Bioinformatics analysis of potential common molecular pathogenesis assumed by intracranial aneurysm, aortic aneurysm and aortic dissection

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Abstract

This study is intended to find possible pathogenesis-related genetic overlap and common molecular mechanisms of intracranial aneurysm, abdominal aortic aneurysm and aortic dissection. Three mRNA microarray datasets, GSE75436 of intracranial aneurysms, GSE7084 of abdominal aortic aneurysm and GSE52093 of aortic dissection were downloaded from Gene Expression Omnibus and detected in silico. DEGs of these three datasets screened through GEO2R, respectively. The overlapping genes were found by Venny mapping. Subsequently, Gene Ontology, Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis were performed using the DAVID database and protein-protein interaction network analyses were conducted by STRING and Cytoscape webpage tool to illustrate the molecular mechanisms in their pathogenesis and progression. This study identified 178 DEGs, including SMTN, MYH11, TAGLN, ACTG2, CNN1, MYLK, LMOD1, MYL9, VCL and ACTC1 in the most significant module. Except for those confirmed biological processes, mesenchyme migration and platelet aggregation are common biological processes shared by genes in the most significant module and the hub genes. Focal adhesion signaling pathway is highlighted in this analysis. The present study identified possible pathogenesis-related genetic overlap and common molecular mechanisms of intracranial aneurysm, abdominal aortic aneurysm and aortic dissection, which may contribute to their diagnosis, treatment and prognostic prediction with a systematic view.

Introduction

Intracranial aneurysm (IA), abdominal aortic aneurysms (AAA) and aortic dissection (AD) have yet lingered as life-threatening diseases. Currently, endovascular intervention and surgical treatment are the two main preventative methods for them. The molecular mechanisms leading to their initiation, progression and rupture remain incompletely interpreted and were discussed respectively in the past. As a result, no safe and effective noninvasive IA, AAA or AD therapies have been identified and implemented in clinical practice by now. AD and thoracic aortic aneurysm (TAA) share common etiologies and feature common pathological characteristics to a great extent¹. Generally IAs have saccular shapes, whereas AAAs and TAAs are more often spindle-shaped; Atherosclerosis plays a more significant role in AAA, compared with IA and TAA^{2,3}. Although these three diseases have different internal molecular mechanisms leading to different clinical manifestations of occurrence and development^{4,5}, they are also related in genetic and pathological processes. For example, the prevalence of IA is higher in patients with AD or aortic aneurysm; Most aneurysms are named according to the local parent vessels, but they are often accompanied with systematic vascular lesions⁶.

Expression microarray technology and bioinformatic analysis for genetic dysfunction research have been extensively applied so far, identifying the differentially expressed genes (DEGs) and signal pathways leading to the pathogenesis and progression of many diseases. In order to understand the common molecular mechanisms among these three diseases better, the author research them via bioinformatics methods. In this study, three mRNA microarray datasets from Gene Expression Omnibus (GEO) were

included and detected to reveal common DEGs among IA, AAA and AD. Subsequently, Gene Ontology(GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis and protein-protein interaction(PPI) network analyses were conducted to illustrate the molecular mechanisms in their pathogenesis and progression.

Materials And Methods

gene expression datasets

Three gene expression profiles datasets, GSE75436, GSE7084 and GSE52093, were identified following key word search of “aneurysm”, “expression profile by array” and “human” in the Gene Expression Omnibus (GEO) (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi>)⁷ and downloaded. Gene expression profile dataset GSE75436 contains 15 IAs wall tissues samples and their matched superficial temporal artery wall tissues samples, based on platform GPL570 (Affymetrix Human Genome U133 Plus 2.0 Array). Gene expression profile dataset GSE7084 includes 8 abdominal aortic aneurysm samples and 7 non-diseased abdominal aortas control samples, based on platform GPL2507 (Illumina Sentrix Human-6 Expression BeadChip). Gene expression profile dataset GSE52093 is composed of 7 dissected ascending aorta samples and 5 normal ascending aorta control samples, based on platform GPL10558 (Illumina HumanHT-12 V4.0 Expression BeadChip).

