Int J Clin Exp Med 2021;14(4):1628-1637
www.ijcem.com /ISSN:1940-5901/IJCEM0118380

Original Article

Bioinformatic identification of key biomarkers in the brain and blood involved in ischemia preconditioning protection against acute ischemic stroke in mice

Yu-Xin Yang[1,2], Mei-Ling Wu[1], Ou Du[1], Wei Duan[3], Jun-Rong Du[1]

[1]Department of Pharmacology, West China School of Pharmacy, Sichuan University, Chengdu, China; [2]The Privis Technology Co., Ltd., Chengdu, China; [3]School of Medicine and Centre for Molecular and Medical Research, Deakin University, Waurn Ponds, Victoria, Australia

Received July 17, 2020; Accepted January 5, 2021; Epub April 15, 2021; Published April 30, 2021

Abstract: Objective: The pathophysiologic processes of ischemic stroke may be implicated in brain damage and circulatory disorders. This study explored the co-biomarkers in the brain and blood that are involved in ischemic preconditioning (IPC) in a mouse model of ischemic stroke induced by transient middle cerebral artery occlusion (MCAO). Methods: GSE32529 datasets were downloaded from Gene Expression Omnibus, which included brain and blood samples from three groups (Control, Model or IPC group). Bioinformatic analysis was applied to identify co-genes in the brain and blood that are involved in ischemia preconditioning (IPC) treatment in MCAO mice. Results: The IPC-related key co-genes, interleukin-6 (*IL-6*), C-C motif chemokine ligand-2 (*CCL2*), tissue inhibitor of metalloproteinase-1 (*TIMP1*), and chemokine CXC motif ligand-1 (CXCL1), were identified among the top 10 hub genes in both the brain and blood of the MCAO mice. Moreover, ischemic stroke-related interference scores of these co-genes ranged from 42.45 to 144.19 in the Comparative Toxicogenomics database, suggesting the involvement of four co-hub genes in ischemic brain injury. Conclusion: The current findings provide novel insight into key co-biomarkers and therapeutic targets that may be useful for the diagnosis of acute ischemic stroke.

Keywords: Acute ischemic stroke, bioinformatics, biomarkers, expression profiles, high-through sequencing, ischemia preconditioning

Introduction

Ischemic stroke is the most common cerebrovascular disease in adults and is a leading cause of death and disability. Thus, there is an increasing demand to develop novel effective strategies for the diagnosis and treatment of acute ischemic stroke. Ischemic preconditioning (IPC) is a widely reported neuroprotective phenomenon in preclinical and clinical settings, in which brief sublethal ischemic exposure can prevent subsequent lethal ischemic brain injury [1, 2]. Since first reported in 1990 [3], cerebral IPC has become a promising model for exploring the molecular mechanisms of endogenous neuroprotection [4, 5]. Over the past three decades, various putative biomarkers of IPC have been identified in ischemic brain tissues in stroke patients and animal models [6]. Nevertheless, no translational applications of these biomarkers for ischemic stroke diagnosis and treatment decisions have been reported. This is at least partly because the specificity of putative biomarkers across studies may be markedly influenced by the severity of ischemia and evaluation time-points after stroke.

Numerous studies have demonstrated that the pathogenesis of ischemic stroke is associated with central and peripheral pathophysiologic processes [7, 8]. Therefore, the identification of common biomarkers of IPC in the brain and blood may provide novel insight into understanding its neuroprotective mechanisms and translation potential. The present study sought to simultaneously identify key co-biomarkers of IPC neuroprotection against acute ischemic stroke in the brain and blood. We downloaded GSE32529 datasets from Gene Expression Omnibus (GEO). Bioinformatics analysis was applied to identify co-genes and potential pathways of IPC in both ischemic brain tissue and

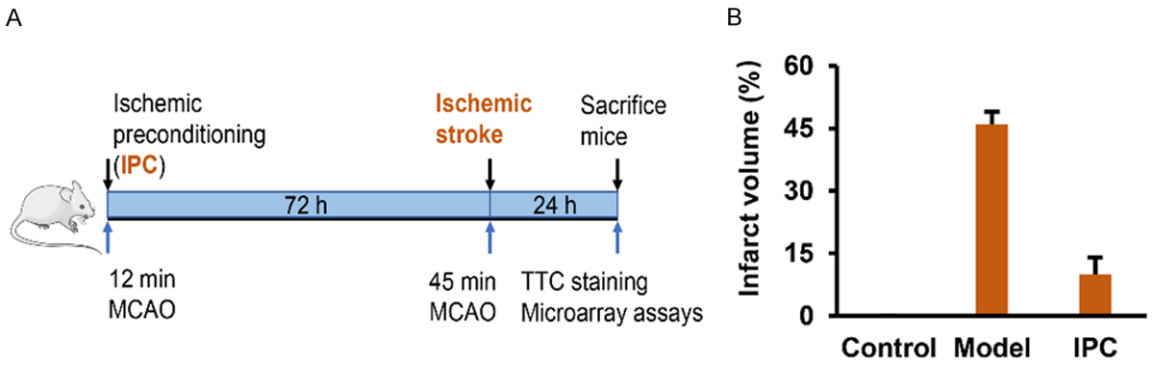

Figure 1. Experimental procedures and IPC-induced protection against ischemic brain injury in a mouse model of focal brain ischemia [9]. A. Temporal schematic diagram of the experiment. B. Ischemic preconditioning (12 min MCAO)-induced protection against cerebral infarct 24 h after 45 min MCAO in mice. Cerebral infarct volume is expressed as a percentage of the ipsilateral hemisphere volume in mice.

blood. We also determined relationships between core co-genes and ischemic stroke in the Comparative Toxicogenomics Database (CTD).

Materials and methods

Data resources

GSE32529 datasets were downloaded from GEO (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE32529), and expression profiling arrays were generated using the GPL1261 (Mouse430_2) Affymetrix Mouse Genome 430 2.0 Array (Affymetrix, Santa Clara, CA, USA). In the GSE32529 datasets, the experimental procedures are described in **Figure 1A**. Ischemic preconditioning significantly reduced the ischemic infarct volume that was induced by transient middle cerebral artery occlusion (MCAO) in mice (**Figure 1B**) [9]. In the present study, we downloaded the original gene expression profile data of the ipsilateral cortex and blood samples of four mice per group that were subjected to sham surgery (Control group), 45 min MCAO (Model group), or IPC (12 min MCAO) followed by 45 min MCAO (IPC group), respectively. We performed data preprocessing and standardized analysis and generated an expression spectrum matrix file that included 12 brain samples, 12 blood samples and 12998 genes per sample for the subsequent analysis.

Identification of differentially expressed genes and clustering analysis

We used the limma package (http://www.bioconductor.org/packages/release/bioc/html/limma.html) in the R language to calculate differentially expressed genes (DEGs) in the brain and blood between the model and control groups and between the IPC and model groups [10]. Values of $P < 0.05$ and [log2 fold change (FC)] > 0.5 were set as thresholds to identify significant DEGs [11]. We calculated and constructed Venn diagrams using the Venn2.1 tool (https://bioinfogp.cnb.csic.es/tools/venny/index.html) for co-DEGs in brain and blood samples between different groups. Short Time-series Expression Miner (STEM) analysis (http://www.cs.cmu.edu/~jernst/stem/) was conducted to explore key DEGs in the brain and blood that are involved in IPC-related protection against ischemic brain injury [12].

Functional and pathway enrichment analyses of key DEGs

To explore the functional classification of key DEGs in IPC-related protection against ischemic stress, we analyzed the Gene Ontology in Biological Process (GOPP) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases for the key brain DEGs, the key blood DEGs, and co-DEGs in both the brain and blood using DAVID (https://david.ncifcrf.gov/tools.jsp) and KEGG pathway map tool [13, 14]. Values of $P < 0.05$ and counts ≥ 2 were set as thresholds to identify significantly enriched functions and pathways for the key DEGs.

Analysis of protein-protein interaction networks of key DEGs

Possible networks of protein-protein interaction (PPI) networks that were encoded by key DEGs were constructed using STRING (http://

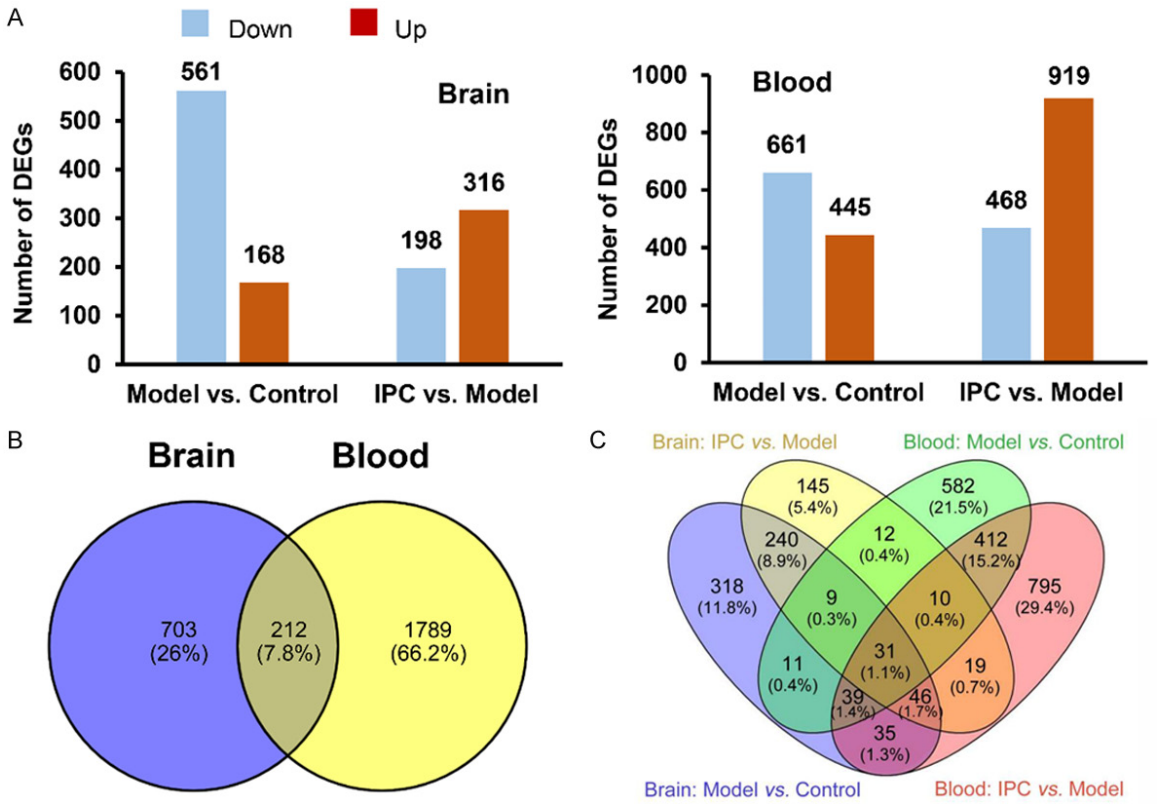

Figure 2. Identification and integrative analysis of differentially expressed genes (DEGs) that are involved in focal brain ischemia and IPC treatment in mice. A. Number of DEGs in either the brain or blood. B. Venn diagram of DEGs in the brain and blood. C. Intersection of DEG expression in the brain and blood that was induced by focal brain ischemia (model group *vs.* control group) and IPC treatment (IPC group *vs.* model group).

string-db.org/), followed by visualization using Cytoscape software (https://cytoscape.org/) [15, 16]. A combined score > 0.4 was set as the significance threshold. The scale function in R language was used to convert the average expression values of the genes into z-scores for each group, followed by setting the node color according to z-scores and the node size according to node connections in PPI networks [17]. In the network, the node represents the corresponding DEG, and the node connection indicates the interacting correlation between two genes.

Identification of key co-DEGs associated with ischemic stroke

To examine the involvement of co-hub genes in ischemic stroke and its clinical prognosis, we analyzed relationships between key co-DEGs and ischemic stroke using the CDT database (http://ctdbase.org/) [18].

