Supplementary Information

The miRNA-mRNA Interactome of murine iPSC-derived Chondrocytes in Response to Inflammatory Cytokines

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Supplementary Figure Legends

Figure S1 Volcano plot visualization shows miRNAs that are differentially expressed compared to controls at each time point (red: $p_{adj} < 0.05$). LFC, $\log_2$(FoldChange).

Figure S2 Volcano plot visualization shows mRNAs that are differentially expressed compared to controls at each time point (red: $p_{adj} < 0.05$, $|LFC| > 1$). LFC, $\log_2$(FoldChange).

Figure S3 From RNA-sequencing analysis, fold changes of miRNAs that are differentially expressed exclusively with **(A)** IL-1β or **(B)** TNF-α from RNA-sequencing analysis. LFC, $\log_2$(FoldChange).

Figure S4 IL-1β miRNA-mRNA interactome at **(A)** 4, **(B)** 12, and **(C)** 24 hours. TNF-α miRNA-mRNA interactome at **(D)** 12 and **(E)** 24 hours. Network of conserved and predicted miRNA-mRNA target pairs that are differentially expressed, are changing expression levels in opposite directions, and have been experimentally validated in response to 1 ng/mL IL-1β or 20 ng/mL TNF-α, respectively. The color of the node indicates the LFC of the gene or miRNA and the size of the node is proportional to the number of connections. The thickness of the line corresponds to the context++ score from the TargetScan database. LFC, $\log_2$(FoldChange).

Table S1 Enriched pathways of genes within each cluster in response to IL-1β. KEGG pathway analysis of the top 5 enriched pathways, ranked by p-value, and their associated genes.

Table S2 Enriched pathways of genes within each cluster in response to TNF-α. KEGG pathway analysis of the top 5 enriched pathways, ranked by p-value, and their associated genes.

Table S3 Enriched pathways of genes in response to IL-1β at each time point. KEGG pathway analysis of the top enriched pathways, ranked by p-value, and their associated genes.

Table S4 Enriched pathways of genes in response to TNF-α at each time point. KEGG pathway analysis of the top enriched pathways, ranked by p-value, and their associated genes.

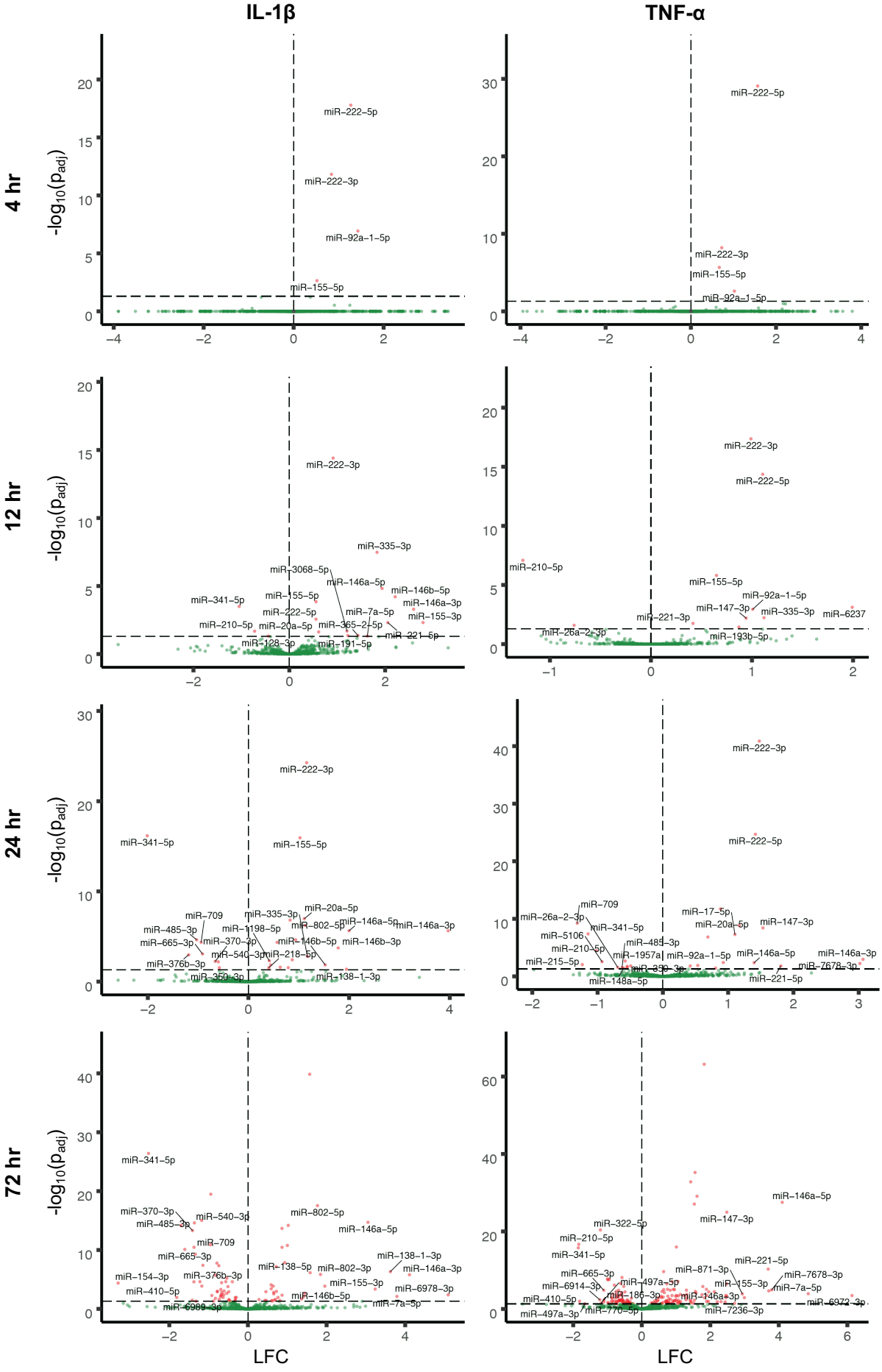
IL-1β
TNF-α
4 hr
12 hr
24 hr
72 hr
-log10(padj)
LFC
miR−222−5p
miR−222−3p
miR−92a−1−5p
miR−155−5p
miR−335−3p
miR−3068−5p
miR−146a−5p
miR−146b−5p
miR−341−5p
miR−7a−5p
miR−146a−3p
miR−155−3p
miR−210−5p
miR−20a−5p
miR−365−2−5p
miR−221−5p
miR−128−3p
miR−191−5p
miR−210−5p
miR−92a−1−5p
miR−147−3p
miR−335−3p
miR−6237
miR−221−3p
miR−26a−2−3p
miR−193b−5p
miR−20a−5p
miR−709
miR−485−3p
miR−1198−5p
miR−802−5p
miR−665−3p
miR−370−3p
miR−540−3p
miR−218−5p
miR−376b−3p
miR−350−3p
miR−138−1−3p
miR−17−5p
miR−5106
miR−1957a
miR−215−5p
miR−148a−5p
miR−7678−3p
miR−322−5p
miR−871−3p
miR−497a−5p
miR−6914−3p
miR−186−3p
miR−770−5p
miR−7236−3p
miR−154−3p
miR−410−5p
miR−6989−3p
miR−6978−3p
miR−7a−5p
miR−6972−3p

