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重度抑郁症发病机制关键基因和信号通路的生物信息学分析

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[摘要] **目的**:通过生物信息学方法分析与重度抑郁症分子生物学机制相关的关键基因和信号通路。**方法**:从美国国家生物技术信息中心网站GEO公共数据库获得脑皮质总mRNA表达谱数据(GSE101521),使用Networkanalyst在线数据库筛选正常组(非精神病人)和抑郁组(抑郁症患者)存在表达差异的基因;利用DAVID和KOBAS在线数据库进行GO功能和KEGG信号通路分析;STRING和Cytoscape软件进行PPI分子网络构建。**结果**:共筛选出41个差异基因,其中39个差异基因上调,2个差异基因下调。GO功能注释富集分析发现差异基因主要参与炎症反应,而KEGG通路分析表明与抑郁相关的最主要通路是IL-17信号通路,TNF信号通路和NOD样受体信号通路。通过蛋白-蛋白互作网络和模块分析筛选出了6个关键基因(*IL6*,*CXCL8*,*IL1B*,*FOS*,*CCL2*和*CXCL2*)。**结论**:本研究筛选出了重度抑郁症涉及免疫系统新的标志物和靶标,其参与了重度抑郁症关键发病机制。

[关键词] 重度抑郁症;差异基因;信号通路;生物信息学
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Identification of core genes and pathways in major depressive disorder by bioinformatic methods

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View from specialist: It is creative, and of certain scientific and educational value.

[ABSTRACT] **Objective**: To identify key genes and pathways associated with the molecular biological mechanisms of major depressive disorder through bioinformatics analysis in the Gene Expression Omnibus (GEO) public database of the National Center for Biotechnology Information website. **Methods**: The whole-transcriptome brain expression profile dataset (GSE101521) was obtained from the GEO database. Differentially-expressed genes (DEGs) in the normal group (non-psychiatric human) and the MDD group (depressive patients) were identified by applying Networkanalyst online database. Gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed to function annotation and enrichment analysis. After that, STRING online database was conducted to protein - protein interaction (PPI) network, and Cytoscape.3.7.2 software was performed to module analysis. **Results**: Out of the 41 DEGs identified from normal tissue samples and MDD, 39 were upregulated and 2 were downregulated. GO enrichment analysis discovered that DEGs were primarily involved in inflammatory response, and KEGG pathway analysis suggested that the most chiefly pathways related to MDD were IL-17 signaling pathway, TNF signaling pathway and NOD-like receptor signaling pathway. Six hub genes (*IL6*, *CXCL8*, *IL1B*, *FOS*, *CCL2*, and *CXCL2*) were identified by PPI network and module analysis. **Conclusion**: Our current study detected novel markers and targets

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involved immune system, which are involved in pivotal biological mechanisms related to the pathogenesis of major depression. Looking forward, these findings still need to be validated in future experimental studies.

[KEYWORDS] Major depressive disorder; Differentially-expressed genes; Signaling pathway; Bioinformatics

重度抑郁症是一种严重威胁全世界人民身心健康的精神类疾病,其主要特征是情绪低落并伴有疲劳、注意力不集中、睡眠障碍和语言障碍的精神障碍综合征[1].尽管人们对重度抑郁症进行了广泛深入的研究,重度抑郁症的发病机制已经取得了十分显著的进展,例如科学家发现单胺类特别是5-羟色胺的缺乏是重度抑郁症的重要发病机制之一[2]。然而越来越多的研究表明,单胺类神经递质的改变不足以解释重度抑郁症的全部发病机制,目前的治疗方案对某些抑郁症患者疗效有限甚至是无效。

重度抑郁症潜在的发病机制中,突触可塑性、表观遗传学和免疫系统起着十分重要的作用。进一步研究重度抑郁症发病机制的分子机制和信号通路,发现重度抑郁症新的诊断和治疗策略,仍极为重要的。幸运的是,随着高通量测序技术的发展,已发现新的核心基因和信号通路与重度抑郁症的发生和进展相关。例如,Jollant等[3]使用外周血转录组学阐明了5-羟色胺和nociceptin系统与抑郁症的活动相关。Hepgul等[4]则通过外周血转录组学分析发现抑郁症与IFN-α分子机制相关的多条证据。Wang等[5]通过分析mRNA的表达谱发现NF-κB信号通路在重度抑郁症的发作和发展中起重要作用。Carboni等[6]发现大脑海马转录因子在抑郁症患者和具有抑郁症症状的动物模型中生长因子信号传导和炎症反应均存在失调现象。因此,研究重度抑郁症的关键基因和信号通路,阐明关键基因和信号通路之间的相互作用网络,是进一步阐明重度抑郁症发病机制的基础。为此,本研究旨在通过运用生物信息学方法分析建立关键基因和信号通路作为重度抑郁症的生物标志物。

1 材料与方法

1.1 数据的获取与差异基因的筛选.