Results

Identification of DEGs in brain and blood

Based on the threshold of [log FC] > 0.5, the significant DEGs in both the brain and blood between different groups were analyzed. We identified 729 DEGs in the brain and 1106 DEGs in the blood in the model group compared with the control group, including 561 and 661 upregulated DEGs in the brain and blood, respectively, and 168 and 445 downregulated DEGs in the brain and blood, respectively (**Figure 2A**). A total of 512 DEGs in the brain and 1387 DEGs in the blood were identified in the IPC group compared with the model group, including 198 and 468 upregulated DEGs in the brain and blood, respectively, and 316 and 919 downregulated DEGs in the brain and blood, respectively (**Figure 2A**). A Venn diagram revealed 915 DEGs in the brain and 2001 DEGs in the blood, including 212 co-DEGs in the brain and blood (**Figure 2B** and **2C**). These findings

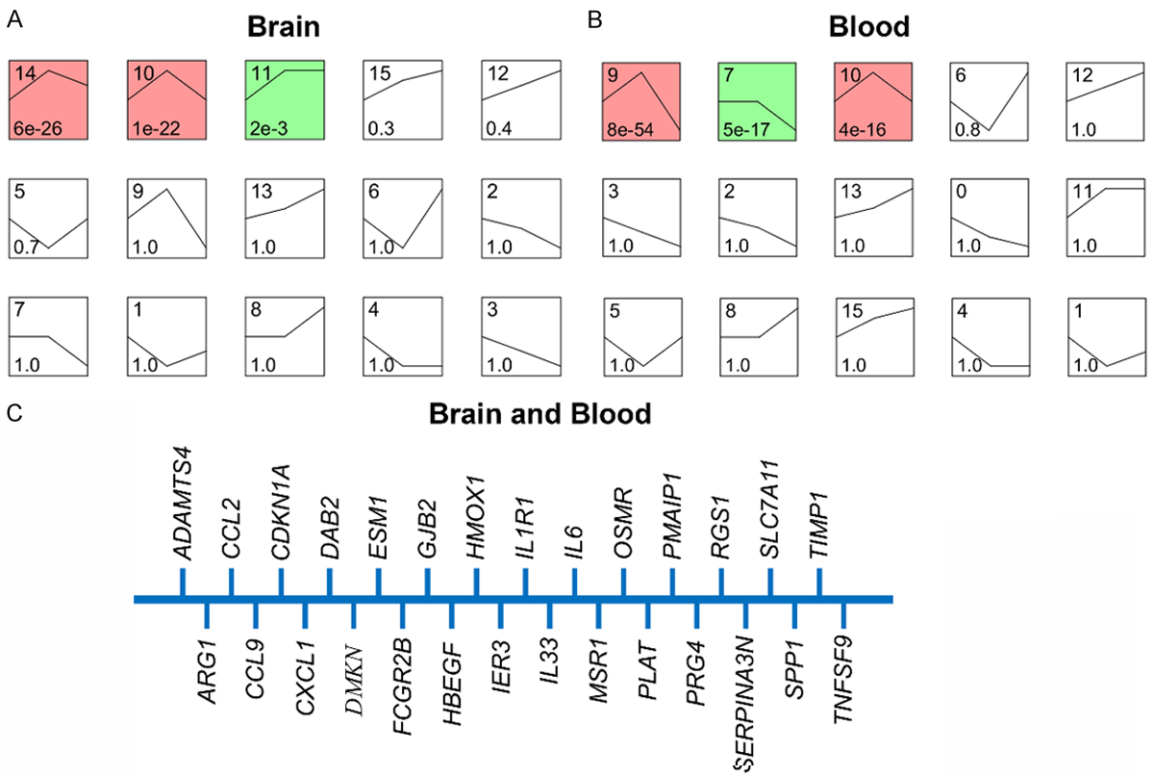

Figure 3. Screening of key DEGs that are involved in IPC treatment in a mouse model of focal brain ischemia by STEM analysis. A, B. Profiles of DEGs in the brain or blood. In each profile (box), the number in the upper left corner is the profile number, and the number in the bottom left corner is the *p* value. Profiles are ordered based on *p* values of the number of genes assigned *vs*. expected. The colored boxes represent significant profiles. Among these, expression patterns of genes that are related to IPC protection are shown in red, and the other expression patterns are shown in green. The full names of the genes in brain profiles 14 and 10 (red) are listed in Table S1, and the full names of blood profiles 9 and 10 (red) are listed in Table S2. C. Intersection of 28 genes in significant profiles in both the brain and blood.

suggest a role of these DEGs in both the brain and blood in post-ischemic brain injury or IPC-induced neuroprotection.

Screening of key DEGs in brain and blood

Based on the 915 DEGs in the brain and 2001 DEGs in the blood that were identified, we applied STEM analysis to further screen key DEGs that are involved in IPC-induced neuroprotection in mice. As shown in **Figure 3**, three significant profiles of DEGs in the brain (profiles 14, 10, and 11; **Figure 3A**) and blood (profiles 9, 7, and 10; **Figure 3B**) were detected. Among these, profiles 14 and 10 in the brain and profiles 9 and 10 in the blood revealed similar expression patterns of DEGs within different groups. Differentially expressed genes significantly increased in the model group compared with the control group, which was markedly inhibited by IPC treatment. Notably, the STEM analysis did not detect IPC neuroprotection that was significantly related to upregulated profiles in this study. STEM analysis identified 182 key genes in profiles 14 and 10 in the brain and 276 key genes in profiles 9 and 10 in the blood. The full names of these key DEGs are shown in Tables S1 and S2. Furthermore, we identified 28 intersecting DEGs in both the brain and blood by integrated clustering analysis (**Figure 3C**). Collectively, these data suggest that the 28 key co-DEGs in the brain and blood may be biomarkers and targets of IPC-induced protection against ischemic brain injury.

Functional and pathway enrichment analysis of key DEGs

GOBP and KEGG were applied for the functional and pathway enrichment analysis of IPC protection that was related to 182 key DEGs in the brain and 276 key DEGs in the blood, respectively. The full names of the key DEGs that corresponded significantly to overrepresented

Table 1. Top 10 enriched Gene Ontology in Biological Process (GOPP) terms in brain after ischemic preconditioning (IPC)

Term	Count	*P* Value
GO: 0006954~inflammatory response	30	4.86E-20
GO: 0006955~immune response	25	3.63E-17
GO: 0050729~positive regulation of inflammatory response	15	3.60E-16
GO: 0071347~cellular response to interleukin-1	15	1.30E-14
GO: 0030593~neutrophil chemotaxis	14	4.33E-14
GO: 0070098~chemokine-mediated signaling pathway	13	6.46E-14
GO: 0071346~cellular response to interferon-gamma	13	9.69E-13
GO: 0006935~chemotaxis	15	3.36E-12
GO: 0071356~cellular response to tumor necrosis factor	13	3.37E-10
GO: 0048247~lymphocyte chemotaxis	9	4.42E-10

Table 2. Top 10 enriched in Gene Ontology in Biological Process (GOPP) terms in blood after ischemic preconditioning (IPC)

Term	Count	*P* Value
GO: 0051384~response to glucocorticoid	12	6.10E-09
GO: 0006955~immune response	19	4.46E-08
GO: 0031424~keratinization	9	4.92E-08
GO: 0006954~inflammatory response	19	1.44E-06
GO: 0060326~cell chemotaxis	9	1.18E-05
GO: 0048661~positive regulation of smooth muscle cell proliferation	9	1.42E-05
GO: 0043123~positive regulation of I-kappaB kinase/NF-kappaB signaling	11	4.19E-05
GO: 0032755~positive regulation of interleukin-6 production	7	7.69E-05
GO: 0030216~keratinocyte differentiation	8	1.71E-04
GO: 0050729~positive regulation of inflammatory response	7	2.26E-04

terms and pathways are shown in Tables S3 and S4, including 281 GOBP terms and 39 KEGG pathways in the brain and 236 GOBP terms and 21 KEGG pathways in the blood. Among these, the top 10 enriched GOBP terms in the brain and blood are shown in **Tables 1** and **2**. The top 10 enriched KEGG pathways in the brain and blood are shown in **Tables 3** and **4**. These results showed that both key DEGs in the brain and blood were mainly enriched in various immune-inflammatory responses and related signaling pathways.

Protein-protein interaction networks and key co-DEGs in brain and blood

In the PPI networks that were constructed using Cytoscape 3.6.1 software, we identified 146 nodes and 1044 connections in the brain and 209 nodes and 701 connections in the blood (Figures S1 and S2), respectively. Moreover, there were 26 protein-encoding co-DEGs in both the brain and blood. Among them, *DMKN* and *GJB2* have not been included in the PPI database (**Figure 4**). The top 10 hub co-DEGs and the corresponding degrees are shown in **Table 5**, among which interleukin-6 (*IL6*), C-C motif chemokine ligand-2 (*CCL2*), tissue inhibitor of metalloproteinase-1 (*TIMP1*), and chemokine CXC motif ligand-1 (CXCL1) were key co-DEGs in both the brain and blood that were associated with IPC neuroprotection. Notably, the present results showed that key co-DEGs significantly increased in the model group compared with the control group, which was markedly inhibited by IPC treatment (**Figure 5**).

Identification of relationships between co-DEGs and ischemic stroke

In the CDT database, three indexes (stroke, brain ischemia, and cerebral infarction) are associated with ischemic stroke and outcome.

Table 3. Top 10 enriched KEGG pathways in brain after ischemic preconditioning (IPC)

Term	Count	*P* Value
mmu04060: Cytokine-cytokine receptor interaction	25	8.18E-16
mmu04668: TNF signaling pathway	13	7.28E-09
mmu05134: Legionellosis	9	4.04E-07
mmu05132: Salmonella infection	10	4.12E-07
mmu05323: Rheumatoid arthritis	10	6.36E-07
mmu05144: Malaria	8	1.71E-06
mmu04620: Toll-like receptor signaling pathway	10	3.74E-06
mmu04062: Chemokine signaling pathway	12	2.68E-05
mmu04010: MAPK signaling pathway	13	5.52E-05
mmu04640: Hematopoietic cell lineage	8	7.91E-05

Table 4. Top 10 enriched KEGG pathways in blood after ischemic preconditioning (IPC)

Term	Count	*P* Value
mmu04060: Cytokine-cytokine receptor interaction	17	3.61E-07
mmu05323: Rheumatoid arthritis	9	2.29E-05
mmu05133: Pertussis	8	9.27E-05
mmu05020: Prion diseases	6	1.03E-04
mmu04668: TNF signaling pathway	9	1.76E-04
mmu04978: Mineral absorption	5	2.37E-03
mmu05142: Chagas disease	7	3.80E-03
mmu04640: Hematopoietic cell lineage	6	7.80E-03
mmu04621: NOD-like receptor signaling pathway	5	9.31E-03
mmu05152: Tuberculosis	8	1.41E-02

Therefore, we investigated the relationship between each of the key co-DEGs (*IL6*, *CCL2*, *TIMP1*, and *CXCL1*) and each ischemic stroke-related index in the CDT database. As shown in **Figure 6**, all interference scores of these genes ranged from 42.45 to 144.19, thus confirming the involvement of four co-hub genes in ischemic brain injury.

Discussion

Post-ischemic gene expression may be influenced by many factors, such as the extent and duration of ischemia and circadian rhythm. To overcome the deviation of brain and blood biomarkers across various studies of IPC treatment for acute ischemic stroke, we investigated candidate core co-genes in the brain and blood based on genomic profile datasets (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE32529) in mice that were subjected to tMCAO using extensive bioinformatic analyses. Consistent with previous reports [19, 20], we identified several upregulated and downregulated DEGs in the brain and blood after acute brain ischemia with or without IPC treatment. Among these genes were 915 DEGs in the brain and 2001 DEGs in the blood, including 212 co-DEGs in both the brain and blood. We also screened 182 key DEGs in the brain and 276 key DEGs in the blood for their involvement in IPC protection against ischemic brain injury. Among these genes were 28 key co-DEGs in both the brain and blood that were related to IPC neuroprotection. In contrast to a previous study [21], all of the identified key genes in the present study were significantly downregulated by IPC. This discrepancy may be attributable to differences in IPC conditions and bioinformatic analysis methods across studies. Additionally, the GOBP and KEGG analyses showed that key IPC-related DEGs were mainly enriched in the various immune-inflammatory responses and related pathways. Furthermore, the PPI topological network analysis identified four key co-DEGs (*IL6*, *CCL2*, *TIMP1*, and *CXCL1*) among the top 10 hub genes in both the brain and blood. We also validated the involvement of four co-genes in ischemic brain injury in the CTD, suggesting their translational potential in clinical practice.

The *IL6* gene encodes the proinflammatory cytokine IL-6, which is implicated in various inflammation-associated disease states, including ischemic stroke [22]. Several studies have reported an increase in *IL6* expression at both the mRNA and protein levels in the brain and blood after acute ischemic stroke in both animal models and patients. Our previous studies showed a significant increase in mRNA levels of IL-6 and other inflammatory cytokines (e.g., tumor necrosis factor a [TNF-α] and IL-1β) in brain tissues 24 h after tMCAO [23, 24]. Clinical studies showed that IL-6 levels in serum and cerebrospinal fluid significantly increased within the first 24 h after stroke onset and that

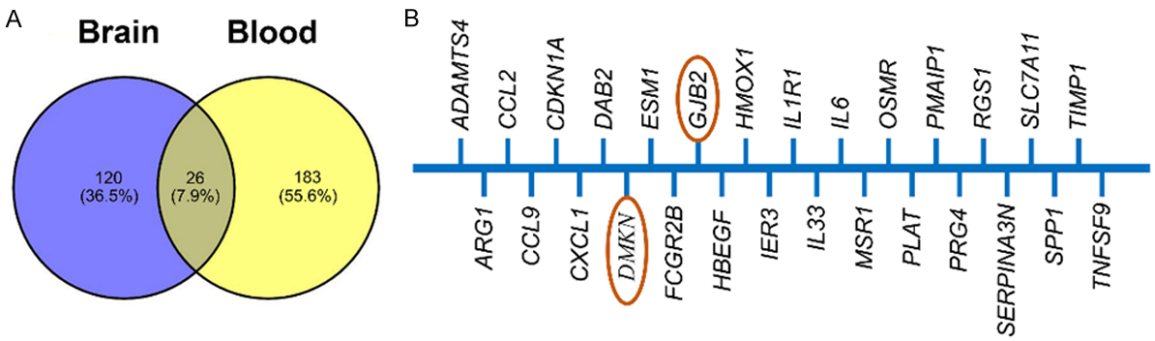

Figure 4. Identification of protein-encoding co-genes in PPI networks for IPC protection in a mouse model of focal brain ischemia. A. Venn diagram of the nodes in the PPI network in either the brain or blood. A total of 26 protein-encoding co-genes were identified in both the brain and blood. B. Two key co-DEGs (*DMKN* and *GJB2*, circled in brown) in the brain and blood were not found in the PPI database.

