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An analysis of plasma reveals proteins in the acute phase response pathway to be candidate diagnostic biomarkers for depression

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ABSTRACT

Globally, depression is one of the most serious debilitating psychiatric mental disorders. In this study, we validated the expression levels of fibrinogen alpha (FGA), fibrinogen beta (FGB), fibrinogen gamma (FGG), Complement factor B (CFB) and serpin family D member 1(SERPIND1) in the acute phase response signaling pathway in plasma samples using enzyme-linked immunosorbent assay (ELISA).Then illuminate the roles of FGA, FGB, FGG, CFB, SERPIND1 in depression using microarray data.

Gene expression dataset GSE98793 was downloaded from the Gene Expression Omnibus database. There were 128 whole blood samples included 64 patients with major depressed patients and 64 healthy controls. Differentially expressed genes (DEGs) were identified, and then protein-protein interaction (PPI) network was constructed to screen crucial genes associated with FGA, FGB, FGG, CFB and SERPIND1. Moreover, gene ontology (GO) biological processes analyses was performed.

The ELISA data showed that the expression levels of FGA, FGB, FGG, CFB and SERPIND1 were up-regulated in depressed patients. The enriched GO terms were predominantly associated with the biological processes including more genes were inflammation related. The PPI network was found these five genes interacted with 11 genes. FGA, FGB, FGG, CFB and SERPIND1 may be important in the pathogenesis of depression.

1. Introduction

In recent years, an increasing number of studies has indicated that using proteomics and bioinformatics is a powerful tool to screen biomarkers for depression (Duman and Aghajanian, 2012; Patel, 2014; Razafsha et al., 2015). A blood test would be a convenient and easier alternative for large-scale implementation. Every day, approximately 500 ml of CSF are absorbed into the blood. (Hye et al., 2006) In patients with MDD, a dysfunction in the blood-brain barrier has been observed, resulting in damage to the blood-brain barrier, facilitating the exchange of proteins between blood and the brain in these patients (Bahn and Chan, 2015; Bot et al., 2015; Niculescu et al., 2015).

Because depression is a multi-factorial disease, it is difficult to obtain a single, specific diagnostic marker. Currently, there is still no accurate conclusion regarding a protein that can be used as a target for treating depression.(Lopresti et al., 2014) This suggests that a set of multiple molecules may be better to understand the various manifestations of depression and thereby improve the ability of diagnostic tests. To better explain the potential etiology of depression, it is critical to understand the molecular pathway. In this regard, biomarkers can

Abbreviations: CSF, cerebrospinal fluid; Fga, fibrinogen alpha; FGB, fibrinogen beta; FGG, fibrinogen gamma; CFB, complement factor b; SERPIND1, serpin family d member 1; ELISA, enzyme-linked immunosorbent assay; HAM-D-17, 17-item hamilton rating scales for depression; IPA, ingenuity pathway analysis; iTRAQ, isobaric tag for relative and absolute quantitation; DEGs, differentially expressed genes; PPI, protein-protein interaction; NCBI, National Center Of Biotechnology Information; HPRD, human protein reference database; Sam, significance analysis of microarrays; GO, gene ontology; TNF-α, tumor necrosis factor α; Il-1, interleukin-1; IL-6, interleukin-6; IL1β, interleukin-1 beta

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provide valuable data not only for individual protein entities but also simultaneously for pathways to understand the disease, thus yielding important information to help guide future therapeutic strategies. (Zhang et al., 2011)

Differentially expressed genes data were obtained from our previous iTRAQ experiment. (Wang et al., 2016) In this study, we analyzed the iTRAQ experiment data using Ingenuity Pathway Analysis. The result found that the top statistically significant canonical pathway is the acute phase response signaling pathway. FGA, FGB, FGG, CFB and SERPIND1 were up-regulated in depressed patients and also paticipate in this pathway. The goal of this study was to further illuminate the mechanisms FGA, FGB, FGG, CFB and SERPIND of by analyzing the microarray data of depression. We selected microarray data GSE98793, which was downloaded from the Gene Expression Omnibus database and was generated from whole blood samples from non-medicated subjects (MDD patients and controls) to screen DEGs. PPI network was constructed to screen crucial genes associated with FGA, FGB, FGG, CFB and SERPIND1. The relationship between the nodes to further explore the possible molecular mechanisms of acute phase response signaling pathway involved in the regulation of depression, and to reveal more potential targets for treatment of depression.