Identifying differentially expressed genes

Gene expression data tables of GSE75436, GSE7084 and GSE52093 were obtained via GEO2R webpage application (<http://www.ncbi.nlm.nih.gov/geo/geo2r/>), which is an R programming languages-based tool for identifying DEGs⁷. In GEO2R, query for each datasets were conducted with defining and assigning “disease” and “control” groups and selecting “Top 250” DEGs, respectively. Difference of p value ≤ 0.05 and $|\log_2 \text{foldchange}| \geq 1$ is considered statistically significant. Common differently expressed genes (cDEGs) of these three datasets, the overlapped genes, are illustrated via Venny mapping (<https://bioinfogp.cnb.csic.es/tools/venny/>).

Functional and pathway enrichment analysis

The Database for Annotation, Visualization and Integrated Discovery Version 6.8 (DAVID) was used to perform GO term and KEGG pathway analysis for the cDEGs (<https://david.ncifcrf.gov/>). Gene Ontology (GO) enrichment annotation is to locate functional gene products at the subcellular structures (cellular component—CC), describe activities that occur at the molecular level (molecular function, MF) and the larger processes accomplished by multiple molecular activities (biological process—BP). The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database, analyzing the potential relevant biological function, provides useful structured information of a gene network. p value < 0.05 and FDR < 0.05 was the cut-off criteria in GO and KEGG pathway analysis.

The PPI networks and analysis of most significant module The Search Tool for the Retrieval of Interacting Genes (STRING) database Version 11.0 (<http://string-db.org/>) is a database of known and predicted PPI, consisting of direct (physical) associations and indirect (functional) associations⁸. Input the gene symbols of cDEGs into the “multiple proteins” selection bar of STRING and then the interactions between proteins encoded by cDEGs acquired with cut-off criterion “combined score > 0.4”. Then Cytoscape Version 3.7.2⁹ were utilized to visualize the PPI network of the cDEGs. Molecular Complex Detection (MCODE) plugin was used to select the most significant module from the PPI network with degree cutoff =2, haircut on, node score cutoff = 0.2, k-score=2, maximum depth=100, and nodes more than 5. The GO and KEGG pathway enrichment analyses for genes in this module were performed using DAVID. **Hub genes selection and analysis.** CytoHubba is a plugin software of Cytoscape. It predicts and explores important nodes and sub-networks in a given network by 12 topological analysis methods including Degree, EPC, MNC, et al. The hub genes, acting more importantly in biological processes than the other DEGs, were selected with degrees ≥ 10 by CytoHubba. Then, the biological process analysis of them was performed and visualized using Biological Networks Gene Ontology tool (BiNGO) plugin of Cytoscape with the significance level 0.02. BiNGO is a software to select statistically overrepresented Gene Ontology (GO) categories in a set of genes or a subgraph of a biological network, and maps the predominant functional themes of a given gene set on the GO hierarchy. GO and KEGG function analysis of these hub genes were performed in DAVID (p value < 0.05).

Results

Identification of DEGs

A total of 1963, 515 and 853 DEGs were extracted from GSE75436, GSE7084 and GSE52093, respectively (Fig. 1A–C). Among them, 178 overlapped DEGs illustrated in Venny map (Fig. 1D)

Functional and pathway enrichment analysis of DEGs

The functional annotation of cDEGs was conducted via DAVID in order to understand the subcellular localization, molecular functions, biological processes of cDEGs. Functional enrichment analysis showed that cDEGs were enriched in cellular components (CC) such as Z disc, focal adhesion, extracellular space, et al; For GO molecular functions (MF), the cDEGs were significantly enriched in actin binding, structural constituent of muscle, actin filament binding, protein kinase activity, et al; Upon biology processes (BP), the cDEGs were significantly enriched in muscle contraction, chemotaxis, cell chemotaxis, cell adhesion, et al. Furthermore, KEGG analysis revealed that cDEGs were significantly enriched in vascular smooth muscle contraction, neurotrophin signaling pathway, cGMP-PKG signaling pathway, osteoclast differentiation, et al. (Top 10 in Fig. 2 A, B, C; Top 13 in Fig. 2 D; Both according to $-\log_{10}(p\text{-value})$).