Table 5. The top 10 hub genes in brain and blood after IPC in a mouse model of focal brain ischemia

Resource	Hub gene	Degree	Resource	Hub gene	Degree
Brain	***IL-6****	82	Blood	***IL-6****	66
	*CCL2**	59		*TNF*	61
	TLR2	58		***CCL2****	37
	TIMP1*	50		*CSF2*	34
	ICAM1	47		***CXCL1****	32
	CXCL1*	44		*PTGS2*	30
	CCL5	43		*CXCL16*	28
	CXCL2	42		*CCR5*	24
	CCL4	42		***TIMP1****	24
	CD44	41		*MMP13*	22

*; The bold types indicate the co-hub genes in both brain and blood.

IL-6 levels were correlated with final infarct size and mortality [25].

In the present study, we found that IPC protection was associated with the downregulation of *IL6* expression in the brain and blood in tMCAO mice. Consistent with the present results, previous studies have shown that *IL6* mRNA levels in the brain and IL-6 content in serum were significantly decreased by IPC protection against acute brain ischemia that was induced by tMCAO or occlusion of the bilateral common carotid arteries in rat [4]. Thus, further clinical research is needed to verify whether systemic and central IL-6 is a biomarker of ischemic stroke.

Numerous studies have indicated that chemokines play important roles in post-stroke neuroinflammation by mediating the recruitment of central glia and peripheral leukocytes to sites of ischemic tissue injury. *CCL2* is a proinflammatory chemokine gene that encodes a member of the CC subfamily of chemokines. During the progression of neuroinflammation-related pathophysiology, CCL2 is widely expressed by resident brain cells and endothelial cells and infiltrates specific subsets of leukocytes, including lymphocytes and macrophages [26]. Thus, CCL2 has been regarded as a key chemokine that is involved in inflammatory brain conditions (e.g., stroke). The *CCL2* gene was reported to be expressed at > 10-fold higher levels in the ischemic hemisphere 24 h after tMCAO in rats [27]. Additionally, a clinical study showed that serum CCL2 levels were significantly elevated in acute ischemic stroke patients compared with the control group [28]. In the present study, IPC protection was associated with the downregulation of *CCL2* expression in the brain and blood 24 h after focal stroke in mice. However, in contrast to the present results, Wacker et al. reported that the upregulation of cerebral *CCL2* expression triggered hypoxic preconditioning-induced protection against focal stroke in mice, the underlying mechanism of which was at least partially related to sphingosine-1-phosphate signaling [29, 30]. These results indicate that *CCL2* gene expression is differentially involved in the effects of different preconditioning stimuli.

CXCL1 is another proinflammatory chemokine-related gene that encodes a member of the CXC subfamily of chemokines. This chemokine is preferentially expressed in various brain cells and has potent neutrophil chemotactic and

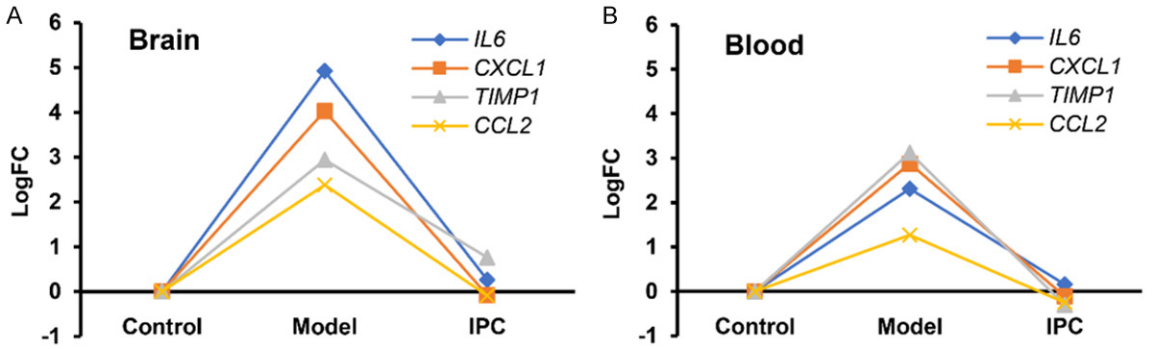

Figure 5. Effects of IPC treatment on expression patterns of key co-biomarkers in the brain and blood in a mouse model of acute focal brain ischemia.

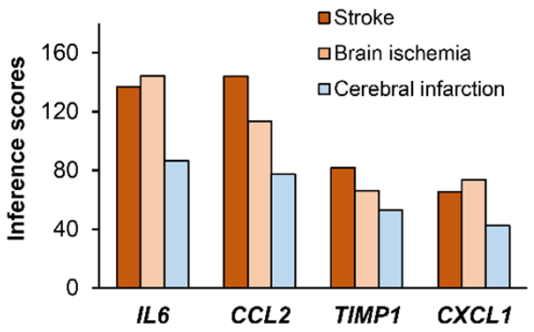

Figure 6. Interaction of key co-biomarkers that were identified in both the brain and blood and ischemic stroke based in the CTD.

activating properties [31]. CXCL1 has been implicated in post-stroke inflammation and cerebral damage by mediating neutrophil accumulation within the ischemic brain region. Similar to *CCL2* expression that is upregulated by ischemic insult, *CXCL1* gene expression was > 10-fold higher in the ischemic hemisphere 24 h after tMCAO in rats [27]. CXCL1 expression was also significantly elevated in serum and cerebrospinal fluid in ischemic stroke patients compared to the controls [32, 33]. Moreover, CXCL1 levels in cerebrospinal fluid were positively correlated with the volume of hypodense areas on brain computed tomography in stroke patients [34]. In the present study, we found that IPC protection was associated with the downregulation of *CXCL1* expression in the brain and blood 24 h after focal stroke in mice. The results indicate that CXCL1 may be a co-biomarker in the brain and blood after acute ischemic stroke.

We also found that IPC protection was accompanied by the downregulation of *TIMP1* expression in both the brain and blood in tMCAO mice. TIMP1 protein functions as an endogenous inhibitor of matrix metalloproteinases, a group of peptidases that are involved in the degradation of the extracellular matrix. The Searchlight Protein Array showed that TIMP1 was upregulated in infarct tissue compared with healthy control areas in ischemic stroke patients [35]. Moreover, *TIMP1* mRNA-expressing monocytes were elevated in patients compared with healthy controls, suggesting an increase in TIMP1 levels in the circulatory system [35, 36]. However, in contrast to the pro-inflammatory properties of three biomarkers that were identified in the present study (*IL6*, *CCL2*, and *CXCL1*), *TIMP1* is proposed to exert neuroprotective effects against ischemic insult. Treatment with recombinant TIMP1 significantly decreased cultured neuronal death that was induced by hypoxia and reoxygenation. TIMP1 overexpression ameliorated blood-brain barrier leakage and infarct volume in a model of transient 2-h focal cerebral ischemia in mice [37]. Studies have shown that *TIMP1* gene expression is highly inducible in response to cytokines and hormones [38]. In the present study, the IPC-induced downregulation of proinflammatory gene expression might contribute to the decrease in *TIMP1* expression. Therefore, the exact function of *TIMP1* in IPC protection needs further exploration.

Conclusion

In summary, we identified the top common target genes, including *IL6*, *CCL2*, *CXCL1*, and *TIMP1*, in both the brain and blood that are involved in IPC protection against ischemic brain injury in tMCAO mice through bioinformat-

ic analyses of data from GSE32529 datasets. Our findings provide novel insights into the key biomarkers that may be useful for the diagnosis and prognosis of acute ischemic stroke as well as possible therapeutic targets.

Acknowledgements

This work was supported by Sichuan Science and Technology Programs (2018SZ0015) and 111 Project of the National Ministry of Education (B18035, China).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jun-Rong Du, Department of Pharmacology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China. Tel: +86-28-85503938; Fax: +86-28-855-01371; E-mail: dujr_1@163.com

References

[1] England TJ, Hedstrom A, O'Sullivan S, Donnelly R, Barrett DA, Sarmad S, Sprigg N and Bath PM. RECAST (Remote Ischemic Conditioning After Stroke Trial): a pilot randomized placebo controlled phase II trial in acute ischemic stroke. Stroke 2017; 48: 1412-1415.

[2] Li S, Hafeez A, Noorulla F, Geng X, Shao G, Ren C, Lu G, Zhao H, Ding Y and Ji X. Preconditioning in neuroprotection: from hypoxia to ischemia. Prog Neurobiol 2017; 157: 79-91.

[3] Hao Y, Xin M, Feng L, Wang X, Wang X, Ma D and Feng J. Review cerebral ischemic tolerance and preconditioning: methods, mechanisms, clinical applications, and challenges. Front Neurol 2020; 11: 812.

[4] Yan Y, Tong F and Chen J. Endogenous BMP-4/ROS/COX-2 mediated IPC and resveratrol alleviated brain damage. Curr Pharm Des 2019; 25: 1030-1039.

[5] McDonough A and Weinstein JR. Correction to: neuroimmune response in ischemic preconditioning. Neurotherapeutics 2018; 15: 511-524.

[6] Stokfisz K, Ledakowicz-Polak A, Zagorski M and Zielinska M. Ischaemic preconditioning - current knowledge and potential future applications after 30 years of experience. Adv Med Sci 2017; 62: 307-316.

[7] Iadecola C and Anrather J. The immunology of stroke: from mechanisms to translation. Nat Med 2011; 17: 796-808.

[8] Patel RAG and McMullen PW. Neuroprotection in the treatment of acute ischemic stroke. Prog Cardiovasc Dis 2017; 59: 542-548.

[9] Stevens SL, Leung PY, Vartanian KB, Gopalan B, Yang T, Simon RP and Stenzel-Poore MP. Multiple preconditioning paradigms converge on interferon regulatory factor-dependent signaling to promote tolerance to ischemic brain injury. J Neurosci 2011; 31: 8456-8463.

[10] Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W and Smyth GK. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res 2015; 43: e47.

[11] Zou R, Zhang D, Lv L, Shi W, Song Z, Yi B, Lai B, Chen Q, Yang S and Hua P. Bioinformatic gene analysis for potential biomarkers and therapeutic targets of atrial fibrillation-related stroke. J Transl Med 2019; 17: 45.

[12] Tripto NI, Kabir M, Bayzid MS and Rahman A. Evaluation of classification and forecasting methods on time series gene expression data. PLoS One 2020; 15: e0241686.

[13] Huang da W, Sherman BT and Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 2009; 4: 44-57.

[14] Kanehisa M, Furumichi M, Tanabe M, Sato Y and Morishima K. KEGG: new perspectives on genomes, pathways, diseases and drugs. Nucleic Acids Res 2017; 45: D353-D361.

[15] Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, Simonovic M, Roth A, Santos A, Tsafou KP, Kuhn M, Bork P, Jensen LJ and von Mering C. STRING v10: protein-protein interaction networks, integrated over the tree of life. Nucleic Acids Res 2015; 43: D447-452.

[16] Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B and Ideker T. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 2003; 13: 2498-2504.

[17] Yang B, Li M, Tang W, Liu W, Zhang S, Chen L and Xia J. Dynamic network biomarker indicates pulmonary metastasis at the tipping point of hepatocellular carcinoma. Nat Commun 2018; 9: 678.

[18] Davis AP, Grondin CJ, Johnson RJ, Sciaky D, King BL, McMorran R, Wiegers J, Wiegers TC and Mattingly CJ. The comparative toxicogenomics database: update 2017. Nucleic Acids Res 2017; 45: D972-D978.

[19] Kim SJ, Moon GJ and Bang OY. Biomarkers for stroke. J Stroke 2013; 15: 27-37.

[20] Kamtchum-Tatuene J and Jickling GC. Blood biomarkers for stroke diagnosis and management. Neuromolecular Med 2019; 21: 344-368.

