-miR-3911	0.004773
hsa-miR-3162-5p	0.004825
hsa-miR-3940-3p	0.004825
hsa-miR-1250-3p	0.004871
hsa-miR-513a-5p	0.004871
hsa-miR-214-3p	0.00488
hsa-miR-147a	0.004884
hsa-miR-6815-5p	0.005002
hsa-miR-3190-5p	0.005073
hsa-miR-6514-3p	0.005105
hsa-miR-3121-3p	0.00516
hsa-miR-3942-5p	0.005166
hsa-miR-4717-3p	0.005166
hsa-miR-6743-5p	0.005166
hsa-miR-4644	0.0053
hsa-miR-4735-5p	0.005338
hsa-miR-7113-5p	0.005352
hsa-let-7a-2-3p	0.005384
hsa-miR-139-5p	0.005384
hsa-miR-432-5p	0.005384

hsa-miR-8082	0.005431
hsa-miR-381-3p	0.005465
hsa-miR-6865-5p	0.005476
hsa-miR-802	0.005476
hsa-miR-380-3p	0.005581
hsa-miR-6734-3p	0.00563
hsa-miR-29b-2-5p	0.005687
hsa-miR-98-3p	0.005687
hsa-let-7g-3p	0.005759
hsa-miR-3174	0.005759
hsa-miR-4775	0.005805
hsa-miR-3680-3p	0.005822
hsa-miR-6131	0.005851
hsa-miR-3184-3p	0.005981
hsa-miR-615-5p	0.005988
hsa-miR-4703-5p	0.00602
hsa-miR-2467-3p	0.006069
hsa-miR-140-3p	0.006083
hsa-miR-513c-3p	0.006083
hsa-miR-4735-3p	0.006154
hsa-miR-4534	0.006309
hsa-miR-5697	0.006309
hsa-miR-4695-5p	0.006322
hsa-let-7b-3p	0.006401
hsa-let-7f-1-3p	0.006401
hsa-miR-3919	0.006428
hsa-miR-6880-5p	0.006492
hsa-miR-6875-3p	0.006495
hsa-miR-4645-3p	0.006517
hsa-miR-5194	0.006566
hsa-miR-5691	0.006566
hsa-miR-6805-3p	0.006566
hsa-miR-4531	0.006782
hsa-miR-6879-3p	0.006782
hsa-miR-8079	0.006782
hsa-miR-5193	0.006825
hsa-miR-1305	0.0069
hsa-miR-200c-3p	0.0069
hsa-miR-3606-3p	0.0069
hsa-miR-4801	0.006998
hsa-miR-1226-5p	0.007085
hsa-miR-6886-3p	0.007085
hsa-miR-7110-3p	0.007285
hsa-miR-3153	0.007289
hsa-miR-6733-5p	0.007289
hsa-miR-6856-5p	0.007294
hsa-miR-148b-5p	0.007328

hsa-miR-6740-5p	0.007328
hsa-miR-4731-3p	0.00745
hsa-miR-1255a	0.007479
hsa-miR-1255b-5p	0.007479
hsa-miR-624-3p	0.007479
hsa-miR-450b-5p	0.007488
hsa-miR-4438	0.007532
hsa-miR-3923	0.007536
hsa-miR-1245a	0.00759
hsa-miR-126-5p	0.00759
hsa-miR-216b-3p	0.00759
hsa-miR-3945	0.007603
hsa-miR-3591-3p	0.007686
hsa-miR-520f-5p	0.007686
hsa-miR-3652	0.007757
hsa-miR-4430	0.007757
hsa-miR-4487	0.007894
hsa-miR-150-5p	0.007987
hsa-miR-518a-5p	0.007991
hsa-miR-5187-5p	0.008067
hsa-miR-18a-3p	0.00812
hsa-miR-4691-5p	0.008137
hsa-miR-4729	0.008294
hsa-miR-1178-3p	0.008321
hsa-miR-4646-3p	0.008321
hsa-miR-4731-5p	0.008416
hsa-miR-6792-3p	0.008426
hsa-let-7a-3p	0.008463
hsa-miR-183-3p	0.008463
hsa-miR-1258	0.00856
hsa-miR-6808-3p	0.00856
hsa-miR-6501-5p	0.008639
hsa-miR-1343-5p	0.008708
hsa-miR-423-3p	0.008721
hsa-miR-766-5p	0.008768
hsa-miR-1304-3p	0.008774
hsa-miR-337-5p	0.008778
hsa-miR-494-5p	0.008845
hsa-miR-34c-3p	0.008854
hsa-miR-4427	0.008854
hsa-miR-34b-5p	0.008925
hsa-miR-335-3p	0.008981
hsa-miR-1180-3p	0.00899
hsa-miR-323a-5p	0.00899
hsa-miR-4639-5p	0.00899
hsa-miR-6732-5p	0.00899
hsa-miR-6748-3p	0.00899

hsa-miR-6758-5p	0.009109
hsa-miR-4255	0.009166
hsa-miR-576-3p	0.009166
hsa-miR-6834-5p	0.009166
hsa-miR-6086	0.009208
hsa-miR-4328	0.009403
hsa-miR-1914-3p	0.009458
hsa-miR-3662	0.009466
hsa-miR-1252-5p	0.009579
hsa-miR-7973	0.00959
hsa-miR-377-5p	0.009629
hsa-miR-126-3p	0.009689
hsa-miR-217	0.009693
hsa-miR-3064-5p	0.009693
hsa-miR-3189-3p	0.009693
hsa-miR-4260	0.009693
hsa-miR-5685	0.009693
hsa-miR-6504-5p	0.009693
hsa-miR-3120-3p	0.009899
hsa-miR-4514	0.009899
hsa-miR-4692	0.009899
hsa-miR-4795-3p	0.009899
hsa-miR-6506-5p	0.00999

Supplementary Table 14 Reporter biomolecules in T cells

T- miRNA	p-value	T-TF	p-value	T-receptor	p-value
hsa-miR-19b-3p	1.07E-05	FOXP3	1.54E-06	EPOR	6.98E-06
hsa-miR-4679	0.00013	AR	1.27E-05	CSF3R	0.000434
hsa-miR-548c-3p	0.000242	ESR1	0.000234	PRLR	0.000673
hsa-miR-187-5p	0.000277	EGR1	0.000768	ITPR1	0.001229
hsa-miR-944	0.000309	GATA2	0.00083	GHR	0.003744
hsa-miR-19a-3p	0.00036	PRDM14	0.00086	MATK	0.004575
hsa-miR-8485	0.000369	NR3C2	0.008024	CD22	0.005295
hsa-miR-6833-5p	0.000523	ZFP36	0.008024	IL1B	0.006872
hsa-miR-3190-3p	0.000578			LEPR	0.007726
hsa-miR-548v	0.000611			PTK6	0.007726
hsa-miR-30b-5p	0.001036				
hsa-miR-30e-5p	0.001045				
hsa-miR-299-5p	0.001111				
hsa-miR-192-5p	0.001428				
hsa-miR-4668-5p	0.001534				
hsa-miR-3127-3p	0.00161				
hsa-miR-4668-3p	0.00161				
hsa-miR-221-3p	0.001805				
hsa-miR-6889-3p	0.002185				
hsa-miR-4766-3p	0.002186				

hsa-miR-6756-3p	0.002597
hsa-miR-130b-3p	0.002707
hsa-miR-30a-5p	0.002781
hsa-miR-141-3p	0.003169
hsa-miR-3182	0.00319
hsa-miR-155-5p	0.003231
hsa-miR-5047	0.003482
hsa-miR-5008-3p	0.003491
hsa-miR-7157-3p	0.003491
hsa-miR-6737-3p	0.003744
hsa-miR-4697-3p	0.004282
hsa-miR-128-3p	0.004295
hsa-miR-4724-5p	0.004458
hsa-miR-6082	0.004575
hsa-miR-603	0.004693
hsa-miR-548av-5p	0.004806
hsa-miR-548k	0.004806
hsa-miR-8054	0.004806
hsa-miR-767-3p	0.005168
hsa-miR-124-3p	0.005414
hsa-miR-30d-5p	0.005498
hsa-miR-107	0.00554
hsa-miR-3140-5p	0.005812
hsa-miR-526b-3p	0.006299
hsa-miR-519d-3p	0.00641
hsa-miR-548ar-3p	0.006432
hsa-miR-548e-3p	0.006432
hsa-miR-548f-3p	0.006432
hsa-miR-6828-3p	0.0065
hsa-miR-548az-3p	0.006596
hsa-miR-130a-3p	0.006753
hsa-miR-548a-3p	0.006762
hsa-miR-20b-5p	0.006908
hsa-miR-218-5p	0.007256
hsa-miR-222-3p	0.007763
hsa-miR-93-5p	0.007798
hsa-miR-4473	0.008006
hsa-miR-566	0.008006
hsa-miR-768-3p	0.008024
hsa-miR-605-5p	0.008635
hsa-miR-214-5p	0.009589
hsa-miR-4643	0.0098

Supplementary Table 15 Reporter biomolecules in CD4⁺ T cells

CD4 ⁺ T miRNA	p-value	CD4 ⁺ T TF	p-value	CD4 ⁺ T receptor	p-value
hsa-miR-21-5p	6.05E-10	ETS1	3.44E-83		
hsa-miR-3938	1.05E-07	GATA2	3.1E-59		
hsa-miR-221-3p	1.12E-06	AR	8.39E-48		
hsa-miR-26a-5p	3.43E-06	YBX1	4.21E-41		
hsa-miR-568	4.02E-06	FOXP3	7.43E-35		
hsa-miR-181a-5p	4.4E-06	GATA1	6.74E-24		
hsa-miR-5580-3p	1.1E-05	E2F4	4.14E-19		
hsa-miR-181c-5p	1.6E-05	PRDM14	1.38E-18		
hsa-miR-484	1.71E-05	TFAP2C	8.29E-09		
hsa-miR-18a-5p	2.71E-05	ESR1	1.17E-08		
hsa-miR-196b-5p	2.83E-05	GATA3	2.6E-07		
hsa-miR-16-5p	2.9E-05	FOXA1	0.000224		
hsa-miR-340-5p	4.52E-05	MYC	0.000985		
hsa-miR-155-5p	5.68E-05	HIF1A	0.000997		
hsa-miR-3194-3p	7.46E-05	TP73	0.007595		
hsa-miR-203a-3p	0.000105				
hsa-miR-126-5p	0.000106				
hsa-miR-4724-5p	0.000112				
hsa-miR-4761-5p	0.000121				
hsa-miR-8485	0.00015				
hsa-miR-1277-5p	0.000153				
hsa-miR-5691	0.000153				
hsa-miR-6805-3p	0.000153				
hsa-miR-30b-5p	0.000157				
hsa-miR-98-5p	0.000162				
hsa-miR-1267	0.000168				
hsa-miR-32-3p	0.00019				
hsa-miR-513c-3p	0.000208				
hsa-miR-513a-3p	0.000229				
hsa-miR-3606-3p	0.00024				
hsa-miR-15b-5p	0.000252				
hsa-miR-181d-5p	0.000256				
hsa-miR-190a-3p	0.000258				
hsa-miR-6734-3p	0.000258				
hsa-miR-6832-3p	0.000268				
hsa-miR-8063	0.000275				
hsa-miR-204-5p	0.000285				
hsa-miR-4755-5p	0.000353				
hsa-miR-144-3p	0.000358				
hsa-miR-33a-5p	0.000372				
hsa-miR-211-5p	0.000392				
hsa-miR-3163	0.000483				
hsa-miR-623	0.000483				
hsa-miR-5011-5p	0.000579				

hsa-miR-4633-3p	0.000586
hsa-miR-6500-5p	0.000586
hsa-miR-5089-5p	0.000609
hsa-miR-1-3p	0.000656
hsa-miR-195-5p	0.000658
hsa-miR-33b-5p	0.000693
hsa-miR-2681-5p	0.000717
hsa-miR-619-5p	0.000764
hsa-miR-30a-5p	0.000791
hsa-miR-129-5p	0.000804
hsa-miR-5696	0.000808
hsa-miR-4700-3p	0.000817
hsa-miR-6506-5p	0.000826
hsa-miR-181b-5p	0.000918
hsa-miR-106b-5p	0.000923
hsa-miR-3667-3p	0.000958
hsa-miR-3682-3p	0.000972
hsa-miR-199a-3p	0.001012
hsa-miR-5006-3p	0.001035
hsa-miR-519b-3p	0.00104
hsa-miR-3685	0.001075
hsa-miR-615-3p	0.001108
hsa-miR-519a-3p	0.001129
hsa-miR-3919	0.001147
hsa-miR-25-3p	0.0012
hsa-miR-590-3p	0.001218
hsa-miR-519c-3p	0.001224
hsa-miR-1279	0.001276
hsa-miR-421	0.001353
hsa-miR-7848-3p	0.001416
hsa-miR-551b-5p	0.00146
hsa-miR-642a-3p	0.001464
hsa-miR-642b-3p	0.001464
hsa-miR-6505-5p	0.001464
hsa-miR-93-5p	0.001531
hsa-miR-222-3p	0.001709
hsa-miR-548c-3p	0.001732
hsa-miR-4762-3p	0.001778
hsa-miR-212-3p	0.001902
hsa-miR-5582-3p	0.001927
hsa-miR-7159-5p	0.002025
hsa-miR-132-3p	0.002049
hsa-miR-19a-3p	0.002161
hsa-miR-1200	0.002182
hsa-miR-4668-5p	0.002184
hsa-miR-20a-5p	0.002196
hsa-miR-548bb-3p	0.00224