2. Methods

2.1. Data mining and pathway analysis

Data were obtained from 154 differentially expressed genes from our previous iTRAQ experiment, (Wang et al., 2016) and they were analyzed using Ingenuity Pathway Analysis (IPA, Ingenuity, USA, http://www.ingenuity.com/). The data packet containing the 154 differentially expressed proteins was converted by IPA to a “fold change” and uploaded into IPA. P-values were calculated using a right-tailed Fisher's exact test. Each identifier was mapped to its corresponding molecule in the Ingenuity Pathway Knowledge Base. The molecular relationship between proteins is presented in a pathway graph.

2.2. ELISA assay

In this study, we tested five proteins (CFB, FGG, FGA, FGB, and SERPIND1) using enzyme-linked immunosorbent assay (ELISA). We didn't analyse other acute phase proteins such as alpha 1-antitrypsin. Previous study was found that major depression may be accompanied by inflammatory changes with higher levels of alpha 1-antitrypsin (Maes et al., 1992). What we choose are the top fold-change proteins in the acute phase response signaling pathway. The plasma samples obtained from depressed patients ($n = 22$) and healthy control subjects ($n = 20$) .

The patient eligibility criteria were previously described in the clinical characteristics of the depressed patients and healthy controls (Wang et al., 2016). All of the participants provided informed consent to be involved in the study, which was approved by the local ethics committee in accordance with the Helsinki Declaration. The patients were diagnosed by trained professional senior specialists in psychiatry and psychology. All participants were free of any co-morbidities as judged by study investigators using clinical or laboratory findings. No females in this study were pregnant, lactating, or menstruating. Guidelines from the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) were used to diagnose depression. The severity of depression was evaluated by the 17-item Hamilton Rating Scale for Depression (HAM-D-17) questionnaire. Only participants with a score higher than 17 in the HAM-D-17 questionnaire were enrolled in the depressive disorder group.

Blood samples (5 ml) were drawn from the antecubital vein by EDTA-lined tubes (BD vacutainer blood collection tubes, 367899, Becton and Dickinson, Sydney, New South Wales) between 7:00 and 9:00 a.m., and followed by centrifugation at 2000 × g for 20 min at 4 °C. Then, the supernatants were stored at −80 °C until analysis.

The human FGA ELISA kit (DER-H5019c, Rapidbio System, Inc., USA), human FGB ELISA kit (DER-H5020c, Rapidbio System, Inc., USA), human FGG ELISA kit (DER-H5022c, Rapidbio System, Inc., 3USA), human CFB ELISA kit (DER-H9002c, Rapidbio System, Inc., USA) and human SERPIND1 ELISA kit (KMS-EL501A, Kamaishu Biological, Inc., China) were used to detect protein levels in the plasma according to the manufacturer's instructions. The absorbance at 450 nm was measured with a microplate reader (DNM-9602, Perlong Medical, China). The variables were tested for normality by a Shapiro-Wilcoxon normality test, and the differences between the studied groups were analyzed by either Student's *t*-test or the Mann-Whitney test. The results from the ELISA data are expressed as the mean ± SD. A *p*-value < 0.05 was considered significant. All of the statistical analyses were performed using Graph Pad Prism (Version 5.0, Graph Pad Software, CA, USA).

2.3. Microarray dataset

Microarray data was accessible at the National Center of Biotechnology Information (NCBI) Gene Expression Omnibus database (http://www.ncbi.nlm.nih.gov/geo) using the series accession number GSE98793. In total, 64 MDD patients and 64 healthy controls were analyzed using basal gene expression in whole blood. This data set was based on the GPL570 platform of the [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array.

2.4. Data normalization and DEG identification

The original microarray data were processed by $\log_2$-fold-change standardization. The differences between the studied groups were analyzed by significance analysis of microarrays (SAM)(Kim et al., 2006; Tusher et al., 2001).The Limma package in R language was used to screen DEGs. The threshold was set as $P < 0.05$ and $|\log(\text{fold-change})| > 0.05$. (Diboun et al., 2006)

2.5. Construction of the PPI network

PPI data were downloaded from the Biological General Repository for Interaction Datasets (BioGRID; http://www.thebiogrid.org) interaction database and Human Protein Reference Database (HPRD; http://www.hprd.org), (Chatr-Aryamontri et al., 2017; Keshava Prasad et al., 2009) and merged into the background PPI network. FGA, FGB, FGG, CFB, and SERPIND1 were mapped into the whole network and the PPI network for the FGA, FGB, FGG, CFB, and SERPIND1 was then visualized with Cytoscape(Shannon et al., 2003).

