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Identifying key genes, pathways and screening therapeutic agents for manganese-induced Alzheimer disease using bioinformatics analysis

JunJun Ling, MD[a,b], Shengyou Yang, MD[c], Yi Huang, MD[d], Dongfeng Wei, PhD[e], Weidong Cheng, PhD[a,*]

Abstract

Alzheimer disease (AD) is a progressive neurodegenerative disease, the etiology of which remains largely unknown. Accumulating evidence indicates that elevated manganese (Mn) in brain exerts toxic effects on neurons and contributes to AD development. Thus, we aimed to explore the gene and pathway variations through analysis of high through-put data in this process.

To screen the differentially expressed genes (DEGs) that may play critical roles in Mn-induced AD, public microarray data regarding Mn-treated neurocytes versus controls (GSE70845), and AD versus controls (GSE48350), were downloaded and the DEGs were screened out, respectively. The intersection of the DEGs of each datasets was obtained by using Venn analysis. Then, gene ontology (GO) function analysis and KEGG pathway analysis were carried out. For screening hub genes, protein–protein interaction network was constructed. At last, DEGs were analyzed in Connectivity Map (CMAP) for identification of small molecules that overcome Mn-induced neurotoxicity or AD development.

The intersection of the DEGs obtained 140 upregulated and 267 downregulated genes. The top 5 items of biological processes of GO analysis were taxis, chemotaxis, cell-cell signaling, regulation of cellular physiological process, and response to wounding. The top 5 items of KEGG pathway analysis were cytokine–cytokine receptor interaction, apoptosis, oxidative phosphorylation, Toll-like receptor signaling pathway, and insulin signaling pathway. Afterwards, several hub genes such as INSR, VEGFA, PRKACB, DLG4, and BCL2 that might play key roles in Mn-induced AD were further screened out. Interestingly, tyrphostin AG-825, an inhibitor of tyrosine phosphorylation, was predicted to be a potential agent for overcoming Mn-induced neurotoxicity or AD development.

The present study provided a novel insight into the molecular mechanisms of Mn-induced neurotoxicity or AD development and screened out several small molecular candidates that might be critical for Mn neurotoxicity prevention and Mn-induced AD treatment.

Abbreviations: AD = Alzheimer disease, APP = amyloid precursor protein, CMAP = Connectivity Map, DEGs = differentially expressed gene, GEO = Gene Expression Omnibus, GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, Mn = manganese, PPI = protein–protein interaction.

Keywords: Alzheimer disease, differentially expressed genes, dysfunctional pathway, function enrichment analysis, manganese

1. Introduction

Alzheimer disease (AD) is a progressive neurodegenerative disease clinically characterized by cognitive impairment,

[a] Department of Traditional Chinese Medicine, Southern Medical University, Guangzhou, [b] Institute of Cancer, Xinqiao Hospital, Third Military Medical University, Chongqing, [c] Department of Medical Image, Guizhou Provincial People's Hospital, [d] Department of Internal Medicine, Affiliated Hospital of Guizhou Medical University, Guiyang, [e] Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, China.

* Correspondence: Weidong Cheng, Department of Traditional Chinese Medicine, Southern Medical University, Guangzhou 510515, China (e-mail: chengweidong888@mail.com).

ultimately leading to dementia in late stage of life. Evidence indicates that genomic, epigenomic, cerebrovascular, metabolic, and environmental factors might contribute to AD.[1] However, despite great progress in basic and clinical research of AD, its etiology remains largely unknown. Notably, the treatments for AD can only improve the symptoms to some extent without hampering the disease progression.[2] Therefore, to find risk factors for AD may help prevent or postpone the onset of this disorder.

Recently, more attention has been focused on the roles of homeostasis of some metal elements in the development of AD.[3] A meta-analysis indicated that higher levels of copper and lower levels of zinc can be found in the serum of patients with AD relative to the controls.[4] Also, environmental exposure to cadmium[5] or arsenic[6] may be a risk factor for AD. Thus, the imbalance of the trace elements in the body might increase the susceptibility to AD.

Manganese (Mn) is an essential heavy metal that is widely spread in the environments such as mineral and soil. It is an indispensable part of several key enzymes that play a role in cell growth and functions. Nevertheless, excess Mn in the body may exert toxic effects on cells. A report showed that elevated Mn in brain may have a relation with progressive cognitive impairment and thus contribute to AD development.[7] Besides, Mn can induce impairment of learning and memory ability.[8] The levels of Mn in the hair of patients with AD are higher than those of

healthy controls.[9] Therefore, high Mn concentration might be a risk factor for AD.