Figure S1

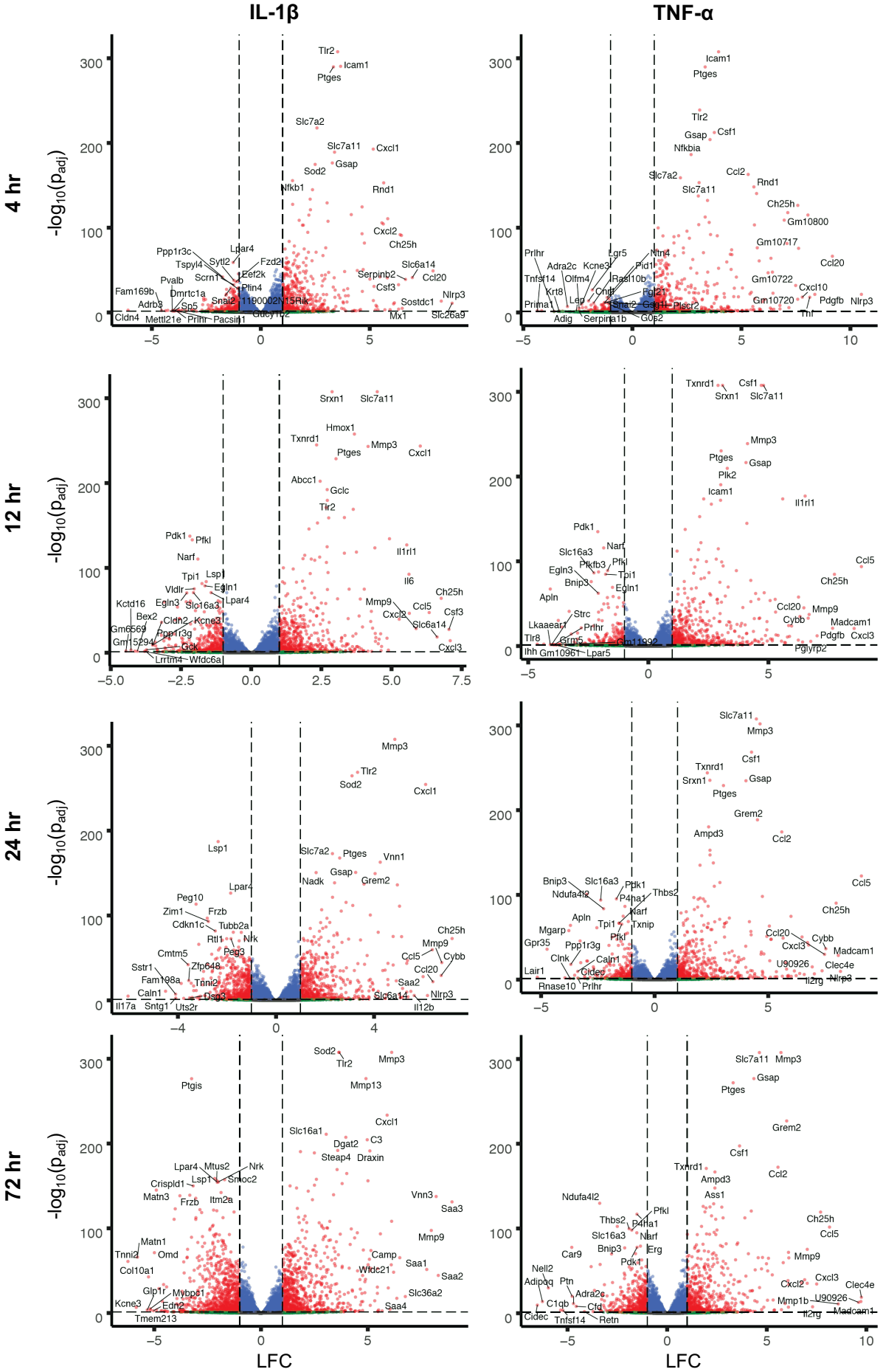

Figure S2

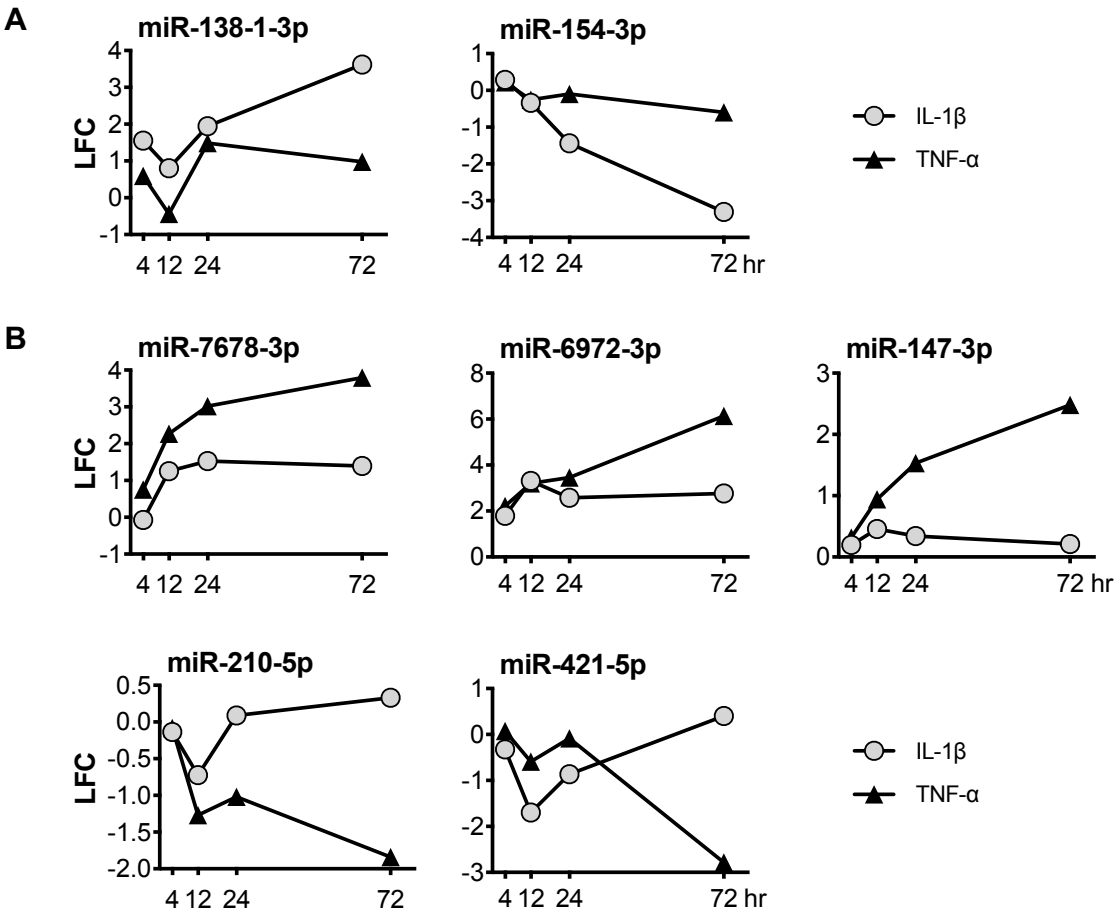
A
miR-138-1-3p
miR-154-3p
LFC
4 12 24 72
4 12 24 72 hr
IL-1β
TNF-α
B
miR-7678-3p
miR-6972-3p
miR-147-3p
miR-210-5p
miR-421-5p