从美国国家生物技术信息中心网站GEO公共数据库下载重度抑郁症脑皮质基因表达谱数据GSE101521(https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi? acc=GSE101521)[7]。此数据是基于Illumina MiSeq人类平台GPL15520的基因表达数据信息。该数据集包括:猝死的非精神病个体中收集的29个大脑背外侧前额叶皮层样本和重度抑郁症死亡患者中收集的30个大脑背外侧前额叶皮层样本。本研究将GSE101521数据集分为两组,即正常组和重度抑郁症组,并提取数据。从GSE101521数据集中选取的counts数据通过edgeR在networkanalyst(https://www.networkanalyst.ca/)进行标准化,并利用networkanalyst筛选正常组和重度抑郁症组之间存在差异的基因。筛选标准设置如下:|log2Fold Change (FC)|>1并且校正后P值<0.05。

1.2 Gene Ontology (GO) 基因功能注释和KEGG信号通路富集分析

使用Database for Annotation, Visualization and Integrated Discovery (DAVID)在线数据库(https://DAVID.ncifcrf.gov/)进行Gene Ontology (GO)基因功能注释富集分析[8,9]。富集分析从生物过程(biological process, BP),细胞成分(cellular components, CC)和分子功能(molecular function, MF)三方面进行。此外,使用KOBAS在线数据库对KEGG信号通路进行分析(http://kobas.cbi.pku.edu.cn/kobas3)[10],筛选标准设置为P值<0.05。KEGG是一个在已知生物过程中整合了基因,化合物和调控网络的数据库,并在整体水平分析了基因功能和基因组。

1.3 蛋白-蛋白互作网络(Protein-protein interaction, PPI)分析

使用STRING 11.0在线软件(https://string-db.org/)[11]进行差异基因的PPI分析,采用Cytoscape 3.7.2[12]对结果进行可视化处理。使用Cytoscape软件的MCODE插件筛选PPI关键模块,Cytoscape的cytohubba插件筛选PPI关键基因。关键模块的筛选标准设置如下:Degree cut-off=2, node score cut-off=0.2, k-core=2和max. depth =100;关键基因的筛选标准设置为degree >10。对得分最高的关键模块中的差异基因再次进行GO功能注释富集分析和KEGG信号通路分析。

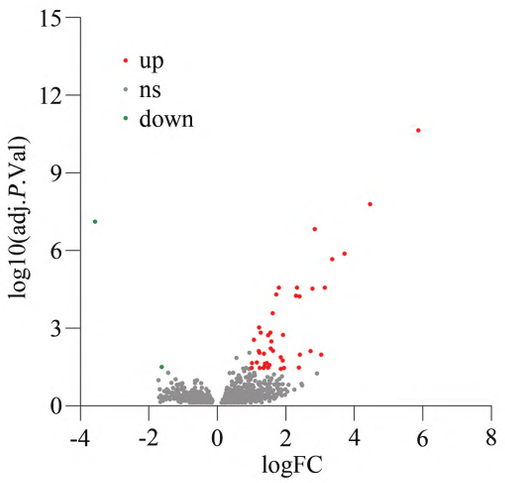
2 结果

2.1 差异基因的筛选

根据校正后P值<0.05和|log2(FC)|>1的筛选标准,共筛选出41个正常组和重度抑郁症组间见有显著差异的基因,其中39个差异基因上调,2个差异基因下调,见图1、表1。

2.2 GO功能注释富集分析和KEGG信号通路富

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红色代表上调表达基因，绿色代表下调差异表达基因，灰色代表无显著差异表达基因