PPI network construction and module analysis

The PPI network of cDEGs was mapped intuitively and expansively to illustrate the possible association between down-stream proteins with 137 nodes and 336 edges (Figure 3A). After MCODE plugin of

Cytoscape processing, the most significant module was selected with nodes=10 and edges=43 (Fig. 3B), consisting of *SMTN* Smoothelin, *MYH11* Myosin Heavy Chain 11, *TAGLN* Transgelin, *ACTG2* actin gamma 2, smooth muscle, *LMOD1* Leiomodin 1, *MYLK* Myosin light chain kinase, *VCL* Vinculin, *CNN1* Calponin 1, *ACTC1* Actin alpha cardiac muscle 1, *MYL9* Myosin light chain 9. Functional enrichment analysis indicated that these genes in the module were enriched in GO terms and KEGG pathways in Table 1

Functional and pathway enrichment analysis of hub genes

A total of 20 hub genes were screened out, and their gene symbols and aliases were shown in Table 2 with PPI network in Fig. 4A. The biological processes resulted from BingGO analysis with different color depths of each node according to their *p* value (Fig. 4B). The functional analysis of hub genes was conducted through DAVID (Table 3). Muscle contraction, smooth muscle contraction, actomyosin structure organization, inflammatory response co-existed in Fig. 4B and Table 3.

Discussion

Thoracic aortic diseases (TADs) include thoracic aortic aneurysms (TAAs) and aortic dissections (ADs), associating with a widely common genetic etiology, and are usually discussed as a whole by many scholars^{10,11}. TADs are different from abdominal aortic aneurysms (AAAs) in clinical features, inheritance modes, et al. But TADs and AAAs share several joint pathogenic processes, for example, proteolytic elastic tissue degeneration and smooth muscle dysfunction⁵. In an autopsy study, these thoracoabdominal artery lesions can co-exist¹². So, there may be same pathogenic molecular mechanisms between TADs and AAAs. The prevalence of IA in patients with aortic dissection or aneurysms is higher than those without^{13,14,15}. Degeneration of the elastic tissue and smooth muscle dysfunction are also explicated in IAs formation and rupture¹⁶. These evidences suggest associations in these diseases pathogenetic process, but still understood unclearly. In this paper, the common differentially expressed genes of the three diseases IA, AD and AAA, and their possible signaling pathways was detected *in silico*, so as to provide basis for future studies.

In this study, to reveal possible common pathogenesis-related genes of IA, AAA and AD, the author selected three microarray profile datasets, GSE75436 of IAs, GSE7084 of AAAs and GSE52093 of ADs. DEGs of these three datasets screened through GEO2R, respectively. In summary, 178 common DEGs of the three datasets were identified. The enrichment analysis demonstrated these DEGs were primarily enriched in biological processes, including muscle cell contraction, cell chemotaxis, cell adhesion and protein localization to cell surface. To date, smooth muscle cells (SMCs), leukocytes, complements, immunoglobulins, cytokines have been affirmed to be contributors to IA pathogenesis. Their roles in the biological processes mentioned above need further investigation. In GO cellular component enrichment analysis, the most enriched component was Z disc, whereas in GO molecular function analysis, it was actin binding. In KEGG pathway analysis, DEGs were mostly enriched in vascular smooth muscle contraction, neurotrophin signaling pathway, cGMP-PKG signaling pathway, osteoclast differentiation,

arginine and proline metabolism, et al. in Fig.2D. Only smooth muscle contraction, Toll-like receptor signaling pathway and cGMP-PKG signaling pathway have been researched extensively by now^{17,18,19}.