2.6. Gene ontology (GO) term enrichment analysis

Functional annotation of DEGs is a necessary and critical step in the analysis of microarray data.The Database for Annotation, Visualization and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov/) is a tool providing a comprehensive set of functional annotation (Sherman et al., 2007). Enriched GO terms from DEGs were identified using DAVID with a threshold of $P < 0.05$.

3. Results

3.1. Pathway analysis

The IPA software identified and analyzed genes eligible for canonical pathways. The top statistically significant canonical pathways was the acute phase response signaling pathway ($^*p < 0.05$), as shown in Fig. 1.

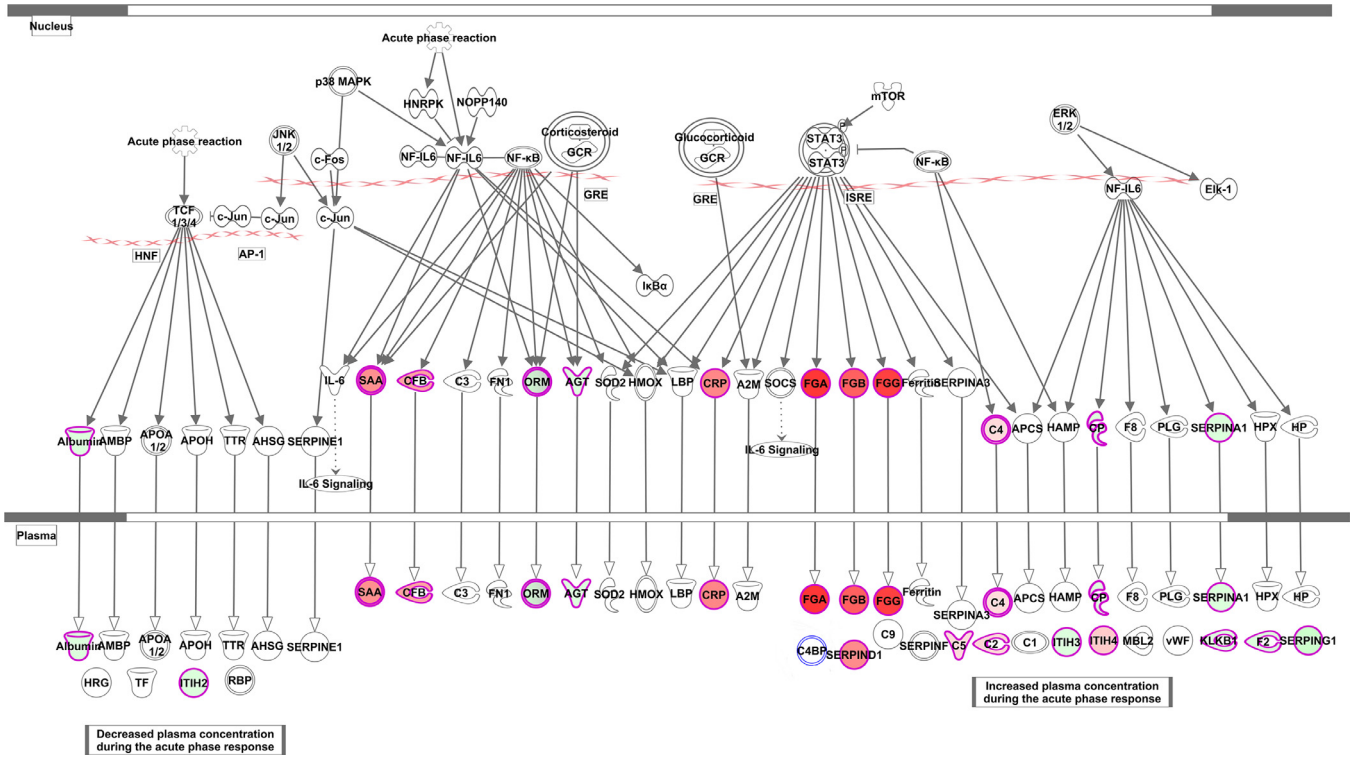

Fig. 1. Graph showing the acute phase response signaling pathway. Red-colored genes represent up-regulation in depressive patients compared to healthy controls; green-colored genes are down-regulated.