[21] Chen L, Huang K, Wang R, Jiang Q, Wu Z, Liang W, Guo R and Wang L. Neuroprotective effects of cerebral ischemic preconditioning in a rat

middle cerebral artery occlusion model: the role of the notch signaling pathway. Biomed Res Int 2018; 2018: 8168720.
[22] Grønhøj MH, Clausen BH, Fenger CD, Lambertsen KL and Finsen B. Beneficial potential of intravenously administered IL-6 in improving outcome after murine experimental stroke. Brain Behav Immun 2017; 65: 296-311.
[23] Kuang X, Wang LF, Yu L, Li YJ, Wang YN, He Q, Chen C and Du JR. Ligustilide ameliorates neuroinflammation and brain injury in focal cerebral ischemia/reperfusion rats: involvement of inhibition of TLR4/peroxiredoxin 6 signaling. Free Radic Biol Med 2014; 71: 165-175.
[24] Zou X, Yang XJ, Gan YM, Liu DL, Chen C, Duan W and Du JR. Neuroprotective effect of phthalide derivative CD21 against ischemic brain injury: involvement of msr1 mediated DAMP peroxiredoxin1 clearance and TLR4 signaling inhibition. J Neuroimmune Pharmacol 2020; [Epub ahead of print].
[25] Beridze M, Sanikidze T, Shakarishvili R, Intskirveli N and Bornstein NM. Selected acute phase CSF factors in ischemic stroke: findings and prognostic value. BMC Neurol 2011; 11: 41.
[26] Cédile O, Wlodarczyk A and Owens T. CCL2 recruits T cells into the brain in a CCR2-independent manner. APMIS 2017; 125: 945-956.
[27] Brait VH, Rivera J, Broughton BR, Lee S, Drummond GR and Sobey CG. Chemokine-related gene expression in the brain following ischemic stroke: no role for CXCR2 in outcome. Brain Res 2011; 1372: 169-179.
[28] He X, Li DR, Cui C and Wen LJ. Clinical significance of serum MCP-1 and VE-cadherin levels in patients with acute cerebral infarction. Eur Rev Med Pharmacol Sci 2017; 21: 804-808.
[29] Wacker BK, Perfater JL and Gidday JM. Hypoxic preconditioning induces stroke tolerance in mice via a cascading HIF, sphingosine kinase, and CCL2 signaling pathway. J Neurochem 2012; 123: 954-962.
[30] Stowe AM, Wacker BK, Cravens PD, Perfater JL, Li MK, Hu R, Freie AB, Stüve O and Gidday JM. CCL2 upregulation triggers hypoxic preconditioning-induced protection from stroke. J Neuroinflammation 2012; 9: 33.
[31] Li Y, Imaizumi T, Matsumiya T, Seya K, Kawaguchi S, Ding J and Ohkuma H. Polyinosinic-polycytidylic acid induces CXCL1 expression in cultured hCMEC/D3 human cerebral microvascular endothelial cells. Neuroimmunomodulation 2020; 27: 38-47.
[32] Park HJ, Yun DH, Kim SK, Chung JH, Lee JS, Park HK, Chon J, Kim DH, Yoo SD and Kim HS. Association of CXCL1 promoter polymorphism with ischaemic stroke in Korean population. Int J Immunogenet 2013; 40: 306-310.
[33] Ormstad H, Aass HC, Lund-Sørensen N, Amthor KF and Sandvik L. Serum levels of cytokines and C-reactive protein in acute ischemic stroke patients, and their relationship to stroke lateralization, type, and infarct volume. J Neurol 2011; 258: 677-685.
[34] Losy J, Zaremba J and Skrobański P. CXCL1 (GRO-alpha) chemokine in acute ischaemic stroke patients. Folia Neuropathol 2005; 43: 97-102.
[35] Lorente L, Martin MM, Ramos L, Caceres JJ, Sole-Violan J, Argueso M, Jimenez A, Borreguero-Leon JM, Orbe J, Rodriguez JA and Paramo JA. Serum tissue inhibitor of matrix metalloproteinase-1 levels are associated with mortality in patients with malignant middle cerebral artery infarction. BMC Neurol 2015; 15: 111.
[36] Lorente L, Martin MM, Ramos L, Argueso M, Caceres JJ, Sole-Violan J, Jimenez A, Borreguero-Leon JM, Gonzalez-Rivero AF, Orbe J, Rodriguez JA and Paramo JA. High serum levels of tissue inhibitor of matrix metalloproteinase-1 during the first week of a malignant middle cerebral artery infarction in non-surviving patients. BMC Neurol 2019; 19: 167.
[37] Tejima E, Guo S, Murata Y, Arai K, Lok J, van Leyen K, Rosell A, Wang X and Lo EH. Neuroprotective effects of overexpressing tissue inhibitor of metalloproteinase TIMP-1. J Neurotrauma 2009; 26: 1935-1941.
[38] Murphy G. Tissue inhibitors of metalloproteinases. Genome Biol 2011; 12: 233.

Table S1. The full names of key DEGs in brain Profiles 14 and 10 in **Figure 3A**

Selected	symbol	SPOT	Profile	Sham	Model	IPC
	1500004A13RIK	ID_1	6	0.00	-0.64	0.53
	3930401B19RIK	ID_6	10	0.00	1.27	-0.38
	A2M	ID_9	11	0.00	2.09	1.58
	ABCA8A	ID_11	8	0.00	0.12	1.41
	ACOD1	ID_18	14	0.00	1.63	0.45
	ADAM8	ID_23	10	0.00	1.91	0.49
	ADAMTS1	ID_24	10	0.00	2.52	-0.51
	ADAMTS4	ID_25	10	0.00	1.13	0.15
	ADAMTSL4	ID_27	14	0.00	1.01	0.35
	ADGRE1	ID_30	13	0.00	0.56	1.52
	ADGRG3	ID_31	10	0.00	1.41	0.20
	AIF1	ID_36	8	0.00	0.14	1.16
	AJUBA	ID_39	6	0.00	-0.54	0.67
	AKAP12	ID_40	10	0.00	1.01	-0.16
	AKR1B8	ID_42	11	0.00	1.11	0.85
	AKR1C14	ID_43	6	0.00	-0.56	0.78
	ANGPT2	ID_50	10	0.00	1.92	-0.24
	ANGPTL4	ID_51	9	0.00	2.22	-1.04
	ARC	ID_60	11	0.00	1.23	1.32
	ARG1	ID_61	10	0.00	1.63	0.36
	ARID5A	ID_65	10	0.00	1.00	-0.03
	ARPC1B	ID_67	14	0.00	1.01	0.36
	ATF3	ID_73	14	0.00	3.81	1.07
	ATP10A	ID_75	5	0.00	-1.14	-0.19
	AVPR1A	ID_79	10	0.00	1.19	0.22
	BAG3	ID_83	10	0.00	1.09	0.16
	BCL3	ID_86	10	0.00	1.92	0.21
	BCL6B	ID_87	9	0.00	1.11	-0.51
	BDNF	ID_89	13	0.00	0.26	1.03
	BIRC3	ID_93	9	0.00	0.75	-0.39
	BLNK	ID_94	10	0.00	1.05	0.19
	BST2	ID_97	12	0.00	0.46	1.09
	BTC	ID_98	10	0.00	1.14	0.01
	C3AR1	ID_102	14	0.00	1.31	0.85
	C77405	ID_104	10	0.00	0.91	-0.21
	C77815	ID_105	10	0.00	0.76	-0.24
	C79246	ID_107	10	0.00	1.70	-0.10
	CASP4	ID_120	14	0.00	1.10	0.54
	CCL11	ID_128	10	0.00	2.16	0.00
	CCL12	ID_129	11	0.00	2.04	2.29
	CCL2	ID_131	10	0.00	2.38	-0.09
	CCL3	ID_132	14	0.00	3.67	1.19
	CCL4	ID_133	14	0.00	2.89	0.88
	CCL5	ID_134	14	0.00	1.25	0.49
	CCL6	ID_135	10	0.00	1.37	0.12
	CCL7	ID_136	10	0.00	2.10	-0.03
	CCL9	ID_138	10	0.00	1.41	-0.02

CCN1	ID_139	10	0.00	2.81	0.56
CCR1	ID_142	10	0.00	1.71	-0.08
CD14	ID_144	10	0.00	2.47	-0.29
CD244A	ID_146	10	0.00	1.85	0.27
CD274	ID_148	14	0.00	1.41	0.86
CD44	ID_151	14	0.00	1.74	0.96
CD48	ID_152	8	0.00	0.16	1.17
CD52	ID_153	12	0.00	0.84	1.89
CD53	ID_154	14	0.00	1.00	0.29
CD72	ID_157	11	0.00	1.16	0.89
CD9	ID_161	14	0.00	1.17	0.70
CDKN1A	ID_165	10	0.00	1.06	-0.24
CEBPD	ID_171	10	0.00	1.51	0.03
CH25H	ID_175	10	0.00	1.37	-0.07
CHAC1	ID_176	9	0.00	0.71	-0.32
CHIL3	ID_179	10	0.00	1.75	0.46
CLCF1	ID_184	14	0.00	1.40	0.68
CLEC4D	ID_190	10	0.00	2.44	-0.78
CLEC7A	ID_192	15	0.00	0.90	1.15
CLIC4	ID_194	14	0.00	1.05	0.31
COL3A1	ID_204	11	0.00	1.28	0.99
CRYBB1	ID_216	6	0.00	-0.59	0.58
CSF2RB2	ID_219	10	0.00	1.12	0.17
CSF3	ID_220	10	0.00	3.54	-0.33
CST7	ID_221	12	0.00	0.88	1.71
CTLA2A	ID_223	9	0.00	1.32	-0.82
CTLA2B	ID_224	10	0.00	1.84	-0.21
CUTAL	ID_230	6	0.00	-0.74	0.29
CXCL1	ID_232	10	0.00	4.03	-0.08
CXCL10	ID_233	11	0.00	2.69	2.42
CXCL2	ID_236	10	0.00	4.98	-0.34
CYLC1	ID_240	10	0.00	0.75	-0.27
CYP11A1	ID_241	7	0.00	-0.16	-1.01
CYP39A1	ID_244	5	0.00	-1.54	-0.28
D7BWG0826E	ID_247	14	0.00	1.10	0.43
DAB2	ID_248	10	0.00	1.15	0.25
DACH2	ID_249	11	0.00	1.31	1.23
DCN	ID_250	10	0.00	1.61	0.35
DDIT4L	ID_252	5	0.00	-1.29	0.17
DIO2	ID_255	9	0.00	0.81	-0.35
DMKN	ID_259	14	0.00	2.14	1.15
EDN1	ID_275	10	0.00	1.48	0.13
EGR2	ID_278	11	0.00	2.07	1.66
EMP1	ID_281	14	0.00	2.76	0.83
ESM1	ID_295	10	0.00	1.80	0.15
FCGR1	ID_310	15	0.00	0.68	1.00
FCGR2B	ID_311	10	0.00	1.34	0.30
FCGR4	ID_313	14	0.00	1.10	0.56
FCRLS	ID_315	11	0.00	1.05	1.27

FGA	ID_317	10	0.00	3.73	0.19
FLNC	ID_322	14	0.00	1.25	0.51
FMOD	ID_327	5	0.00	-1.20	0.29
FOS	ID_329	14	0.00	2.13	1.22
FOSL1	ID_330	14	0.00	2.27	0.96
FPR2	ID_331	9	0.00	0.72	-0.35
GABRR2	ID_343	2	0.00	-0.35	-1.21
GADD45A	ID_344	10	0.00	1.07	0.23
GADD45B	ID_345	14	0.00	1.59	0.74
GADD45G	ID_346	10	0.00	1.37	0.17
GBP2	ID_347	14	0.00	1.93	1.30
GBP3	ID_348	11	0.00	1.90	1.82
GBP6	ID_349	14	0.00	1.45	0.81
GEM	ID_353	10	0.00	1.73	0.36
GFAP	ID_355	11	0.00	1.43	1.42
GH	ID_358	1	0.00	-1.51	-0.60
GIMAP6	ID_359	9	0.00	0.72	-0.64
GJB2	ID_361	14	0.00	1.25	0.52
GLIPR2	ID_363	14	0.00	1.54	0.65
GLYCAM1	ID_364	11	0.00	1.62	1.25
GM20186	ID_367	10	0.00	1.11	-0.16
GPR34	ID_376	6	0.00	-1.01	1.40
GPR35	ID_377	14	0.00	1.33	0.39
GPR84	ID_379	14	0.00	1.45	1.04
HBEGF	ID_393	14	0.00	1.32	0.49
HMGB2	ID_404	10	0.00	1.13	0.11
HMOX1	ID_406	14	0.00	3.35	1.79
HOXC8	ID_408	10	0.00	1.34	0.14
HSPA1A	ID_412	10	0.00	3.62	0.51
HSPA1B	ID_413	10	0.00	3.17	0.24
HSPB1	ID_415	14	0.00	1.97	1.03
ICAM1	ID_422	10	0.00	1.51	-0.18
IDO1	ID_424	1	0.00	-1.07	-0.54
IER3	ID_426	14	0.00	1.20	0.35
IFI204	ID_427	15	0.00	1.10	1.67
IFI27L2A	ID_429	12	0.00	0.57	1.23
IFI44	ID_431	13	0.00	0.41	1.13
IFIT1	ID_434	15	0.00	1.39	2.21
IFIT3	ID_436	15	0.00	0.95	1.28
IFITM3	ID_439	11	0.00	1.01	0.79
IGF2BP2	ID_443	10	0.00	1.30	0.26
IGFBP1	ID_444	10	0.00	1.32	0.11
IGFBP3	ID_445	10	0.00	1.86	-0.37
IIGP1	ID_449	14	0.00	1.65	1.16
IL11	ID_450	10	0.00	3.16	0.24
IL1R1	ID_453	10	0.00	1.06	0.01
IL1R2	ID_454	10	0.00	1.26	0.06
IL2RG	ID_457	11	0.00	1.06	0.81
IL33	ID_458	14	0.00	2.36	1.44