hsa-miR-548h-3p	0.00224
hsa-miR-548z	0.00224
hsa-miR-5680	0.002276
hsa-miR-548ac	0.002302
hsa-miR-4760-5p	0.002324
hsa-miR-8061	0.002324
hsa-miR-30d-5p	0.002399
hsa-miR-548d-3p	0.00243
hsa-miR-6778-3p	0.002441
hsa-miR-892b	0.002508
hsa-miR-3671	0.002578
hsa-miR-17-5p	0.002705
hsa-miR-4301	0.002727
hsa-miR-10a-5p	0.002776
hsa-miR-3065-5p	0.00278
hsa-miR-579-3p	0.002795
hsa-miR-329-3p	0.002915
hsa-miR-362-3p	0.002915
hsa-miR-519d-3p	0.003016
hsa-miR-664b-3p	0.003025
hsa-miR-4795-3p	0.003049
hsa-miR-3678-3p	0.003224
hsa-miR-6847-3p	0.003269
hsa-miR-20b-5p	0.003385
hsa-miR-342-3p	0.003401
hsa-miR-627-3p	0.003401
hsa-miR-664a-3p	0.003403
hsa-miR-7853-5p	0.003403
hsa-miR-367-3p	0.003435
hsa-miR-3156-5p	0.003579
hsa-miR-218-5p	0.003593
hsa-miR-3613-3p	0.003638
hsa-miR-4735-3p	0.003781
hsa-miR-367-5p	0.003805
hsa-miR-548az-5p	0.003822
hsa-miR-548t-5p	0.003822
hsa-miR-30c-5p	0.003862
hsa-miR-603	0.003862
hsa-miR-4639-5p	0.004083
hsa-miR-6732-5p	0.004083
hsa-miR-5008-3p	0.004116
hsa-miR-7157-3p	0.004116
hsa-miR-4446-5p	0.004123
hsa-miR-101-3p	0.004129
hsa-miR-539-5p	0.004205
hsa-miR-363-3p	0.00435
hsa-miR-105-5p	0.004403

hsa-miR-3941	0.004413
hsa-miR-3670	0.004494
hsa-miR-6737-3p	0.004494
hsa-miR-206	0.004625
hsa-miR-6777-3p	0.004625
hsa-miR-513b-3p	0.004633
hsa-let-7a-5p	0.004636
hsa-miR-15a-5p	0.004817
hsa-miR-3646	0.004907
hsa-miR-4435	0.005004
hsa-miR-191-5p	0.005231
hsa-miR-4760-3p	0.005231
hsa-miR-613	0.005231
hsa-miR-6817-3p	0.005314
hsa-miR-3667-5p	0.005314
hsa-miR-103a-3p	0.005406
hsa-miR-5190	0.005549
hsa-miR-3155a	0.005592
hsa-miR-3155b	0.005592
hsa-miR-6514-5p	0.005592
hsa-miR-19b-3p	0.005901
hsa-miR-192-5p	0.005975
hsa-miR-4698	0.006027
hsa-miR-3190-3p	0.006149
hsa-miR-6854-5p	0.006221
hsa-miR-34a-5p	0.006306
hsa-miR-150-5p	0.006363
hsa-miR-33a-3p	0.006382
hsa-miR-4756-3p	0.006402
hsa-miR-199a-5p	0.00662
hsa-miR-618	0.006712
hsa-miR-767-3p	0.006712
hsa-miR-92a-3p	0.006844
hsa-miR-32-5p	0.006896
hsa-miR-3140-3p	0.006983
hsa-miR-335-3p	0.007009
hsa-miR-4776-3p	0.007287
hsa-miR-532-3p	0.007517
hsa-miR-7-5p	0.007585
hsa-miR-4639-3p	0.007633
hsa-miR-4735-5p	0.007646
hsa-miR-1249-3p	0.007693
hsa-miR-607	0.00772
hsa-miR-4768-5p	0.007764
hsa-miR-6504-3p	0.007764
hsa-miR-6833-3p	0.007764
hsa-miR-30e-5p	0.00792

hsa-miR-605-5p	0.00792
hsa-miR-4789-3p	0.007994
hsa-miR-6083	0.008115
hsa-miR-4433b-3p	0.008129
hsa-miR-92b-3p	0.008165
hsa-miR-6814-5p	0.008177
hsa-let-7f-1-3p	0.00825
hsa-miR-4798-3p	0.008312
hsa-miR-6797-3p	0.008317
hsa-miR-375	0.008532
hsa-miR-6128	0.008551
hsa-miR-624-3p	0.008551
hsa-miR-145-5p	0.008568
hsa-miR-378a-5p	0.008776
hsa-miR-6076	0.0089
hsa-miR-8083	0.0089
hsa-miR-18b-5p	0.008936
hsa-miR-548av-5p	0.009041
hsa-miR-548k	0.009041
hsa-miR-8054	0.009041
hsa-miR-6868-3p	0.009112
hsa-miR-7854-3p	0.009293
hsa-miR-1272	0.009435
hsa-miR-4709-5p	0.009898
hsa-miR-122-5p	0.009911

Supplementary Table 16 Reporter biomolecules in CD8⁺ T cells

CD8 ⁺ T miRNA	p-value	CD8 ⁺ T TF	p-value	CD8 ⁺ T receptor	p-value
hsa-miR-15b-5p	3.97E-08	ETS1	1.3E-15	CDK5	0.001101
hsa-miR-21-5p	1.42E-07	YBX1	3.47E-06	KDM6B	0.001925
hsa-miR-8485	2.8E-07	FOXP3	3.83E-06	KMT2B	0.002199
hsa-miR-195-5p	4.75E-07	GATA2	0.001154	EHMT2	0.006621
hsa-miR-19b-3p	5.67E-07	AR	0.003686	WDR5	0.009749
hsa-miR-30c-5p	8.21E-07	GATA1	0.004737		
hsa-miR-329-3p	1.09E-06				
hsa-miR-362-3p	1.09E-06				
hsa-miR-16-5p	1.7E-06				
hsa-miR-30a-5p	1.91E-06				
hsa-miR-17-5p	2.51E-06				
hsa-miR-218-5p	2.56E-06				
hsa-miR-15a-5p	2.86E-06				
hsa-miR-30b-5p	5.17E-06				
hsa-miR-373-3p	6.33E-06				
hsa-miR-3941	6.54E-06				
hsa-miR-92a-3p	1.12E-05				
hsa-miR-340-5p	1.26E-05				

hsa-miR-877-3p	1.86E-05
hsa-miR-1-3p	2.76E-05
hsa-miR-19a-3p	2.99E-05
hsa-miR-216b-3p	3.11E-05
hsa-miR-190a-3p	3.18E-05
hsa-miR-6828-5p	3.19E-05
hsa-miR-106a-5p	3.56E-05
hsa-miR-106b-5p	3.69E-05
hsa-miR-603	4.09E-05
hsa-miR-93-5p	4.43E-05
hsa-miR-539-3p	4.59E-05
hsa-miR-4524a-5p	4.87E-05
hsa-miR-4524b-5p	4.87E-05
hsa-miR-6838-5p	4.89E-05
hsa-miR-5011-5p	5.39E-05
hsa-miR-130b-5p	5.85E-05
hsa-miR-424-5p	6.27E-05
hsa-miR-320b	7.92E-05
hsa-miR-223-5p	7.97E-05
hsa-miR-30d-5p	7.99E-05
hsa-miR-365a-5p	8.42E-05
hsa-miR-497-5p	8.48E-05
hsa-miR-302c-3p	8.71E-05
hsa-miR-1277-5p	8.88E-05
hsa-miR-33a-5p	0.000117
hsa-miR-320c	0.000136
hsa-miR-20b-5p	0.000137
hsa-miR-526b-3p	0.000146
hsa-miR-4724-5p	0.00015
hsa-miR-519d-3p	0.000153
hsa-miR-103a-3p	0.000159
hsa-miR-302b-3p	0.00018
hsa-miR-20a-5p	0.000191
hsa-miR-365b-5p	0.000195
hsa-miR-4506	0.000204
hsa-miR-4259	0.000222
hsa-miR-302a-3p	0.000242
hsa-miR-410-3p	0.000243
hsa-miR-30e-5p	0.000263
hsa-miR-769-5p	0.000265
hsa-miR-181b-5p	0.00027
hsa-miR-582-5p	0.000289
hsa-miR-3199	0.000304
hsa-miR-8052	0.000304
hsa-miR-520c-3p	0.000317
hsa-miR-302d-3p	0.000348
hsa-miR-181c-5p	0.000366

hsa-miR-646	0.000382
hsa-miR-485-3p	0.000386
hsa-miR-186-5p	0.000388
hsa-miR-548n	0.000412
hsa-miR-302e	0.000414
hsa-miR-520a-3p	0.000434
hsa-miR-520d-3p	0.000434
hsa-miR-503-5p	0.000436
hsa-miR-32-5p	0.000437
hsa-miR-6079	0.000461
hsa-miR-708-5p	0.000461
hsa-miR-520e	0.000476
hsa-miR-5571-5p	0.000479
hsa-miR-320a	0.000494
hsa-miR-3681-5p	0.000496
hsa-miR-6849-5p	0.000496
hsa-miR-4429	0.000511
hsa-miR-155-5p	0.000513
hsa-miR-4649-3p	0.000524
hsa-miR-34a-5p	0.000535
hsa-miR-520b	0.000545
hsa-miR-375	0.000557
hsa-miR-302f	0.000572
hsa-miR-512-3p	0.000651
hsa-miR-26b-5p	0.000666
hsa-miR-320d	0.000667
hsa-miR-6834-3p	0.000674
hsa-miR-26a-5p	0.000675
hsa-miR-372-3p	0.00071
hsa-miR-548ah-5p	0.000713
hsa-miR-5680	0.000748
hsa-miR-3609	0.000751
hsa-miR-548az-5p	0.000757
hsa-miR-548t-5p	0.000757
hsa-miR-101-3p	0.000773
hsa-miR-590-3p	0.00084
hsa-miR-642a-3p	0.000861
hsa-miR-642b-3p	0.000861
hsa-miR-193a-3p	0.000888
hsa-miR-5585-5p	0.000923
hsa-miR-4684-5p	0.000982
hsa-miR-6083	0.001001
hsa-miR-1273e	0.00101
hsa-miR-5095	0.00101
hsa-miR-5692a	0.001043
hsa-miR-676-5p	0.001053
hsa-miR-4469	0.001106

hsa-miR-567	0.001124
hsa-miR-5096	0.001134
hsa-miR-4440	0.001188
hsa-miR-657	0.001188
hsa-miR-5696	0.001213
hsa-miR-6776-3p	0.001226
hsa-miR-548c-3p	0.001262
hsa-miR-1305	0.001321
hsa-miR-1184	0.001323
hsa-miR-107	0.001357
hsa-miR-3658	0.001382
hsa-miR-7151-3p	0.001432
hsa-miR-8064	0.001462
hsa-miR-192-5p	0.001492
hsa-miR-5698	0.001503
hsa-miR-3163	0.001529
hsa-miR-1322	0.001543
hsa-miR-615-3p	0.001645
hsa-miR-511-3p	0.001649
hsa-miR-10a-5p	0.001672
hsa-miR-466	0.001681
hsa-miR-548f-5p	0.001706
hsa-miR-519b-3p	0.001737
hsa-miR-548aj-5p	0.001799
hsa-miR-548g-5p	0.001799
hsa-miR-548x-5p	0.001799
hsa-miR-4731-5p	0.001818
hsa-miR-124-3p	0.001833
hsa-miR-302b-5p	0.001834
hsa-miR-125b-5p	0.001845
hsa-miR-181d-5p	0.001889
hsa-miR-3934-3p	0.001921
hsa-miR-519a-3p	0.001989
hsa-miR-7856-5p	0.002
hsa-miR-369-3p	0.002033
hsa-miR-2116-5p	0.002065
hsa-miR-4740-3p	0.00219
hsa-miR-671-5p	0.002225
hsa-miR-5693	0.002242
hsa-miR-143-5p	0.002259
hsa-miR-519c-3p	0.002271
hsa-miR-579-3p	0.002293
hsa-miR-4639-5p	0.002331
hsa-miR-4485-5p	0.002335
hsa-miR-4306	0.002351
hsa-miR-6867-5p	0.002427
hsa-miR-27b-3p	0.002444

hsa-miR-5582-3p	0.002457
hsa-miR-6507-5p	0.002493
hsa-miR-195-3p	0.002513
hsa-miR-513a-3p	0.002513
hsa-miR-297	0.002515
hsa-miR-421	0.002516
hsa-miR-27a-3p	0.002541
hsa-miR-4477a	0.002582
hsa-miR-6891-3p	0.002609
hsa-miR-3668	0.002624
hsa-miR-4539	0.002624
hsa-miR-4776-3p	0.002624
hsa-miR-664b-3p	0.00264
hsa-miR-101-5p	0.002664
hsa-miR-7-2-3p	0.002672
hsa-miR-3606-3p	0.002673
hsa-miR-4465	0.002681
hsa-miR-4672	0.002693
hsa-miR-4525	0.002788
hsa-miR-4795-3p	0.002788
hsa-miR-5010-5p	0.002788
hsa-miR-1297	0.002856
hsa-miR-3672	0.002867
hsa-miR-4677-5p	0.002877
hsa-miR-513b-3p	0.002943
hsa-miR-4640-3p	0.002985
hsa-miR-6499-3p	0.003058
hsa-miR-5739	0.003074
hsa-miR-16-2-3p	0.003101
hsa-miR-1257	0.003107
hsa-miR-5579-3p	0.003241
hsa-miR-92b-3p	0.003251
hsa-miR-129-5p	0.003339
hsa-miR-302d-5p	0.003373
hsa-miR-6506-5p	0.003427
hsa-miR-5590-3p	0.00345
hsa-miR-1910-3p	0.003472
hsa-miR-552-5p	0.003523
hsa-miR-574-5p	0.003563
hsa-miR-5089-5p	0.003588
hsa-miR-4729	0.00362
hsa-miR-613	0.00367
hsa-miR-377-3p	0.003722
hsa-miR-4483	0.003757
hsa-miR-6511a-5p	0.003779
hsa-miR-4715-5p	0.00382
hsa-miR-299-5p	0.003846