The mechanisms of Mn exerting toxic effects on neurons are still not clear. Previous evidence only concentrated on any certain molecular gene or pathway, without considering that multiple genes and pathways are involved in this process. Thus, in the present study, we aimed to explore the gene and pathway variations through analysis of high through-put data.

To screen the differentially expressed genes (DEGs) that may play critical roles in Mn-induced AD, public microarray data regarding Mn-treated neurocytes versus controls, and AD versus controls, were downloaded and analyzed by using bioinformatics methods. Then, the functions of the candidate genes were further evaluated.

2. Materials and methods

2.1. Data source

Datasets were retrieved and obtained from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/). The study type was restricted to Expression profiling by array, and human species. As a result, 2 datasets (GSE70845 and GSE48350) were selected and downloaded for further analysis. GSE70845 contained 6 specimens that were divided into 2 groups, namely, Mn-treated nerve cells and the controls. GSE48350 comprised 253 specimens (80 AD cases and 173 controls).

2.2. Screening of DEGs

To screen the DEGs, the data of the selected 2 datasets were submitted to GEO2R web tool[10] for analysis, respectively. The results were downloaded in text format, in which the genes that met the cutoff criteria of $P < .05$ and |fold change >1.2 were selected as DEGs.

2.3. Acquiring the intersection of DEGs

To screen genes that expressed differentially both in the Mn-treated nerve cells versus controls, and in AD versus healthy brain tissues, the intersection of the DEGs originated from the above two expression profiles (GSE70845 and GSE48350) was obtained by using Venn analysis.[11] The intersection of DEGs originated from 2 GEO datasets (GSE70845 and GSE48350) were used in the subsequent analysis.

2.4. Functional enrichment analysis of DEGS

To explore the possible functions of the DEGs, gene ontology (GO) function analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed by using Gather tool.[12] For both analyses, a P value of <.05 was considered as statistically significant, respectively.

2.5. Protein–protein interaction network construction

To screen the possible hub genes/proteins that might be critical in the progression of Mn-induced AD, the DEGs were submitted to STRING and Cytoscape tools, respectively, to predict their interaction relationship.

In the STRING tool, a combined score of not <0.40 (median confidence score) was considered significant. The hub genes/proteins were selected on the basis of its relationship with other genes/proteins, which were sorted by the betweenness value in the network.

2.6. Identification of small molecules that overcome Mn-induced AD

The CMAP database (http://www.broad.mit.edu/cmap/) contains whole genomic expression profiles for small active molecular inferences, containing 6100 classes of small molecular interference experiments and 7056 expression profiles.[13] The DEGs were submitted to CMAP for analysis. Compounds with negative connectivity enrichment scores, which imply a mode of action by the matched compounds to reverse the expression direction of query genes, were selected as potential therapeutic agents for Mn-induced neurotoxicity or AD development.

3. Results

3.1. DEGs screened from the selected 2 GEO datasets

Two GEO datasets (GSE70845 and GSE48350) were downloaded from GEO database (Table 1).

GSE70845 dataset contains 6 specimens (three specimens of SHSY5Y cells treated with sublethal concentration of Mn 100 μ mol/L for 24 hours and 3 controls). Thus, specimens in the GSE70845 dataset were classified as 2 groups (Mn-treated group and the control group). Compared to the control group, 1778 upregulated and 1379 downregulated DEGs were screened from Mn-treated group in the GSE70845.

GSE48350 dataset is an AD gene expression profile, containing 80 AD specimens and 173 healthy controls. There were 1346 upregulated DEGs and 2572 downregulated DEGs obtained from the comparison of the AD group and control group (Table 2).

3.2. The intersection of DEGs

To acquire the DEGs that play a role in Mn-induced AD, venn analysis was used to obtain the DEGs both in the comparison of AD vs normal tissues, and in the comparison of Mn-treated nerve cells versus controls. As shown in Figure 1, a total of 140 upregulated and 267 downregulated DEGs were obtained.