IL6	ID_460	10	0.00	4.92	0.26
IRF7	ID_466	13	0.00	0.26	1.04
IRGM1	ID_469	14	0.00	1.61	0.65
IRX3	ID_471	10	0.00	1.78	-0.21
ITGB2	ID_477	14	0.00	1.08	0.65
ITM2A	ID_478	6	0.00	-1.29	0.51
JUN	ID_480	9	0.00	0.72	-0.33
KCNE4	ID_486	10	0.00	1.72	-0.05
KLK6	ID_497	11	0.00	1.79	1.35
LAIR1	ID_503	13	0.00	0.28	1.12
LCN2	ID_508	9	0.00	1.57	-1.15
LGALS3	ID_512	11	0.00	3.31	2.58
LIF	ID_516	10	0.00	1.62	0.19
LOX	ID_521	10	0.00	1.13	-0.02
LOXL1	ID_522	14	0.00	1.40	0.54
LY86	ID_532	13	0.00	0.37	1.64
LYVE1	ID_535	14	0.00	1.72	0.56
MAFF	ID_538	10	0.00	1.22	-0.22
MAP3K6	ID_540	9	0.00	0.96	-0.41
MARVELD2	ID_543	9	0.00	0.64	-0.40
MMP12	ID_557	14	0.00	3.71	1.14
MMP3	ID_559	10	0.00	4.60	0.10
MPEG1	ID_562	15	0.00	1.13	1.49
MS4A6C	ID_568	10	0.00	1.03	0.12
MS4A6D	ID_569	14	0.00	1.25	0.36
MSN	ID_571	14	0.00	1.30	0.67
MSR1	ID_572	10	0.00	1.45	0.34
MVP	ID_579	10	0.00	1.00	-0.18
MX1	ID_580	13	0.00	0.50	1.20
MYC	ID_581	10	0.00	1.39	0.29
MYD88	ID_582	10	0.00	1.05	0.25
MYL9	ID_585	5	0.00	-0.92	0.12
NAIP5	ID_592	13	0.00	0.29	1.11
NCF4	ID_597	14	0.00	1.12	0.38
NEAT1	ID_599	15	0.00	0.83	1.11
NFKBIZ	ID_610	10	0.00	1.28	0.25
NID1	ID_612	10	0.00	1.05	0.07
NR4A2	ID_626	1	0.00	-1.43	-0.47
OASL2	ID_630	12	0.00	0.88	1.76
ODC1	ID_631	10	0.00	1.11	0.24
OGN	ID_632	5	0.00	-1.34	0.26
OLFML3	ID_634	8	0.00	-0.34	1.09
OSMR	ID_641	14	0.00	1.52	0.96
P2RY12	ID_644	6	0.00	-0.54	0.88
PARP3	ID_652	14	0.00	1.07	0.55
PDE6B	ID_660	10	0.00	1.32	0.21
PDPN	ID_665	14	0.00	1.56	1.09
PF4	ID_670	14	0.00	2.56	1.39
PGLYRP1	ID_671	9	0.00	0.56	-0.60

PLA2G4A	ID_679	14	0.00	1.25	0.71
PLAT	ID_682	10	0.00	1.10	-0.40
PLAUR	ID_683	10	0.00	1.84	0.03
PLD4	ID_685	6	0.00	-0.62	0.72
PLEK	ID_686	14	0.00	1.08	0.48
PLIN2	ID_690	14	0.00	2.17	0.94
PLIN4	ID_691	9	0.00	0.38	-0.82
PLSCR1	ID_694	14	0.00	1.15	0.36
PLSCR2	ID_695	12	0.00	0.59	1.15
PLTP	ID_696	6	0.00	-0.67	0.56
PMAIP1	ID_697	10	0.00	1.10	-0.20
PRELP	ID_706	6	0.00	-0.76	0.36
PRG4	ID_707	10	0.00	1.77	0.03
PRL	ID_708	1	0.00	-1.01	-0.55
PROCR	ID_709	14	0.00	2.20	0.67
PROS1	ID_710	14	0.00	1.07	0.49
PTGR1	ID_718	12	0.00	0.62	1.10
PTH2R	ID_719	5	0.00	-1.01	0.06
PTX3	ID_724	14	0.00	3.99	1.62
RAB20	ID_727	14	0.00	1.10	0.37
RGS1	ID_743	10	0.00	2.58	-0.13
RHOC	ID_749	10	0.00	1.00	-0.05
RHOJ	ID_750	10	0.00	2.00	0.36
RPE65	ID_756	14	0.00	1.39	0.97
RRBP1	ID_761	14	0.00	1.22	0.59
RSAD2	ID_762	11	0.00	1.24	1.43
RTP4	ID_765	15	0.00	0.64	1.02
S100A4	ID_768	11	0.00	1.31	1.43
S100A8	ID_770	14	0.00	2.72	1.08
S100A9	ID_771	14	0.00	2.60	1.04
SAA3	ID_774	10	0.00	2.63	-0.32
SCARA5	ID_776	10	0.00	1.18	-0.02
SCN10A	ID_777	4	0.00	-1.11	-1.02
SELP	ID_781	10	0.00	2.38	-0.22
SELPLG	ID_782	6	0.00	-0.66	0.36
SERPINA3N	ID_784	14	0.00	2.25	1.27
SERPINB1A	ID_785	8	0.00	0.17	1.01
SERPINB6B	ID_788	6	0.00	-1.35	0.66
SERPINH1	ID_791	14	0.00	1.21	0.86
SLAMF9	ID_798	12	0.00	0.56	1.11
SLC10A6	ID_799	10	0.00	2.60	0.09
SLC14A1	ID_802	11	0.00	1.34	1.24
SLC15A1	ID_803	10	0.00	1.08	-0.21
SLC15A3	ID_804	14	0.00	1.24	0.58
SLC22A6	ID_814	5	0.00	-0.88	0.27
SLC22A8	ID_815	5	0.00	-1.39	-0.02
SLC38A5	ID_820	6	0.00	-1.05	1.26
SLC43A3	ID_823	14	0.00	1.42	0.42
SLC44A3	ID_824	14	0.00	1.49	0.74

SLC7A11	ID_827	14	0.00	1.52	0.98
SLC7A12	ID_828	9	0.00	0.64	-0.37
SLCO1A4	ID_830	5	0.00	-1.36	-0.18
SLCO1C1	ID_831	5	0.00	-1.19	-0.06
SLFN2	ID_833	14	0.00	1.13	0.50
SLFN4	ID_834	14	0.00	2.35	1.38
SMPDL3B	ID_838	10	0.00	1.01	0.23
SOCS3	ID_842	10	0.00	2.57	0.14
SOX7	ID_848	14	0.00	1.14	0.50
SPIDR	ID_854	10	0.00	1.25	0.27
SPP1	ID_855	14	0.00	2.08	0.66
SRGN	ID_856	10	0.00	1.14	-0.09
STEAP4	ID_865	10	0.00	1.00	-0.10
SYNPO	ID_873	10	0.00	1.09	0.27
TBX21	ID_877	10	0.00	1.00	-0.29
TEAD1	ID_878	10	0.00	1.16	0.30
TENT5C	ID_879	13	0.00	0.34	1.02
TFPI2	ID_884	14	0.00	1.38	0.58
TGFBI	ID_885	14	0.00	1.66	0.90
TGIF1	ID_886	14	0.00	1.51	0.42
TGM1	ID_887	10	0.00	2.21	0.48
THBD	ID_888	10	0.00	1.11	0.20
TIMP1	ID_891	10	0.00	2.94	0.76
TLR1	ID_896	14	0.00	1.09	0.73
TLR2	ID_897	14	0.00	1.26	0.89
TM4SF1	ID_899	14	0.00	1.30	0.75
TMBIM1	ID_902	14	0.00	1.10	0.50
TNC	ID_909	14	0.00	3.01	1.06
TNFAIP2	ID_910	10	0.00	1.73	0.02
TNFRSF12A	ID_911	14	0.00	1.55	0.59
TNFRSF1A	ID_912	14	0.00	1.35	0.55
TNFSF9	ID_914	10	0.00	1.87	0.09
TRIM30A	ID_928	15	0.00	0.91	1.23
TSLP	ID_933	14	0.00	1.41	0.62
TUBB6	ID_938	14	0.00	2.80	1.03
UCP2	ID_944	9	0.00	0.79	-0.40
UPP1	ID_950	14	0.00	1.20	0.52
USP18	ID_954	12	0.00	1.49	2.66
VIM	ID_957	11	0.00	1.14	1.25
ZFP36	ID_976	10	0.00	2.08	-0.42

Table S2. The full names of key DEGs in blood Profiles 9 and 10 in **Figure 3B**

Selected	Symbol	SPOT	Profile	Sham	Model	IPC
	1300017J02RIK	ID_1	0	0.00	-1.13	-1.45
	1700097N02RIK	ID_5	6	0.00	-0.44	0.57
	1700102P08RIK	ID_6	12	0.00	0.49	1.09
	1810055G02RIK	ID_9	14	0.00	1.08	0.42
	2810004N23RIK	ID_17	12	0.00	0.61	1.15
	4932441J04RIK	ID_24	4	0.00	-1.05	-1.06

AADAC	ID_28	8	0.00	0.30	3.21
ABCD2	ID_35	7	0.00	0.05	-1.01
ACKR3	ID_46	10	0.00	2.16	0.48
ACPP	ID_51	9	0.00	1.45	-0.89
ADAM28	ID_56	10	0.00	1.07	-0.06
ADAMDEC1	ID_58	9	0.00	0.79	-0.67
ADAMTS4	ID_59	10	0.00	2.19	-0.58
ADAP2	ID_61	9	0.00	1.10	-0.70
ADGRF1	ID_67	7	0.00	0.23	-1.63
AGRN	ID_82	7	0.00	0.19	-0.84
AI661453	ID_86	7	0.00	0.43	-1.55
AIF1	ID_89	7	0.00	0.34	-1.59
AIF1L	ID_90	7	0.00	-0.19	-2.05
AJUBA	ID_91	10	0.00	1.05	-0.09
AKR1B7	ID_98	9	0.00	1.44	-1.06
ALDH1A7	ID_104	1	0.00	-1.36	-0.74
ALDH3A1	ID_106	10	0.00	1.06	-0.03
ALPL	ID_110	9	0.00	1.45	-1.53
ANLN	ID_121	7	0.00	0.18	-0.86
ANXA3	ID_122	9	0.00	1.11	-1.33
ANXA9	ID_125	9	0.00	0.87	-0.91
APOC2	ID_138	9	0.00	0.71	-1.02
APOD	ID_139	10	0.00	1.23	0.20
APOH	ID_141	1	0.00	-1.17	-0.75
AQP1	ID_144	3	0.00	-0.54	-1.10
AQP5	ID_147	7	0.00	0.84	-2.36
ARF2	ID_150	9	0.00	0.91	-0.47
ARG1	ID_153	9	0.00	2.48	-1.55
ARHGAP39	ID_155	6	0.00	-0.52	0.60
ARHGEF28	ID_159	0	0.00	-0.74	-1.03
ARL4C	ID_163	6	0.00	-0.55	0.57
ARRDC4	ID_170	9	0.00	0.35	-0.69
ASB11	ID_175	2	0.00	-0.32	-1.70
ASPA	ID_179	9	0.00	1.57	-0.91
ATG9B	ID_183	7	0.00	0.22	-0.93
AZGP1	ID_198	8	0.00	-0.29	1.73
B4GALT6	ID_205	10	0.00	1.00	-0.22
BACE2	ID_206	7	0.00	0.20	-1.21
BCAT1	ID_217	10	0.00	1.17	0.26
BCL2L15	ID_222	9	0.00	1.09	-2.49
BHLHE40	ID_227	10	0.00	0.94	-0.14
BSPRY	ID_239	9	0.00	1.18	-0.58
C1QA	ID_246	10	0.00	1.54	-0.39
C1QB	ID_247	9	0.00	1.42	-1.69
C1QC	ID_249	9	0.00	1.47	-1.64
C78704	ID_257	9	0.00	0.45	-0.69
CABLES1	ID_261	9	0.00	0.90	-0.71
CALML3	ID_267	9	0.00	0.97	-1.69
CAMKK1	ID_269	9	0.00	0.78	-0.37