Figure S3

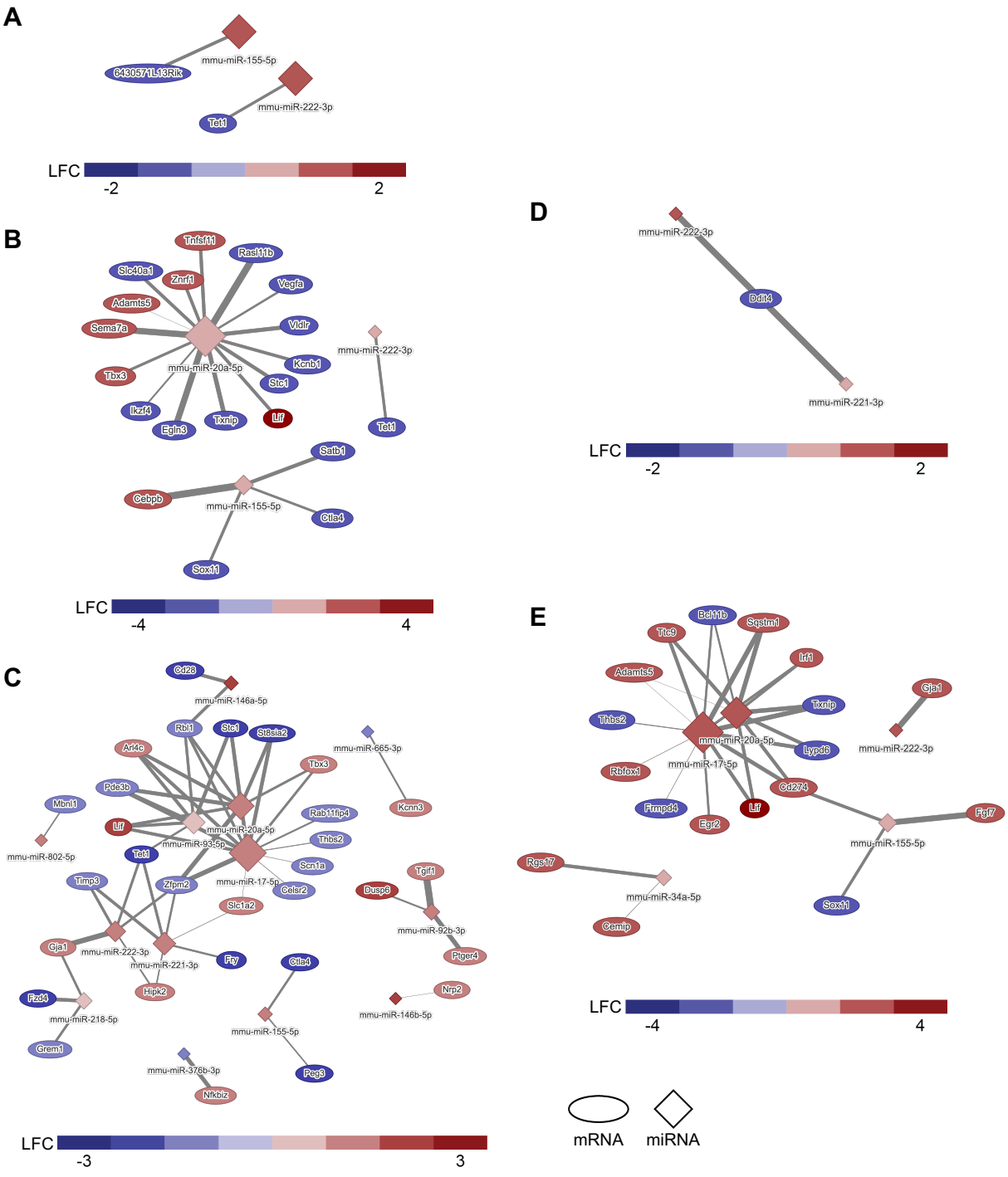
A
mmu-miR-155-5p
6430571L13Rik
mmu-miR-222-3p
Tet1
LFC
-2
2
B
Tnfsf11
Rasl11b
Slc40a1
Znrf1
Vegfa
Adamts5
Sema7a
Vldlr
mmu-miR-222-3p
mmu-miR-20a-5p
Kcnb1
Tbx3
Stc1
Ikzf4
Egln3
Txnip
Lif
Tet1
Satb1
Cebpb
mmu-miR-155-5p
Ctla4
Sox11
LFC
-4
4
C
Cd28
mmu-miR-146a-5p
Rbl1
Stc1
St8sia2
Ari4e
mmu-miR-665-3p
Tbx3
Pde3b
Kcnn3
Mbnl1
Rab11fip4
Lif
mmu-miR-20a-5p
Thbs2
mmu-miR-93-5p
mmu-miR-802-5p
Tet1
Scn1a
Timp3
Zfpm2
mmu-miR-17-5p
Celsr2
Tgif1
Dusp6
Slc1a2
mmu-miR-92b-3p
Gja1
mmu-miR-222-3p
Ptger4
mmu-miR-221-3p
Fzd4
Hipk2
Nrp2
mmu-miR-218-5p
mmu-miR-146b-5p
Grem1
mmu-miR-155-5p
mmu-miR-376b-3p
Peg3
Nfkbiz
LFC
-3
3
D
mmu-miR-222-3p
Ddit4
mmu-miR-221-3p
LFC
-2
2
E
Bcl11b
Sqstm1
Ttc9
Irf1
Adamts5
Gja1
Txnip
Thbs2
mmu-miR-20a-5p
mmu-miR-222-3p
Lypd6
Rbfox1
mmu-miR-17-5p
Cd274
Fmnpd4
Lif
Egr2
Fgf7
mmu-miR-155-5p
Rgs17
mmu-miR-34a-5p
Sox11
Cemip
LFC
-4
4
mRNA
miRNA

Figure S4

Table S1 Enriched pathways of genes within each cluster in response to IL-1β.