3.3. Functional annotation and pathway enrichment of DEGs

To annotate the biological processes of DEGs, they were clustered through GO analysis. The results showed that the DEGs were associated with multiple biological processes. The top 5 were taxis, chemotaxis, cell-cell signaling, regulation of cellular physiological process, and response to wounding. Then, we conducted KEGG pathway enrichment analysis (Fig. 2A). The DEGs were enriched in multiple KEGG pathway analysis, mainly including cytokine-cytokine receptor interaction, apoptosis, oxidative phosphorylation, Toll-like receptor signaling pathway, and insulin signaling pathway (Fig. 2B).

Table 1

Gene expression datasets used in this study.

GEO accession	Data type	Case/control	Sample type	Year
GSE70845	mRNA-array	3/3	Cell line (SHSY5Y)	2016
GSE48350	mRNA-array	80/173	Human brain tissue	2014

Table 2

The most significant up- and downregulated DEGs in GSE70845 and GSE48350.

GSE70845				GSE48350			
ID	Gene symbol	Fold change	*P*	ID	Gene symbol	Fold change	*P*
Upregulated				Up-regulated			
11763055_x_at	EEF1A1	2.499168197	5.80E-03	1558620_at	ZNF621	8.320736717	7.40E-92
200010_PM_at	RPL11	2.46050884	1.22E-03	224588_at	XIST	5.298875019	7.34E-04
11757552_x_at	ARPC3	2.416912091	3.33E-03	206552_s_at	TAC1	4.41206532	1.58E-19
11715421_a_at	CCT2	2.326122863	8.15E-03	202018_s_at	LTF	2.412157099	3.08E-07
11720311_a_at	XRCC5	2.294394865	1.52E-02	208451_s_at	C4B_2	2.34029194	1.45E-06
11725930_s_at	HSPA5	2.290418138	9.39E-04	212063_at	CD44	2.188643563	1.22E-04
11720757_a_at	IVNS1ABP	2.288824745	5.94E-04	211919_s_at	CXCR4	2.174462562	2.90E-09
11755205_a_at	HSPH1	2.273868777	1.30E-04	229259_at	GFAP	2.026147902	1.80E-05
11750093_a_at	PRICKLE4	2.233958368	2.69E-04	204846_at	CP	2.008270314	7.39E-04
11757113_a_at	SNHG1	2.189890905	1.96E-02	217028_at	CXCR4	1.965429098	3.19E-07
Downregulated				Down-regulated			
11753872_x_at	MT3	−3.359876024	4.23E-06	1556366_s_at	LY86-AS1	−2.023122433	1.99E-07
11715204_x_at	HIST2H2AC	−3.362068223	1.38E-06	242372_s_at	MFSD4A	−2.03370374	3.30E-06
11757262_at	SCARNA20	−3.410604105	6.79E-07	224650_at	MAL2	−2.039086801	9.32E-07
11718141_at	DKK1	−3.416790282	3.84E-04	210315_at	SYN2	−2.063200575	1.57E-04
11715132_x_at	HIST1H2BH	−4.298036397	4.39E-07	1553410_a_at	ABCC12	−2.071117968	1.18E-08
11757120_at	EIF4A2	−4.499037213	9.59E-07	204338_s_at	RGS4	−2.093880546	1.34E-03
11734659_a_at	FOS	−4.57393131	4.53E-07	213921_at	SST	−2.206367085	6.50E-06
11757127_at	SNORA23	−5.268798477	1.12E-06	240532_at	SLC32A1	−2.218953554	2.96E-06
11757164_s_at	SNORA32	−5.862452385	6.46E-06	223913_s_at	MIR7-3HG	−2.228416325	3.12E-10
11763956_at	SCARNA14	−10.60595039	5.09E-07	205625_s_at	CALB1	−2.264264443	4.59E-06

DEGs = differentially expressed gene.