CAR6	ID_274	10	0.00	1.48	-0.10
CARD10	ID_275	6	0.00	-0.36	0.70
CASP14	ID_278	4	0.00	-1.56	-1.41
CBLC	ID_281	9	0.00	0.70	-0.52
CBLN3	ID_283	0	0.00	-0.64	-1.09
CBR4	ID_286	9	0.00	0.87	-0.41
CCL12	ID_298	10	0.00	1.02	-0.07
CCL2	ID_299	10	0.00	1.27	-0.25
CCL20	ID_300	10	0.00	1.45	0.12
CCL5	ID_304	6	0.00	-0.31	0.74
CCL9	ID_305	9	0.00	0.81	-0.93
CCN1	ID_306	7	0.00	1.01	-2.79
CCN2	ID_307	9	0.00	0.93	-1.19
CCR2	ID_313	7	0.00	0.18	-1.07
CCR5	ID_315	9	0.00	0.85	-1.01
CD163	ID_319	9	0.00	2.48	-1.53
CD38	ID_332	9	0.00	0.78	-0.32
CD40	ID_333	6	0.00	-0.49	0.58
CD59A	ID_336	6	0.00	-0.46	0.67
CDCA7L	ID_346	6	0.00	-0.58	0.74
CDCP1	ID_347	9	0.00	1.11	-0.86
CDH1	ID_348	11	0.00	1.70	1.53
CDK6	ID_354	7	0.00	-0.13	-1.24
CDKN1A	ID_355	10	0.00	1.01	-0.05
CDO1	ID_357	9	0.00	0.69	-1.59
CEACAM1	ID_360	9	0.00	0.75	-0.50
CENPH	ID_366	0	0.00	-0.73	-1.05
CENPM	ID_367	10	0.00	1.21	-0.24
CERS4	ID_375	8	0.00	0.02	1.77
CES1D	ID_376	12	0.00	0.76	1.71
CFP	ID_379	9	0.00	0.53	-0.52
CHAC1	ID_380	7	0.00	-0.25	-1.53
CHEK2	ID_387	1	0.00	-1.03	-0.38
CIITA	ID_395	6	0.00	-0.43	0.65
CLCA3A1	ID_403	6	0.00	-0.51	0.84
CLCA3B	ID_404	7	0.00	-0.23	-1.94
CLDN1	ID_405	9	0.00	0.68	-0.34
CLDN23	ID_408	7	0.00	-0.11	-1.76
CLDN4	ID_410	10	0.00	1.12	-0.20
CLEC10A	ID_412	7	0.00	0.54	-1.69
CLEC4N	ID_416	9	0.00	0.76	-0.45
CLEC5A	ID_417	9	0.00	0.61	-1.02
CLEC7A	ID_418	6	0.00	-1.39	0.69
CLTRN	ID_425	4	0.00	-1.29	-1.52
CMA1	ID_428	5	0.00	-0.89	0.17
COL18A1	ID_439	8	0.00	-0.25	1.16
COL1A1	ID_440	9	0.00	0.55	-0.69
COPRS	ID_445	10	0.00	1.09	0.20
CPA2	ID_449	1	0.00	-1.09	-0.67

CR2	ID_451	6	0.00	-0.98	1.05
CRCT1	ID_454	7	0.00	-0.27	-1.90
CREM	ID_458	10	0.00	1.03	0.27
CRIP3	ID_459	5	0.00	-1.11	0.27
CRYAB	ID_463	7	0.00	0.34	-1.07
CRYBG1	ID_464	14	0.00	1.04	0.45
CSF2	ID_469	10	0.00	3.15	-0.14
CST6	ID_473	9	0.00	0.73	-1.63
CSTB	ID_475	9	0.00	0.75	-0.61
CTDSPL	ID_476	10	0.00	1.00	-0.26
CTNND1	ID_479	14	0.00	1.12	0.37
CTNND2	ID_480	9	0.00	0.54	-0.69
CTSF	ID_482	2	0.00	-0.38	-1.48
CTSL	ID_484	10	0.00	1.12	-0.38
CTTNBP2NL	ID_486	9	0.00	0.50	-0.59
CX3CR1	ID_492	1	0.00	-1.17	-0.64
CXCL1	ID_493	10	0.00	2.88	-0.11
CXCL16	ID_494	9	0.00	1.34	-1.04
CXCR5	ID_498	6	0.00	-0.40	0.80
CYP11A1	ID_502	11	0.00	1.01	0.75
CYP2S1	ID_506	8	0.00	-0.44	1.59
CYP3A13	ID_507	9	0.00	0.94	-0.53
CYSLTR1	ID_511	9	0.00	0.43	-1.10
CYSRT1	ID_512	7	0.00	0.10	-1.77
DAB2	ID_519	9	0.00	0.98	-0.49
DBNDD2	ID_526	10	0.00	1.35	-0.21
DEFB1	ID_536	9	0.00	0.99	-1.82
DIO1	ID_543	4	0.00	-1.66	-1.61
DLEU2	ID_548	6	0.00	-0.87	0.43
DMKN	ID_552	9	0.00	2.56	-1.16
DMXL1	ID_554	6	0.00	-0.79	0.72
DNASE2A	ID_559	5	0.00	-1.13	-0.17
DOK2	ID_562	9	0.00	0.37	-0.70
DPPA5A	ID_569	1	0.00	-1.59	-0.56
DRC1	ID_572	8	0.00	-0.23	1.59
DTX1	ID_578	6	0.00	-0.50	0.73
DUOXA2	ID_580	10	0.00	1.36	-0.21
DUSP14	ID_581	3	0.00	-0.76	-1.33
DUSP19	ID_582	0	0.00	-0.72	-1.01
ECT2	ID_594	12	0.00	0.47	1.10
EDNRB	ID_597	10	0.00	0.94	-0.16
EEF2K	ID_598	5	0.00	-1.14	-0.28
EGR1	ID_605	7	0.00	0.56	-1.66
EHF	ID_606	10	0.00	1.38	-0.46
ELANE	ID_610	10	0.00	1.25	-0.11
ELF3	ID_612	7	0.00	0.38	-1.44
ELOVL3	ID_614	13	0.00	0.75	3.22
ENPP2	ID_624	10	0.00	1.04	-0.22
ENPP3	ID_625	9	0.00	0.40	-0.95

EOMES	ID_627	8	0.00	-0.32	1.27
EPHA2	ID_629	9	0.00	0.98	-1.41
EPHB3	ID_631	7	0.00	0.13	-0.99
EPN3	ID_634	7	0.00	0.16	-1.01
EPS8L2	ID_638	9	0.00	0.66	-1.35
EREG	ID_641	10	0.00	1.83	-0.32
ERRFI1	ID_648	9	0.00	0.47	-0.98
ESM1	ID_651	9	0.00	0.42	-0.67
ESYT3	ID_653	9	0.00	0.51	-1.09
ETL4	ID_655	9	0.00	0.51	-0.51
F10	ID_662	10	0.00	0.81	-0.29
FABP7	ID_667	7	0.00	0.61	-2.25
FAM110A	ID_671	7	0.00	0.03	-1.03
FAM83H	ID_683	9	0.00	0.68	-0.37
FASN	ID_685	8	0.00	0.20	1.40
FCER1A	ID_692	14	0.00	1.50	0.57
FCER2A	ID_693	6	0.00	-1.88	0.77
FCGR1	ID_694	7	0.00	0.36	-1.58
FCGR2B	ID_695	10	0.00	1.08	-0.24
FFAR2	ID_702	9	0.00	1.04	-0.75
FGFR2	ID_706	10	0.00	1.29	0.07
FLNB	ID_715	11	0.00	1.36	1.02
FN1	ID_719	7	0.00	0.04	-1.28
FOLR1	ID_721	7	0.00	0.15	-1.33
FOLR2	ID_722	7	0.00	0.34	-2.10
FOSB	ID_723	11	0.00	1.12	0.87
FOXA1	ID_725	9	0.00	1.31	-1.23
FOXC1	ID_726	7	0.00	0.08	-1.22
FRK	ID_729	9	0.00	1.05	-1.94
FXYD3	ID_736	10	0.00	1.16	0.13
GALNT3	ID_745	9	0.00	0.73	-0.66
GATM	ID_751	9	0.00	1.81	-0.76
GCA	ID_754	9	0.00	0.84	-0.57
GDPD1	ID_760	9	0.00	0.58	-0.43
GFAP	ID_764	9	0.00	1.26	-0.58
GINS1	ID_773	14	0.00	1.63	0.49
GJA1	ID_775	10	0.00	3.08	0.20
GJB2	ID_776	10	0.00	1.81	-0.45
GLRP1	ID_779	4	0.00	-1.21	-1.15
GM11567	ID_781	10	0.00	1.21	-0.42
GM20186	ID_784	14	0.00	1.18	0.61
GM20559	ID_785	6	0.00	-0.60	0.44
GMNN	ID_795	10	0.00	0.87	-0.16
GPC4	ID_808	8	0.00	0.01	1.08
GPR34	ID_814	6	0.00	-0.53	0.84
GPR87	ID_818	7	0.00	0.69	-2.23
GRAMD3	ID_825	10	0.00	1.04	0.25
GRHL1	ID_829	9	0.00	0.40	-0.78
GSTA4	ID_841	9	0.00	1.16	-1.20

GTF2F1	ID_846	10	0.00	1.03	0.27
H1F0	ID_858	7	0.00	0.47	-1.44
HBEGF	ID_869	9	0.00	1.21	-1.31
HEBP1	ID_873	3	0.00	-0.52	-1.10
HEMGN	ID_878	1	0.00	-1.04	-0.70
HFE	ID_880	9	0.00	0.34	-0.76
HILPDA	ID_883	10	0.00	1.36	0.30
HMOX1	ID_890	9	0.00	0.55	-0.48
HSCB	ID_904	3	0.00	-0.56	-1.03
HSPA1A	ID_909	2	0.00	-0.69	-2.07
HVCN1	ID_921	6	0.00	-0.45	0.63
ICOSL	ID_925	6	0.00	-0.47	0.60
ID2	ID_927	7	0.00	0.12	-0.92
ID4	ID_928	10	0.00	1.45	0.37
IER3	ID_930	9	0.00	1.29	-0.61
IFI202B	ID_931	9	0.00	1.03	-1.01
IFI204	ID_932	7	0.00	0.13	-1.02
IFIT1	ID_937	3	0.00	-0.55	-1.03
IGHM	ID_949	5	0.00	-1.02	0.26
IL1A	ID_966	9	0.00	1.54	-1.05
IL1F6	ID_968	9	0.00	1.69	-1.22
IL1R1	ID_970	10	0.00	1.88	-0.32
IL1RN	ID_972	9	0.00	0.63	-0.44
IL23A	ID_973	10	0.00	1.15	-0.34
IL33	ID_975	10	0.00	2.06	-0.47
IL6	ID_977	10	0.00	2.31	0.16
INHBA	ID_983	10	0.00	2.44	0.18
INMT	ID_984	5	0.00	-0.82	0.26
IRF6	ID_991	14	0.00	1.12	0.43
ITGAE	ID_994	6	0.00	-0.60	0.50
ITIH5	ID_1002	6	0.00	-0.61	0.67
KCNA1	ID_1014	10	0.00	1.13	0.08
KCNE3	ID_1017	0	0.00	-0.85	-1.17
KCNK1	ID_1019	13	0.00	0.58	2.54
KLK10	ID_1040	9	0.00	0.73	-1.13
KLK11	ID_1041	9	0.00	1.04	-1.44
KLK6	ID_1043	9	0.00	0.66	-0.60
KLRA17	ID_1044	5	0.00	-2.11	0.17
KLRB1A	ID_1048	6	0.00	-1.04	0.51
KLRG1	ID_1049	5	0.00	-1.40	0.50
KRT13	ID_1053	9	0.00	0.68	-0.98
KRT14	ID_1054	10	0.00	1.27	0.22
KRT16	ID_1056	9	0.00	1.78	-0.80
KRT19	ID_1057	9	0.00	1.38	-1.68
KRT23	ID_1058	7	0.00	-0.10	-1.59
KRT6A	ID_1061	9	0.00	1.17	-1.63
KRT6B	ID_1062	9	0.00	0.69	-1.75
KRT7	ID_1063	7	0.00	0.64	-1.87
KRT75	ID_1064	9	0.00	0.54	-0.78