图1 差异表达基因火山图

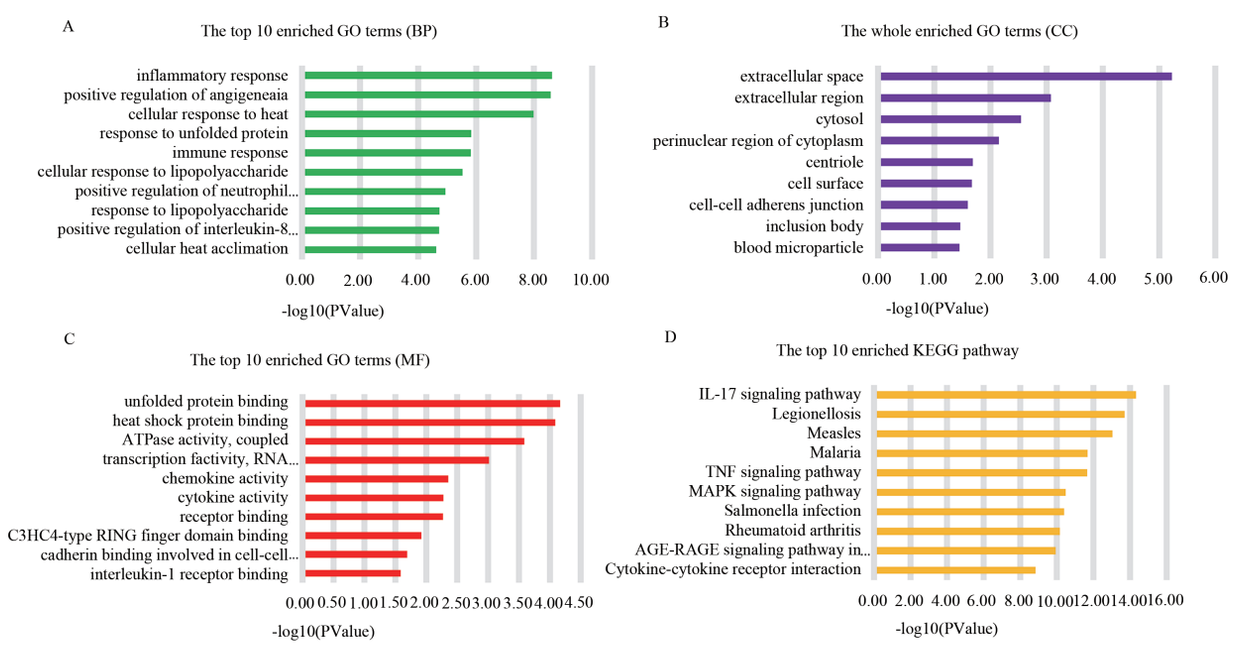
Fig 1 Volcano plot of genes with different expressions

集分析结果

使用DAVID在线数据库对41个显著差异基因进行GO功能注释富集分析。在生物过程（BP）方面，差异基因主要富集在炎性反应，血管生成的阳性调节和细胞对热的反应，见图2A。在细胞成分（CC）方面，差异基因主要富集在细胞外间隙，细胞外基质和胞液，见图2B。在分子功能（MF）方面，差异基因主要富集在未折叠蛋白结合和热休克蛋白结合，见图2C。KEGG信号通路富集分析结果显示，显著差异基因主要富集在IL-17信号通路，军团菌病和麻疹，见图2D。GO功能注释富集分析和KEGG信号通路富集分析结果显示，与抑郁最相关的生物学功能是炎症反应。

2.3 蛋白-蛋白互作网络（Protein-protein interaction，PPI）分析

为了筛选出了与重度抑郁症最为相关的差异基因，本研究使用STRING 11.0在线数据库进行PPI分析，将41个差异基因映射到PPI中，共包含28个节点和108条线，见图3A。PPI分析结果显示，28个差异基因对抑郁症的发病机制有影响。应用Cytoscape软件中的MCODE插件筛选出了PPI中3个群集。其中，集群1得分最高（分数＝8.222），包含10个节点（FOS、SELE、ATF3、CXCL8、TNFAIP3、IL-6、IL-1B、C5AR1、CCL2、CXCL2）和37条连接线，见图3B；群集2包含4个节点和6条连接线（分数＝4.000），见图3C；群集3包含3个节点和3条连接线（得分＝3.000）（图3D）。



（A）前10位差异表达基因GO功能分析结果（生物功能）；（B）前10位差异表达基因GO功能分析结果（细胞成分）；（C）前10位差异表达基因GO功能分析结果（分子功能）；（D）前10位差异表达基因KEGG信号通路富集分析结果。