3.2. Proteins validated by ELISA

There were no significant differences between the two groups in terms of their demographic characteristics, age, sex and body mass index (BMI) ($p > 0.05$). The detailed demographic and clinical characteristics of the recruited subjects are summarized in Table 1.

We didn't analyse other acute phase proteins such as Alpha 1-antitrypsin, because previous study found that major depression may be accompanied by inflammatory changes with higher levels of alpha 1-antitrypsin. What we choose are the top fold-change proteins in the acute phase response signaling pathway ($p < 0.05$), as shown in Table 2.

ELISA was employed to evaluate FGA, FGB, FGG, CFB and SERPIND1 in the acute phase response signaling pathway. FGA, FGB, CFB and SERPIND1 data were assumed to be normally distributed. Student's *t*-test was used to analyze the between-group variances of FGA, FGB, CFB and SERPING1. FGG data were not normally distributed and compared between-group variances using the Mann-Whitney *U* test. The results showed that, compared with healthy controls, FGA, FGB, FGG, CFB and SERPIND1 were up-regulated in depressed patients

Table 1
Detailed clinical information of each cohort[a].

	Depressed patients	Healthy controls	P[b]
sample size	22	20	
sex(M/F)	9/13	9/11	1
age(year)[c]	46.23 ± 6.01	42.40 ± 7.55	0.15
BMI[c]	23.12 ± 2.55	23.84 ± 2.55	0.44
HDRS scores[c]	20.82 ± 2.28	6.15 ± 1.09	0.00

[a] Abbreviations: M, male; F, female; BMI, body mass index; HDRS, Hamilton depression rating scale.

[b] Two-tailed *t*-test for continuous variables (age, BMI, and HDRS scores); Chi-square analysis for categorical variables (sex). [c]Values expressed as means ± SDs.

Table 2
The top fold-change proteins in the acute phase response signaling pathway. ($P < 0.05$).

Protein name	Molecular Weight	p-Value	Fold-change
FGA	95 kDa	0.001022797	2.6
FGB	56 kDa	0.014263482	2.4
FGG	52 kDa	0.000697777	2.6
CFB	86 kDa	1.33701E−06	1.6
SERPIND1	57 kDa	3.07838E−05	1.8

(*$p < 0.05$), as shown in Fig. 2.

3.3. Identification of DEGs

After data normalization, 2113 genes were identified as DEGs between depressed patients and healthy controls samples based on the threshold of adjusted *$p < 0.05$ and $|\log(\text{fold-change})| > 0.05$, including 918 downregulated and 1196 upregulated genes . NUP85 was the most significantly upregulated gene; HAO1was the most significantly downregulated gene. The top 15 significantly upregulated and downregulated genes are listed in Table 3.

3.4. PPI network

A PPI network (118 nodes and 8521 edges) was constructed. Blue nodes correspond to DEPs from the microarray dataset, whereas red nodes correspond to the genes of the five proteins in the acute phase response signaling pathway (FGA, FGB, FGG, CFB, and SERPIND1). These five genes interacted with 11 genes (e.g., RANBP3, SH3BP5, PCDH1, TTR). The results of the PPI network analysis are presented in Fig. 3.