KRT8	ID_1065	13	0.00	0.69	1.85
LAMP5	ID_1077	1	0.00	-1.00	-0.53
LCAT	ID_1085	9	0.00	0.66	-0.60
LCE3A	ID_1086	7	0.00	0.27	-1.43
LCE3C	ID_1087	9	0.00	0.44	-1.09
LDHC	ID_1091	10	0.00	3.32	-0.35
LGMN	ID_1099	9	0.00	0.80	-0.51
LIPG	ID_1103	9	0.00	1.06	-2.47
LMO7	ID_1107	7	0.00	0.35	-1.98
LPAR1	ID_1115	10	0.00	1.10	0.24
LPL	ID_1116	8	0.00	-0.12	2.04
LRATD1	ID_1117	7	0.00	0.58	-1.61
LRP4	ID_1120	9	0.00	0.87	-0.44
LRRN1	ID_1125	10	0.00	1.00	-0.09
LSR	ID_1128	7	0.00	0.32	-0.90
LSS	ID_1129	13	0.00	0.33	1.20
LTA	ID_1130	6	0.00	-0.71	0.91
LTBP2	ID_1133	6	0.00	-0.67	0.62
LY6F	ID_1136	6	0.00	-0.37	0.93
LYVE1	ID_1143	5	0.00	-1.01	-0.20
MAFB	ID_1144	9	0.00	0.63	-0.86
MAL	ID_1153	9	0.00	0.61	-1.56
MAL2	ID_1154	9	0.00	1.09	-2.04
MALL	ID_1156	9	0.00	1.26	-1.41
MANF	ID_1158	9	0.00	0.37	-0.74
MAPK12	ID_1166	6	0.00	-0.44	0.99
MBOAT1	ID_1173	9	0.00	0.63	-0.77
MCPT8	ID_1179	10	0.00	2.55	0.66
MCUB	ID_1180	7	0.00	0.30	-1.16
MERTK	ID_1189	7	0.00	0.30	-0.92
MLXIPL	ID_1202	10	0.00	1.10	0.10
MMP13	ID_1205	10	0.00	1.52	-0.54
MMP14	ID_1206	9	0.00	0.93	-0.95
MMP23	ID_1207	7	0.00	-0.06	-1.18
MOBP	ID_1211	10	0.00	2.68	0.32
MOG	ID_1212	10	0.00	1.71	-0.16
MOGAT1	ID_1213	12	0.00	0.97	2.22
MR1	ID_1222	7	0.00	0.22	-0.91
MRAS	ID_1223	5	0.00	-1.38	-0.31
MRC1	ID_1224	9	0.00	1.23	-1.15
MRPL45	ID_1228	14	0.00	1.09	0.36
MS4A3	ID_1236	10	0.00	2.14	-0.19
MS4A4C	ID_1237	1	0.00	-1.22	-0.68
MS4A6C	ID_1239	7	0.00	0.10	-0.93
MS4A6D	ID_1240	7	0.00	0.15	-0.87
MS4A8A	ID_1242	7	0.00	-0.06	-1.34
MSMB	ID_1246	1	0.00	-1.06	-0.49
MSR1	ID_1247	9	0.00	0.62	-1.13
MST1R	ID_1249	9	0.00	1.01	-0.93

MT1	ID_1250	10	0.00	0.87	-0.25
MT2	ID_1251	9	0.00	1.39	-1.87
MUC1	ID_1259	9	0.00	0.88	-1.02
MUC20	ID_1261	9	0.00	0.64	-1.73
MUC4	ID_1262	9	0.00	1.13	-1.28
MUCL2	ID_1263	9	0.00	2.25	-1.25
MX1	ID_1268	3	0.00	-0.90	-1.84
MYCBPAP	ID_1274	2	0.00	-0.33	-1.17
MYOZ2	ID_1283	3	0.00	-0.55	-1.13
MYT1	ID_1284	14	0.00	1.27	0.48
MYZAP	ID_1285	9	0.00	0.59	-0.72
NAIP1	ID_1291	7	0.00	0.12	-1.75
NCAM1	ID_1297	9	0.00	0.40	-0.69
NCR1	ID_1302	6	0.00	-0.73	1.32
NEFH	ID_1314	6	0.00	-0.62	0.64
NET1	ID_1318	9	0.00	0.75	-0.56
NLRP3	ID_1331	5	0.00	-0.93	0.33
NLRP6	ID_1332	1	0.00	-1.28	-0.45
NPL	ID_1342	9	0.00	1.24	-0.55
NR4A1	ID_1347	11	0.00	0.91	1.09
NRARP	ID_1348	15	0.00	0.74	1.15
NRBP2	ID_1349	10	0.00	1.57	0.42
NRSN1	ID_1352	10	0.00	1.42	-0.02
NT5E	ID_1355	9	0.00	0.82	-0.99
NUPR1	ID_1367	10	0.00	1.25	0.30
OASL2	ID_1373	5	0.00	-1.10	0.24
OBP1A	ID_1375	9	0.00	1.84	-1.35
OCLN	ID_1376	7	0.00	0.08	-1.37
OCSTAMP	ID_1377	9	0.00	1.10	-0.46
OLR1	ID_1384	4	0.00	-1.02	-1.01
OSMR	ID_1393	9	0.00	1.15	-0.43
P2RY14	ID_1405	10	0.00	2.26	0.33
P2RY2	ID_1406	9	0.00	0.58	-0.99
PADI1	ID_1411	2	0.00	-0.50	-1.25
PANK1	ID_1415	13	0.00	0.67	2.06
PARD6B	ID_1419	7	0.00	0.14	-1.51
PATJ	ID_1427	14	0.00	1.16	0.74
PAWR	ID_1428	9	0.00	1.19	-0.51
PBP2	ID_1430	9	0.00	1.60	-0.92
PCOLCE	ID_1440	7	0.00	0.58	-1.81
PDK4	ID_1454	7	0.00	-0.04	-2.66
PERP	ID_1458	10	0.00	0.89	-0.18
PEX11A	ID_1459	12	0.00	0.74	1.33
PFN2	ID_1465	14	0.00	1.20	0.34
PHGR1	ID_1470	1	0.00	-1.09	-0.76
PHLDA1	ID_1471	9	0.00	0.40	-1.07
PKD2	ID_1495	9	0.00	0.62	-0.56
PLAGL1	ID_1504	10	0.00	1.20	0.14
PLAT	ID_1505	9	0.00	1.17	-2.34

PLEKHA6	ID_1511	9	0.00	0.73	-0.38
PLEKHA7	ID_1512	9	0.00	0.69	-0.48
PLEKHB1	ID_1513	10	0.00	2.48	0.63
PLEKHG6	ID_1514	7	0.00	0.06	-1.23
PLEKHS1	ID_1515	9	0.00	0.82	-1.66
PLET1	ID_1516	9	0.00	1.16	-1.26
PLK2	ID_1520	9	0.00	0.69	-0.87
PLLP	ID_1522	7	0.00	0.13	-1.36
PLPP1	ID_1524	2	0.00	-0.22	-1.03
PLS3	ID_1526	7	0.00	0.33	-1.49
PLXDC1	ID_1530	1	0.00	-1.68	-1.16
PMAIP1	ID_1532	9	0.00	0.74	-0.62
PPL	ID_1564	9	0.00	1.06	-0.93
PRDM1	ID_1570	9	0.00	0.91	-0.80
PRG4	ID_1572	10	0.00	1.70	-0.22
PRKCG	ID_1575	13	0.00	0.29	1.01
PRKCH	ID_1576	10	0.00	1.39	0.20
PRR15	ID_1590	10	0.00	1.09	0.03
PRSS22	ID_1593	7	0.00	0.41	-1.95
PRSS23	ID_1594	7	0.00	-0.36	-2.21
PRSS32	ID_1596	9	0.00	0.40	-1.05
PRSS8	ID_1598	7	0.00	-0.14	-1.38
PRTN3	ID_1599	9	0.00	0.43	-1.03
PSAPL1	ID_1601	8	0.00	-0.02	2.37
PSCA	ID_1603	7	0.00	0.45	-1.54
PSD3	ID_1604	5	0.00	-1.24	-0.21
PSORS1C2	ID_1612	10	0.00	2.53	-0.21
PTGDS	ID_1614	10	0.00	2.16	-0.35
PTGS2	ID_1617	10	0.00	1.89	-0.03
PTPRF	ID_1625	11	0.00	1.24	1.41
PUS7	ID_1629	12	0.00	0.46	1.05
QSER1	ID_1637	13	0.00	0.32	1.03
RAB17	ID_1638	3	0.00	-0.71	-1.24
RAB25	ID_1641	9	0.00	0.67	-0.43
RAI14	ID_1650	10	0.00	1.44	-0.01
RALGPS2	ID_1652	6	0.00	-0.59	0.45
RASL11B	ID_1662	10	0.00	1.24	-0.40
RASSF7	ID_1664	7	0.00	0.23	-1.35
RASSF8	ID_1665	9	0.00	0.38	-0.95
RBP1	ID_1673	9	0.00	1.38	-0.78
RDH16	ID_1679	7	0.00	0.38	-2.22
RGS1	ID_1690	10	0.00	1.13	-0.10
RHD	ID_1697	2	0.00	-0.55	-1.52
RHOU	ID_1702	9	0.00	1.16	-0.57
RHPN2	ID_1703	7	0.00	0.47	-1.42
RIPK4	ID_1713	7	0.00	0.19	-1.48
RIPPLY3	ID_1714	9	0.00	0.65	-1.47
RND3	ID_1719	7	0.00	0.32	-1.26
RNF183	ID_1725	9	0.00	0.57	-0.49

RYR1	ID_1759	11	0.00	1.01	0.89
S100A14	ID_1760	9	0.00	0.72	-1.95
S100A4	ID_1763	9	0.00	0.81	-0.62
SAA3	ID_1769	7	0.00	0.64	-1.90
SARDH	ID_1775	2	0.00	-0.48	-1.38
SASH1	ID_1777	9	0.00	1.51	-0.64
SBK1	ID_1778	6	0.00	-0.64	1.05
SCARA3	ID_1781	10	0.00	1.20	0.30
SCD1	ID_1784	6	0.00	-0.62	1.19
SCD3	ID_1785	13	0.00	0.84	3.28
SCEL	ID_1786	7	0.00	0.18	-1.47
SCG5	ID_1788	10	0.00	1.14	0.23
SCGB1B2	ID_1789	9	0.00	1.09	-1.97
SCIN	ID_1790	11	0.00	1.71	1.57
SDC1	ID_1795	14	0.00	1.41	0.47
SDC4	ID_1797	10	0.00	1.84	0.42
SDCBP2	ID_1798	9	0.00	0.77	-1.26
SDF2L1	ID_1799	9	0.00	0.41	-0.97
SEC24D	ID_1802	9	0.00	0.56	-0.60
4-Sep	ID_1813	10	0.00	1.45	-0.25
SERPINA3N	ID_1815	10	0.00	1.15	-0.21
SERPINB11	ID_1816	9	0.00	1.03	-2.08
SERPINB8	ID_1821	7	0.00	0.34	-1.23
SH2D3C	ID_1831	6	0.00	-0.36	0.66
SH3GL3	ID_1833	10	0.00	0.88	-0.18
SLC11A2	ID_1842	9	0.00	0.71	-0.39
SLC13A2	ID_1846	2	0.00	-0.49	-1.27
SLC15A1	ID_1848	3	0.00	-0.80	-1.83
SLC16A11	ID_1849	2	0.00	-0.31	-1.34
SLC1A1	ID_1852	9	0.00	1.65	-1.07
SLC25A48	ID_1860	2	0.00	-0.47	-1.34
SLC26A4	ID_1861	9	0.00	0.67	-0.35
SLC27A2	ID_1862	4	0.00	-1.55	-1.37
SLC28A3	ID_1864	9	0.00	0.93	-1.11
SLC41A2	ID_1880	12	0.00	0.83	1.45
SLC44A4	ID_1881	7	0.00	0.47	-1.74
SLC45A3	ID_1882	9	0.00	0.94	-0.41
SLC5A1	ID_1885	9	0.00	0.99	-1.31
SLC5A8	ID_1888	10	0.00	1.76	-0.45
SLC6A1	ID_1889	10	0.00	2.47	-0.04
SLC6A13	ID_1890	7	0.00	0.24	-0.77
SLC6A14	ID_1891	9	0.00	1.41	-1.70
SLC6A20A	ID_1892	10	0.00	0.99	-0.33
SLC6A3	ID_1893	6	0.00	-0.90	0.48
SLC7A11	ID_1897	10	0.00	1.49	-0.10
SLURP1	ID_1905	7	0.00	0.63	-2.67
SMPDL3B	ID_1909	7	0.00	0.29	-1.03
SNAP25	ID_1912	10	0.00	1.08	-0.27
SPA17	ID_1925	4	0.00	-1.03	-0.96