	Pathway	P-value	Genes
1	ECM-receptor interaction	1.11×10^{-12}	*Sdc4; Lamb3; Gp1bb; Lama3; Tnc; Lamc2; Hmmr; Thbs2; Thbs1; Gp5; Col2a1; Reln; Sv2c; Col4a1; Col6a2; Chad; Col9a1; Col9a3; Col9a2; Cd44*
	TNF signaling pathway	2.66×10^{-10}	*Edn1; Ccl12; Csf2; Ccl20; Lif; Pik3cb; Nod2; Ptgs2; Tnf; Sele; Cxcl2; Nfkb1; Cx3cl1; Icam1; Cxcl10; Creb3l2; Ccl2; Junb; Map3k5; Creb5*
	PI3K-Akt signaling pathway	1.48×10^{-8}	*Pkn3; Lama3; Pdgfb; Tnc; Il6ra; Lamc2; Pik3cb; Fgf1; Thbs2; Areg; Fgf2; Thbs1; Pik3r5; Reln; Erbb4; Creb3l2; Chad; Fgf21; Lamb3; Igf2; Nfkb1; Ereg; Col2a1; Col4a1; Col6a2; Fgf18; Col9a1; Bcl2; Gnb3; Col9a3; Kras; Col9a2; Fgfr3; Creb5*
	Fluid shear stress and atherosclerosis	2.95×10^{-8}	*Edn1; Ccl12; Sdc4; Cav1; Pdgfb; Calml3; Plat; Pik3cb; Tnf; Prkcz; Sele; Nfkb1; Klf2; Actg1; Icam1; Nppc; Trpv4; Bcl2; Ccl2; Map3k5*
	Protein digestion and absorption	1.53×10^{-7}	*Col17a1; Col15a1; Col27a1; Kcne3; Eln; Col11a1; Col11a2; Slc1a5; Col2a1; Slc7a8; Col4a1; Col6a2; Col9a1; Col9a3; Col9a2*
2	Cytokine-cytokine receptor interaction	1.03×10^{-3}	*Gdf10; Il33; Bmp2; Mstn; Il1r1; Tnfsf10; Tnfsf8; Osmr; Prlr; Il13ra1; Bmp15*
	NOD-like receptor signaling pathway	3.96×10^{-3}	*Gsdmd; Gbp5; Oas3; Casp4; Tnfaip3; Gbp2; Nfkbib; Gbp3*
	Influenza A	4.85×10^{-3}	*Socs3; H2-dmb2; Il33; Rsad2; Oas3; Tnfsf10; Nfkbib*
	Notch signaling pathway	2.24×10^{-2}	*Lfng; Rbpjl; Notch4*
	Epstein-Barr virus infection	2.35×10^{-2}	*Rbpjl; H2-dmb2; Oas3; Tnfaip3; H2-q10; Tlr2; Nfkbib*
3	Drug Metabolism	4.00×10^{-3}	*Ces2e; Gsto1; Gstp2; Gstp1; Aox1; Upb1; Xdh*
	IL-17 Signaling Pathway	5.35×10^{-3}	*Ccl7; Traf5; Cxcl1; Traf2; Ikbke; Cxcl5*
	Glycosphingolipid Biosynthesis	7.89×10^{-3}	*Fut9; St8sia1; A4galt; Ggta1*
	TNF Signaling Pathway	1.31×10^{-2}	*Jag1; Irf1; Ccl5; Traf5; Cxcl1; Traf2*
	Cytokine-cytokine Receptor Interaction	1.45×10^{-2}	*Ccr1; Il21; Cxcl9; Acvr1c; Ccl7; Ifngr2; Ccl5; Cxcl1; Il13ra2; Eda2r; Cxcl5*
4	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	4.78×10^{-5}	*Dsp; Ryr2; Cacng8; Itgb3; Itga10; Tcf7; Pkp2; Itga7; Sgcg; Itga9*
	Glutathione metabolism	1.03×10^{-4}	*Gclc; Gsta4; Gsta3; Gss; G6pdx; Gsr; Gsta1; Pgd; Gclm*
	Cytokine-cytokine receptor interaction	4.50×10^{-4}	*Il11; Csf3; Csf1; Gdf15; Il4ra; Il1f9; Cxcl3; Ngf; Il2rg; Cxcl14; Il17rb; Bmp6; Bmp3; Il1rl1; Il6; Il18rap; Il7; Tnfsf4; Cd27; Il12rb1*
	Rheumatoid arthritis	8.19×10^{-4}	*Mmp1b; Il11; Il6; Csf1; Cd80; Cd28; Atp6v0a4; Atp6v0e2; Atp6v1c2*
	Hematopoietic cell lineage	1.83×10^{-3}	*Il11; Cd24a; Csf3; Il6; Csf1; Il7; Itgb3; Il4ra; Cd14*
5	Metabolism of xenobiotics by cytochrome P450	2.52×10^{-11}	*Cbr2; Gstm2; Ugt2b34; Ugt1a1; Gstt4; Mgst1; Mgst2; Gstt1; Ugt1a6a; Ugt1a6b; Ugt1a7c; Hsd11b1; Adh1; Ugt1a5; Cyp1b1; Ugt1a2; Cyp2f2; Gstm7; Gstm6*
	Pathways in cancer	9.36×10^{-10}	*Lamc3; Il23r; Calml4; Gli2; Fgf7; Il12b; Rac3; Pim2; Ifnar2; Pdgfra; Prkcb; Hgf; Mmp2; Wnt16; Mmp9; Pgf; Runx1; Plcb4; Il3ra; Pparg; Il6st; Birc3; Camk2b; Epas1; Lama1; Gstt4; Mgst1; Mgst2; Gstt1; Lpar3; Csf2rb; Adcy1; Lpar4; Rasgrp2; Kng2; Egfr; Kng1; Adcy5; Gng2; Abl1; Egln1; Gstm2; Fzd2; Fzd4; Tgfb3; Fzd8; Vegfd; Lamb1; Igf1; Nfkbia; Cxcl12; Kitl; Fas; Gstm7; Gstm6; Fgf10*
	Drug metabolism	1.70×10^{-8}	*Gstm2; Ugt2b34; Maob; Ugt1a1; Gstt4; Mgst1; Mgst2; Fmo1; Gstt1; Nme4; Ugt1a6a; Ugt1a7c; Ugt1a6b; Adh1; Nat1; Ces2g; Ces1f; Ugt1a5; Ugt1a2; Gstm7; Gstm6*
	Chemical carcinogenesis	9.54×10^{-8}	*Gstm2; Ugt2b34; Ugt1a1; Gstt4; Mgst1; Mgst2; Gstt1; Ugt1a6a; Ugt1a6b; Ugt1a7c; Hsd11b1; Adh1; Nat1; Ugt1a5; Cyp1b1; Ugt1a2; Gstm7; Gstm6*
	Cytokine-cytokine receptor interaction	1.43×10^{-6}	*Acvrl1; Amhr2; Il23r; Csf2rb; Cxcl13; Acvr1b; Cxcl15; Ccl9; Ccl8; Ccl6; Ccl27a; Tnfsf11; Il12b; Ccr10; Ifnar2; Tnfsf14; Tnfsf15; Il10rb; Tgfb3; Il34; Tnfrsf9; Lifr; Inhbb; Il17re; Il17ra; Edar; Cxcl12; Il3ra; Tnfsf9; Fas; Il6st; Tnfrsf21*

Table S2 Enriched pathways of genes within each cluster in response to TNF-α.

	Pathway	P-value	Genes
1	TNF signaling pathway	8.39×10^{-4}	*Mapk10; Ccl12; Vcam1; Irf1; Ccl2; Fas; Birc3*
	Cytokine-cytokine receptor interaction	2.55×10^{-3}	*Il33; Ccl12; Bmp2; Acvr1c; Fas; Ccl2; Il17re; Tnfrsf11a; Gdf6; Prlr; Il12rb2*
	Malaria	4.62×10^{-3}	*Ccl12; Vcam1; Hgf; Ccl2*
	Hippo signaling pathway	6.66×10^{-3}	*Wnt10a; Bmp2; Lef1; Gdf6; Wnt16; Nkd1; Actg1*
	Wnt signaling pathway	6.89×10^{-3}	*Mapk10; Wnt10a; Lef1; Rspo3; Wnt16; Lgr5; Nkd1*
2	Influenza A	1.14×10^{-6}	*H2-eb1; Rsad2; Ddx58; Pik3cd; Oas1a; H2-aa; Oas1g; Ifih1; Oas2; Oas3; Tnfsf10; Irf7; Hspa1b*
	Epstein-Barr virus infection	3.30×10^{-5}	*Entpd1; H2-eb1; Syk; Ddx58; H2-q6; Oas1a; Pik3cd; Isg15; H2-aa; Oas1g; Oas2; Oas3; Irf7*
	NOD-like receptor signaling pathway	4.91×10^{-5}	*Gsdmd; Panx1; Gbp7; Aim2; Ifi204; Oas2; Oas3; Irf7; Oas1a; Tmem173; Oas1g; Gbp3*
	Measles	5.03×10^{-5}	*Ifih1; Ddx58; Oas2; Oas3; Irf7; Pik3cd; Oas1a; Il2rg; Hspa1b; Oas1g*
	Cytokine-cytokine receptor interaction	1.03×10^{-4}	*Cxcl9; Csf1; Ngf; Tnfrsf1b; Il2rg; Cxcl14; Cxcl15; Il1rl1; Ccl9; Il1rl2; Il18rap; Tnfsf4; Tnfsf10; Il12rb1*
3	TNF signaling pathway	1.87×10^{-12}	*Edn1; Cebpb; Csf2; Ccl20; Lif; Tnfaip3; Cxcl1; Nod2; Ptgs2; Tnf; Sele; Cxcl2; Nfkb1; Cx3cl1; Icam1; Nfkbia; Cxcl10; Il6; Creb3l3; Junb; Creb5*
	Cytokine-cytokine receptor interaction	2.45×10^{-11}	*Cntfr; Il1rn; Cd40; Csf3; Csf2; Il20rb; Cxcr4; Cxcl1; Cxcr6; Tnf; Cxcl2; Cx3cl1; Cxcl5; Bmp15; Tnfsf11; Il11; Tnfsf15; Ccl20; Tnfrsf19; Lif; Bmp8a; Il19; Gdf5; Bmp4; Cxcl10; Il6; Il23a; Il7; Lep; Tnfsf9; Inha; Il17a*
	Protein digestion and absorption	3.20×10^{-11}	*Col15a1; Col27a1; Kcne3; Eln; Col11a1; Col22a1; Col12a1; Col11a2; Col1a1; Col3a1; Col2a1; Col1a2; Slc7a8; Col5a1; Col9a1; Col9a3; Col9a2; Kcnn4*
	IL-17 signaling pathway	2.93×10^{-9}	*Csf3; Cebpb; Csf2; Ccl20; Tnfaip3; Cxcl1; Ptgs2; Cxcl2; Tnf; Cxcl5; Nfkb1; Nfkbia; Fosl1; Cxcl10; Il6; Il17a*
	ECM-receptor interaction	6.19×10^{-9}	*Lama2; Tnc; Thbs2; Thbs4; Col1a1; Col2a1; Reln; Col1a2; Sv2b; Chad; Itga11; Col9a1; Col9a3; Col9a2; Cd44*
4	Metabolism of xenobiotics by cytochrome P450	2.62×10^{-10}	*Gstm1; Gsto1; Gstt4; Mgst1; Mgst2; Ugt1a6a; Ugt1a6b; Ugt1a7c; Aldh1a3; Aldh3a1; Gsta4; Gsta3; Ugt1a5; Cyp1b1*
	Chemical carcinogenesis	3.27×10^{-8}	*Gstm1; Gsto1; Gstt4; Mgst1; Mgst2; Ugt1a6a; Ugt1a6b; Ugt1a7c; Aldh1a3; Aldh3a1; Gsta4; Gsta3; Ugt1a5; Cyp1b1*
	Drug metabolism	5.84×10^{-8}	*Gstm1; Gsto1; Gstt4; Mgst1; Mgst2; Ugt1a6a; Ugt1a7c; Ugt1a6b; Aldh3a1; Aldh1a3; Ces2e; Gsta4; Gsta3; Ugt1a5; Xdh*
	IL-17 signaling pathway	1.68×10^{-7}	*Mmp1b; Mmp3; Cxcl3; Mmp9; Mapk13; Mapk11; Mmp13; Traf4; Ccl7; Traf5; Ikbkg; Ikbke; S100a8*
	Pathways in cancer	1.02×10^{-6}	*Mmp1b; Csf1r; Notch3; Il23r; Gstt4; Mgst1; Mgst2; Adcy1; Calml4; Lpar4; Fgf7; Casp7; Fgf9; Pmaip1; Ikbkg; Bid; Gstm1; Fzd4; Gsto1; Gadd45a; Ifngr2; Fzd6; Vegfc; Traf1; Mmp9; Traf4; Gsta4; Gsta3; Col4a4; Traf5; Mdm2; Pparg*
5	Proximal tubule bicarbonate reclamation	5.81×10^{-5}	*Fxyd2; Atp1a2; Atp1b1; Slc38a3*
	Mineral absorption	7.01×10^{-5}	*Fxyd2; Trf; Atp1a2; Mt2; Atp1b1*
	Cytokine-cytokine receptor interaction	1.58×10^{-4}	*Gdf10; Il15ra; Bmp3; Tnfsf14; Mstn; Amhr2; Il15; Ccl5; Cxcl13; Ccr3; Il27ra*
	Carbohydrate digestion and absorption	8.34×10^{-4}	*Fxyd2; Atp1a2; Amy1; Atp1b1*
	Intestinal immune network for IgA production	8.34×10^{-4}	*H2-dmb2; Il15ra; Il15; Madcam1*