hsa-miR-331-5p	0.003846
hsa-miR-606	0.003846
hsa-miR-5697	0.003929
hsa-miR-940	0.003978
hsa-miR-18a-3p	0.004034
hsa-miR-6504-3p	0.004065
hsa-miR-4659a-5p	0.00408
hsa-miR-4659b-5p	0.00408
hsa-miR-5590-5p	0.00408
hsa-miR-224-3p	0.004085
hsa-miR-374c-5p	0.004164
hsa-miR-3662	0.004241
hsa-miR-142-5p	0.004258
hsa-miR-607	0.004258
hsa-miR-548aw	0.004273
hsa-miR-190a-5p	0.004316
hsa-miR-513c-3p	0.004343
hsa-miR-100-5p	0.004442
hsa-miR-146a-3p	0.004615
hsa-miR-545-5p	0.004615
hsa-miR-10b-5p	0.004662
hsa-miR-7-1-3p	0.004681
hsa-miR-4634	0.004699
hsa-miR-6787-3p	0.004712
hsa-miR-1293	0.004805
hsa-miR-4689	0.004805
hsa-miR-4710	0.004805
hsa-miR-522-3p	0.004805
hsa-miR-6778-3p	0.004817
hsa-miR-619-5p	0.004843
hsa-miR-454-3p	0.004917
hsa-miR-5189-3p	0.004951
hsa-miR-6739-5p	0.004961
hsa-miR-5010-3p	0.005101
hsa-miR-6858-5p	0.005199
hsa-miR-6864-3p	0.005203
hsa-miR-4644	0.005276
hsa-miR-181a-5p	0.005277
hsa-miR-510-3p	0.005347
hsa-miR-4504	0.005379
hsa-miR-655-5p	0.005383
hsa-miR-4753-3p	0.005426
hsa-miR-192-3p	0.005428
hsa-miR-3665	0.005428
hsa-miR-4665-5p	0.005428
hsa-miR-548ao-5p	0.0055
hsa-miR-4796-3p	0.005543

hsa-miR-6509-5p	0.005664
hsa-miR-3653-3p	0.005751
hsa-miR-655-3p	0.005842
hsa-miR-6839-3p	0.005977
hsa-miR-4272	0.006004
hsa-miR-6072	0.006004
hsa-miR-620	0.006004
hsa-miR-25-3p	0.006014
hsa-miR-1224-5p	0.006067
hsa-miR-548s	0.006151
hsa-miR-4262	0.006208
hsa-miR-6873-3p	0.006247
hsa-miR-4482-3p	0.006541
hsa-miR-4670-3p	0.006541
hsa-miR-548ax	0.006541
hsa-miR-8084	0.006541
hsa-miR-1827	0.006567
hsa-miR-4662a-5p	0.00658
hsa-miR-6736-3p	0.006595
hsa-miR-4435	0.006618
hsa-miR-4766-5p	0.006627
hsa-miR-494-3p	0.006627
hsa-miR-193b-3p	0.00672
hsa-miR-3115	0.006797
hsa-miR-3925-5p	0.006845
hsa-let-7e-5p	0.006907
hsa-miR-5001-3p	0.006907
hsa-miR-548b-3p	0.006986
hsa-miR-3616-5p	0.007014
hsa-miR-4496	0.007014
hsa-miR-6089	0.007067
hsa-miR-3145-3p	0.00711
hsa-miR-9-5p	0.007143
hsa-miR-183-5p	0.007178
hsa-miR-3158-5p	0.007286
hsa-miR-3117-3p	0.00743
hsa-miR-3682-3p	0.007436
hsa-miR-526b-5p	0.007544
hsa-miR-3187-3p	0.007892
hsa-miR-3152-5p	0.007957
hsa-miR-3976	0.007957
hsa-miR-4720-3p	0.008054
hsa-miR-144-3p	0.008167
hsa-miR-186-3p	0.008229
hsa-miR-6084	0.008235
hsa-miR-3671	0.008348
hsa-miR-543	0.008572

hsa-miR-1321	0.008614
hsa-miR-4698	0.008614
hsa-miR-4756-5p	0.008614
hsa-miR-367-5p	0.008617
hsa-miR-147a	0.00864
hsa-miR-382-5p	0.008647
hsa-miR-573	0.008647
hsa-miR-24-3p	0.008692
hsa-miR-17-3p	0.008838
hsa-miR-4270	0.008838
hsa-miR-4268	0.008846
hsa-miR-653-5p	0.008846
hsa-miR-139-5p	0.009035
hsa-miR-33b-5p	0.009035
hsa-miR-2113	0.009035
hsa-miR-3190-3p	0.009035
hsa-miR-580-3p	0.009035
hsa-miR-6754-5p	0.009349
hsa-miR-145-3p	0.00942
hsa-miR-6804-5p	0.009427
hsa-miR-3618	0.009472
hsa-miR-185-5p	0.00949
hsa-miR-200b-3p	0.009574
hsa-miR-6895-3p	0.009574
hsa-miR-5589-5p	0.009652
hsa-miR-4448	0.009689
hsa-miR-6508-5p	0.009689
hsa-miR-4474-5p	0.009754
hsa-miR-4441	0.009879
hsa-miR-6875-3p	0.009936

Supplementary Table 17 Reporter biomolecules in NK cells

NK miRNA	p-value	NK TF	p-value	NK receptor	p-value
hsa-miR-21-5p	2.45E-07	PRDM14	7.06E-06	HDAC6	0.000835
hsa-miR-8485	2.43E-06	AR	1.27E-05	EGFR	0.000982
hsa-miR-5011-5p	5E-05	ETS1	1.69E-05	PTEN	0.002327
hsa-miR-6883-3p	7.06E-05	TFAP2C	0.00225	LYN	0.003876
hsa-miR-4762-3p	8.63E-05	FOXA1	0.002995	ADA	0.009674
hsa-miR-1277-5p	0.000128	FOXP3	0.003147		
hsa-miR-6873-3p	0.000142	E2F4	0.004824		
hsa-miR-335-3p	0.000152	MEOX2	0.00518		
hsa-miR-942-5p	0.000281	NR1I2	0.00892		
hsa-miR-214-3p	0.000296	TP63	0.009956		
hsa-miR-33b-5p	0.000298				
hsa-miR-302a-5p	0.000315				
hsa-miR-6797-3p	0.000377				

hsa-miR-192-5p	0.000389
hsa-miR-494-3p	0.000418
hsa-miR-6076	0.000452
hsa-miR-215-5p	0.000467
hsa-miR-4291	0.000472
hsa-miR-190a-3p	0.000523
hsa-miR-7110-3p	0.00053
hsa-miR-519c-3p	0.000557
hsa-miR-574-5p	0.000589
hsa-miR-140-5p	0.000604
hsa-miR-891b	0.000636
hsa-miR-519b-3p	0.000724
hsa-miR-33a-3p	0.000733
hsa-miR-380-5p	0.000738
hsa-miR-302c-3p	0.00076
hsa-miR-145-5p	0.000769
hsa-miR-519a-3p	0.000846
hsa-miR-106b-5p	0.000848
hsa-miR-3591-3p	0.000855
hsa-miR-519d-3p	0.000919
hsa-miR-510-3p	0.001051
hsa-miR-5588-3p	0.001074
hsa-miR-1343-3p	0.001085
hsa-miR-6783-3p	0.001085
hsa-miR-7151-3p	0.001163
hsa-miR-4729	0.001207
hsa-miR-33a-5p	0.001224
hsa-miR-520h	0.001275
hsa-miR-761	0.001285
hsa-miR-6817-3p	0.001342
hsa-miR-5096	0.001351
hsa-miR-5095	0.001395
hsa-miR-4670-3p	0.001507
hsa-miR-342-3p	0.001575
hsa-miR-4775	0.001581
hsa-miR-21-3p	0.001665
hsa-miR-520g-3p	0.001692
hsa-miR-511-3p	0.00174
hsa-miR-22-3p	0.001972
hsa-miR-103a-3p	0.001979
hsa-miR-4263	0.002069
hsa-miR-6867-5p	0.002131
hsa-miR-5692b	0.002165
hsa-miR-5692c	0.002165
hsa-miR-520c-3p	0.002192
hsa-miR-4456	0.002242
hsa-miR-20b-5p	0.002248

hsa-miR-4678	0.002345
hsa-miR-29b-3p	0.002399
hsa-miR-6794-3p	0.002472
hsa-miR-3619-5p	0.002502
hsa-miR-656-3p	0.002502
hsa-miR-4755-3p	0.002531
hsa-miR-4677-3p	0.002655
hsa-miR-645	0.002676
hsa-miR-302a-3p	0.002745
hsa-miR-372-3p	0.002745
hsa-miR-520a-3p	0.002823
hsa-miR-3692-3p	0.00294
hsa-miR-7161-3p	0.0031
hsa-miR-563	0.003128
hsa-miR-873-5p	0.003133
hsa-miR-3191-5p	0.003214
hsa-miR-155-5p	0.003333
hsa-miR-455-5p	0.003357
hsa-miR-520b	0.003386
hsa-miR-2052	0.003545
hsa-miR-615-3p	0.003589
hsa-miR-302d-3p	0.003634
hsa-miR-6852-5p	0.003658
hsa-miR-106a-5p	0.003687
hsa-miR-4760-5p	0.003757
hsa-miR-8061	0.003757
hsa-miR-329-3p	0.003879
hsa-miR-29c-3p	0.00389
hsa-miR-567	0.004007
hsa-miR-302e	0.004162
hsa-miR-3145-5p	0.004221
hsa-miR-4700-3p	0.004221
hsa-miR-556-5p	0.004246
hsa-miR-6742-3p	0.004271
hsa-miR-223-3p	0.004286
hsa-miR-520d-3p	0.004308
hsa-miR-5696	0.004338
hsa-miR-576-5p	0.004382
hsa-miR-7-2-3p	0.004448
hsa-miR-4698	0.004587
hsa-miR-520e	0.004611
hsa-miR-548ah-3p	0.004691
hsa-miR-548am-3p	0.004691
hsa-miR-143-3p	0.004732
hsa-miR-3941	0.004769
hsa-miR-6090	0.00478
hsa-miR-526b-3p	0.005087

hsa-miR-5580-3p	0.005095
hsa-miR-302b-3p	0.005097
hsa-miR-548j-3p	0.005121
hsa-miR-4662a-5p	0.00513
hsa-miR-376a-5p	0.005223
hsa-miR-4310	0.005258
hsa-miR-7157-5p	0.005258
hsa-miR-4789-5p	0.00533
hsa-miR-548ae-3p	0.005346
hsa-miR-548aj-3p	0.005346
hsa-miR-548aq-3p	0.005346
hsa-miR-548x-3p	0.005346
hsa-miR-331-5p	0.005361
hsa-miR-8063	0.005405
hsa-miR-1468-3p	0.005464
hsa-miR-337-3p	0.005484
hsa-miR-362-3p	0.005559
hsa-miR-329-5p	0.005606
hsa-miR-218-5p	0.005635
hsa-miR-551b-5p	0.005681
hsa-miR-4438	0.005762
hsa-miR-630	0.005784
hsa-miR-224-3p	0.006092
hsa-miR-2114-5p	0.006107
hsa-miR-4683	0.006387
hsa-miR-29a-3p	0.006453
hsa-miR-508-5p	0.006644
hsa-miR-17-5p	0.006874
hsa-miR-522-3p	0.00711
hsa-miR-16-5p	0.007129
hsa-miR-7-1-3p	0.007521
hsa-miR-3681-5p	0.007642
hsa-miR-6849-5p	0.007642
hsa-miR-6857-3p	0.007801
hsa-miR-1270	0.007837
hsa-miR-6787-3p	0.007917
hsa-miR-30a-5p	0.007994
hsa-miR-9-5p	0.008125
hsa-miR-3177-5p	0.008202
hsa-miR-4423-3p	0.008202
hsa-miR-6126	0.008202
hsa-miR-620	0.008522
hsa-miR-4484	0.008545
hsa-miR-7976	0.008545
hsa-miR-431-5p	0.008753
hsa-miR-548p	0.008864
hsa-miR-4463	0.00905

hsa-miR-4503	0.00905
hsa-miR-744-5p	0.009154
hsa-miR-365b-3p	0.009248
hsa-miR-8084	0.009248
hsa-miR-1225-3p	0.009319
hsa-miR-20a-5p	0.009589
hsa-miR-181d-3p	0.009749
hsa-miR-616-3p	0.00975
hsa-miR-320c	0.009803
hsa-miR-23a-5p	0.009909
hsa-miR-3658	0.009909