3.4. Protein–protein interaction network of DEGs

String and cytoscape loaded with cytoHubba plugin were used to predict protein interactions and construct network topology of DEGs, respectively. In the network, hub genes were ranked by betweenness (Table 3 and Fig. 3). The top 5 genes were *INSR*, *VEGFA*, *PRKACB*, *DLG4*, and *BCL2* (ranked by degree: *VEGFA*, *ENO2*, *DLG4*, *BCL2*, and *INSR*), indicating that they might play essential roles in Mn-induced neurotoxicity or AD development.
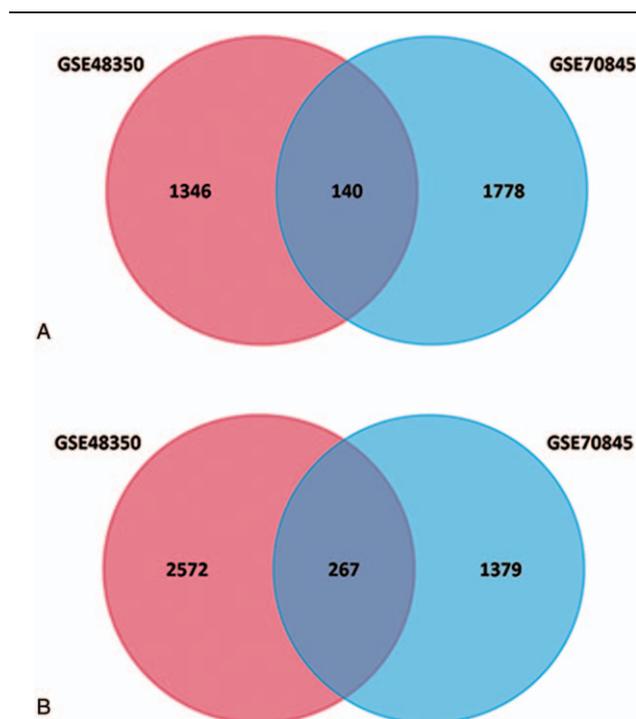
3.5. CMAP analysis

For the purpose of exploring small molecules that might reverse the biological process, DEGs were submitted to CMAP for analysis. *P* values, permutated results, and enrichment scores were used to analyze the perturbagens from the CMAP. As shown in Table 4, the most top related small molecules ranked by negative enrichment scores were listed. Tyrphostin AG-825, an inhibitor of tyrosine phosphorylation, with the highest negative enrichment score, might have a potential to reverse the biological process of Mn-induced neurotoxicity or AD development.

4. Discussion

In the present study, we aimed to explore the possible molecular mechanisms underlying Mn-induced AD by using bioinformatic methods. The results showed that a total of 140 upregulated and 267 downregulated DEGs were screened out from 2 GEO datasets. The GO analysis indicated that these genes were mainly enriched in items such as taxis, chemotaxis, cell-cell signaling, regulation of cellular physiological process, and response to wounding. Although the pathway analysis showed that some pathways such as cytokine-cytokine receptor interaction, apoptosis, oxidative phosphorylation, Toll-like receptor signaling pathway, and insulin signaling pathway may be involved in the biological process of Mn-induced AD. Afterwards, protein–protein interaction (PPI) analysis revealed that several genes/proteins such as *INSR*, *VEGFA*, *PRKACB*, *DLG4*, and *BCL2* may be the hub genes that may play key roles during the
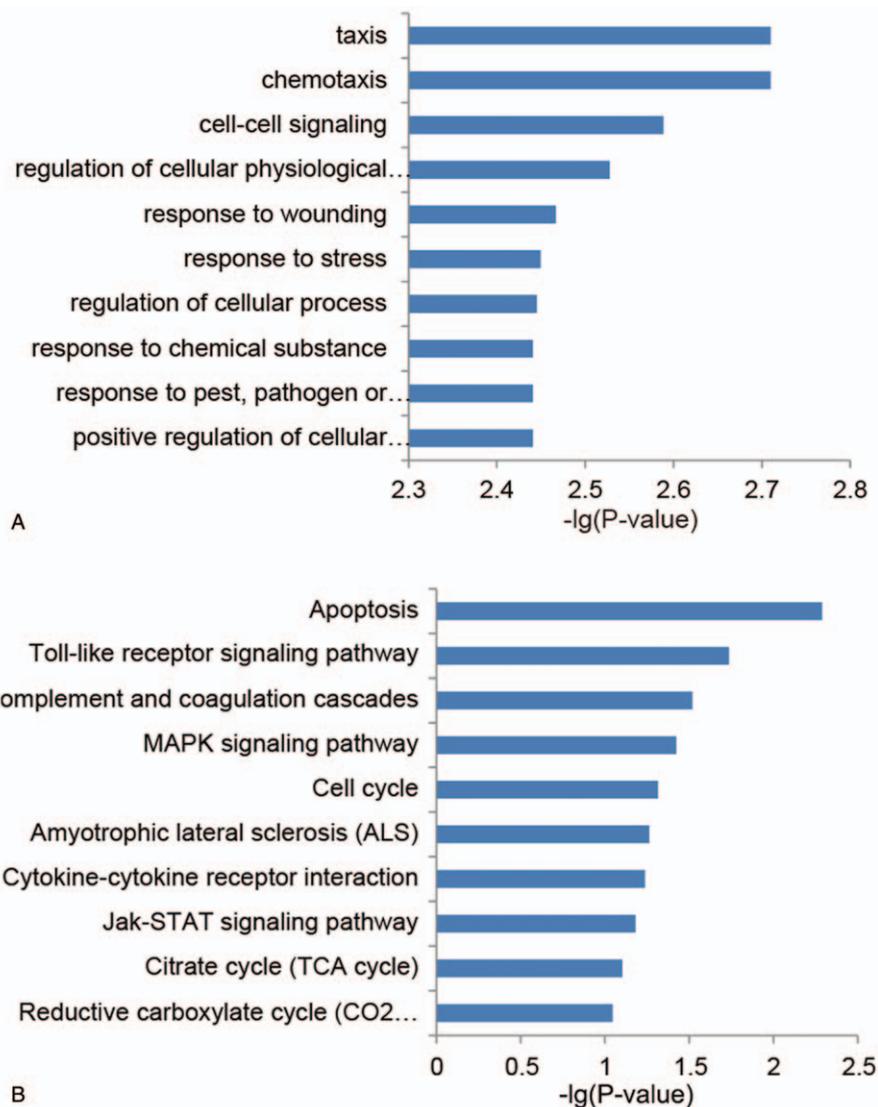