Table S3 Enriched pathways of genes in response to IL-1β at each time point.

	Pathway	P-value	Genes
4 hr	TNF signaling pathway	6.37×10^{-23}	*Cebpb; Csf2; Csf1; Tnfaip3; Cxcl1; Nod2; Cxcl3; Ptgs2; Tnf; Cxcl2; Cx3cl1; Icam1; Socs3; Ccl5; Ccl2; Junb; Edn1; Vcam1; Ccl20; Mmp3; Lif; Ifi47; Traf1; Sele; Mmp9; Nfkb1; Nfkbia; Cxcl10; Mapk11; Il6; Irf1; Bcl3; Fas; Creb5; Birc3*
	Cytokine-cytokine receptor interaction	4.90×10^{-19}	*Il21; Il1rn; Cd40; Csf3; Cxcl9; Csf2; Mstn; Csf1; Il1f9; Cxcl1; Cxcl3; Tnf; Cxcl2; Cx3cl1; Cxcl5; Cxcl16; Il18rap; Tnfsf10; Tnfsf11; Il12b; Tnfrsf8; Il13ra2; Il19; Il17re; Osmr; Il4ra; Il20rb; Il2rg; Acvr1b; Il1rl1; Il1rl2; Acvr1c; Ccl7; Ccl5; Ccl2; Ccr10; Tslp; Tnfsf14; Tnfsf15; Ccl20; Tgfb3; Tnfrsf9; Lif; Cxcl10; Bmp2; Il6; Il7; Tnfsf4; Fas; Tnfsf8*
	IL-17 signaling pathway	4.45E-16	*Mmp1b; Csf3; Cebpb; Csf2; Tnfaip3; Cxcl1; Cxcl3; Ptgs2; Cxcl2; Tnf; Cxcl5; Ccl7; Ccl2; Ikbke; Ccl20; Mmp3; Il17re; Mmp9; Nfkb1; Nfkbia; Fosl1; Mapk11; Cxcl10; Il6; Mmp13; S100a8*
	NOD-like receptor signaling pathway	1.02×10^{-7}	*Tnfaip3; Cxcl1; Nod2; Cxcl3; Tnf; Cxcl2; Ccl5; Casp4; Nlrp3; Ccl2; Gbp2; Ikbke; Camp; Gbp3; Gsdmd; Gbp5; Ifi207; Ifi204; Ripk2; Cybb; Nfkb1; Nfkbia; Mapk11; Il6; Aim2; Birc3*
	Rheumatoid arthritis	1.14×10^{-7}	*Mmp1b; H2-eb1; Csf2; Csf1; Tgfb3; Ccl20; Mmp3; Tnf; Cxcl5; Icam1; Il6; Ccl5; Cd28; Tnfsf11; Ccl2; Tlr2*
	NF-kappa B signaling pathway	3.49×10^{-7}	*Cd40; Vcam1; Tnfsf14; Tnfaip3; Traf1; Ptgs2; Tnf; Cxcl2; Nfkb1; Icam1; Nfkb2; Relb; Nfkbia; Plau; Tnfsf11; Card14; Birc3*
12 hr	Cytokine-cytokine receptor interaction	1.06×10^{-15}	*Il21; Il1rn; Csf3; Cxcl9; Mstn; Csf1; Amhr2; Il1f9; Cxcl1; Cxcl3; Tnf; Cxcl14; Cxcl2; Eda2r; Cx3cl1; Cxcl5; Bmp15; Il18rap; Ccl27a; Tnfsf11; Il13ra2; Il11; Ngf; Prlr; Ccl12; Il4ra; Csf2rb; Il2rg; Il1rl1; Il1rl2; Ccl9; Ccl7; Ccl5; Ccl2; Il12rb1; Ccr1; Gdf10; Il33; Tnfsf15; Ccl20; Gdf15; Tnfrsf9; Lif; Bmp2; Il6; Il7; Tnfsf4; Tnfsf9; Cd27; Fas; Tnfsf8; Il17a*
	TNF signaling pathway	5.77×10^{-13}	*Cebpb; Ccl12; Csf1; Tnfaip3; Cxcl1; Nod2; Cxcl3; Ptgs2; Tnf; Cxcl2; Cx3cl1; Icam1; Ccl5; Ccl2; Mlkl; Ccl20; Mmp3; Lif; Traf1; Sele; Mmp9; Nfkbia; Mapk11; Il6; Irf1; Fas; Creb5; Birc3*
	IL-17 signaling pathway	7.89×10^{-11}	*Mmp1b; Csf3; Cebpb; Ccl12; Ccl20; Mmp3; Tnfaip3; Cxcl1; Cxcl3; Ptgs2; Cxcl2; Tnf; Mmp9; Cxcl5; Nfkbia; Fosl1; Mapk11; Il6; Mmp13; Ccl7; Ccl2; S100a8; Il17a*
	Pathways in cancer	4.39×10^{-9}	*Mmp1b; Calml4; Gli1; Fgf7; Bdkrb1; Prkcb; Gsto1; Dcc; Dapk2; Mitf; Traf1; Wnt16; Mmp9; Agtr1a; Rarb; Met; Birc3; Ptger4; Camk2b; Gstp2; Epas1; Gstp1; Notch4; Tcf7; Pdgfb; Il4ra; Pdgfa; Lpar3; Csf2rb; Lpar4; Ptgs2; Il2rg; Hmox1; Pmaip1; Bid; Il12rb1; Egln1; Arnt2; Nqo1; Wnt10a; Egln3; Nos2; Wnt7b; Txnrd1; Fzd8; Vegfc; Igf1; Nfkb2; Vegfa; Nfkbia; Bmp2; Il6; Gsta4; Gsta3; Il7; Gsta1; Mdm2; Fas; Gstm7; Fgfr3*
	Rheumatoid arthritis	2.50×10^{-8}	*Mmp1b; Il11; Ccl12; Csf1; Ccl20; Cd80; Mmp3; Tnf; Cxcl5; Icam1; Vegfa; H2-dmb2; Il6; Ccl5; Ctla4; Tnfsf11; Ccl2; Tlr2; Il17a*
24 hr	TNF signaling pathway	2.81×10^{-16}	*Cebpb; Csf1; Tnfaip3; Cxcl1; Nod2; Cxcl3; Tnf; Cxcl2; Cx3cl1; Icam1; Socs3; Ccl5; Creb3l2; Ccl2; Junb; Ccl20; Mmp3; Lif; Ifi47; Traf2; Traf1; Sele; Mmp9; Nfkbia; Cxcl10; Mapk11; Il6; Irf1; Bcl3; Traf5; Fas; Creb5; Birc3*
	IL-17 signaling pathway	3.01×10^{-15}	*Mmp1b; Csf3; Cebpb; Traf3ip2; Tnfaip3; Cxcl1; Cxcl3; Cxcl2; Tnf; Cxcl5; Ccl7; Ccl2; Ikbke; Ccl20; Mmp3; Traf2; Mmp9; Il17rb; Nfkbia; Fosl1; Mapk11; Cxcl10; Il6; Mmp13; Traf5; Lcn2; Il17d; S100a8; Il17a*
	Cytokine-cytokine receptor interaction	8.17×10^{-15}	*Il1rn; Cd40; Csf3; Cxcl9; Mstn; Csf1; Il23r; Il1f9; Cxcl1; Cxcl3; Tnf; Cxcl14; Cxcl2; Cx3cl1; Cxcl15; Cxcl5; Bmp15; Il18rap; Tnfsf11; Il12b; Il13ra2; Ifngr2; Il19; Osmr; Prlr; Il17rb; Edar; Il6st; Tnfrsf21; Il4ra; Il2rg; Acvr1b; Il1rl1; Il1rl2; Ccl9; Ccl7; Ccl5; Ccl2; Gdf10; Il33; Tnfsf15; Ccl20; Tnfrsf9; Lif; Cxcl10; Bmp2; Il6; Cxcl12; Cd27; Fas; Tnfsf8; Il17d; Il17a*
