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REVIEW ARTICLE

Systems Genomics Support for Immune and Inflammation Hypothesis of Depression

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Abstract: ***Background***: Immune system plays an important role in brain development and function. With the discovery of increased circulating inflammatory cytokine levels in depression over two decades ago, evidence implicating immune system alterations in the disease has increasingly accumulated.

Objective: To assess the underlying etiology and pathophysiology, a brief overview of the hypothesis free genomic, transcriptomic and proteomic studies in depression is presented here in order to specifically examine if the immune and inflammation hypothesis of depression is supported.

Results: It is observed that genes identified in genome-wide association studies, and genes showing differential expression in transcriptomic studies in human depression do separately overrepresent processes related to both development as well as functioning of the immune system, and inflammatory response. These processes are also enriched in differentially expressed genes reported in animal models of antidepressant treatment. It is further noted that some of the genes identified in genome sequencing and proteomic analyses in human depression, and transcriptomic studies in chronic social defeat stress, an established animal model of depression, relate to immune and inflammatory pathways.

Conclusion: In conclusion, integrative genomics evidence supports the immune and inflammation hypothesis of depression.

Keywords: Antidepressant, depression, genome-wide association, immune, inflammation, proteomic, transcriptomic.

INTRODUCTION

Immune system plays an important role in brain development and function, by positively modulating, under normal conditions, neural plasticity, neurogenesis, and learning and memory [1]. This role is accomplished through intricate mechanisms involving non-neuronal brain cells with immune functions, peripheral immune cells, neurons, and neural precursor cells [1]. Complex interactions among neuronal and non-neuronal cells mediated by neuro-transmitters, inflammatory cytokines, and growth factors mainly underlie these mechanisms [1]. Following the initial discovery of increased levels of circulating inflammatory cytokines in depression [2-4], evidence implicating immune system alterations in the disease has increasingly been obtained in the last twenty five years [5-14]. Both environmental and genetic factors may potentially contribute to the development of depression *via* affecting immune and inflammatory processes [15]. Medical illness, obesity, childhood trauma, stress, poor sleep, and gastrointestinal inflammation are examples of environmental factors that are considered to raise the susceptibility to depression by causing chronic exposure to elevated levels of inflammatory cytokines [15]. With regard to genetic factors, hypothesis driven candidate gene analyses and unbiased genome-wide studies have provided evidence for the association of several immune and inflammation related genes in depression [16-18]. As hypothesis free genome level analyses provide powerful means to statistically identify potential molecular pathways underlying etiology and pathophysiology of complex disorders, this article aims at overviewing the available genomic, transcriptomic and proteomic data in depression to specifically examine if the immune and inflammation hypothesis of the disease is supported. Besides human studies, an overview of transcriptomic analyses in animal models of depression and antidepressant treatment is also provided in order to investigate whether preclinical data is consistent with the said hypothesis.

GENOME-WIDE ASSOCIATION STUDIES IN HUMAN DEPRESSION

With several genome-wide association studies in depression reported [19], a recent large scale pathway based analysis of single nucleotide polymorphisms (SNPs) underlying genetic risk has notably identified statistically significant association of immune pathway, besides neuronal signaling, synaptic and histone methylation pathways, in major depressive disorder (MDD), as also in bipolar disorder

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Table 1. Genome-wide association genes in depression overrepresenting immune and inflammation related processes.