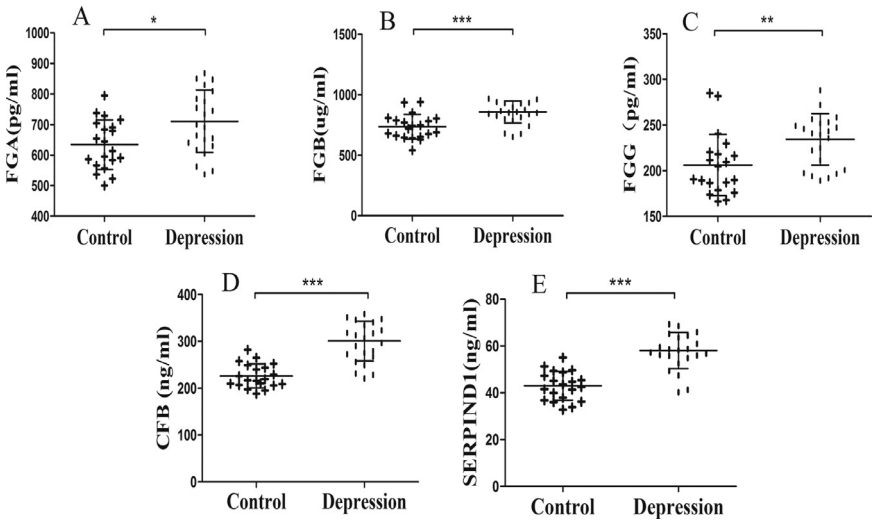

Fig. 2. ELISA quantification: (A) FGA (*p < 0.05, Student's t-test), (B) FGB (***p < 0.0001, Student's t-test), (C) FGG (**p < 0.001, Mann-Whitney U test), (D) CFB (***p < 0.0001, Student's t -test with Welch's correction), (E) SERPIND1 (***p < 0.0001, Student's t-test).

Table 3
The top 15 significantly upregulated and downregulated genes that presented differential expression are detailed below.

Gene ID	Fold Change	Log2 Fold Change	*P*-value
HAO1	0.435177948	−1.200322642	0.02650903
LOC100288152	0.717442274	−0.479065339	0.000188636
PRKG2	0.738426937	−0.437472912	0.006147677
CTSK	0.752243815	−0.410727754	0.000708022
SLC10A4	0.760546139	−0.394892322	0.016296176
AC068138.1	0.761149966	−0.393747365	0.000316177
RNF19A	0.764605861	−0.387211837	0.005657011
C10orf107	0.765791685	−0.3849761	0.004027005
SHKBP1	0.766128406	−0.384341881	0.000192704
ZNF674	0.772226445	−0.372904135	0.002505779
LOC101928716	0.77666876	−0.364628657	0.000575759
LOC101928002	0.777207042	−0.363629123	0.009148976
RP11-1081M5.2	0.778777399	−0.360717079	0.001659263
ALS2CR12	0.78012562	−0.358221643	0.009306496
DPM2	0.784246443	−0.350621015	0.000326936
NUP85	1.658791427	0.730132496	0.001648518
PSMD14	1.60341234	0.681145482	0.003742781
UNC45B	1.590427546	0.66941465	0.000302737
KRT25	1.542224938	0.625013202	0.003892533
C2orf42	1.416625787	0.502458709	0.001078829
NDST3	1.414628238	0.500422965	0.017211947
LOC101929272	1.393504424	0.478717582	5.97E−05
C8orf60	1.369890503	0.454060581	0.048520523
SPATA8	1.359119497	0.442672307	0.0072415
TNFRSF13B	1.35329643	0.436477886	3.17E−05
ZNF486	1.329585412	0.410976458	0.000121656
PTPN20B	1.328249281	0.409525931	0.000696089
NFKBIB	1.323392668	0.404241192	0.014847242
SEC14L5	1.31970914	0.400219999	0.000101535
HSPB1	1.310662782	0.390296545	0.000262435

3.5. GO enrichment analysis

To obtain insights into their potential biological roles, GO term enrichment analysis was performed on the DEGs and FGA, FGB, FGG, CFB and SERPIND. GO terms were predominantly associated with the biological processes of regulation of heterotypic cell-cell adhesiona and negative regulation of endothelial cell apoptotic process , as shown in Fig. 4.

4. Discussion

Depression is a widespread and debilitating mental disorder. Currently, there are no practical biomarkers available to accurately aid clinical diagnosis. In this study, the enriched GO terms were suspected that the biological processes of heterotypic cell-cell adhesiona and negative regulation of endothelial cell apoptotic process including more inflammation genes (e.g., IL10, IL1, IL4, TNF) may be associated with depression. We demonstrated that FGA, FGG, FGB, CFB and SERPIND1 were up-regulated in plasma from depressed patients. Finally, potential target genes (e.g.NRANBP3, SH3BP5, PCDH1, TTR) interacted with these five genes were identified from the PPI network. CFB and SERPIND1 in the acute phase response signaling pathway are the first to be reported as differentially expressed up-regulated proteins in plasma from depressed patients. These proteins, which in the acute phase response signaling pathway provide additional information on pathways that are affected in disease pathobiology, will promote further investigation of the disease.