SMCs contractile dysfunction (dedifferentiation) refers to the degeneration from an initial contractile status to an inflammatory and matrix remodeling status under the stimulation of the cellular and extracellular environment. It is an integral part of the inflammatory response along with subsequent cell death. It is a key predisposing process of aortic dissection, aortic aneurysms and intracranial aneurysms^{20,21,22,23}. Genes in the most significant module of Fig. 3B are all embedded in hub genes of Fig. 4A, suggesting that their biological function is particularly important. They are all associated with SMC contraction, but only MYH11 and MYLK have been validated to be predisposing genes of aneurysmal diseases and AD further^{5,24}.

Smoothelin- α (SMTN- α) Myosin Heavy Chain 11 (MYH11 or SMMHC), Transgelin (TAGLN or SM22- α) and CNN1 are SMC differentiation biomarkers that function importantly in SMC contraction. SMTN family are composed of SMTN- α , SMTN- β and SMTNL1. SMTN was expressed in tunica media SMCs of normal arteries, but unexpressed in the media SMCs of saccular intracranial aneurysm (sIA); Meanwhile, sIA SMCs showed significant decrease of MYH11 expression²⁵. It's reported that MYH11 mutation correlated with thoracic aortic aneurysms, dissections and *de novo* intracranial aneurysm formation²⁶. TAGLN is an actin binding enzyme of the calponin family, performing actin binding and actin bundling activities. Loss of TAGLN promotes thoracic aortic aneurysm and aortic dissection progression in vivo²⁷. But no association with its roles and other vascular diseases has been reported yet.

in vitro experiments implicated that ACTG2, a target of miR-193a-3p, participated in the development of AD²⁸. Feng J reported CNN1 was downregulated in aortic dissection vascular smooth muscle cells which might be a key pathogenetic gene in vascular diseases²⁹. LMOD1 is a highly specific contractile gene for smooth muscle lineages. myosin light chain 9 (MYL9) is involved in inflammatory response, which is a main biological process of aneurysmal diseases³⁰. Defects of cytoskeleton proteins VCL and actin ACTC1 are the cause of dilated cardiomyopathy. These genes in the most significant module except MYH11 and MYLK have not been discussed in aneurysmal diseases and need continuous research in the future.

In this study, smooth muscle contraction, actomyosin structure organization, mesenchyme migration and platelet aggregation are common biological processes shared by genes in the most significant module and hub genes. Smooth muscle contraction, actomyosin structure organization are important in preventing aneurysm (or dissections) pathogenesis, validated by many researches⁵. Our findings are in accordance with previously reported data on the role of vascular SMCs in aneurysm pathogenesis. Nevertheless, mesenchyme migration and platelet aggregation have not been understood completely. Platelet aggregation and thrombosis are the subsequent events of elastin integrity loss after AAA initiation. Expounded by quite limited articles, platelet aggregation plays a significant role in AAA onset and progression, and platelet inhibitors can attenuate aneurysm formation in rat AAA model, though

lacking of clinical evidence³¹. Inflammatory factors TGF β released during platelet aggregation, can promote the transformation of SMC phenotype from contractile status to inflammatory status, along with inflammatory responses, thereby contribute to aneurysm formation³². These evidences lead us to speculate on a positive feedback between aneurysm pathogenesis and platelet aggregation.

Focal adhesion signaling pathway co-exhibited in Fig 2D, Table 1–Table 3. Focal adhesions function as the transmembrane signal transduction interface between extracellular matrix and intracellular cytoskeleton, and has not been elucidated extensively in aneurysm pathogenesis. Testin (TES), a focal adhesion scaffold protein, was validated as a potential contributor to TAA onset³³. THSD1, a novel nascent adhesion protein, is provided likely to cause intracranial aneurysm in both familial and sporadic patients³⁴. *MYL9*, *VCL* and *MYLK* mined in this article may play significant roles in aneurysmal diseases pathology via focal adhesion pathway, which worthy of further investigation.