Supplementary Table 18 Reporter biomolecules in NKT cells

NKT- miRNA	p-value	NKT-TF	p-value	NKT receptor	p-value
hsa-miR-511-3p	2.17E-06	AR	0.000528	SRC	0.000971
hsa-miR-223-5p	2.21E-05	PRDM14	0.002724	PRKDC	0.001603
hsa-miR-6741-5p	6.73E-05	YBX1	0.006239	RAF1	0.004576
hsa-miR-1277-5p	8.13E-05			ABL1	0.006927
hsa-miR-590-3p	9.97E-05				
hsa-miR-376a-3p	0.000103				
hsa-miR-103a-3p	0.00011				
hsa-miR-375	0.000162				
hsa-miR-5011-5p	0.000181				
hsa-let-7a-3p	0.000183				
hsa-miR-4517	0.000249				
hsa-miR-3689a-3p	0.000277				
hsa-miR-3689b-3p	0.000277				
hsa-miR-3689c	0.000277				
hsa-miR-337-3p	0.000297				
hsa-miR-1273h-5p	0.000297				
hsa-miR-6780a-5p	0.000308				
hsa-miR-6779-5p	0.000319				
hsa-miR-98-3p	0.000328				
hsa-miR-9-5p	0.000344				
hsa-miR-30b-3p	0.000354				
hsa-let-7b-3p	0.000392				
hsa-let-7f-1-3p	0.000392				
hsa-miR-574-5p	0.000506				
hsa-miR-190a-3p	0.000556				
hsa-miR-6799-5p	0.000571				
hsa-miR-4659a-3p	0.000724				
hsa-miR-4659b-3p	0.000724				
hsa-miR-21-5p	0.000772				
hsa-miR-340-5p	0.000785				
hsa-miR-10a-3p	0.000793				
hsa-miR-548aw	0.000797				

hsa-miR-384	0.000885
hsa-miR-4753-3p	0.000901
hsa-miR-3976	0.000912
hsa-miR-924	0.000912
hsa-miR-6867-5p	0.000919
hsa-miR-1468-3p	0.000958
hsa-miR-107	0.001045
hsa-miR-100-3p	0.001056
hsa-miR-202-5p	0.001108
hsa-miR-4728-5p	0.001142
hsa-miR-203a-3p	0.001188
hsa-miR-376b-3p	0.001217
hsa-miR-6813-3p	0.00123
hsa-miR-130b-5p	0.001256
hsa-miR-6516-5p	0.001256
hsa-miR-514a-5p	0.001299
hsa-miR-4662a-5p	0.001352
hsa-miR-5584-5p	0.001361
hsa-miR-6785-5p	0.001419
hsa-miR-6883-5p	0.001419
hsa-miR-4724-3p	0.001442
hsa-miR-5580-3p	0.001459
hsa-miR-1307-3p	0.001488
hsa-miR-4802-3p	0.00151
hsa-miR-192-5p	0.001517
hsa-miR-19b-3p	0.001526
hsa-miR-30b-5p	0.001545
hsa-miR-503-5p	0.001569
hsa-miR-149-3p	0.00179
hsa-miR-1301-3p	0.001828
hsa-miR-5585-5p	0.00183
hsa-miR-3689f	0.001879
hsa-miR-640	0.002021
hsa-miR-8073	0.002051
hsa-miR-3689a-5p	0.002132
hsa-miR-3689b-5p	0.002132
hsa-miR-3689e	0.002132
hsa-miR-221-5p	0.002196
hsa-miR-2681-5p	0.002196
hsa-miR-1279	0.002213
hsa-miR-4670-5p	0.002237
hsa-miR-16-5p	0.002323
hsa-miR-4746-3p	0.002408
hsa-miR-3672	0.002465
hsa-miR-6864-3p	0.002465
hsa-miR-4705	0.00251
hsa-miR-548f-5p	0.002624

hsa-miR-4528	0.002647
hsa-miR-3122	0.002681
hsa-miR-3913-5p	0.002681
hsa-miR-335-5p	0.002682
hsa-miR-19a-3p	0.002723
hsa-miR-548aj-5p	0.002732
hsa-miR-548g-5p	0.002732
hsa-miR-548x-5p	0.002732
hsa-miR-567	0.002735
hsa-miR-26a-5p	0.002887
hsa-miR-6875-3p	0.00296
hsa-miR-424-5p	0.003063
hsa-miR-377-5p	0.003075
hsa-miR-130b-3p	0.003122
hsa-miR-7977	0.003172
hsa-miR-548s	0.003183
hsa-miR-3650	0.003239
hsa-miR-497-5p	0.003242
hsa-miR-4635	0.003288
hsa-miR-6512-5p	0.003363
hsa-miR-218-5p	0.003459
hsa-miR-6808-5p	0.003476
hsa-miR-5684	0.003498
hsa-miR-3187-3p	0.003638
hsa-miR-4638-5p	0.003638
hsa-miR-4639-5p	0.00369
hsa-miR-921	0.00369
hsa-miR-30a-5p	0.00369
hsa-miR-2117	0.003782
hsa-miR-3682-5p	0.003782
hsa-miR-8079	0.003786
hsa-miR-374b-5p	0.00395
hsa-miR-6826-5p	0.003979
hsa-miR-383-3p	0.004074
hsa-miR-15a-5p	0.004104
hsa-miR-450a-1-3p	0.004257
hsa-miR-1245a	0.004302
hsa-miR-4676-5p	0.004302
hsa-miR-6821-3p	0.004305
hsa-miR-32-5p	0.004371
hsa-miR-3685	0.004394
hsa-miR-576-5p	0.004394
hsa-miR-33b-3p	0.004504
hsa-miR-6499-3p	0.004556
hsa-miR-3161	0.004579
hsa-miR-5047	0.004678
hsa-miR-221-3p	0.004697

hsa-miR-3591-5p	0.004704
hsa-miR-3691-3p	0.004704
hsa-miR-4491	0.004809
hsa-miR-4657	0.004809
hsa-miR-548c-3p	0.004958
hsa-miR-1-3p	0.005017
hsa-miR-6892-5p	0.005075
hsa-miR-6893-5p	0.005267
hsa-miR-4666a-3p	0.005371
hsa-miR-519e-3p	0.005694
hsa-miR-302f	0.005737
hsa-miR-769-5p	0.005737
hsa-miR-8063	0.00585
hsa-miR-4310	0.006182
hsa-miR-7157-5p	0.006182
hsa-miR-27b-5p	0.006195
hsa-miR-4677-5p	0.006251
hsa-miR-515-3p	0.006363
hsa-miR-5698	0.006374
hsa-miR-30c-1-3p	0.00705
hsa-miR-4475	0.007082
hsa-miR-4273	0.007181
hsa-miR-7156-5p	0.007181
hsa-miR-6790-3p	0.007211
hsa-miR-32-3p	0.007283
hsa-miR-6858-3p	0.007283
hsa-miR-7106-5p	0.007312
hsa-miR-4468	0.007336
hsa-miR-599	0.007336
hsa-miR-6890-3p	0.0074
hsa-miR-3613-3p	0.007437
hsa-miR-3973	0.007452
hsa-miR-4520-2-3p	0.00751
hsa-miR-5590-3p	0.007566
hsa-let-7a-2-3p	0.007654
hsa-miR-4742-3p	0.007687
hsa-miR-935	0.007718
hsa-miR-2054	0.007738
hsa-miR-3121-3p	0.007828
hsa-miR-155-5p	0.007967
hsa-miR-606	0.008065
hsa-miR-6741-3p	0.008105
hsa-miR-3156-3p	0.008106
hsa-miR-381-3p	0.008106
hsa-miR-6885-3p	0.008106
hsa-miR-142-3p	0.008155
hsa-let-7g-3p	0.008166

hsa-miR-188-5p	0.008247
hsa-miR-3194-3p	0.008247
hsa-miR-373-3p	0.008323
hsa-miR-5589-5p	0.008433
hsa-miR-588	0.008466
hsa-miR-215-5p	0.008523
hsa-miR-6838-5p	0.008653
hsa-miR-1298-3p	0.00868
hsa-miR-676-3p	0.00868
hsa-miR-374b-3p	0.008702
hsa-miR-3616-5p	0.008731
hsa-miR-142-5p	0.008782
hsa-miR-6086	0.008936
hsa-miR-3689d	0.008998
hsa-miR-6513-5p	0.009044
hsa-miR-887-5p	0.009082
hsa-miR-6866-3p	0.009261
hsa-miR-4736	0.009459
hsa-miR-6507-5p	0.009459
hsa-miR-6087	0.00947
hsa-miR-7106-3p	0.009503
hsa-miR-302b-3p	0.009549
hsa-miR-6807-5p	0.00955
hsa-miR-4686	0.009561
hsa-miR-6740-5p	0.009561
hsa-miR-6779-3p	0.009561
hsa-miR-195-5p	0.009909
hsa-miR-940	0.009963

Supplementary Table 19 Reporter biomolecules in neutrophil cells

Neutrophils miRNA	p-value	Neutrophils TF	p-value	Neutrophils receptor	p-value
hsa-miR-16-5p	6.61E-12	ETS1	1.04E-15	SRC	0.002426
hsa-miR-15b-5p	1.02E-09	GATA1	1.25E-05	BIRC2	0.002644
hsa-miR-19b-3p	1.55E-09	FOXP3	1.6E-05	GRM8	0.006898
hsa-miR-21-5p	4.32E-09	AR	5.72E-05	ITPR1	0.007634
hsa-miR-195-5p	5.06E-09	YBX1	0.00022	BIRC6	0.008819
hsa-miR-92a-3p	2.48E-08	GATA2	0.000392	BIRC3	0.008936
hsa-miR-15a-5p	3.77E-08				
hsa-miR-19a-3p	1.14E-07				
hsa-miR-192-5p	4.36E-07				
hsa-miR-103a-3p	4.62E-07				
hsa-miR-497-5p	5.15E-07				
hsa-miR-519d-3p	5.29E-07				
hsa-miR-93-5p	7.95E-07				
hsa-miR-20a-5p	9.94E-07				

hsa-miR-579-3p	1.43E-06
hsa-miR-664b-3p	1.8E-06
hsa-miR-181c-5p	2.05E-06
hsa-miR-4435	2.22E-06
hsa-miR-26a-5p	2.22E-06
hsa-miR-20b-5p	2.65E-06
hsa-miR-181b-5p	2.84E-06
hsa-miR-424-5p	3.31E-06
hsa-miR-181d-5p	3.5E-06
hsa-miR-877-3p	6.25E-06
hsa-miR-3613-3p	7.53E-06
hsa-miR-526b-5p	7.92E-06
hsa-miR-4635	8.46E-06
hsa-miR-6838-5p	9.58E-06
hsa-miR-221-3p	9.75E-06
hsa-miR-615-3p	1.14E-05
hsa-miR-455-3p	1.18E-05
hsa-miR-552-5p	1.2E-05
hsa-miR-181a-5p	1.38E-05
hsa-miR-10a-5p	1.65E-05
hsa-miR-215-5p	1.79E-05
hsa-miR-106b-5p	2.02E-05
hsa-miR-5696	2.06E-05
hsa-miR-17-5p	2.2E-05
hsa-miR-3187-3p	2.46E-05
hsa-miR-769-5p	2.84E-05
hsa-miR-107	3.13E-05
hsa-miR-410-3p	3.24E-05
hsa-miR-568	3.44E-05
hsa-miR-190a-3p	4.3E-05
hsa-miR-548ar-3p	4.37E-05
hsa-miR-548e-3p	4.37E-05
hsa-miR-548f-3p	4.37E-05
hsa-miR-548az-3p	4.77E-05
hsa-miR-548a-3p	5.21E-05
hsa-miR-205-3p	5.34E-05
hsa-miR-1184	5.61E-05
hsa-miR-590-3p	6.32E-05
hsa-miR-548s	6.66E-05
hsa-miR-708-5p	6.95E-05
hsa-miR-1-3p	7.58E-05
hsa-miR-548c-3p	7.6E-05
hsa-miR-377-5p	8.91E-05
hsa-miR-539-5p	9.58E-05
hsa-miR-3910	9.95E-05
hsa-miR-218-5p	0.000111
hsa-miR-154-5p	0.000115

hsa-miR-30c-5p	0.000124
hsa-miR-6086	0.000129
hsa-miR-5582-3p	0.000132
hsa-miR-3934-5p	0.000142
hsa-let-7b-5p	0.000149
hsa-miR-646	0.00015
hsa-miR-548f-5p	0.000151
hsa-miR-588	0.000154
hsa-miR-1245b-3p	0.000154
hsa-miR-130b-3p	0.000155
hsa-miR-124-3p	0.000159
hsa-miR-548aj-5p	0.00016
hsa-miR-548g-5p	0.00016
hsa-miR-548x-5p	0.00016
hsa-miR-128-3p	0.000174
hsa-miR-340-5p	0.000181
hsa-miR-106a-5p	0.000192
hsa-miR-6788-3p	0.000198
hsa-miR-526b-3p	0.000211
hsa-miR-3163	0.000221
hsa-miR-6837-3p	0.000221
hsa-miR-548at-5p	0.000222
hsa-miR-548az-5p	0.000241
hsa-miR-548t-5p	0.000241
hsa-miR-140-3p	0.000254
hsa-miR-374a-5p	0.000264
hsa-miR-186-5p	0.00028
hsa-miR-4540	0.000283
hsa-miR-1468-3p	0.000285
hsa-miR-4262	0.000289
hsa-miR-1272	0.000304
hsa-miR-1277-5p	0.000316
hsa-miR-130a-3p	0.000322
hsa-miR-6516-5p	0.000324
hsa-miR-5187-5p	0.000332
hsa-miR-519a-3p	0.000339
hsa-let-7e-5p	0.000345
hsa-let-7c-3p	0.00036
hsa-miR-3192-5p	0.00037
hsa-miR-4465	0.00037
hsa-miR-8485	0.000381
hsa-miR-503-5p	0.000389
hsa-miR-1297	0.000397
hsa-miR-5011-5p	0.000405
hsa-miR-1252-3p	0.000409
hsa-miR-373-3p	0.000415
hsa-miR-605-5p	0.000439