The "acute phase response signaling pathway" is related to inflammatory reactions induced in response to infection or tissue injury (Kushner, 1988) .In recent years, inflammatory response dysfunction and inflammatory markers have been identified to be closely related to depression (Maes et al., 2016; Miller and Raison, 2016; Moylan et al., 2013). Several clinical studies have confirmed that the expression levels of inflammatory markers, such as interleukin-1(IL-1), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), interleukin 2 receptor (IL-2R), C-reactive protein (CRP), and acute phase reactants, were significantly elevated in depressed subjects compared with non-depressed subjects (Demir et al., 2015; Eyre et al., 2016; Liu et al., 2012; Maes, 1993; Sluzewska et al., 1996). A community study with a large sample size (2,861 individuals) reported that depressive symptoms have a positive relationship with the levels of TNF-α, IL-6, and CRP. TNF -α, IL-1β and IL-6 increased in blood are associated with suicidal behavior and ideation (Janelidze et al., 2011; O'Donovan et al., 2013). In addition, there is extensive evidence demonstrating that diseases of the central nervous system can cause activation of a potent peripheral acute phase response, which leads to inflammation and damage to the central nervous system (Rajkovic et al., 2016). In our previous study, the level of CRP and serum amyloid A1 both of which in the acute phase response signaling pathway, are increased in depressed patients (Wang et al., 2016). Therefore, it is possible that the identification of proteins in the acute phase response signaling pathway may ultimately provide new biomarkers for depression.

Fibrinogen is a 340-kDa glycoprotein that is mainly synthesized in hepatocytes. It has a dimer that circulates in plasma and is composed of three pairs of polypeptide chains, denoted α, β and γ. These chains are