图2 差异表达基因GO功能注释富集分析和KEGG信号通路分析

Fig 2 GO and KEGG enrichment analyses of DEGs

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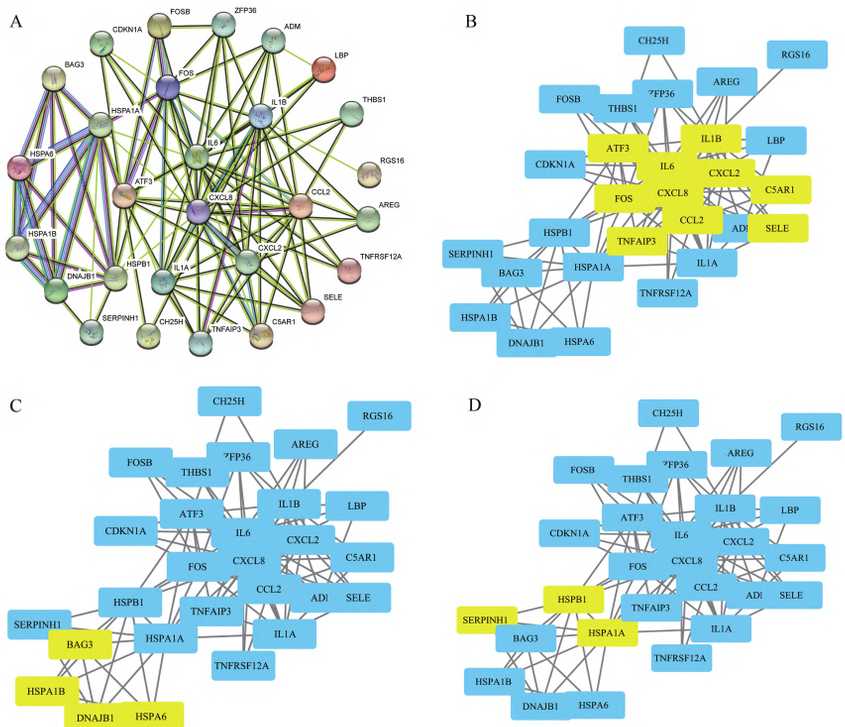
表1　正常组和重度抑郁组之间差异表达基因

Tab 1　Genes showing significant expressions between the normal and MDD groups.