Figure 1. Intersection of the up- and downregulated differentially expressed gene (DEGs) from GSE70845 and GSE48350. (A) Upregulated DEGs. (B) Downregulated DEGs.

Figure 2. The top 10 GO (A) and KEGG (b) pathway enrichment analysis.

biological process. Furthermore, using the CMAP tool, a small molecule, Tyrphostin AG-825, was predicted to be a potential agent for preventing or overcoming the Mn-induced neurodegeneration.

Previous studies have explored the possible molecular mechanisms of Mn-induced neurodegeneration. For example, a recent report indicated that Mn can induce oxidative stress and dopaminergic toxicity in nerve cells.[14] Pathways such as iNOS/NF-κB and HO-1/Nrf2 may play a role in Mn-induced oxidative stress.[15] In addition, P53 signaling might also be involved in this process.[16] Nevertheless, although these researchers endeavored to investigate the molecular mechanisms of Mn-induced neurotoxicology, they only concerned any certain gene or pathway indicated by the literature. Although in the present study, we screened the DEGs based on microarray data from the public database. To our knowledge, we for the first time screened the DEGs and selected the hub genes/proteins during Mn-induced AD by using bioinformatics methods.

Through functional enrichment analysis, we observed that some items may have an association with Mn-induced AD. For

example, GO analysis showed that the DEGs may have a relationship with taxis, chemotaxis, cell-cell signaling, regulation of cellular physiological process, and response to wounding. The results indicated that cell mobility, interaction, and signaling might play a role in the Mn-induced biological process. Moreover, KEGG pathway enrichment analysis showed that the DEGs may be enriched in pathways such as cytokine-cytokine receptor interaction, apoptosis, oxidative phosphorylation, Toll-like receptor signaling pathway, and insulin signaling pathway, suggesting that cell interaction, oxidative stress, and pathways related to cell apoptosis may be the major cell signaling pathways.

To screen the genes/proteins that might play central roles in the biological process, PPI analysis was conducted. As a result, a series of hub genes (proteins) have been shown to form a local network, of which, several genes/proteins such as *INSR*, *VEGFA*, *PRKACB*, *DLG4*, and *BCL2* have been implied to have high betweennesses relative to other genes/proteins, indicating that these genes/proteins might play critical roles in Mn-induced AD. INSR (insulin receptor) was involved in insulin signaling. Evidence indicated that insulin signaling deficiencies or resistance

Table 3

The top 5 hub genes in the PPI network.