	Pathways in cancer	7.02×10^{-9}	*Mmp1b; Lamc3; Il23r; Calml3; Lamc2; Calml4; Fgf2; Gli2; Fgf7; Ednrb; Il12b; Rac3; Bdkrb1; Pim2; Gsto1; Dapk2; Ifngr2; Traf2; Traf1; Mmp9; Runx1; Traf5; Il6st; Met; Birc3; Ptger4; Camk2b; Epas1; Lama1; Ptger2; Il4ra; Mgst1; Pdgfa; Mgst2; Gstt1; Lpar3; Adcy1; Lpar4; Il2rg; Rasgrp2; Gng2; Wnt11; Bid; Fgf21; Fzd1; Arnt2; Egln3; Fzd2; Nos2; Fzd4; Fzd9; Vegfc; Lamb1; Nfkb2; Nfkbia; Bmp2; Il6; Cxcl12; Gsta4; Gsta3; Fgf18; Fas; Fgfr3*
	Rheumatoid arthritis	1.75×10^{-8}	*Mmp1b; Csf1; Ccl20; Cd80; Itgb2; Mmp3; Tnf; Cxcl5; Icam1; H2-dmb2; Il6; Cxcl12; Ccl5; Cd28; Ctla4; Tnfsf11; Ccl2; Tlr2; Atp6v1c2; Il17a*
72 hr	Cytokine-cytokine receptor interaction	2.21×10^{-16}	*Acvrl1; Il21; Il1rn; Cd40; Csf3; Cxcl9; Mstn; Il23r; Cxcl1; Tnfrsf13c; Cxcl13; Cxcl3; Cxcl14; Cxcl2; Cx3cl1; Cxcl15; Cxcl5; Bmp15; Il18rap; Tnfsf11; Il12b; Il13ra2; Il13ra1; Ifnar2; Il11; Il1r1; Il19; Lifr; Osmr; Ngf; Il17rb; Il17ra; Edar; Il3ra; Il6st; Tnfrsf21; Il4ra; Il20rb; Il6ra; Tnfrsf11b; Il2rg; Acvr1b; Il1rl2; Ccl9; Ccl8; Ccl7; Ccl6; Ccl5; Ccl2; Il12rb1; Gdf10; Il33; Tnfsf14; Tnfsf15; Ccl20; Il10rb; Gdf15; Il34; Tnfrsf9; Lif; Inhbb; Gdf5; Bmp6; Inhbe; Cxcl10; Bmp3; Bmp2; Il6; Cxcl12; Cd27; Fas; Tnfsf8; Il17d*
	ECM-receptor interaction	7.86×10^{-12}	*Lamc3; Lama1; Itgb3; Lama3; Lamc2; Hmmr; Thbs2; Thbs1; Comp; Reln; Sv2c; Ibsp; Chad; Itgb8; Lamb3; Gp1bb; Itga1; Lamb1; Npnt; Col2a1; Col4a1; Col6a2; Itga10; Itga8; Col9a1; Itga7; Sdc1; Col9a3; Col9a2; Cd44*
	Pathways in cancer	5.42×10^{-9}	*Mmp1b; Lamc3; Il23r; Calml3; Lamc2; Pik3cb; Fgf1; Fgf2; Fgf7; Ednrb; Il12b; Rac3; Bdkrb1; Pim2; Il13ra1; Ifnar2; Pdgfra; Prkcb; Dapk2; Hgf; Mmp2; Traf2; Mmp9; Pgf; Runx1; Plcb4; Col4a1; Il3ra; Pparg; Il6st; Birc3; Ptger4; Epas1; Lama1; Gstt4; Lama3; Il4ra; Mgst1; Mgst2; Tgfa; Il6ra; Gstt1; Lpar3; Adcy1; Lpar4; Adcy8; Il2rg; Rasgrp2; Kng2; Egfr; Kng1; Adcy5; Rasgrp3; Gng2; Wnt11; Abl1; Hes1; Il12rb1; Fgf21; Fzd1; Gstm2; Jag1; Jup; Lamb3; Nos2; Fzd4; Fzd6; Fzd9; Igf2; Vegfc; Vegfd; Lamb1; Igf1; Esr2; Nfkb2; Nfkbia; Bmp2; Il6; Cxcl12; Kitl; Gsta3; Fgf18; Bcl2; Fas; Kras; Gstm7; Fgfr3; Gstm6; Fgf10*
	IL-17 signaling pathway	1.26×10^{-8}	*Mmp1b; Csf3; Cebpb; Traf3ip2; Tnfaip3; Cxcl1; Cxcl3; Cxcl2; Cxcl5; Ccl7; Ccl2; Ikbke; Ccl20; Mmp3; Traf2; Mmp9; Il17rb; Il17ra; Nfkbia; Fosl1; Mapk11; Cxcl10; Il6; Mmp13; Lcn2; Il17d; S100a8*
	PI3K-Akt signaling pathway	4.67×10^{-8}	*Csf3; Lamc3; Itgb3; Lamc2; Pik3cb; Fgf1; Fgf2; Comp; Gys1; Fgf7; Ibsp; Itgb8; Ifnar2; Pdgfra; Hgf; Itga1; Osmr; Ngf; Pgf; Ereg; Col2a1; Col4a1; Col6a2; Il3ra; Itga8; Itga7; Sgk3; Tlr2; Creb5; Pkn3; Lama1; Lama3; Il4ra; Tgfa; Lpar3; Il6ra; Lpar4; Il2rg; Thbs2; Thbs1; Egfr; Reln; Gng2; Erbb4; Chad; Fgf21; Ntrk2; Lamb3; Igf2; Vegfc; Vegfd; Lamb1; Igf1; Il6; Kitl; Itga10; Fgf18; Col9a1; Bcl2; Col9a3; Kras; Col9a2; Fgfr3; Fgf10*
	TNF signaling pathway	6.79×10^{-8}	*Cebpb; Tnfaip3; Cxcl1; Pik3cb; Nod2; Cxcl3; Cxcl2; Cx3cl1; Socs3; Ccl5; Ccl2; Junb; Map3k5; Vcam1; Jag1; Ccl20; Mmp3; Lif; Ifi47; Traf2; Mmp9; Nfkbia; Cxcl10; Mapk11; Il6; Bcl3; Fas; Creb5; Birc3*
	Cell adhesion molecules (CAMs)	8.61×10^{-8}	*Cd274; H2-t23; Cd40; Cntnap1; H2-t22; Nlgn1; Nrxn1; H2-q6; H2-k1; Itgb2; H2-q7; H2-q4; Vsir; H2-dmb2; Ctla4; Itgb8; Madcam1; Jam2; Ntng1; Ntng2; Cadm3; H2-eb1; Vcam1; Icosl; L1cam; H2-aa; Selp; Cldn11; Cldn10; Vcan; Cd6; Cldn7; Cntn1; Cd28; Itga8; Sdc1; Siglec1; H2-q10*
	Protein digestion and absorption	1.80×10^{-7}	*Kcnk5; Col17a1; Col15a1; Kcne3; Col14a1; Eln; Col11a1; Col11a2; Atp1a3; Atp1a2; Slc1a5; Slc8a1; Col10a1; Col27a1; Mme; Slc8a3; Col2a1; Slc7a8; Col4a1; Col6a2; Col5a3; Fxyd2; Col9a1; Col9a3; Col9a2*