Ensembl gene ID	Gene symbol	logFC	*P* value	adj. *P* val	Up/down−regulated
ENSG00000173110	*HSPA6*	5.873 7	7.23E−16	2.30E−11	up−regulated
ENSG00000225217	*HSPA7*	4.462 6	9.99E−13	1.59E−08	up−regulated
ENSG00000255823	*MTRNR2L8*	−3.573 6	7.15E−12	7.58E−08	down−regulated
ENSG00000149257	*SERPINH1*	2.847 7	1.86E−11	1.48E−07	up−regulated
ENSG00000169429	*CXCL8*	3.715 8	2.09E−10	1.33E−06	up−regulated
ENSG00000007908	*SELE*	3.134 1	7.36E−09	2.74E−05	up−regulated
ENSG00000108691	*CCL2*	2.327 8	7.73E−09	2.74E−05	up−regulated
ENSG00000125538	*IL1B*	2.403 1	2.37E−08	5.79E−05	up−regulated
ENSG00000261441	*AC124068.2*	2.723 9	5.78E−06	0.0075 57	up−regulated
ENSG00000136244	*IL6*	3.035 5	9.60E−06	0.0103 55	up−regulated
ENSG00000129988	*LBP*	2.378	4.43E−05	0.0332 71	up−regulated
ENSG00000162772	*ATF3*	1.800 9	7.74E−09	2.74E−05	up−regulated
ENSG00000170345	*FOS*	1.722 3	1.73E−08	5.00E−05	up−regulated
ENSG00000118503	*TNFAIP3*	1.618	1.14E−07	0.000 26	up−regulated
ENSG00000138135	*CH25H*	1.221 2	4.45E−07	0.000 943	up−regulated
ENSG00000132002	*DNAJB1*	1.269	7.87E−07	0.001 479	up−regulated
ENSG00000204389	*HSPA1A*	1.55	7.90E−07	0.001 479	up−regulated
ENSG00000217527	*RPS16P5*	1.916 3	1.04E−06	0.001 83	up−regulated
ENSG00000204388	*HSPA1B*	1.488 6	1.12E−06	0.001 876	up−regulated
ENSG00000198805	*PNP*	1.073 4	1.76E−06	0.002 802	up−regulated
ENSG00000166592	*RRAD*	1.578 5	2.12E−06	0.003 215	up−regulated
ENSG00000125740	*FOSB*	1.564 6	4.16E−06	0.006 012	up−regulated
ENSG00000115008	*IL1A*	1.622 5	5.33E−06	0.007 372	up−regulated
ENSG00000137801	*THBS1*	1.212 4	5.94E−06	0.007 557	up−regulated
ENSG00000106211	*HSPB1*	1.233 8	7.34E−06	0.008 704	up−regulated
ENSG00000124762	*CDKN1A*	1.361 7	8.49E−06	0.009 652	up−regulated
ENSG00000081041	*CXCL2*	1.854 7	1.27E−05	0.013 026	up−regulated
ENSG00000105825	*TFPI2*	1.910 5	1.80E−05	0.017 307	up−regulated
ENSG00000197405	*C5AR1*	1.151 3	2.20E−05	0.020 577	up−regulated
ENSG00000143333	*RGS16*	1.011 2	2.47E−05	0.022 019	up−regulated
ENSG00000128016	*ZFP36*	1.392 4	2.71E−05	0.023 341	up−regulated
ENSG00000006327	*TNFRSF12A*	1.520 2	3.15E−05	0.026 388	up−regulated
ENSG00000151929	*BAG3*	1.381 3	3.57E−05	0.029 147	up−regulated
ENSG00000146410	*MTFR2*	1.384 1	3.84E−05	0.030 542	up−regulated
ENSG00000214814	*FER1L6*	−1.625 8	4.04E−05	0.031 33	down−regulated
ENSG00000139151	*PLCZ1*	1.480 9	4.50E−05	0.033 271	up−regulated
ENSG00000148926	*ADM*	1.352 5	5.00E−05	0.034 381	up−regulated
ENSG00000146904	*EPHA1*	1.007 1	5.14E−05	0.034 381	up−regulated
ENSG00000133874	*RNF122*	1.235 8	5.19E−05	0.034 381	up−regulated
ENSG00000109321	*AREG*	1.855 1	5.83E−05	0.036 681	up−regulated
ENSG00000230650	*AC140479.2*	1.827 4	6.89E−05	0.042 138	up−regulated

在群集1中，Cytoscape软件的cytohubba插件将6个基因（*IL-6*、*CXCL8*、*IL-1B*、*FOS*、*CCL2*、*CXCL2*）筛选为关键基因（degree＞10）。对得分最高的集群1中的显著差异基因进行GO功能注释富集分析和KEGG信号通路富集分析。结果显示，对于GO功能注释富集分析，群集1的差异基因大部分在炎症反应和免疫反应中富集，见图4A。KEGG信号通路富集分析表明，群集1的差异基因主要富集在

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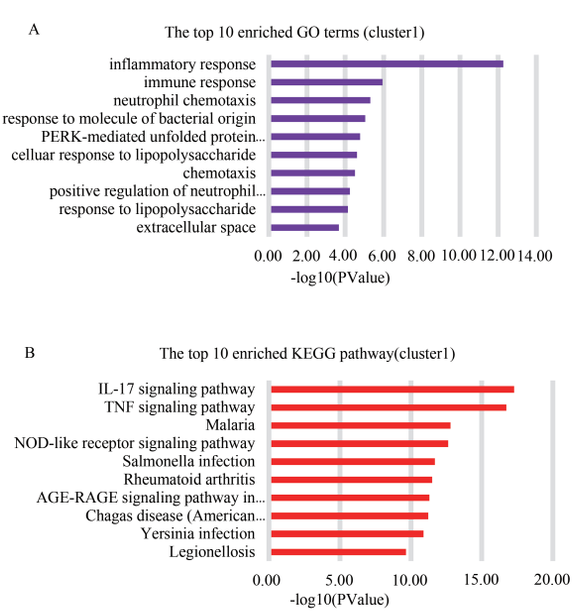


（A）蛋白－蛋白互作网络。带有颜色的节点代表蛋白，连接线代表蛋白之间的相互联系；（B）蛋白－蛋白互作网络集群1；（C）蛋白－蛋白互作网络集群2；（D）蛋白－蛋白互作网络集群3。