Genetic variation is an important factor of vascular diseases, and the understanding of its role is gradually enriched. It can lead to biological degeneration in blood vessels, including cellular and tissue events contributing to intracranial and aortic aneurysms (or dissection), which may provide new therapeutic targets. Genetic testing is regular procedure of clinical diagnosis and treatment. The genes discussed in this paper, may be developed as potential predictors of systemic aneurysms in genetic test or targets of vascular therapy.

There are some limitations to this study. The first one is merely single-aspect analysis. Other methods, e.g. gene set enrichment analysis (GSEA), can provide understanding of genes function from another aspect. The second one is lacking experimental and clinical feature validation, such as in vitro and in vivo experiments, patients' age, sex, different types of aneurysms, and so on. And in addition, the sample count of each group is limited. False-positive incidences in independent microarray analysis hinder reliable data acquisition.

To date, genetic sharing among IA, AAA, and AD has been considered mainly within families^{35,36}, but possible genetic correlations in sporadic aneurysmal cases are also worthy of attention. Therefore, further research focusing on the aforementioned hub genes and biological processes calls for more evidences with a systematic view.

Conclusion

This article aiming to find possible pathogenesis-related genetic overlap of IA, AAA and AD, identified 178 DEGs, which include *SMTN*, *MYH11*, *TAGLN*, *ACTG2*, *CNN1*, *MYLK*, *LMOD1*, *MYL9*, *VCL* and *ACTC1* in the the most significant module. Except for those confirmed biological processes, mesenchyme migration and platelet aggregation are common biological processes shared by genes in the most significant module and the hub genes. Focal adhesion signaling pathway highlighted in this analysis, has not been elucidated extensively in aneurysm pathogenesis by now. Basic and clinical experiments are needed to

verify all of these results that may contribute to the diagnosis, treatment and prognostic prediction of IA, AAA and AD with a systematic view.

Declarations

Compliance with ethical standards

Conflicts of interest

The authors declare no conflict of interest related to the content of this article

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Availability of data and material: Open

Code availability: Not applicable

Authors' contributions: Chao Zhao conceived and designed the study. Xinchun Cui , Guodong Liu, Jianlong Li, Jinxing Liu and Junliang Shang performed data processing. Chao Zhao, Shuai Wang and Ronghua Shi wrote the paper. Chao Zhao and Aihong Wu reviewed and edited the manuscript. All authors read and approved the manuscript.

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Tables

Table 1 GO terms and KEGG pathways analysis of genes in the most significant module

Category	Term	PValue	Genes	FDR
GOTERM_BP_DIRECT	GO:0006936~muscle contraction	1.18E-09	<i>LMOD1, MYH11, MYL9, VCL, ACTG2, MYLK</i>	5.90E-08
GOTERM_BP_DIRECT	GO:0006939~smooth muscle contraction	3.89E-05	<i>SMTN, MYH11, MYLK</i>	9.72E-04
GOTERM_BP_DIRECT	GO:0090131~mesenchyme migration	0.002677295	<i>ACTC1, ACTG2</i>	0.044621583
GOTERM_BP_DIRECT	GO:0031032~actomyosin structure organization	0.014381856	<i>CNN1, ACTC1</i>	0.1797732
GOTERM_BP_DIRECT	GO:0070527~platelet aggregation	0.021766485	<i>MYL9, VCL</i>	0.217664854
GOTERM_BP_DIRECT	GO:0007517~muscle organ development	0.046713293	<i>TAGLN, SMTN</i>	0.389277442
KEGG_PATHWAY	hsa04270:Vascular smooth muscle contraction	0.002773761	<i>MYL9, ACTG2, MYLK</i>	0.052701458
KEGG_PATHWAY	hsa04510:Focal adhesion	0.00840762	<i>MYL9, VCL, MYLK</i>	0.055276053
KEGG_PATHWAY	hsa04810:Regulation of actin cytoskeleton	0.008727798	<i>MYL9, VCL, MYLK</i>	0.055276053