hsa-miR-199a-3p	0.000441
hsa-miR-320c	0.000487
hsa-miR-1279	0.000496
hsa-miR-548ae-3p	0.00051
hsa-miR-548aj-3p	0.00051
hsa-miR-548aq-3p	0.00051
hsa-miR-548x-3p	0.00051
hsa-let-7c*	0.00052
hsa-miR-155-5p	0.000549
hsa-miR-501-5p	0.000552
hsa-miR-32-5p	0.000553
hsa-miR-4701-5p	0.000555
hsa-miR-6728-5p	0.000557
hsa-miR-125a-3p	0.000564
hsa-miR-548d-5p	0.000566
hsa-miR-519b-3p	0.000595
hsa-miR-891b	0.000607
hsa-miR-216b-3p	0.000628
hsa-miR-4684-5p	0.000632
hsa-miR-4699-5p	0.000636
hsa-miR-559	0.000641
hsa-miR-548p	0.000648
hsa-miR-26b-5p	0.000674
hsa-miR-302c-5p	0.000698
hsa-miR-3665	0.0007
hsa-miR-4505	0.0007
hsa-miR-4724-5p	0.000718
hsa-miR-513a-3p	0.000721
hsa-miR-1185-1-3p	0.000745
hsa-miR-4524a-5p	0.000768
hsa-miR-4524b-5p	0.000768
hsa-miR-125a-5p	0.000768
hsa-miR-519c-3p	0.000776
hsa-miR-2467-3p	0.000783
hsa-miR-5681a	0.00081
hsa-miR-6792-5p	0.000872
hsa-miR-5787	0.000883
hsa-miR-367-3p	0.00091
hsa-let-7f-5p	0.000919
hsa-miR-3978	0.000929
hsa-miR-1185-2-3p	0.000953
hsa-miR-3675-3p	0.000953
hsa-miR-548ah-5p	0.001036
hsa-miR-3609	0.001083
hsa-miR-548a-5p	0.001105
hsa-miR-548ab	0.001105
hsa-miR-548ad-5p	0.001105

hsa-miR-548ae-5p	0.001105
hsa-miR-548ak	0.001105
hsa-miR-548am-5p	0.001105
hsa-miR-548ap-5p	0.001105
hsa-miR-548aq-5p	0.001105
hsa-miR-548ar-5p	0.001105
hsa-miR-548as-5p	0.001105
hsa-miR-548au-5p	0.001105
hsa-miR-548ay-5p	0.001105
hsa-miR-548b-5p	0.001105
hsa-miR-548bb-5p	0.001105
hsa-miR-548c-5p	0.001105
hsa-miR-548h-5p	0.001105
hsa-miR-548i	0.001105
hsa-miR-548j-5p	0.001105
hsa-miR-548o-5p	0.001105
hsa-miR-548w	0.001105
hsa-miR-548y	0.001105
hsa-miR-652-3p	0.001151
hsa-miR-4418	0.001172
hsa-miR-509-3-5p	0.001172
hsa-miR-556-5p	0.001177
hsa-miR-3942-3p	0.001206
hsa-miR-656-3p	0.001206
hsa-miR-548bb-3p	0.00121
hsa-miR-548h-3p	0.00121
hsa-miR-548z	0.00121
hsa-miR-548ac	0.001266
hsa-miR-3129-5p	0.001273
hsa-miR-6842-3p	0.001273
hsa-miR-8067	0.001273
hsa-miR-509-5p	0.001293
hsa-miR-32-3p	0.001302
hsa-miR-34a-5p	0.001309
hsa-miR-30a-5p	0.001317
hsa-miR-3666	0.001332
hsa-miR-4295	0.001332
hsa-miR-425-5p	0.00137
hsa-let-7f-2-3p	0.001377
hsa-miR-548d-3p	0.001385
hsa-miR-363-3p	0.001398
hsa-miR-4762-5p	0.001404
hsa-miR-761	0.001404
hsa-miR-199b-3p	0.001416
hsa-miR-98-5p	0.001484
hsa-miR-606	0.001496
hsa-miR-513c-3p	0.001498

hsa-miR-3127-3p	0.00151
hsa-miR-25-3p	0.001542
hsa-miR-520f-3p	0.001635
hsa-miR-3606-3p	0.001778
hsa-miR-301b-3p	0.001815
hsa-miR-4775	0.001829
hsa-miR-548ah-3p	0.001829
hsa-miR-548am-3p	0.001829
hsa-miR-3924	0.001868
hsa-miR-6507-5p	0.001875
hsa-miR-4474-3p	0.001933
hsa-miR-30b-5p	0.001937
hsa-miR-301a-3p	0.001955
hsa-miR-374b-5p	0.001963
hsa-miR-548j-3p	0.001995
hsa-miR-138-2-3p	0.002049
hsa-miR-593-3p	0.002051
hsa-miR-1296-5p	0.002071
hsa-miR-1256	0.002115
hsa-miR-33b-3p	0.002115
hsa-miR-5579-3p	0.002115
hsa-miR-6739-3p	0.002117
hsa-miR-548aw	0.002118
hsa-miR-5096	0.002123
hsa-miR-583	0.002187
hsa-miR-6814-5p	0.002187
hsa-miR-205-5p	0.002277
hsa-miR-493-3p	0.002328
hsa-miR-9-5p	0.002329
hsa-miR-6839-3p	0.002332
hsa-miR-454-3p	0.002333
hsa-miR-4796-3p	0.002362
hsa-miR-302f	0.002371
hsa-miR-3672	0.002381
hsa-miR-6864-3p	0.002381
hsa-miR-3662	0.002455
hsa-miR-6895-3p	0.002458
hsa-miR-4503	0.002587
hsa-miR-3612	0.0026
hsa-let-7d-5p	0.002607
hsa-miR-4729	0.00263
hsa-miR-519e-3p	0.002796
hsa-miR-10b-5p	0.002807
hsa-miR-650	0.002846
hsa-miR-5580-3p	0.00289
hsa-miR-1267	0.002954
hsa-miR-95-5p	0.002954

hsa-miR-375	0.002978
hsa-miR-330-3p	0.002991
hsa-miR-30e-5p	0.003032
hsa-miR-506-3p	0.003063
hsa-miR-6866-3p	0.003109
hsa-miR-3619-5p	0.003161
hsa-miR-1252-5p	0.003186
hsa-miR-3617-3p	0.003191
hsa-miR-3663-3p	0.003191
hsa-miR-515-3p	0.003191
hsa-miR-183-5p	0.003256
hsa-miR-8066	0.003364
hsa-miR-3529-5p	0.003481
hsa-miR-4662a-3p	0.003481
hsa-miR-421	0.003609
hsa-miR-576-3p	0.003633
hsa-miR-7159-3p	0.003633
hsa-miR-302c-3p	0.003642
hsa-miR-6511a-5p	0.003654
hsa-miR-129-5p	0.003711
hsa-miR-4459	0.003713
hsa-let-7b-3p	0.003793
hsa-miR-6508-5p	0.003824
hsa-miR-3156-3p	0.003848
hsa-miR-6756-3p	0.003873
hsa-miR-4755-3p	0.003902
hsa-let-7g-5p	0.00393
hsa-miR-30d-5p	0.003954
hsa-miR-6818-3p	0.003968
hsa-miR-6794-3p	0.004063
hsa-miR-3685	0.004222
hsa-miR-892b	0.004285
hsa-miR-382-5p	0.004347
hsa-miR-548ap-3p	0.004484
hsa-miR-548t-3p	0.004484
hsa-miR-8063	0.004488
hsa-miR-4662a-5p	0.004561
hsa-miR-6723-5p	0.004574
hsa-miR-4272	0.004641
hsa-miR-548aa	0.004717
hsa-miR-4653-3p	0.004741
hsa-miR-5100	0.004741
hsa-miR-100-5p	0.004912
hsa-miR-4672	0.004932
hsa-miR-6780a-3p	0.004937
hsa-miR-520g-3p	0.004945
hsa-miR-92b-3p	0.004969

hsa-miR-4301	0.005018
hsa-miR-4482-3p	0.005018
hsa-miR-4670-3p	0.005018
hsa-miR-4537	0.005107
hsa-miR-142-3p	0.005148
hsa-miR-331-5p	0.00523
hsa-miR-7156-3p	0.005236
hsa-let-7i-5p	0.00525
hsa-miR-1273g-3p	0.00526
hsa-miR-603	0.005277
hsa-miR-548n	0.00531
hsa-miR-7844-5p	0.00545
hsa-miR-4789-5p	0.005518
hsa-miR-361-3p	0.005553
hsa-miR-208a-5p	0.005606
hsa-miR-208b-5p	0.005606
hsa-miR-4671-3p	0.005606
hsa-miR-520h	0.005761
hsa-miR-548at-3p	0.005839
hsa-miR-548ay-3p	0.005839
hsa-miR-203a-3p	0.005885
hsa-miR-335-3p	0.005885
hsa-miR-633	0.005923
hsa-miR-4667-3p	0.005945
hsa-miR-1910-3p	0.006018
hsa-miR-4512	0.006042
hsa-miR-517-5p	0.006042
hsa-miR-4263	0.006284
hsa-miR-1290	0.006315
hsa-miR-2681-5p	0.006373
hsa-miR-4795-3p	0.006373
hsa-miR-764	0.006423
hsa-miR-642a-3p	0.006425
hsa-miR-642b-3p	0.006425
hsa-miR-377-3p	0.006651
hsa-miR-5683	0.006753
hsa-miR-130b-5p	0.006802
hsa-miR-1260b	0.006835
hsa-miR-548o-3p	0.006841
hsa-miR-412-5p	0.006898
hsa-miR-139-3p	0.006957
hsa-miR-3158-5p	0.006957
hsa-miR-298	0.006962
hsa-miR-4311	0.007009
hsa-miR-101-3p	0.007011
hsa-miR-4676-3p	0.007149
hsa-miR-6807-3p	0.007149

hsa-miR-3150a-3p	0.007179
hsa-miR-6763-5p	0.007179
hsa-miR-1263	0.007213
hsa-miR-3174	0.007246
hsa-miR-374c-5p	0.007246
hsa-miR-25-5p	0.007293
hsa-miR-599	0.007293
hsa-miR-30e-3p	0.007351
hsa-miR-4668-3p	0.007351
hsa-miR-30d-3p	0.007397
hsa-miR-1178-3p	0.007547
hsa-miR-3166	0.007547
hsa-miR-4646-3p	0.007547
hsa-miR-3160-3p	0.007608
hsa-miR-488-3p	0.007608
hsa-miR-671-5p	0.007755
hsa-miR-607	0.007766
hsa-miR-1247-3p	0.007776
hsa-miR-378a-5p	0.007901
hsa-miR-892c-3p	0.007905
hsa-miR-6858-3p	0.008055
hsa-miR-4458	0.0081
hsa-miR-4500	0.0081
hsa-miR-4639-5p	0.008221
hsa-miR-1323	0.008259
hsa-miR-188-5p	0.008259
hsa-miR-98-3p	0.008259
hsa-miR-5691	0.008306
hsa-miR-6805-3p	0.008306
hsa-miR-324-3p	0.008343
hsa-miR-4753-3p	0.008551
hsa-miR-4477a	0.00861
hsa-miR-6838-3p	0.008705
hsa-miR-3129-3p	0.008714
hsa-miR-212-3p	0.008735
hsa-miR-7850-5p	0.008735
hsa-miR-196a-5p	0.00875
hsa-miR-376a-3p	0.008774
hsa-miR-655-5p	0.008875
hsa-miR-3926	0.008928
hsa-miR-6515-3p	0.008998
hsa-miR-188-3p	0.009004
hsa-miR-558	0.009004
hsa-miR-6885-3p	0.009004
hsa-miR-3120-5p	0.009023
hsa-miR-4793-3p	0.009027
hsa-miR-544a	0.009062

hsa-miR-7703	0.009108
hsa-miR-4282	0.009227
hsa-let-7f-1-3p	0.009311
hsa-miR-7159-5p	0.009391
hsa-miR-3607-3p	0.00947
hsa-miR-655-3p	0.00947
hsa-let-7a-5p	0.009532
hsa-miR-491-3p	0.009576
hsa-miR-499a-5p	0.009576
hsa-miR-5583-5p	0.009576
hsa-miR-4663	0.009691
hsa-miR-1273e	0.009845