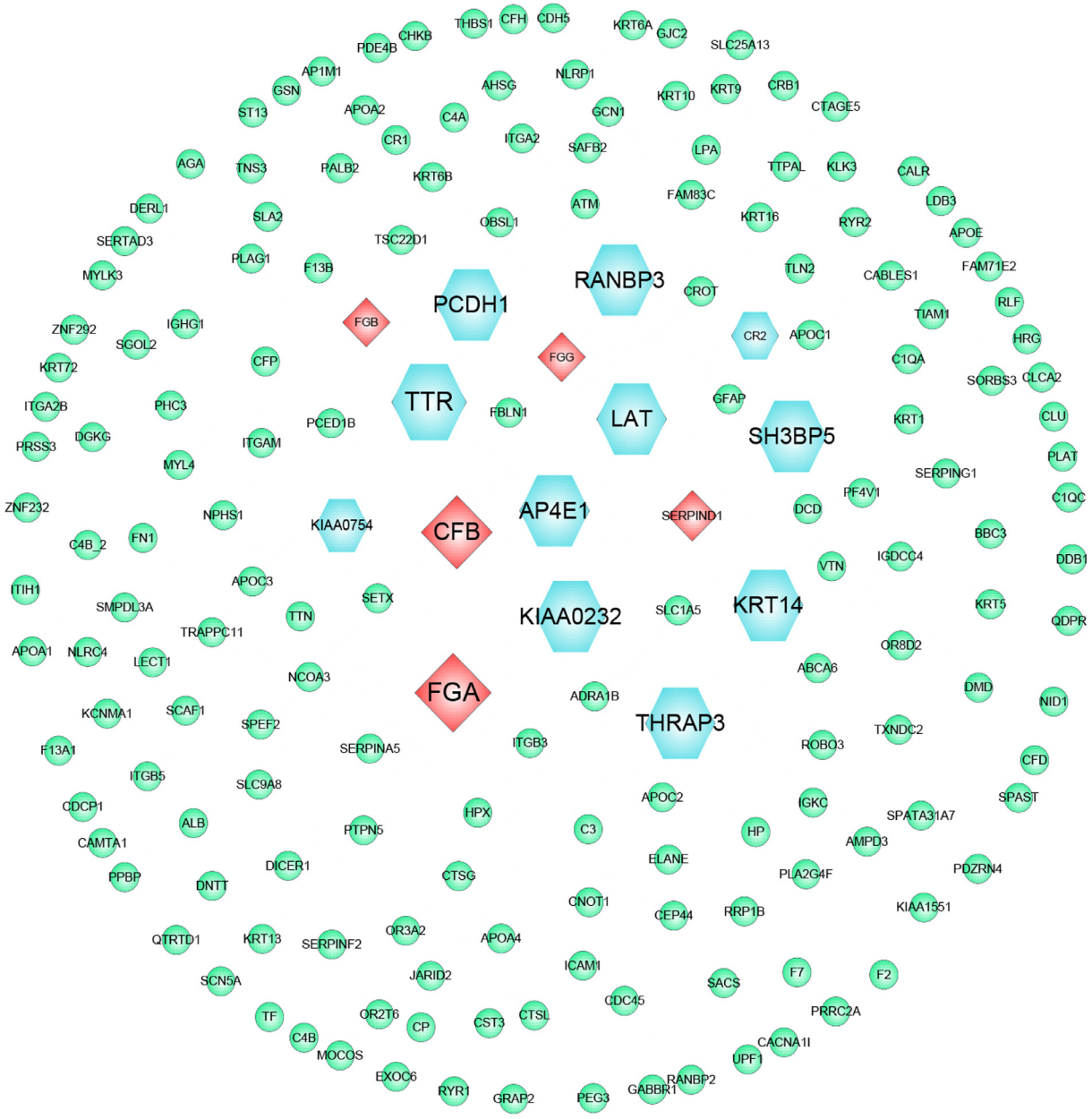

Fig. 3. A display of the biological process attributed to the genes (DEPs from the microarray dataset, FGA, FGB, FGG, CFB and SERPIND1) in network.

encoded by FGA, FGB and FGG. Fibrinogen is essential for blood coagulation, inflammation, and angiogenesis. Previous studies have shown that in patients with MDD, the plasma fibrinogen levels increased,(Maes et al., 1997; Wium-Andersen et al., 2013) although conflicting results have also been reported(Baune et al., 2010; Doulalas et al., 2006; Matthews et al., 2007). The increased fibrinogen levels might have caused axonal damage and subsequent depressive disorder (Hattori et al., 2015). Fibrinogen is also an acute phase reactant in vivo that helps regulate inflammatory cellular reactions (Lolis and Bucala, 2003). Patients with increased fibrinogen can damage the blood brain barrier induced by neuroinflammation, which is in accordance with the mild inflammation hypothesis in the etiology of major depressed disorder (Krishnadas and Cavanagh, 2012; Rosenblat et al., 2014). We found that patients with depression had high plasma fibrinogen levels compared with the controls. Further studies are needed to examine the possible relationship between fibrinogen levels and depression.

The complement system plays an important role in host defense against infection by coordinating events during inflammation and bridging innate and adaptive immune responses (Lolis and Bucala, 2003). Proteins involved in complement system activation could be interesting candidates to stratify treatment-resistant depression at the molecular level(Ruland et al., 2016). Complement activation is initiated by three sub-pathways, namely, the classical pathway, alternative pathway and lectin pathway. CFB plays a key role in the alternate pathway (Wagner and Frank, 2010). CFB induces cell injury. Moreover, complement can promote toll-like receptor-induced IL-6 production (Fang et al., 2009). The secretion of CFB seems to be affected by pro-inflammatory cytokines, such as L1β, TNF-α, and interferon γ (IFNγ) (Sumiyoshi et al., 1997). Pro-inflammatory cytokines, such as IL-1β and TNF-α, can up-regulate the corresponding transporter to change the extra-cellular serotonin (5-HT) concentrations (Hirschfeld, 2000; Ramamoorthy et al., 1995). In this way, pro-inflammatory cytokines can directly reduce 5-HT levels, which are associated with symptoms of depression (Allison and Ditor, 2015).