Table S4 Enriched pathways of genes in response to TNF-α at each time point.

	Pathway	P-value	Genes
4 hr	TNF signaling pathway	1.73×10^{-27}	*Cebpb; Ccl12; Csf2; Csf1; Tnfaip3; Pik3cd; Cxcl1; Nod2; Cxcl3; Ptgs2; Tnf; Cxcl2; Cx3cl1; Icam1; Ccl5; Ccl2; Edn1; Vcam1; Mlkl; Il15; Ccl20; Mmp3; Lif; Ifi47; Traf1; Sele; Mmp9; Nfkb1; Nfkbia; Mapk10; Cxcl10; Mapk11; Il6; Irf1; Fas; Birc3*
	Cytokine-cytokine receptor interaction	1.44×10^{-22}	*Il1rn; Cd40; Csf3; Cxcl9; Csf2; Csf1; Il1f9; Cxcl1; Cxcl3; Tnf; Cxcl2; Cx3cl1; Cxcl5; Cxcl16; Il18rap; Tnfsf11; Il13ra2; Il15ra; Il15; Tnfrsf19; Il23a; Csf1r; Ccl12; Il20rb; Cxcr4; Cxcr6; Tnfrsf11a; Il2rg; Il1rl1; Il1rl2; Ccl9; Ccl7; Ccl5; Ccl2; Il12rb2; Tslp; Tnfsf14; Tnfsf15; Ccl20; Il10rb; Lif; Cxcl10; Bmp2; Il6; Il7; Tnfsf4; Lep; Fas; Il17a*
	IL-17 signaling pathway	1.59×10^{-18}	*Mmp1b; Csf3; Cebpb; Ccl12; Csf2; Tnfaip3; Cxcl1; Cxcl3; Ptgs2; Cxcl2; Tnf; Cxcl5; Ccl7; Ccl2; Ccl20; Mmp3; Mmp9; Nfkb1; Nfkbia; Mapk10; Fosl1; Mapk11; Cxcl10; Il6; Mmp13; Il17a*
	Rheumatoid arthritis	6.64×10^{-12}	*Mmp1b; Ccl12; Csf2; Csf1; Il15; Ccl20; Mmp3; Tnfrsf11a; Tnf; H2-aa; Cxcl5; Icam1; Il6; Il23a; Ccl5; Tnfsf11; Ccl2; Tlr2; Il17a*
	NF-kappa B signaling pathway	2.41×10^{-10}	*Cd40; Vcam1; Tnfsf14; Syk; Tnfaip3; Tnfrsf11a; Traf1; Ptgs2; Tnf; Cxcl2; Nfkb1; Malt1; Icam1; Nfkb2; Relb; Nfkbia; Plau; Tnfsf11; Birc3*
12 hr	TNF signaling pathway	9.65×10^{-20}	*Ccl12; Csf1; Tnfaip3; Pik3cd; Cxcl1; Nod2; Cxcl3; Ptgs2; Tnf; Cxcl2; Cx3cl1; Icam1; Ccl5; Ccl2; Edn1; Vcam1; Mlkl; Ccl20; Mmp3; Lif; Ifi47; Traf1; Sele; Mmp9; Nfkbia; Cxcl10; Mapk11; Il6; Irf1; Traf5; Fas; Creb5; Birc3*
	Cytokine-cytokine receptor interaction	1.48×10^{-15}	*Ccl12; Csf3; Cxcl9; Csf1; Amhr2; Il1f9; Cxcr4; Cxcl1; Cxcl3; Il2rg; Tnf; Cxcl2; Cx3cl1; Cxcl15; Cxcl5; Cxcl16; Il1rl1; Il1rl2; Ccl9; Il18rap; Acvr1c; Ccl7; Ccl5; Tnfsf10; Ccl2; Il13ra2; Gdf10; Il15ra; Il11; Tslp; Tnfsf14; Ccl20; Gdf15; Tnfrsf9; Lif; Gdf6; Ngf; Cxcl10; Bmp2; Il6; Il7; Tnfsf4; Tnfsf9; Fas; Tnfrsf25; Inha; Il17a*
	IL-17 signaling pathway	2.38×10^{-13}	*Mmp1b; Csf3; Ccl12; Ccl20; Mmp3; Tnfaip3; Cxcl1; Cxcl3; Ptgs2; Cxcl2; Tnf; Mmp9; Cxcl5; Nfkbia; Fosl1; Mapk11; Cxcl10; Il6; Mmp13; Ccl7; Traf5; Ccl2; S100a8; Il17a*
	NOD-like receptor signaling pathway	2.56×10^{-11}	*Ccl12; Oas1a; Tnfaip3; Cxcl1; Nod2; Cxcl3; Tnf; Cxcl2; Oas1g; Ccl5; Nlrp3; Ccl2; Gbp2; Camp; Gbp3; Gsdmd; Gbp5; Gbp7; Ifi207; Ifi204; Ripk2; Cybb; Tmem173; Nfkbia; Mapk11; Il6; Aim2; Oas2; Oas3; Traf5; Irf7; Txnip; Birc3*
	Epstein-Barr virus infection	2.89×10^{-11}	*H2-t22; H2-q6; H2-k1; H2-q4; Oas1a; Tnfaip3; Pik3cd; Tnf; Icam1; Oas1g; Relb; Bid; Entpd1; H2-eb1; Syk; Gadd45a; Ddx58; Isg15; H2-aa; Nfkb2; Tapbp; Nfkbia; Cxcl10; Mapk11; Il6; Oas2; Oas3; Traf5; Cyct; Irf7; Fas; Cd247; Nfkbie; Cd44; Tlr2*
	Rheumatoid arthritis	8.78×10^{-9}	*Mmp1b; Il11; Ccl12; H2-eb1; Csf1; Ccl20; Cd80; Mmp3; Tnf; H2-aa; Cxcl5; Icam1; Vegfa; Il6; Ccl5; Ccl2; Tlr2; Il17a*
24 hr	TNF signaling pathway	3.06×10^{-18}	*Csf1; Tnfaip3; Cxcl1; Nod2; Cxcl3; Tnf; Cxcl2; Cx3cl1; Icam1; Creb3l3; Ccl5; Ccl2; Edn1; Vcam1; Mlkl; Ccl20; Mmp3; Lif; Ifi47; Traf1; Sele; Mmp9; Mapk13; Nfkbia; Cxcl10; Mapk11; Irf1; Traf5; Fas; Birc3*
	Cytokine-cytokine receptor interaction	1.89×10^{-13}	*Csf1r; Cxcl9; Csf1; Il23r; Il1f9; Cxcr4; Cxcl1; Cxcl13; Cxcl3; Il2rg; Tnf; Cxcl2; Cx3cl1; Il27ra; Cxcl16; Il1rl1; Il1rl2; Ccl9; Il18rap; Acvr1c; Ccl7; Ccl5; Ccl2; Il13ra2; Ccr3; Il15ra; Il33; Tslp; Ccl20; Gdf15; Lif; Ngf; Bmp4; Cxcl10; Bmp3; Bmp2; Tnfsf4; Lep; Tnfsf9; Fas; Il17a*