p value ≤ 0.05

Table 2 information of hub genes

Gene symbol	Full name	Aliases
<i>VCL</i>	vinculin	<i>CMD1W, CMH15, HEL114, MV, MVCL</i>
<i>CXCL8</i>	C-X-C motif chemokine ligand 8	<i>GCP-1, GCP1, IL8, LECT, LUCT, LYNAP, MDNCF, MONAP, NAF, NAP-1, NAP1</i>
<i>SPP1</i>	secreted phosphoprotein 1	<i>BNSP, BSPI, ETA-1, OPN</i>
<i>MYH11</i>	myosin heavy chain 11	<i>AAT4, FAA4, SMHC, SMMHC</i>
<i>TAGLN</i>	Transgelin	<i>SM22, SM22-alpha, SMCC, TAGLN1, WS3-10</i>
<i>ACTC1</i>	actin alpha cardiac muscle 1	<i>ACTC, ASD5, CMD1R, CMH11, LVNC4</i>
<i>FLNA</i>	filamin A	<i>ABP-280, ABPX, CSBS, CVD1, FGS2, FLN, FMD, MNS, NHBP, OPD, XLVD</i>
<i>SPI1</i>	Spi-1 proto-oncogene	<i>OF, PU.1, SFPI1, SPI-1, SPI-A</i>
<i>MYL9</i>	myosin light chain 9	<i>LC20, MLC-2C, MLC2, MRLC1, MYRL2</i>
<i>MYLK</i>	myosin light chain kinase	<i>AAT7, KRP, MLCK, MLCK1, MLCK210, MMIHS, MSTP083, smMLCK</i>
<i>ITGAX</i>	integrin subunit alpha X	<i>CD11C, SLEB6</i>
<i>ACTG2</i>	actin gamma 2, smooth muscle	<i>ACT, ACTA3, ACTE, ACTL3, ACTSG, VSCM</i>
<i>LMOD1</i>	leiomodoin 1	<i>1D, 64kD, D1, SM-LMOD, SMLMOD</i>
<i>MYH10</i>	myosin heavy chain 10	<i>NMMHC-IIB, NMMHCB</i>
<i>LILRB2</i>	leukocyte immunoglobulin like receptor B2	<i>CD85D, ILT-4, ILT4, LIR-2, LIR2, MIR-10, MIR1</i>
<i>CXCL1</i>	C-X-C motif chemokine ligand 1	<i>FSP, GRO1, GROa, MGSA, MGSA-a, NAP-3, SCYB1</i>
<i>SMTN</i>	smoothelin	none
<i>OLR1</i>	oxidized low density lipoprotein receptor 1	<i>CLEC8A, LOX1, LOXIN, SCARE1, SLOX1</i>
<i>CCL5</i>	C-C motif chemokine ligand 5	<i>D17S136E, RANTES, SCYA5, SIS-delta, SISd, TCP228, eoCP</i>
<i>CNN1</i>	calponin 1	<i>HEL-S-14, SMCC, Sm-Calp</i>