SERPIND1, also known as heparin cofactor II (HCII), is a member of

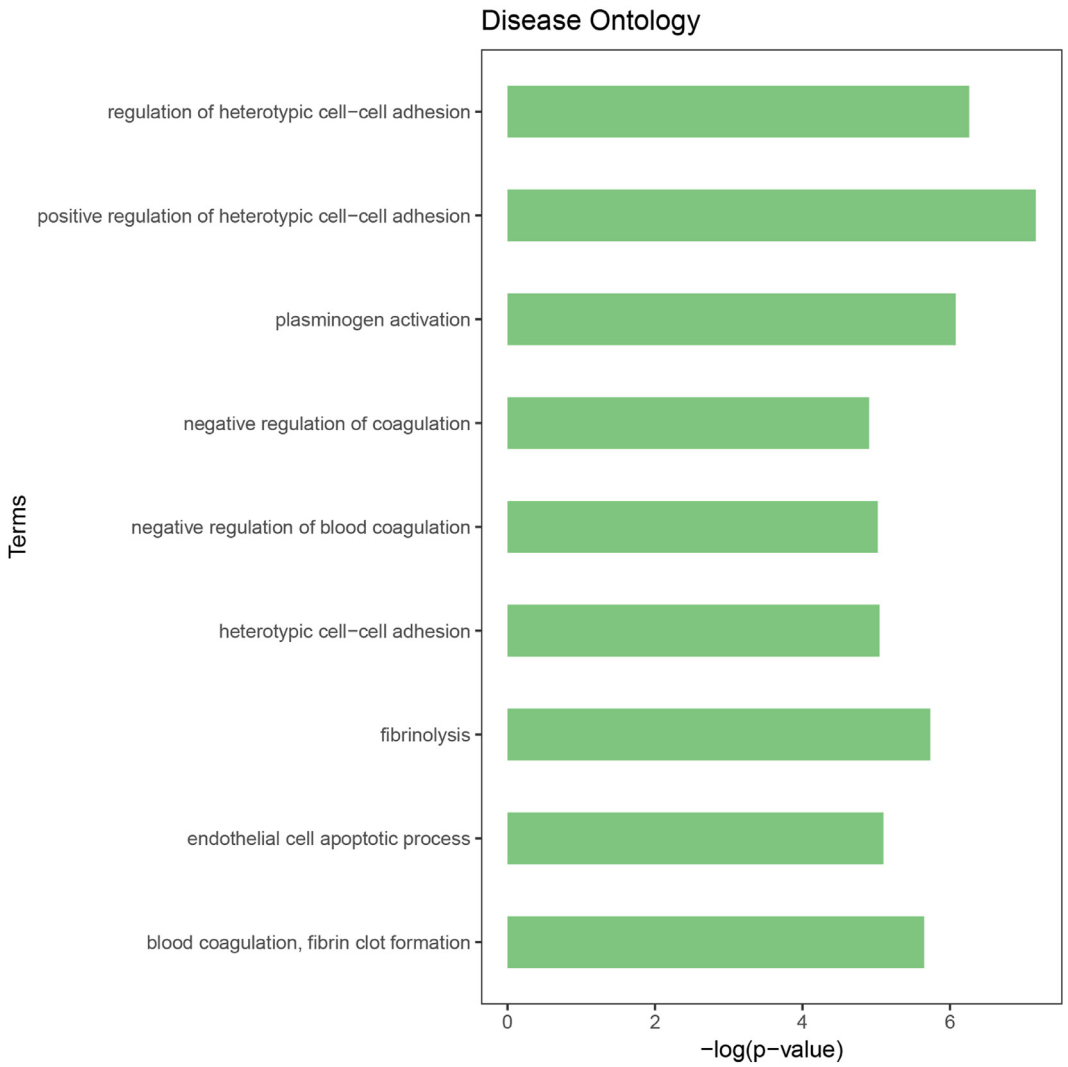

Fig. 4. An overview of the protein-protein interaction network. Blue nodes correspond to DEPs from the microarray dataset, whereas red nodes correspond to FGA, FGB, FGG, CFB and SERPIND1. The connecting lines represent the relationships.

the family of serine protease inhibitors. HCII has antithrombin activity in the inflammatory reaction (Corral et al., 2004; Wang et al., 2005). Thrombin activity, which is regulated by HCII, is the key to inhibit arterial thrombosis, which is associated with disseminated intravascular coagulation and inflammatory diseases (He et al., 2002; Noda et al., 2002). HCII has been identified as differentially abundant in plasma and is also related to cognitive or neuroimaging markers, which indicates that it may be involved in the pathology of the cerebrovascular component in Alzheimer's disease (Muenchhoff et al., 2016). HCII was first detected as up-regulated in plasma in depressed patients, which suggests that there is value in studying it further.

Author contributions

Conceived and designed the experiment: Qi Wang, Taiming Wei, Jian Zhang. Performed the experiments: Xiaojie Su, Yongqing Ding, Chunquan Li, Xiwu Zhao, Wenhai Jiang. Analyzed the data: Shanshan shi, Chunyue yu, Yanan Sun, Min Liu. Wrote the paper: Qi Wang, Chunyue yu, Taiming Wei.

Conflict of interest

The authors declare that they have no competing interest.
All authors have contributed to and approved the final manuscript.

Role of the funding source

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.11.069.

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