	NOD-like receptor signaling pathway	4.99×10^{-12}	*Oas1a; Tnfaip3; Cxcl1; Nod2; Cxcl3; Tnf; Cxcl2; Ccl5; Nlrp3; Ccl2; Gbp2; Camp; Gbp3; Gsdmd; Gbp5; Gbp7; Ifi207; Ifi204; Ripk2; Cybb; Tmem173; Mapk13; Nfkbia; Mapk11; Aim2; Oas2; Oas3; Traf5; Irf7; Txnip; Nfkbib; Birc3*
	IL-17 signaling pathway	9.66×10^{-11}	*Mmp1b; Ccl20; Mmp3; Tnfaip3; Cxcl1; Cxcl3; Cxcl2; Tnf; Mmp9; Mapk13; Nfkbia; Fosl1; Mapk11; Cxcl10; Mmp13; Ccl7; Traf5; Ccl2; S100a8; Il17a*
	Epstein-Barr virus infection	4.34×10^{-10}	*H2-t22; H2-q6; H2-k1; H2-q7; H2-q4; Oas1a; Tnfaip3; Tnf; Icam1; Relb; Bid; Syk; Gadd45a; Isg15; H2-aa; Nfkb2; Tapbp; Mapk13; Nfkbia; Cxcl10; Mapk11; Oas2; Oas3; Traf5; Irf7; Fas; Cd247; Nfkbie; Cd44; Tlr2; Nfkbib*
72 hr	TNF signaling pathway	3.35×10^{-20}	*Cebpb; Ccl12; Csf1; Tnfaip3; Cxcl1; Nod2; Cxcl3; Tnf; Cxcl2; Cx3cl1; Icam1; Casp7; Creb3l3; Ccl5; Ccl2; Ikbkg; Junb; Edn1; Vcam1; Mlkl; Ccl20; Mmp3; Lif; Ifi47; Traf1; Tnfrsf1b; Sele; Mmp9; Mapk13; Nfkbia; Mapk10; Cxcl10; Mapk11; Il6; Irf1; Fas; Creb5; Birc3*
	Cytokine-cytokine receptor interaction	9.89×10^{-16}	*Cntfr; Cxcl9; Mstn; Csf1; Il23r; Il1f9; Cxcl1; Cxcl3; Tnf; Cxcl14; Cxcl2; Cx3cl1; Cxcl15; Cxcl16; Bmp15; Il18rap; Il13ra2; Il11; Ifngr2; Il19; Il17re; Tnfrsf1b; Ngf; Prlr; Csf1r; Ccl12; Il20rb; Cxcr4; Tnfrsf11a; Il2rg; Il1rl1; Il1rl2; Ccl9; Ccl8; Ccl7; Ccl5; Ccl2; Il12rb1; Gdf10; Tslp; Tnfsf14; Tnfsf15; Ccl20; Gdf15; Il34; Tnfrsf9; Lif; Bmp8a; Gdf5; Cxcl10; Bmp2; Il6; Tnfsf4; Lep; Tnfsf9; Fas*
	IL-17 signaling pathway	4.44×10^{-12}	*Mmp1b; Cebpb; Ccl12; Tnfaip3; Cxcl1; Cxcl3; Cxcl2; Tnf; Ccl7; Ccl2; Ikbkg; Ikbke; Ccl20; Mmp3; Il17re; Mmp9; Mapk13; Nfkbia; Mapk10; Fosl1; Mapk11; Cxcl10; Il6; Mmp13; Traf4; S100a8*
	Fluid shear stress and atherosclerosis	1.04×10^{-10}	*Ccl12; Prkaa2; Gstt4; Pdgfb; Mgst1; Calml3; Calml4; Tnf; Prkcz; Actg1; Icam1; Nppc; Hmox1; Ccl2; Ikbkg; Mef2c; Edn1; Vcam1; Gstm1; Cav3; Gsto1; Sele; Mmp9; Ass1; Mapk13; Vegfa; Mapk10; Mapk11; Gsta4; Gsta3; Gsta1*
	ECM-receptor interaction	9.57×10^{-10}	*Lama2; Lamc3; Itga2; Tnc; Lamc2; Thbs2; Thbs4; Col1a1; Col2a1; Reln; Col1a2; Ibsp; Sv2b; Col4a4; Chad; Itga11; Col9a1; Itgb7; Col9a3; Col9a2; Cd44; Itga9*
	Pathways in cancer	1.38×10^{-9}	*Mmp1b; Lamc3; Il23r; Calml3; Lamc2; Calml4; Gli1; Fgf7; Casp7; Bdkrb1; Ikbkg; Edn1; Gsto1; Dapk2; Ifngr2; Itga2; Traf1; Mmp9; Agtr1a; Traf4; Col4a4; Met; Birc3; Camk2b; Csf1r; Notch3; Lama2; Ptger2; Gstt4; Pdgfb; Mgst1; Cxcr4; Adcy1; Lpar4; Il2rg; Hmox1; Pmaip1; Gng8; Bid; Il12rb1; Egln1; Arnt2; Wnt10a; Egln3; Fzd2; Gstm1; Gadd45b; Nos2; Fzd4; Gadd45a; Txnrd1; Fzd6; Fzd8; Vegfc; Agt; Nfkb2; Vegfa; Nfkbia; Mapk10; Bmp2; Il6; Gsta4; Gsta3; Gsta1; Mdm2; Fas; Fgfr3*
	Protein digestion and absorption	5.02×10^{-9}	*Col18a1; Col15a1; Col27a1; Kcne3; Eln; Col11a1; Col22a1; Col11a2; Atp1a3; Atp1b1; Slc8a1; Col1a1; Col3a1; Col2a1; Col1a2; Slc7a8; Col5a1; Col4a4; Col5a3; Col9a1; Col9a3; Col9a2*
	PI3K-Akt signaling pathway	1.26×10^{-8}	*Csf1; Lamc3; Tnc; Lamc2; Areg; Fgf7; Creb3l3; Ibsp; Itgb7; Ikbkg; Syk; Itga2; Ngf; Prlr; Ereg; Col2a1; Col4a4; Ddit4; Met; Epha2; Tlr2; Creb5; Itga9; Csf1r; Prkaa2; Lama2; Pdgfb; Lpar4; Il2rg; Thbs2; Thbs4; Pik3r5; Reln; Chad; Gng8; Pck1; Angpt4; Vegfc; Vegfa; Col1a1; Il6; Col1a2; Ppp2r2c; Itga11; Col9a1; Mdm2; Col9a3; Col9a2; Fgfr3*
	Pertussis	2.07×10^{-7}	*C1qb; C1qa; Nos2; Itgb2; Calml3; Calml4; Tnf; C2; Mapk13; C3; Mapk10; Mapk11; Casp7; Il6; C1s1; Irf1; Nlrp3; C1qc*
	Rheumatoid arthritis	2.09×10^{-7}	*Mmp1b; Il11; Ccl12; Csf1; Ccl20; Cd80; H2-dma; Itgb2; Mmp3; Tcirg1; Tnfrsf11a; Tnf; Icam1; Vegfa; H2-dmb2; Il6; Ccl5; Ccl2; Tlr2*