SPARC	ID_1927	9	0.00	0.59	-0.43
SPATS2	ID_1929	9	0.00	0.59	-0.60
SPDEF	ID_1931	10	0.00	1.17	-0.28
SPG20	ID_1933	11	0.00	1.14	1.02
SPNS2	ID_1935	7	0.00	0.32	-1.22
SPP1	ID_1938	9	0.00	1.07	-1.21
SPRED1	ID_1939	9	0.00	0.69	-0.53
SPRR1A	ID_1940	7	0.00	0.87	-2.38
SPRR1B	ID_1941	10	0.00	3.17	-0.89
SPRR2D	ID_1942	9	0.00	2.50	-1.04
SPRR2F	ID_1943	9	0.00	1.17	-2.48
SPRR2H	ID_1944	9	0.00	1.15	-2.07
SQLE	ID_1952	15	0.00	0.84	1.29
STAP2	ID_1974	9	0.00	0.55	-0.96
STAR	ID_1975	4	0.00	-1.03	-1.08
STFA3	ID_1978	11	0.00	1.33	1.41
SWAP70	ID_1992	6	0.00	-1.03	0.56
SYCP3	ID_1995	12	0.00	0.51	1.12
SYT13	ID_1998	13	0.00	0.55	1.71
TBC1D8	ID_2009	9	0.00	1.23	-0.60
TBX21	ID_2010	6	0.00	-0.94	0.42
TCF7L2	ID_2014	9	0.00	1.17	-0.49
TCIM	ID_2015	15	0.00	1.53	1.91
TEAD1	ID_2020	7	0.00	0.08	-2.26
TFEC	ID_2028	9	0.00	1.12	-1.00
TGM2	ID_2034	10	0.00	0.92	-0.26
THA1	ID_2035	9	0.00	0.76	-0.46
TIMP1	ID_2041	10	0.00	3.12	-0.30
TJP1	ID_2044	9	0.00	0.44	-1.14
TM7SF2	ID_2048	14	0.00	1.04	0.69
TMEFF1	ID_2052	11	0.00	1.31	1.08
TMEM106A	ID_2053	9	0.00	0.35	-0.77
TMEM176A	ID_2060	7	0.00	-0.24	-1.91
TMEM176B	ID_2061	7	0.00	-0.22	-1.53
TMEM246	ID_2069	5	0.00	-1.15	-0.16
TMEM30B	ID_2071	7	0.00	0.29	-1.38
TMEM45A	ID_2074	10	0.00	1.71	-0.34
TMEM45B	ID_2075	7	0.00	0.13	-1.23
TMEM87A	ID_2079	9	0.00	0.45	-0.93
TMPRSS4	ID_2085	9	0.00	0.70	-1.44
TNF	ID_2086	10	0.00	1.44	-0.36
TNFAIP6	ID_2089	12	0.00	0.55	1.01
TNFRSF23	ID_2093	9	0.00	0.64	-0.99
TNFSF9	ID_2098	10	0.00	0.88	-0.22
TPBG	ID_2107	9	0.00	1.23	-0.50
TPPP3	ID_2110	10	0.00	0.99	-0.21
TRAF5	ID_2114	6	0.00	-0.60	0.43
TREX2	ID_2122	9	0.00	0.49	-1.21
TRIM13	ID_2126	10	0.00	1.09	0.28

TRIM15	ID_2127	10	0.00	1.28	-0.41
TRIM2	ID_2128	10	0.00	0.99	-0.08
TRIM47	ID_2131	6	0.00	-0.53	0.69
TRIP10	ID_2134	9	0.00	0.65	-0.90
TRP53INP2	ID_2136	9	0.00	0.67	-0.66
TSPAN1	ID_2142	7	0.00	0.14	-1.98
TSPAN17	ID_2143	5	0.00	-1.03	-0.26
TSPAN3	ID_2145	10	0.00	0.91	-0.28
TSPAN8	ID_2148	7	0.00	0.26	-0.95
TTC30B	ID_2159	6	0.00	-0.61	0.61
TTC39C	ID_2160	9	0.00	0.62	-0.67
TUBB2B	ID_2168	5	0.00	-1.19	-0.04
TUBB4A	ID_2170	10	0.00	1.57	-0.08
TXNRD1	ID_2178	10	0.00	1.23	-0.23
UBE2E2	ID_2183	7	0.00	0.46	-1.30
UPB1	ID_2195	6	0.00	-1.24	0.65
VASN	ID_2207	9	0.00	0.42	-0.62
VCAN	ID_2208	7	0.00	0.12	-1.58
VDR	ID_2209	10	0.00	1.03	-0.07
VIP	ID_2211	5	0.00	-1.08	-0.20
VLDLR	ID_2213	9	0.00	0.61	-0.60
VNN1	ID_2215	7	0.00	0.03	-1.43
VNN3	ID_2216	6	0.00	-0.73	0.55
WDPCP	ID_2221	5	0.00	-1.00	-0.25
WFDC2	ID_2225	9	0.00	1.85	-1.57
WFDC5	ID_2226	9	0.00	0.49	-0.91
WFS1	ID_2227	7	0.00	-0.05	-1.41
WWC1	ID_2229	9	0.00	0.55	-0.47
WWTR1	ID_2230	7	0.00	0.44	-1.22
ZFP185	ID_2255	9	0.00	0.91	-0.93
ZFP521	ID_2266	1	0.00	-1.40	-0.50
ZFP53	ID_2267	9	0.00	0.53	-0.50
ZFP94	ID_2276	6	0.00	-0.48	0.54
ZMYND19	ID_2284	15	0.00	0.63	1.01
ZWILCH	ID_2288	11	0.00	1.03	0.89

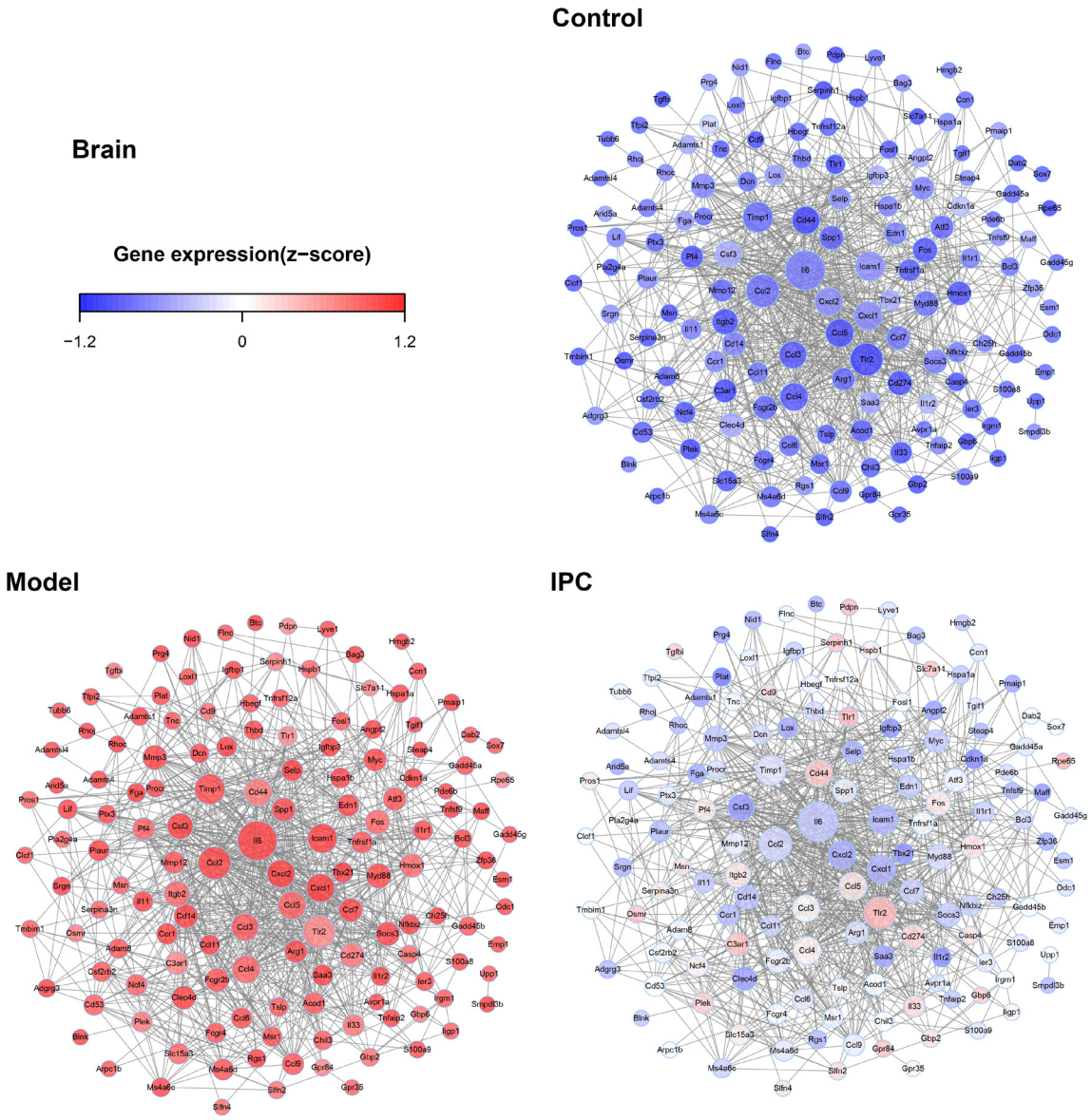

Figure S1. Protein-protein interaction networks encoded by key DEGs in the brain in a mouse model of focal brain ischemia. The networks were constructed using STRING analysis and Cytoscape software. The node represents the corresponding gene, and the lines indicate the node connection. The color and size of the map nodes are determined by the z-scores of gene expression and the number of node connections, respectively.

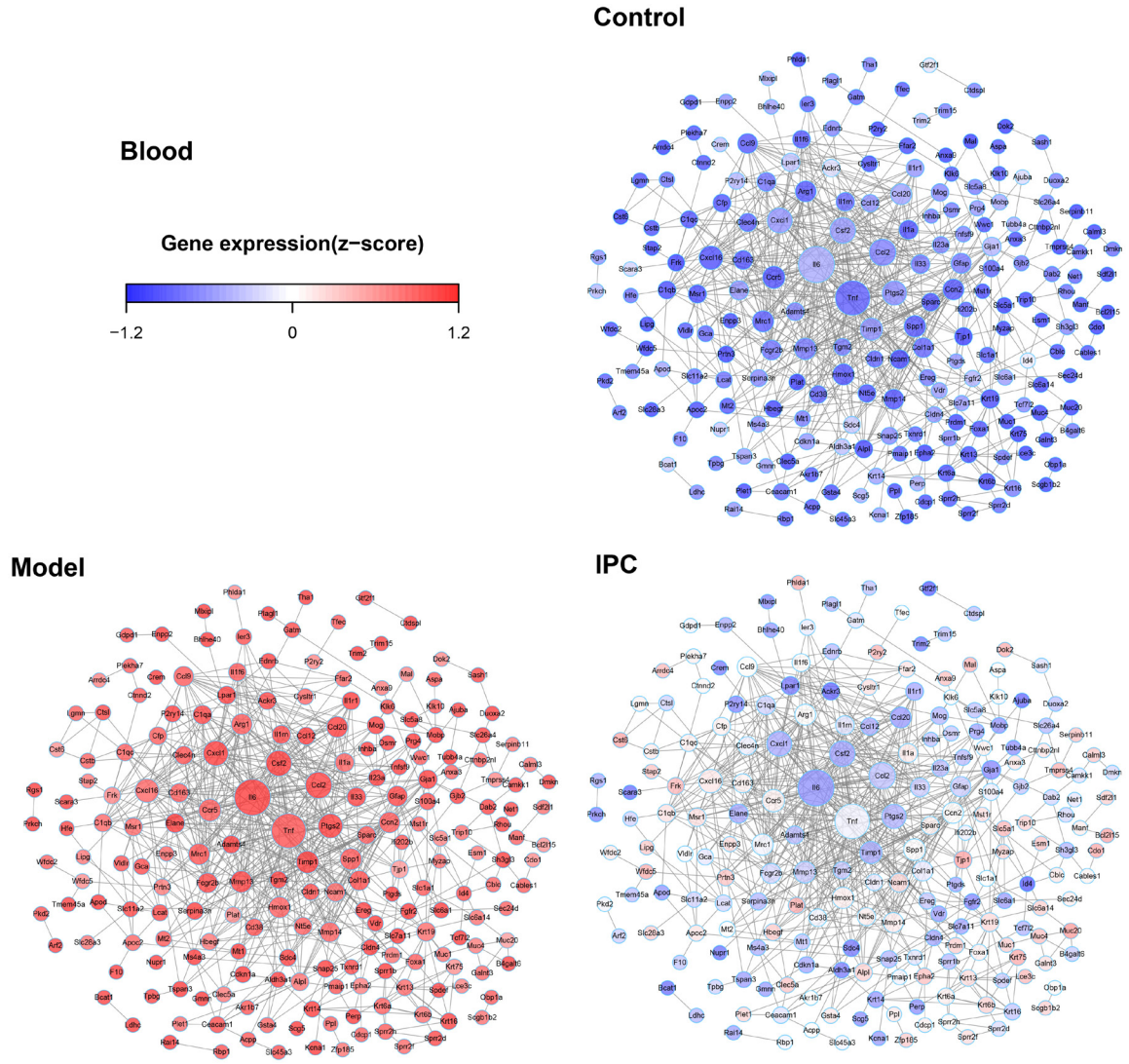

Figure S2. Protein-protein interaction networks encoded by key differentially expressed genes (DEGs) in the blood in a mouse model of focal brain ischemia. The networks were constructed using STRING analysis and Cytoscape software. The node represents the corresponding gene, and the lines indicate the node connection. The color and size of the map nodes are determined by the z-scores of gene expression and the number of node connections, respectively.