Supplementary Table 20 Reporter biomolecules in monocyte cells

Monocyte miRNA	p-value	Monocyte TF	p-value	Monocytes receptor	p-value
hsa-miR-4747-5p	0.000361	GATA2	0.007804		
hsa-miR-5196-5p	0.000361				
hsa-miR-6511a-3p	0.00051				
hsa-miR-3149	0.000519				
hsa-miR-6511b-3p	0.000551				
hsa-miR-3115	0.000652				
hsa-miR-153-5p	0.001121				
hsa-miR-26a-5p	0.001211				
hsa-miR-1307-3p	0.001454				
hsa-miR-4693-3p	0.001488				
hsa-miR-6890-3p	0.001696				
hsa-miR-6873-5p	0.001926				
hsa-miR-4772-3p	0.002086				
hsa-miR-1304-3p	0.002236				
hsa-miR-4304	0.002268				
hsa-miR-340-5p	0.002763				
hsa-miR-146a-5p	0.003177				
hsa-miR-4433a-3p	0.003255				
hsa-miR-5680	0.003396				
hsa-miR-1237-3p	0.003442				
hsa-miR-1207-3p	0.003585				
hsa-miR-6784-3p	0.003799				
hsa-miR-6862-3p	0.004021				
hsa-miR-6505-5p	0.004252				
hsa-miR-9-5p	0.004729				
hsa-miR-155-5p	0.004739				
hsa-miR-1273d	0.004893				
hsa-miR-4638-5p	0.004935				
hsa-miR-3921	0.004997				
hsa-miR-433-5p	0.005135				
hsa-miR-4653-5p	0.005264				

hsa-miR-6741-3p	0.005335
hsa-miR-19a-3p	0.005614
hsa-miR-6861-5p	0.005638
hsa-miR-8485	0.00585
hsa-miR-3200-5p	0.006451
hsa-miR-378a-3p	0.006667
hsa-miR-4485-5p	0.006879
hsa-miR-411-5p	0.007131
hsa-miR-1229-3p	0.007323
hsa-miR-629-5p	0.007333
hsa-miR-553	0.007468
hsa-miR-4284	0.007487
hsa-miR-186-3p	0.007704
hsa-miR-431-5p	0.008924
hsa-miR-4654	0.009848

Supplementary Table 21 Reporter metabolites in synovial tissues

Synovial Tissues GSE1919 Reporter Metabolites	p-value
3,4-dihydroxymandelaldehyde	3.24E-03
3,4-dihydroxyphenylacetaldehyde	3.24E-03
3-hydroxykynurenamine	3.24E-03
3-methoxy-4-hydroxyphenylacetaldehyde	3.24E-03
3-methoxy-4-hydroxyphenylglycolaldehyde	3.24E-03
3-methoxytyramine	3.24E-03
4,6-dihydroxyquinoline	3.24E-03
4,8-dihydroxyquinoline	3.24E-03
4-hydroxyphenylacetaldehyde	3.24E-03
5-hydroxyindoleacetaldehyde	3.24E-03
5-hydroxykynurenamine	3.24E-03
adrenaline	3.24E-03
dopamine	3.24E-03
indole-3-acetaldehyde	3.24E-03
L-metanephrine	3.24E-03
methylamine	3.24E-03
methylimidazole-acetaldehyde	3.24E-03
N4-acetylaminoethanol	3.24E-03
N-acetylputrescine	3.24E-03
N-methylhistamine	3.24E-03
noradrenaline	3.24E-03
normetanephrine	3.24E-03
phenethylamine	3.24E-03
phenylacetaldehyde	3.24E-03
serotonin	3.24E-03
tryptamine	3.24E-03

tyramine	3.24E-03
(10Z)-heptadecenoyl-CoA	3.13E-02
(13Z)-octadecenoyl-CoA	3.13E-02
(7Z)-octadecenoyl-CoA	3.13E-02
(7Z)-tetradecenoyl-CoA	3.13E-02
(9E)-octadecenoyl-CoA	3.13E-02
(9E)-tetradecenoyl-CoA	3.13E-02
5-tetradecenoyl-CoA	3.13E-02
7-hexadecenoyl-CoA	3.13E-02
9-heptadecenoyl-CoA	3.13E-02
activation-ppara	3.13E-02
cis-vaccenoyl-CoA	3.13E-02
heptadecanoyl-CoA	3.13E-02
myristoyl-CoA	3.13E-02
oleoyl-CoA	3.13E-02
palmitoleoyl-CoA	3.13E-02
palmitoyl-CoA	3.13E-02
stearoyl-CoA	3.13E-02

Synovial Tissues GSE55235 Reporter Metabolites	p-value
Synovial Tissues GSE55457 Reporter Metabolites	p-value
de-Fuc form of PA6 (wo peptide linkage)	7.16E-03
de-Fuc form of PA6	7.16E-03
keratan sulfate I, degradation product 1	7.16E-03
n2m2nm	7.16E-03
n2m2nmasn	7.16E-03
N4-(acetyl-beta-D-glucosaminy)asparagine	7.16E-03
N-acetyl-beta-D-glucosaminyamine	7.16E-03
AMP	2.23E-02
Synovial Tissues GSE77298 Reporter Metabolites	p-value
2-deoxy-D-ribose-1-phosphate	1.36E-02
deoxyadenosine	1.36E-02
deoxyguanosine	1.36E-02
hypoxanthine	1.36E-02
thymidine	1.36E-02

Supplementary Table 22 Reporter metabolites in blood cells

Blood Cells GSE93272 Reporter Metabolites	p-value
ubiquinol	2.04E-02
ubiquinone	3.76E-02
ferricytochrome C	3.76E-02

Supplementary Table 23 Reporter metabolites in macrophage cells

Macrophage Cells GSE10500 Reporter Metabolites	p-value
fructose-6-phosphate	1.04E-03
(alpha-D-mannosyl)2-beta-D-mannosyl-N-acetylglucosamine	3.07E-03
beta-1,4-mannose-N-acetylglucosamine	5.58E-03
mannose	5.58E-03
(5S,6S)-epoxy-(15R)-hydroxy-ETE	5.80E-03
1,2-dihydronaphthalene-1,2-diol	5.80E-03
11,12-DHET	5.80E-03
15-epi-lipoxin B5	5.80E-03
1-nitro-5,6-dihydroxy-dihydronaphthalene	5.80E-03
5(S),6(S)-epoxy-15(R)-HEPE	5.80E-03
5,6-DHET	5.80E-03
5,6-epoxytetraene	5.80E-03
8,9-DHET	5.80E-03
9,10-hydroxyoctadec-12(Z)-enoate	5.80E-03
aflatoxin B1 diol	5.80E-03
bromobenzene-2,3-dihydrodiol	5.80E-03
bromobenzene-3,4-dihydrodiol	5.80E-03
lipoxin A4	5.80E-03
lipoxin B4	5.80E-03
trans-5,6-dihydro-5,6-dihydroxy-7	5.80E-03
trioxilin A3	5.80E-03
glycyl-tRNA(gly)	5.85E-03
tRNA(gly)	5.85E-03
11-cis-retinol	6.17E-03
11-cis-retinyl-palmitate	6.17E-03
1-lysolecithin pool	6.17E-03
9-cis-retinol	6.17E-03
retinyl-ester	6.17E-03
succinate	9.55E-03
hepoxilin A3	1.08E-02
fructose-1,6-bisphosphate	1.08E-02
2-acyl-1-(1-alkenyl)-sn-glycero-3-phosphate	1.56E-02
choline	1.56E-02
ethanolamine	1.56E-02
PC-LD pool	1.56E-02
phosphatidate-LD-PC pool	1.56E-02
phosphatidate-LD-PE pool	1.56E-02
phosphatidate-LD-PS pool	1.56E-02
12(S)-HHT	1.69E-02
malonic-dialdehyde	1.69E-02
thromboxane A2	1.69E-02
PC-LD pool	2.08E-02
urea	2.10E-02
6-deoxy-L-galactose	2.13E-02

de-Fuc form of PA6	2.13E-02
keratan sulfate I, degradation product 1	2.13E-02
keratan sulfate I	2.13E-02
PA6	2.13E-02
bilirubin	2.91E-02
pyruvate	3.11E-02
succinate semialdehyde	3.11E-02
N-acetylglucosamine	3.13E-02
galactose	3.74E-02
fructose-2,6-bisphosphate	3.77E-02
L-tryptophanyl-tRNA(trp)	4.24E-02
tRNA(trp)	4.24E-02
(11Z)-docosenoyl-CoA	4.37E-02
(13Z)-eicosenoyl-CoA	4.37E-02
(13Z,16Z)-docosadienoyl-CoA	4.37E-02
(2E)-docosenoyl-CoA	4.37E-02
(2E)-eicosenoyl-CoA	4.37E-02
(2E)-heneicosenoyl-CoA	4.37E-02
(2E)-hexacosenoyl-CoA	4.37E-02
(2E)-nonadecenoyl-CoA	4.37E-02
(2E)-octadecenoyl-CoA	4.37E-02
(2E)-tetracosenoyl-CoA	4.37E-02
(2E)-tricosenoyl-CoA	4.37E-02
(8Z,11Z)-eicosadienoyl-CoA	4.37E-02
(9Z,12Z,15Z,18Z)-tetracosatetraenoyl-CoA	4.37E-02
(9Z,12Z,15Z,18Z,21Z)-tetracosapentaenoyl-CoA	4.37E-02
10,13,16-docosatrienoyl-CoA	4.37E-02
12,15,18,21-tetracosatetraenoyl-CoA	4.37E-02
13,16,19-docosatrienoyl-CoA	4.37E-02
2-trans-7,10,13,16,19-all-cis-docosaheptaenoyl-CoA	4.37E-02
2-trans-9,12,15,18,21-all-cis-tetracosahexaenoyl-CoA	4.37E-02
2-trans-9,12,15,18-all-cis-tetracosapentaenoyl-CoA	4.37E-02
eicosa-(2E,8Z,11Z,14Z,17Z)-pentaenoyl-CoA	4.37E-02
hexacosanoyl-CoA	4.37E-02
hexacosenoyl-CoA	4.37E-02
trans,cis,cis,cis,cis-2,10,13,16,19-docosapentaenoyl-CoA	4.37E-02
trans,cis,cis,cis,cis-2,12,15,18,21-tetracosapentaenoyl-CoA	4.37E-02
trans,cis,cis,cis-2,10,13,16-docosatetraenoyl-CoA	4.37E-02
trans,cis,cis,cis-2,11,14,17-eicosatetraenoyl-CoA	4.37E-02
trans,cis,cis,cis-2,13,16,19-docosatetraenoyl-CoA	4.37E-02
trans,cis,cis-2,11,14-eicosatrienoyl-CoA	4.37E-02
trans,cis,cis-2,13,16-docasatrienoyl-CoA	4.37E-02
trans,cis-2,11-docosadienoyl-CoA	4.37E-02
trans,cis-2,11-eicosadienoyl-CoA	4.37E-02
trans,cis-2,13-docosadienoyl-CoA	4.37E-02
trans,cis-2,13-eicosadienoyl-CoA	4.37E-02
trans,cis-2,15-tetracosadienoyl-CoA	4.37E-02

trans,cis-2,17-hexacosadienoyl-CoA	4.37E-02
trans,cis-2,8,11-eicosatrienoyl-CoA	4.37E-02
trans,cis-2,9-eicosadienoyl-CoA	4.37E-02
trans-2-cis,cis,cis-8,11,14-eicosatetraenoyl-CoA	4.37E-02
tricosanoyl-CoA	4.37E-02
CDP-diacylglycerol-CL pool	4.55E-02
CDP-diacylglycerol-LD-PI pool	4.55E-02
CTP	4.55E-02
phosphatidate-CL pool	4.55E-02
phosphatidate-LD-PI pool	4.55E-02
chondroitin sulfate C (GalNAc6S-GlcA), degradation product 1	4.74E-02
chondroitin sulfate C (GalNAc6S-GlcA), degradation product 3	4.74E-02
chondroitin sulfate C (GalNAc6S-GlcA), degradation product 4	4.74E-02
chondroitin sulfate C (GalNAc6S-GlcA), free chain	4.74E-02
chondroitin sulfate D (GlcNAc6S-GlcA2S), degradation product 1	4.74E-02
chondroitin sulfate D (GlcNAc6S-GlcA2S), degradation product 4	4.74E-02
chondroitin sulfate D (GlcNAc6S-GlcA2S), degradation product 5	4.74E-02
chondroitin sulfate D (GlcNAc6S-GlcA2S), free chain	4.74E-02
chondroitin sulfate E (GalNAc4,6diS-GlcA), degradation product 2	4.74E-02
chondroitin sulfate E (GalNAc4,6diS-GlcA), degradation product 6	4.74E-02
F1alpha	4.74E-02
keratan sulfate I, degradation product 11	4.74E-02
keratan sulfate I, degradation product 14	4.74E-02
keratan sulfate I, degradation product 17	4.74E-02
keratan sulfate I, degradation product 20	4.74E-02
keratan sulfate I, degradation product 23	4.74E-02
keratan sulfate I, degradation product 26	4.74E-02
keratan sulfate I, degradation product 29	4.74E-02
keratan sulfate I, degradation product 32	4.74E-02
keratan sulfate I, degradation product 35	4.74E-02
keratan sulfate I, degradation product 38	4.74E-02
keratan sulfate I, degradation product 39	4.74E-02
keratan sulfate I, degradation product 40	4.74E-02
keratan sulfate I, degradation product 41	4.74E-02
keratan sulfate I, degradation product 8	4.74E-02
keratan sulfate II (core 2-linked), degradation product 5	4.74E-02
keratan sulfate II (core 2-linked), degradation product 8	4.74E-02
keratan sulfate II (core 2-linked), degradation product 9	4.74E-02
n2m2mn	4.74E-02
CTP	4.77E-02
Macrophage Cells GSE97779 Reporter Metabolites	p-value
6-deoxy-L-galactose	2.36E-03
de-Fuc form of PA6	2.36E-03
keratan sulfate I, degradation product 1	2.36E-03
keratan sulfate I	2.36E-03
PA6	2.36E-03