Node name	Betweenness	Degree	Closeness	Clustering coefficient
INSR	10052.43	16	97.01667	0.10833
VEGFA	6684.931	21	96.51667	0.10952
PRKACB	5822.166	14	86.83333	0.05495
DLG4	5737.729	18	92.23333	0.09804
BCL2	5625.714	17	95.9	0.14706

PPI = protein–protein interaction.

may have a relation with the progression of neurodegenerative disorders like AD. Insulin is accumulated as oligomers in hyperphosphorylated tau-bearing neurons in AD. The cells accumulating insulin show signs of insulin resistance and decreased insulin receptor levels.[17] VEGFA (vascular endothelial growth factor A) is a factor that has a close relationship with angiogenesis and microvascular function. However, microvascular dysfunction is considered an integral part of AD pathogenesis, with VEGFA involved.[18] The excess VEGFA in the brain of AD patients can damage neurons, blood vessels, and other components of the neurovascular units.[19] PRKACB (protein kinase A subunits Cβ) is a subunit of PKA that has been widely studied in signal transduction research.[20] It can play a role in tau phosphorylation.[21] The *DLG4* gene encodes for post-synaptic

density protein 95 (PSD95), a major synaptic protein that clusters glutamate receptors and is critical for plasticity. PSD95 is a player in memory and its levels are lowered in aging and neurodegenerative disorders, such as AD.[22] BCL-2 is a well-known factor that suppresses cell apoptosis. It is involved in the pathological process of AD and acts as a protective factor.[23] Taken together, the above evidence supported the notion that the hub genes might play critical roles in Mn-induced AD. However, it is still unknown whether these above hub genes can be used as potential targets for disease prevention and therapy. Future evaluations for the potential roles of the hub genes are warranted.

To predict the agent that might reverse the DEGs profiles, the DEGs were submitted to CMAP tool[24] for analysis. Consequently, a list of agents was screened out, of which Tyrphostin AG-825, a specific tyrphostin inhibitor of ErbB2,[25,26] had the highest negative enrichment score. Evidence showed that AG-825 have tumor suppressive function for multiple ErbB2-over-expressing cancer cells.[25,26] Meanwhile, Bo-Jeng Wang et al[27] found that ErbB2 may play a critical role in the pathogenesis of AD. The expression of ErbB2 is considered dormant during adulthood but reactivated during the pathogenesis of AD. The activated ErbB2 contributes to the accumulation of amyloid precursor protein (APP) C-terminal fragments (99-residue CTF [C99]) by blocking its autophagy-mediated clearance. At the meantime, APP-C99 can be converted to
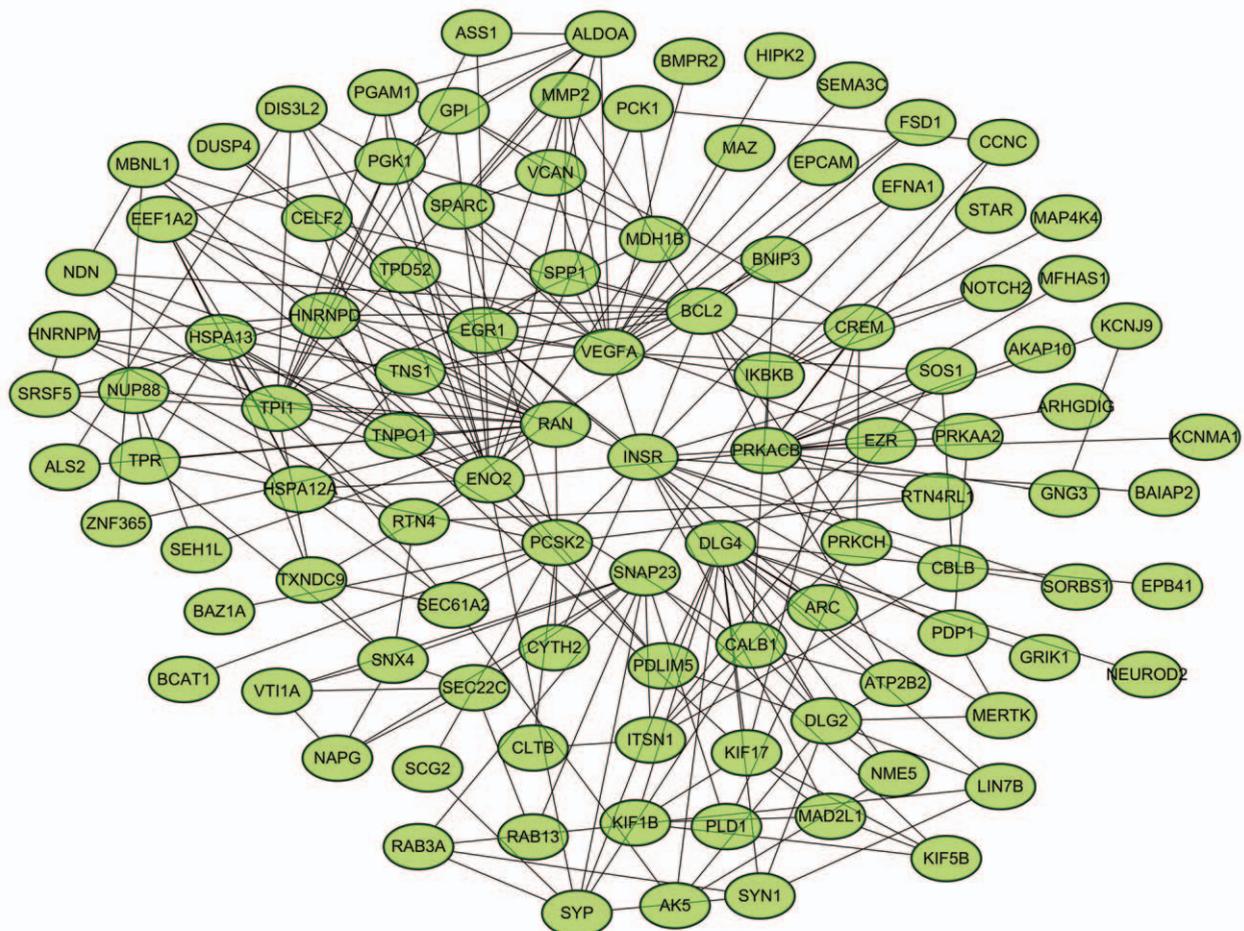