图3　差异表达基因蛋白－蛋白互作网络和MCODE集群

Fig 3　PPI network analysis of DEGs and MCODE clusters

IL-17信号转导通路，TNF信号通路和NOD样受体信号通路。全部6个关键基因（*CCL2*、*CXCL2*、*FOS*、*CXCL8*、*IL-6*和*IL-1B*）都被定位在IL-17信号通路上，5个关键基因（*CXCL2*、*CCL2*、*IL-1B*、*FOS*、*IL-6*）被定位在TNF信号上通路，见图4B。此外，还筛选出了5个关键基因（*CCL2*、*CXCL2*、*CXCL8*、*IL-6*和*IL-1B*）与群集1中的NOD样受体信号通路相关。



（A）集群1前10位GO功能富集结果；（B）集群1前10位KEGG信号通路富集结果。

图4　集群1的GO功能和KEGG信号通路富集分析

Fig 4　GO and KEGG enrichment analyses of cluster 1

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3 讨论

本研究筛选出了41个显著差异基因，进行了PPI分析和模块分析，筛选出了关键基因（*IL-6*、*CXCL8*、*IL-1B*、*FOS*、*CCL2*、*CXCL2*），KEGG信号通路分析结果表明，与重度抑郁症相关的最主要信号通路是IL-17信号通路，TNF信号通路和NOD样受体信号通路。本研究确定了可能参与重度抑郁症发病机制的免疫系统新的标志物和靶标。

随着高通量测序技术的发展，转录组学和下一代测序技术已经产生了大量的数据集，包括lncRNA、miRNA和mRNA表达谱。许多研究者通过使用生物信息学技术，筛选出大量核心基因和信号通路来预测重度抑郁症潜在的发病机制。与其他文献不同的是，本研究从GEO公共数据库获得了重度抑郁症患者脑皮质转录组表达谱的数据集（GSE101521），并应用生物信息学分析筛选出了与重度抑郁症最为相关的新的关键基因和信号通路。本研究利用DAVID在线数据库和KOBAS在线数据库进行GO功能注释富集分析和KEGG信号通路富集分析。DAVID对显著差异基因进行GO富集功能注释的结果以及KEGG信号通路富集分析结果表明，与重度抑郁症患者发病机制最为相关的关键功能标志是炎症反应。差异基因GO功能注释富集分析主要与生物过程有关，包括炎症反应，血管生成的正调节，细胞对热的反应，对未折叠蛋白的反应，免疫反应，细胞对脂多糖的反应等。

此外，本研究发现，显著差异表达基因富集到与重度抑郁症相关的KEGG信号通路是IL-17信号通路，TNF信号通路和NOD样受体信号通路。本研究部分结果与之前的研究结果一致，表明免疫和炎性反应是与重度抑郁症发病机制最为相关的生物学反应系统[13-15]。脑中炎性因子和炎症激活的增加在重度抑郁症的发病机制中起着十分重要的作用[16]。一些组学研究还表明了IL-17信号通路和TNF信号通路与抑郁症有关[17,18]。TNF-α通过NF-κB信号通路和促炎性细胞因子调节小胶质细胞的活化，在神经炎症中起关键作用[19]。IL-17信号触发细胞因子和趋化因子进而激活NF-κB信号通路[20]，抑制IL-17细胞因子家族可能对中枢神经系统的致病条件有益[21,22]。NF-κB信号级联反应也可以激活NOD样受体[23]，NOD样受体炎性体的活化和激活导致人类巨噬细胞随后释放IL-1B[24]. 因此，结合文献和本研究结果，笔者推测，NF-κB信号级联和NOD样受体信号的激活可能引起IL-17信号和TNF信号失调，并导致包括释放细胞因子和趋化因子（IL-1B、IL-6、CCL2、CXCL2）在内的一系列的免疫炎症反应，这在重度抑郁症的发病机制中至关重要

本研究结果表明，通过IL-17信号通路，TNF信号通路和NOD样受体信号通路激活了参与重度抑郁症发病机制中的关键基因（*IL-6*、*CXCL8*、*IL-1B*、*FOS*、*CCL2*、*CXCL2*），表明这些新的标志物和靶标参与了重度抑郁症的免疫炎症发病机制。不过，确切结论仍需实验研究验证。

参考文献

1 Serretti A, Mandelli L, Enrico L, et al. Depressive syndrome in major psychoses: A study on 1351 subjects [J]. Psychiat Res, 2004, 127(1-2): 85-99.