(5S,6S)-epoxy-(15R)-hydroxy-ETE	3.62E-03
1,2-dihydronaphthalene-1,2-diol	3.62E-03
11,12-DHET	3.62E-03
12,13-hydroxyoctadec-9(z)-enoate	3.62E-03
14,15-DHET	3.62E-03
15-epi-lipoxin A4	3.62E-03
15-epi-lipoxin A5	3.62E-03
15-epi-lipoxin B4	3.62E-03
15-epi-lipoxin B5	3.62E-03
1-nitro-5,6-dihydroxy-dihydronaphthalene	3.62E-03
5(S),6(S)-epoxy-15(R)-HEPE	3.62E-03
5,6-DHET	3.62E-03
5,6-epoxytetraene	3.62E-03
8,9-DHET	3.62E-03
9,10-hydroxyoctadec-12(Z)-enoate	3.62E-03
aflatoxin B1 diol	3.62E-03
bromobenzene-2,3-dihydrodiol	3.62E-03
bromobenzene-3,4-dihydrodiol	3.62E-03
lipoxin A4	3.62E-03
lipoxin B4	3.62E-03
trans-5,6-dihydro-5,6-dihydroxy-7	3.62E-03
trioxilin A3	3.62E-03
12(13)-EpOME	6.91E-03
1a,11b-dihydro-4,9-dimethylbenz[a]anthra[3,4-b]oxirene	6.91E-03
5,6-EET	6.91E-03
7,12-dimethylbenz[a]anthracene 5,6-oxide	6.91E-03
8,9-EET	6.91E-03
9(10)-EpOME	6.91E-03
benzo[a]pyrene-7,8-oxide	6.91E-03
trans-3,4-dihydro-3,4-dihydroxy-7,12-dimethylbenz[a]anthracene	6.91E-03
2-deoxy-D-ribose-1-phosphate	1.41E-02
ribose-1-phosphate	1.41E-02
deoxyguanosine	1.75E-02
thymidine	1.75E-02
lactaldehyde	1.79E-02
11,12-EET	1.89E-02
14,15-EET	1.89E-02
GM2A-GM2	2.10E-02
PC-LD pool	2.38E-02
GM2A	2.46E-02
20-oxo-LTB4	2.46E-02
20-oxo-LTE4	2.46E-02
3alpha,7alpha-dihydroxy-5beta-cholestan-26-al	2.46E-02
5-hydroxyindoleacetaldehyde	2.46E-02
retinol	2.53E-02
L-lactate	2.54E-02
(1R,2S)-naphthalene 1,2-oxide	2.94E-02

(1S,2R)-naphthalene 1,2-oxide	2.94E-02
1-nitronaphthalene-5,6-oxide	2.94E-02
aflatoxin B1-exo-8,9-epoxide	2.94E-02
benzo[a]pyrene-7,8-diol	2.94E-02
bromobenzene-2,3-oxide	2.94E-02
bromobenzene-3,4-oxide	2.94E-02
chondroitin sulfate C (GalNAc6S-GlcA), degradation product 1	3.08E-02
chondroitin sulfate C (GalNAc6S-GlcA), degradation product 3	3.08E-02
chondroitin sulfate C (GalNAc6S-GlcA), degradation product 4	3.08E-02
chondroitin sulfate C (GalNAc6S-GlcA), free chain	3.08E-02
chondroitin sulfate D (GlcNAc6S-GlcA2S), degradation product 1	3.08E-02
chondroitin sulfate D (GlcNAc6S-GlcA2S), degradation product 4	3.08E-02
chondroitin sulfate D (GlcNAc6S-GlcA2S), degradation product 5	3.08E-02
chondroitin sulfate D (GlcNAc6S-GlcA2S), free chain	3.08E-02
chondroitin sulfate E (GalNAc4,6diS-GlcA), degradation product 2	3.08E-02
chondroitin sulfate E (GalNAc4,6diS-GlcA), degradation product 6	3.08E-02
F1alpha	3.08E-02
keratan sulfate I, degradation product 11	3.08E-02
keratan sulfate I, degradation product 14	3.08E-02
keratan sulfate I, degradation product 17	3.08E-02
keratan sulfate I, degradation product 20	3.08E-02
keratan sulfate I, degradation product 23	3.08E-02
keratan sulfate I, degradation product 26	3.08E-02
keratan sulfate I, degradation product 29	3.08E-02
keratan sulfate I, degradation product 32	3.08E-02
keratan sulfate I, degradation product 35	3.08E-02
keratan sulfate I, degradation product 38	3.08E-02
keratan sulfate I, degradation product 39	3.08E-02
keratan sulfate I, degradation product 40	3.08E-02
keratan sulfate I, degradation product 41	3.08E-02
keratan sulfate I, degradation product 8	3.08E-02
keratan sulfate II (core 2-linked), degradation product 5	3.08E-02
keratan sulfate II (core 2-linked), degradation product 8	3.08E-02
keratan sulfate II (core 2-linked), degradation product 9	3.08E-02
n2m2mn	3.08E-02
retinal	3.22E-02
ascorbate	3.53E-02
inositol	3.57E-02
hypoxanthine	3.73E-02
nicotinamide ribonucleoside	3.73E-02
nicotinate D-ribonucleoside	3.73E-02
nicotinate	3.73E-02
xanthine	3.73E-02
xanthosine	3.73E-02
deoxyuridine	3.79E-02
uridine	3.79E-02
acyl-CoA-LD-SM pool	3.81E-02

ceramide pool	3.81E-02
CoA	3.81E-02
dihydroceramide pool	3.81E-02
fatty acid-LD-TG1 pool	3.81E-02
phytoceramide pool	3.81E-02
phytosphingosine	3.81E-02
sphinganine	3.81E-02
sphingosine	3.81E-02
glyceraldehyde	4.83E-02
5beta-cholestane-3alpha,7alpha,12alpha,24s,25-pentol	4.87E-02
zinc	4.88E-02

Supplementary Table 24 Reporter metabolites in T cells

T Cells Naïve-GSE65010 Reporter Metabolites	p-value
1-(1-alkenyl)-sn-glycero-3-phosphate	1.88E-02
1-(1-alkenyl)-sn-glycero-3-phosphoethanolamine	1.88E-02
ethanolamine	1.88E-02

Supplementary Table 25 Reporter metabolites in CD4⁺ T cells

CD4 ⁺ T Cells GSE93776 Naive Reporter Metabolites	p-value
1D-myo-inositol-1,3,4,5-tetrakisphosphate	2.12E-04
1D-myo-inositol-1,3,4-trisphosphate	2.12E-04
13,14-dihydro-15-oxo-lipoxin A4	1.27E-02
15-oxo-lipoxin A4	1.27E-02
3alpha,7alpha,12alpha,25-tetrahydroxy-5beta-cholestane-24-one	1.27E-02
3-hydroxypropionyl-CoA	1.27E-02
4-methyl-2-oxopentanoate	1.27E-02
4-oxo-9-cis-retinoate	1.27E-02
5beta-cholestane-3alpha,7alpha,12alpha,24s,25-pentol	1.27E-02
9-cis-4-oxo-13,14-dihydro-retinoate	1.27E-02
alpha-hydroxyisocaproic acid	1.27E-02
3-oxopropionyl-CoA	1.27E-02
CD4 ⁺ T Cells GSE56649 Reporter Metabolites	p-value
O-phosphoprotamine	3.21E-03
protamine	3.21E-03
carnosine	1.17E-02
O-phosphoprotamine	4.28E-02

Supplementary Table 26 Reporter metabolites in CD8⁺ T cells

CD8 ⁺ T Cells GSE93776 Naïve Reporter Metabolites	p-value
Pi	5.20E-04
appA	1.59E-03
pyridoxamine	2.57E-03
pyridoxamine-phosphate	2.57E-03
pyridoxine	2.57E-03
succinate	1.43E-02
nicotinamide D-ribonucleotide	2.39E-02
GDP	4.12E-02
1-pyrroline-5-carboxylate	4.60E-02

Supplementary Table 27 Reporter metabolites in NKT cells

NKT Cells GSE93776 Reporter Metabolites	p-value
PEP	2.87E-05
pyruvate	1.60E-04
2-trans,6-trans-farnesal	1.80E-02
farnesylcysteine	1.80E-02
PAPS	2.35E-02
PPi	2.45E-02
1-phosphatidyl-1D-myo-inositol-5-phosphate	4.17E-02
1-phosphatidyl-myo-inositol-3,5-bisphosphate	4.17E-02

Supplementary Table 28 Reporter metabolites in NK cells

NK Cells GSE93776 Reporter Metabolites	p-value
PEP	2.87E-05
2-trans,6-trans-farnesal	1.80E-02
farnesylcysteine	1.80E-02
PAPS	2.35E-02
PPi	2.45E-02
1-phosphatidyl-1D-myo-inositol-5-phosphate	4.17E-02
1-phosphatidyl-myo-inositol-3,5-bisphosphate	4.17E-02

Supplementary Table 29 Reporter metabolites in neutrophil cells

Neutrophils Cells GSE93776 Reporter Metabolites	p-value
succinate	4.50E-03
cholesterol	5.98E-03
1,2-diacylglycerol-LD-TAG pool	7.05E-03
(11Z)-docosenoyl-CoA	1.01E-02
(11Z,14Z)-eicosadienoyl-CoA	1.01E-02
(11Z,14Z,17Z)-eicosatrienoyl-CoA	1.01E-02
(13Z)-octadecenoyl-CoA	1.01E-02
(13Z,16Z)-docosadienoyl-CoA	1.01E-02
(24R,25R)3alpha,7alpha,12alpha,24-tetrahydroxy-5beta-cholestanoyl-CoA	1.01E-02
(3S)-3-hydroxy-cis,cis-palmito-7,10-dienoyl-CoA	1.01E-02
(3S)-3-hydroxydodec-cis-6-enoyl-CoA	1.01E-02
(3S)-3-hydroxylinoleoyl-CoA	1.01E-02
(4Z,7Z,10Z,13Z,16Z)-docosapentaenoyl-CoA	1.01E-02
(4Z,7Z,10Z,13Z,16Z,19Z)-docosaheptaenoyl-CoA	1.01E-02
(5Z,8Z,11Z)-eicosatrienoyl-CoA	1.01E-02
(5Z,8Z,11Z,14Z,17Z)-eicosapentaenoyl-CoA	1.01E-02
(6Z,9Z)-octadecadienoyl-CoA	1.01E-02
(6Z,9Z,12Z,15Z)-octadecatetraenoyl-CoA	1.01E-02
(7Z)-octadecenoyl-CoA	1.01E-02
(7Z,10Z,13Z,16Z)-docosatetraenoyl-CoA	1.01E-02
(7Z,10Z,13Z,16Z,19Z)-docosapentaenoyl-CoA	1.01E-02
(8Z,11Z)-eicosadienoyl-CoA	1.01E-02
(8Z,11Z,14Z,17Z)-eicosatetraenoyl-CoA	1.01E-02
(9E)-octadecenoyl-CoA	1.01E-02
(9E)-tetradecenoyl-CoA	1.01E-02
(S)-3-hydroxy-11-cis-octadecenoyl-CoA	1.01E-02
(S)-3-hydroxy-2-methylbutyryl-CoA	1.01E-02
(S)-3-hydroxy-7-hexadecenoyl-CoA	1.01E-02
(S)-3-hydroxybutyryl-CoA	1.01E-02
(S)-3-hydroxydodecanoyl-CoA	1.01E-02
(S)-3-hydroxyhexadecanoyl-CoA	1.01E-02
(S)-3-hydroxyoleyleoyl-CoA	1.01E-02
(S)-3-hydroxypalmitoleoyl-CoA	1.01E-02
(S)-3-hydroxytetradecanoyl-CoA	1.01E-02
(S)-hydroxydecanoyl-CoA	1.01E-02
(S)-hydroxyhexanoyl-CoA	1.01E-02
(S)-hydroxyoctanoyl-CoA	1.01E-02
10,13,16,19-docosatetraenoyl-CoA	1.01E-02
10,13,16-docosatrienoyl-CoA	1.01E-02
13,16,19-docosatrienoyl-CoA	1.01E-02
18,20-dioxo-20-CoA-LTB4	1.01E-02
20-CoA-20-oxo-18r-hydroxy-LTB4	1.01E-02
2-methyl-3-oxopropanoate	1.01E-02