Figure 3. PPI network of differentially expressed gene (DEGs). Hexagons and ellipses were used to represent nodes and lines were used to represented edges. The ellipses represented the top 10 DEGs ranked by betweenness and the Hexagons represented others.

CMAP name	Mean	N	Enrichment	Percent non-null
Tyrphostin AG-825	−0.832	1	−0.997	100
Azacitidine	−0.837	3	−0.995	100
GW-8510	−0.851	4	−0.995	100
Irinotecan	−0.799	3	−0.993	100
H-7	−0.78	4	−0.99	100
Mycophenolic acid	−0.758	3	−0.988	100
Alsterpaullone	−0.758	3	−0.976	100
Tomelukast	−0.621	1	−0.969	100
Decitabine	−0.62	1	−0.969	100
MS-275	−0.722	2	−0.964	100

CMAP = Connectivity Map.

amyloid-β byγ-secretase-mediated proteolytical processes.[28] Furthermore, the inhibition of ErbB2 could significantly improve the cognitive functions of APP/presenilin-1 transgenic mice.[27] Thus, the evidence led us to hypothesize that AG-825 might be an potential agent reversing the DEGs profiles and thus overcoming Mn-induced AD. However, the future validation investigations are warranted to test this hypothesis.

In conclusion, the study provides preliminary investigation for the mechanisms underlying Mn-induced AD. DEGs were screened out by computational bioinformatics methods based on microarray data. Then, the aberrant pathways involved in this process were identified. Afterwards, several key hub genes were screened out. Using the CMAP tool, tyrphostin AG-825 that might have a potential to reverse the biological process have been predicted and analyzed. The results of the present study may give a valuable clue for both the basic research and clinical treatment of heavy metal-induced neurodegeneration diseases. However, future validation experiments are warranted to test the findings.

Author contributions

Conceptualization: Junjun Ling, Weidong Cheng.
Data curation: Weidong Cheng.
Formal analysis: Junjun Ling.
Investigation: Shengyou Yang, Yi Huang, Dongfeng Wei.
Project administration: Junjun Ling, Shengyou Yang, Yi Huang.
Resources: Dongfeng Wei.
Validation: Shengyou Yang, Yi Huang, Dongfeng Wei.
Writing – original draft: Junjun Ling.
Writing – review & editing: Junjun Ling.

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