Table 3 GO-BP terms and KEGG pathways analysis of hub genes by DAVID

Category	Term	p value	Genes	FDR
GOTERM_BP_DIRECT	GO:0006936~muscle contraction	1.03551E-07	<i>LMOD1, MYH11, MYL9, VCL, ACTG2, MYLK</i>	.44381E-05
GOTERM_BP_DIRECT	GO:0006939~smooth muscle contraction	0.00018359	<i>SMTN, MYH11, MYLK</i>	0.021663567
GOTERM_BP_DIRECT	GO:0031032~actomyosin structure organization	0.000418626	<i>CNN1, ACTC1, MYH10</i>	0.032931935
GOTERM_BP_DIRECT	GO:0006954~inflammatory response	0.000756701	<i>CXCL8, CCL5, SPP1, OLR1, CXCL1</i>	0.044645332
GOTERM_BP_DIRECT	GO:0070527~platelet aggregation	0.000968797	<i>FLNA, MYL9, VCL</i>	0.045727235
GOTERM_BP_DIRECT	GO:0007155~cell adhesion	0.001540961	<i>ITGAX, SPP1, OLR1, MYH10, VCL</i>	0.060611131
GOTERM_BP_DIRECT	GO:0070098~chemokine-mediated signaling pathway	0.00287718	<i>CXCL8, CCL5, CXCL1</i>	0.097002068
GOTERM_BP_DIRECT	GO:0090131~mesenchyme migration	0.005645339	<i>ACTC1, ACTG2</i>	0.166537488
GOTERM_BP_DIRECT	GO:0006935~chemotaxis	0.008257674	<i>CXCL8, CCL5, CXCL1</i>	0.212825632
GOTERM_BP_DIRECT	GO:0042119~neutrophil activation	0.009018035	<i>CXCL8, CCL5</i>	0.212825632
GOTERM_BP_DIRECT	GO:0006955~immune response	0.011248555	<i>CXCL8, CCL5, CXCL1, LILRB2</i>	0.241332632
GOTERM_BP_DIRECT	GO:0045744~negative regulation of G-protein coupled receptor protein signaling pathway	0.013498108	<i>CXCL8, CCL5</i>	0.245042583
GOTERM_BP_DIRECT	GO:0055003~cardiac myofibril assembly	0.013498108	<i>ACTC1, MYH10</i>	0.245042583
GOTERM_BP_DIRECT	GO:0030048~actin filament-based movement	0.01907122	<i>ACTC1, MYH10</i>	0.321486275
GOTERM_BP_DIRECT	GO:0090023~positive regulation of neutrophil chemotaxis	0.024614495	<i>CXCL8, CXCL1</i>	0.341707103
GOTERM_BP_DIRECT	GO:0034394~protein localization to cell surface	0.024614495	<i>FLNA, VCL</i>	0.341707103
GOTERM_BP_DIRECT	GO:0034113~heterotypic cell-cell adhesion	0.024614495	<i>ITGAX, LILRB2</i>	0.341707103
GOTERM_BP_DIRECT	GO:0051928~positive regulation of calcium ion transport	0.029027734	<i>CCL5, MYLK</i>	0.380585846
GOTERM_BP_DIRECT	GO:0044344~cellular response to fibroblast growth factor stimulus	0.033422052	<i>CXCL8, CCL5</i>	0.415137061
KEGG_PATHWAY	hsa04510: Focal adhesion	0.000822324	<i>SPP1, FLNA, MYL9, VCL, MYLK</i>	0.040293871
KEGG_PATHWAY	hsa04621: NOD-like receptor signaling Pathway	0.006385846	<i>CXCL8, CCL5, CXCL1</i>	0.146216068
KEGG_PATHWAY	hsa04810: Regulation of actin cytoskeleton	0.00972744	<i>ITGAX, MYL9, VCL, MYLK</i>	0.146216068
KEGG_PATHWAY	hsa05132: Salmonella infection	0.013640314	<i>CXCL8, FLNA, CXCL1</i>	0.146216068
KEGG_PATHWAY	hsa04530: Tight junction	0.014920007	<i>MYH11, MYH10, MYL9</i>	0.146216068
KEGG_PATHWAY	hsa04620: Toll-like receptor signaling pathway	0.021671707	<i>CXCL8, CCL5, SPP1</i>	0.176985607
KEGG_PATHWAY	hsa04270: Vascular smooth muscle contraction	0.02606472	<i>MYL9, ACTG2, MYLK</i>	0.182453038

p value ≤0.05

Figures

Figure 1

a Volcano Plot of GSE75436 b Volcano Plot of GSE7084 c Volcano Plot of GSE52093 d DEGs in Venny map

Figure 2

a cellular components(CC) b molecular functions(MF) c biology processes(BP) d KEGG pathway

Figure 3

a PPI network of common DEGs b the most significant module

Figure 4
a PPI network of 20 hub genes b biological processes by BingGO analysis

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