2-methylacetoacetyl-CoA	1.01E-02
3(S),12(R)-dihydroxy-5-oxo-eicosa-(8E,10E,14Z)-trienoyl-CoA	1.01E-02
3(S),12(S)-dihydroxy-5-oxo-eicosa-(8E,10E,14Z)-trienoyl-CoA	1.01E-02
3(S),5(S),12(R)-trihydroxy-eicosa-8-trans-6,14-cis-trienoyl-CoA	1.01E-02
3(S),6(R)-dihydroxy-tetradec-(8Z)-enoate	1.01E-02
3(S),6(S)-dihydroxy-tetradec-(8Z)-enoate	1.01E-02
3(S),8(R)-dihydroxy-(6E,10Z)-hexadecadienoate	1.01E-02
3(S),8(S)-dihydroxy-(6E,10Z)-hexadecadienoate	1.01E-02
3(S)-hydroxy-(5Z,8Z)-tetradecadienoyl-CoA	1.01E-02
3(S)-hydroxy-(6Z,9Z,12Z)-octadecatrienoyl-CoA	1.01E-02
3(S)-hydroxy-11-cis-eicosenoyl-CoA	1.01E-02
3(S)-hydroxy-13-cis-docosenoyl-CoA	1.01E-02
3(S)-hydroxy-13-cis-eicosenoyl-CoA	1.01E-02
3(S)-hydroxy-2(S),6-dimethyl-heptanoyl-CoA	1.01E-02
3(S)-hydroxy-4(R),8-dimethyl-nonanoyl-CoA	1.01E-02
3(S)-hydroxy-4-methyl-pentanoyl-CoA	1.01E-02
3(S)-hydroxy-dihomo-gamma-linolenoyl-CoA	1.01E-02
3,5-dioxo-12(R)-hydroxy-eicosa-(8E,10E,14Z)-trienoyl-CoA	1.01E-02
3,5-dioxo-12(S)-hydroxy-eicosa-(8E,10E,14Z)-trienoyl-CoA	1.01E-02
3alpha,7alpha,12alpha-trihydroxy-5beta-24-oxocholestanoyl-CoA	1.01E-02
3-hydroxydocosanoyl-CoA	1.01E-02
3-hydroxyeicosanoyl-CoA	1.01E-02
3-hydroxyheneicosanoyl-CoA	1.01E-02
3-hydroxyheptadecanoyl-CoA	1.01E-02
3-hydroxyheptanoyl-CoA	1.01E-02
3-hydroxyisobutyrate	1.01E-02
3-hydroxynonadecanoyl-CoA	1.01E-02
3-hydroxynonanoyl-CoA	1.01E-02
3-hydroxyoctadecanoyl-CoA	1.01E-02
3-hydroxypentadecanoyl-CoA	1.01E-02
3-hydroxypentanoyl-CoA	1.01E-02
3-hydroxytridecanoyl-CoA	1.01E-02
3-hydroxyundecanoyl-CoA	1.01E-02
3-oxo-(2S)-methylisocapryloyl-CoA	1.01E-02
3-oxo-(6Z,9Z,12Z)-octadecatrienoyl-CoA	1.01E-02
3-oxo-11-cis-eicosenoyl-CoA	1.01E-02
3-oxo-11-cis-octadecenoyl-CoA	1.01E-02
3-oxo-13cis-docosenoyl-CoA	1.01E-02
3-oxo-13-cis-eicosenoyl-CoA	1.01E-02
3-oxo-4(R),8-dimethyl-nonanoyl-CoA	1.01E-02
3-oxo-4-methyl-pentanoyl-CoA	1.01E-02
3-oxo-5(S),12(R)-dihydroxy-eicosa-8-trans-6,14-cis-trienoyl-CoA	1.01E-02
3-oxo-6(R)-hydroxy-tetradec-8-cis-enoate	1.01E-02
3-oxo-6(S)-hydroxy-tetradec-(8Z)-enoate	1.01E-02
3-oxo-7-hexadecenoyl-CoA	1.01E-02
3-oxo-8(R)-hydroxy-hexadeca-(6E,10Z)-dienoate	1.01E-02
3-oxo-8(S)-hydroxy-hexadeca-(6E,10Z)-dienoate	1.01E-02

3-oxo-cis,cis-5,8-tetradecadienoyl-CoA	1.01E-02
3-oxo-cis,cis-7,10-hexadecadienoyl-CoA	1.01E-02
3-oxodecanoyl-CoA	1.01E-02
3-oxo-dihomo-gamma-linolenoyl-CoA	1.01E-02
3-oxodocosanoyl-CoA	1.01E-02
3-oxododecanoyl-CoA	1.01E-02
3-oxoeicosanoyl-CoA	1.01E-02
3-oxoheneicosanoyl-CoA	1.01E-02
3-oxoheptadecanoyl-CoA	1.01E-02
3-oxoheptanoyl-CoA	1.01E-02
3-oxohexanoyl-CoA	1.01E-02
3-oxolaur-6-cis-enoyl-CoA	1.01E-02
3-oxolinoleoyl-CoA	1.01E-02
3-oxomyrist-5-enoyl-CoA	1.01E-02
3-oxomyrist-7-enoyl-CoA	1.01E-02
3-oxononadecanoyl-CoA	1.01E-02
3-oxononanoyl-CoA	1.01E-02
3-oxooctadecanoyl-CoA	1.01E-02
3-oxooctanoyl-CoA	1.01E-02
3-oxooleoyl-CoA	1.01E-02
3-oxopalmitoleoyl-CoA	1.01E-02
3-oxopalmitoyl-CoA	1.01E-02
3-oxopentadecanoyl-CoA	1.01E-02
3-oxopentanoyl-CoA	1.01E-02
3-oxotetradecanoyl-CoA	1.01E-02
3-oxotridecanoyl-CoA	1.01E-02
3-oxoundecanoyl-CoA	1.01E-02
9-eicosenoyl-CoA	1.01E-02
cis-(3S)-hydroxytetradec-5-enoyl-CoA	1.01E-02
cis-(3S)-hydroxytetradec-7-enoyl-CoA	1.01E-02
FAD	1.01E-02
FADH2	1.01E-02
linolenoyl-CoA	1.01E-02
cholesterol-STAR	1.02E-02
STAR	1.02E-02
11beta-hydroxyandrost-4-ene-3,17-dione	1.05E-02
11beta-hydroxyprogesterone	1.05E-02
17alpha,20alpha-dihydroxycholesterol	1.05E-02
17alpha-hydroxypregnenolone	1.05E-02
17alpha-hydroxyprogesterone	1.05E-02
20-hydroxycholesterol	1.05E-02
21-deoxycortisol	1.05E-02
4-androstene-3,17-dione	1.05E-02
acetaldehyde	1.05E-02
acetate	1.05E-02
cortisol	1.05E-02
dehydroepiandrosterone	1.05E-02

pregnenolone	1.05E-02
progesterone	1.05E-02
pyruvate	1.35E-02
L-lactate	1.58E-02
10-formyl-THF	2.25E-02
5,10-methenyl-THF	2.25E-02
5,10-methylene-THF	2.25E-02
formate	2.25E-02
THF	2.25E-02
acetaldehyde	3.87E-02

Supplementary Table 30 Reporter metabolites in monocyte cells

Monocyte Cells GSE93776 Reporter Metabolites	p-value
1,2-diacylglycerol-LD-PE pool	8.22E-03
1,2-diacylglycerol-LD-PS pool	8.22E-03
1-alkenyl-2-acylglycerol	8.22E-03
1-alkyl-2-acylglycerol	8.22E-03
1-alkyl-2-acylglycerophosphoethanolamine	8.22E-03
CDP-ethanolamine	8.22E-03
O-1-alk-1-enyl-2-acyl-sn-glycero-3-phosphoethanolamine	8.22E-03
PE-LD pool	8.22E-03
PE-PS-LD pool	8.22E-03
CMP	1.52E-02
1-phosphatidyl-1D-myo-inositol-3-phosphate	4.01E-02
1-phosphatidyl-1D-myo-inositol-5-phosphate	4.01E-02
1-phosphatidyl-myo-inositol-3,5-bisphosphate	4.01E-02
phosphatidylinositol-3,5-bisphosphate	4.01E-02
PI pool	4.01E-02

Supplementary Table 31 Enrich KEGG pathways of reporter metabolite for each data set

Synovial Tissue GSE55457	
Annotation	p-value
Purine metabolism	2.57E-02
Metabolic pathways	4.06E-01
Biosynthesis of secondary metabolites	2.85E-01
mTOR signaling pathway	1.95E-03
Parkinson's disease	3.63E-03
Blood Cells GSE93272	
Annotation	p-value
Pyrimidine metabolism	4.23E-06

Metabolic pathways	6.67E-02
Neuroactive ligand-receptor interaction	1.03E-01

Macrophage Cells GSE10500

Annotation	p-value
Pyrimidine metabolism	7.90E-04
Metabolic pathways	6.67E-02
Vitamin B6 metabolism	2.65E-02

Macrophage Cells GSE97779

Annotation	p-value
Pyrimidine metabolism	3.26E-02
Metabolic pathways	1.65E-01
Vitamin B6 metabolism	1.78E-02

CD4⁺ T Cells GSE56649

Annotation	p-value
Oxidative phosphorylation	4.46E-03
Purine metabolism	2.57E-02
Metabolic pathways	4.06E-01
Biosynthesis of secondary metabolites	2.85E-01
Calcium signaling pathway	2.79E-03
Neuroactive ligand-receptor interaction	3.57E-02
Lysosome	1.12E-03
Endocytosis	1.67E-03
Type II diabetes mellitus	1.67E-03
Parkinson's disease	3.63E-03
Hypertrophic cardiomyopathy (HCM)	1.39E-03

CD8⁺ T Cells GSE93776 naïve

Annotation	p-value
Oxidative phosphorylation	2.52E-06
Metabolic pathways	1.79E-03
ABC transporters	1.63E-01
Parkinson's disease	1.29E-06
Purine metabolism	5.31E-04
Biosynthesis of secondary metabolites	6.39E-01
Neuroactive ligand-receptor interaction	1.40E-03
Lysosome	1.96E-05
Endocytosis	4.88E-05
Calcium signaling pathway	1.94E-02
Type II diabetes mellitus	1.17E-02
Hypertrophic cardiomyopathy (HCM)	9.73E-03
Pyrimidine metabolism	5.30E-03
Riboflavin metabolism	4.03E-02

NKT Cells GSE93776

Annotation	p-value
Propanoate metabolism	2.00E-02
Nicotinate and nicotinamide metabolism	2.44E-02
Metabolic pathways	1.65E-01
Oxidative phosphorylation	8.90E-03
Purine metabolism	5.07E-02
Biosynthesis of secondary metabolites	4.89E-01
Neuroactive ligand-receptor interaction	7.01E-02
Lysosome	2.23E-03
Endocytosis	3.34E-03
Parkinson's disease	7.24E-03

NK Cells GSE93776

Annotation	p-value
Propanoate metabolism	2.00E-02
Nicotinate and nicotinamide metabolism	2.44E-02
Metabolic pathways	1.65E-01
Oxidative phosphorylation	8.90E-03
Purine metabolism	5.07E-02
Biosynthesis of secondary metabolites	4.89E-01
Neuroactive ligand-receptor interaction	7.01E-02
Lysosome	2.23E-03
Endocytosis	3.34E-03
Parkinson's disease	7.24E-03

Neutrophils Cells GSE93776

Annotation	p-value
Riboflavin metabolism	5.86E-03
Metabolic pathways	4.06E-01

Monocytes Cells GSE93776

Annotation	p-value
Purine metabolism	6.42E-05
MAPK signaling pathway	5.57E-03
Calcium signaling pathway	4.19E-05
Chemokine signaling pathway	5.57E-03
Oocyte meiosis	4.46E-03
Vascular smooth muscle contraction	2.76E-02
Gap junction	1.22E-02
Leukocyte transendothelial migration	4.46E-03
Long-term potentiation	7.79E-03
Olfactory transduction	5.57E-03
Taste transduction	1.44E-02
Insulin signaling pathway	4.46E-03

GnRH signaling pathway	6.68E-03
Progesterone-mediated oocyte maturation	4.46E-03
Melanogenesis	6.68E-03
Aldosterone-regulated sodium reabsorption	8.90E-03
Vasopressin-regulated water reabsorption	2.23E-03
Prion diseases	3.34E-03
Vibrio cholerae infection	1.00E-02
Chagas disease	7.79E-03
Dilated cardiomyopathy	4.46E-03
Oxidative phosphorylation	2.91E-07
Metabolic pathways	1.86E-01
Biosynthesis of secondary metabolites	3.22E-01
Neuroactive ligand-receptor interaction	7.24E-03
Lysosome	5.60E-06
Endocytosis	1.40E-05
Parkinson's disease	1.49E-07
Type II diabetes mellitus	6.68E-03
Hypertrophic cardiomyopathy (HCM)	5.57E-03
ABC transporters	9.67E-02



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EDUCATION AND TRAINING

2018- ... Adana Science and Technology University, Department of Bioengineering
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2010-2011 Universida de Lisboa Statistics and operations research department
2007-2012 Cukurova University Department of Statistics
Graduated

Organizational / managerial skills

Articles Comertpay Betul, Gov Esra, 2020, Identification of key biomolecules in
rheumatoid arthritis through the reconstruction of comprehensive disease-
specific biological networks, Autoimmunity, 10.1080/08916934.2020.1722107
Project 2020- ... Turkey Institutes of Health Presidency (TÜSEB)- 3436, A holistic perspective on
cancer diseases with system biology and bioinformatics analysis methods:
Determination of Molecular Target and Biomarker Candidates, scholarship student.

Reports	Comertpay Betul, Gov Esra, 2019, Identification of Molecular Targets and Signatures in Rheumatoid Arthritis Using Human Protein Interaction Network, 2nd International Eurasian Conference on Biological and Chemical Sciences (poster presentation) Nour Zarkawi, Betul Comertpay, Esra Gov, 2019, Key genes and pathways of prostate cancer via system biology perspective, 6. Bioengineering Turkey Summit (poster presentation)
License thesis	Normal Distribution I examined economic data using normal distribution methods and forecasting methods
Undergraduate studies	Whales- Finding difficult to estimate data with point estimates and signaling methods and comparing their realities and making risk analyses
Computer skills	R, python, SQL, SPSS and C ++