2 Heim C, Newport D, Mletzko T, et al. The link between childhood trauma and depression: Insights from HPA axis studies in humans [J]. J Psyneuen, 2008, 33(6): 693-710.

3 Jollant F, Perreira F, Fiori LM, et al. Neural and molecular correlates of psychological pain during major depression, and its link with suicidal ideas[J]. Prog Neuro-Psychopharmacol Biol Psychiatry, 2020, 109909.

4 Hepgul N, Cattaneo A, Agarwal K, et al. Transcriptomics in interferon-alpha-treated patients identifies inflammation-, neuroplasticity- and oxidative stress-related signatures as predictors and correlates of depression[J]. NPP, 2016, 41(10): 2502-2511.

5 Wang H, Zhang M, Xie Q, et al. Identification of diagnostic markers for major depressive disorder by cross-validation of data from whole blood samples [J]. Peer J, 2019, 7:e7171.

6 Carboni L, Marchetti L, Lauria M, et al. Cross-species evidence from human and rat brain transcriptome for growth factor signaling pathway dysregulation in major depression [J].NPP, 2018, 43(10): 2134-2145.

7 Pantazatos SP, Huang YY, Rosoklija GB, et al. Whole-transcriptome brain expression and exon-usage profiling in major depression and suicide: Evidence for altered glial, endothelial and ATPase activity [J]. Mol Psychiatry, 2017, 22(5): 760-773.

8 Huang DW, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources [J]. Nat Protoc, 2009, 4(1): 44-57.

9 Huang DW, Sherman BT, Lempicki RA. Bioinformatics enrichment tools: Paths toward the comprehensive

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functional analysis of large gene lists [J]. Nucleic Acids Res, 2009, 37(1): 1-13.

10 Xie C, Mao X, Huang J, et al. KOBAS 2.0: A web server for annotation and identification of enriched pathways and diseases [J]. Nucleic Acids Res, 2011, 39: W316-W322.

11 Szklarczyk D, Franceschini A, Wyder S, et al. STRING v10: Protein-protein interaction networks, integrated over the tree of life [J]. Nucleic Acids Res, 2015, 43: D447-D452.

12 Shannon P, Markiel A, Ozier O, et al. Cytoscape: A software environment for integrated models of biomolecular interaction networks [J]. Genome Res, 2003, 13 (11): 2498-2504.

13 Fleshner M, Frank M, Maier SF. Danger signals and inflammasomes: Stress-evoked sterile inflammation in mood disorders [J]. NPP, 2017, 42(1): 36-45.

14 Kiecolt-glaser JK, Derry HM, Fagundes CP. Inflammation: Depression fans the flames and feasts on the heat [J]. Am J Psychiatry, 2015, 172(11): 1075-1091.

15 Miller AH, Raison CL. The role of inflammation in depression: From evolutionary imperative to modern treatment target [J]. Nat Rev Immunol, 2016, 16 (1): 22-34.

16 Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression [J]. Psychol Bull, 2014, 140 (3): 774-815.

17 Yi Y, Liu Y, Wu K, et al. The core genes involved in the promotion of depression in patients with ovarian cancer [J]. Oncol Lett, 2019, 18(6): 5995-6007.

18 An T, He ZC, Zhang XQ, et al. Baduanjin exerts antidiabetic and anti-depression effects by regulating the expression of mRNA, lncRNA, and circRNA [J]. Chin Med, 2019, 14:3.

19 Kong X, Zhang Z, Fu T, et al. TNF-alpha regulates microglial activation *via* the NF-kappaB signaling pathway in systemic lupus erythematosus with depression [J]. Int J Biologic Macromolecul, 2019, 125:892-900.

20 Gu C, Wu L, Li X. IL-17 family: Cytokines, receptors and signaling [J]. Cytokine, 2013, 64(2): 477-485.

21 Ari W, Judith H, Tommy R. The role of IL-17 in CNS diseases [J]. Acta Neuropathol, 2015, 129 (5): 625-637.

22 Qia Y, Liu C, Hartupee J, et al. The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease [J]. Nat Immunol, 2007, 8(3): 247-256.

23 Choi AJ, Ryter SW. Inflammasomes: Molecular regulation and implications for metabolic and cognitive diseases [J]. Molecul Cells, 2014, 37(6): 441-448.

24 Engin A. The pathogenesis of obesity-associated adipose tissue inflammation[J]. Adv Exp Med Biol, 2017, 960: 221-245.

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