Immune Response	Innate Immune Response	Immune System Process	Immune System Development
ADCY2	*ADCY2*	*ADCY2*	*BCL2*
ADCY9	*ADCY9*	*ADCY9*	*CHUK*
ATG12	*ATG12*	*ATG12*	*ETV6*
BCL2	*BCL2*	*BCL2*	*HDAC9*
CAMK2G	*CAMK2G*	*CADM1*	*NOTCH2*
CHUK	*CHUK*	*CAMK2G*	*NOTCH4*
EGFR	*EGFR*	*CHUK*	*PIK3R1*
ENPP1	*ERBB4*	*DBH*	*PLCG2*
ERBB4	*FGF6*	*DNM2*	*PPARG*
FGF6	*GRIN2A*	*EGFR*	*SYK*
GRIN2A	*HLA-DQA1*	*ENPP1*	*TNF*
HFE	*HLA-DQA2*	*ERBB4*	*ZAP70*
HLA-DOB	*HLA-DQB1*	*ETV6*	
HLA-DQA1	*HLA-DRA*	*FGF6*	
HLA-DQA2	*HSP90B1*	*GRIN2A*	
HLA-DQB1	*IFIT1*	*HDAC9*	
HLA-DRA	*ITPR1*	*HFE*	
HSP90B1	*ITPR2*	*HLA-DOB*	
IFIT1	*MAPK1*	*HLA-DQA1*	
ITPR1	*PIK3R1*	*HLA-DQA2*	
ITPR2	*PLCG2*	*HLA-DQB1*	
MAPK1	*PLD2*	*HLA-DRA*	
PIK3R1	*PPARG*	*HSP90B1*	
PLCG2	*PPP3R1*	*IFIT1*	
PLD2	*PRKCA*	*ITGA1*	
PPARG	*PRKCE*	*ITPR1*	
PPP3R1	*SPTBN1*	*ITPR2*	
PRKCA	*SYK*	*LRMP*	
PRKCE	*VAV3*	*MAPK1*	
PVRL1	*ZAP70*	*NOTCH2*	
SPTBN1		*NOTCH4*	
SYK		*PIK3R1*	
TNF		*PLCG2*	
VAV3		*PLD2*	
ZAP70		*PMAIP1*	
		PPARG	

Table 1. contd….

Immune Response	Innate Immune Response	Immune System Process	Immune System Development
		PPP3R1	
		PRKCA	
		PRKCE	
		PVRL1	
		RAB8B	
		SIRPG	
		SPTBN1	
		SYK	
		TNF	
		VAV3	
		ZAP70	

and schizophrenia [20]. This analysis of association data from over 60,000 subjects, encompassing the three neuropsychiatric diseases mentiond above, is based on the observation that loci showing nominal but not genome-wide significance in original studies may considerably contribute to disease susceptibility. It reports a total of 159 depression associated genes as overrepresenting the aforementioned pathways [20]. In order to gain further insight into immune and inflammation hypothesis of depression, overrepresentation of biological process categories in these genes was reexamined by this author using gene ontology tool [21]. Interestingly, several immune and inflammation related processes, besides others, showed enrichment at nominal 0.05 p value cut-off. Some of the processes with a large number of genome-wide association genes are listed here (Table **1**). It is apparent from this list that depression associated genes relate to both development as well as functioning of the immune system. Other significant processes identified in this secondary analysis include positive regulation of chronic inflammatory response, negative regulation of cytokine secretion involved in immune response, regulation of B cell mediated immunity, activation of immune response, activation of innate immune response etc.

WHOLE GENOME SEQUENCING IN HUMAN DEPRESSION

Besides SNP based genome-wide association studies, a low coverage whole genome sequencing analysis has also been carried out in depression [22]. This study comprises sequencing of over 5,000 subjects with recurrent MDD and a matching number of subjects that were screened to exclude MDD as the discovery cohort, and replication of signals in an independent sample of over 3,000 participants each. The analysis led to the identification of two risk loci at genome-wide significance, one near *SIRT1*, the gene encoding a member of the sirtuin family of proteins, and the other in an intron of *LHPP*, the gene encoding a phosphatase [22]. The *SIRT1* association was further supported by analysis of another 4,000 subjects with melancholia, a severe MDD subtype. Interestingly, *SIRT1* is categorized in gene ontology under, besides others, regulation of adaptive immune response, negative regulation of I-kappaB kinase/NF-kappaB signaling, and negative regulation of NF-kappaB transcription factor activity. This further supports the genetic evidence implicating immune and inflammatory pathways in depression.

TRANSCRIPTOMIC ANALYSES IN HUMAN DEPRESSION

Several transcriptome profiling of postmortem brain samples have been reported in depression (Table **2**). Unlike association of genetic variations, gene expression alterations in a disease may potentially be confounded by downstream effects of etiological factors and therapeutic interventions [20]. Moreover, the transcriptomic studies that have been reported in depression represent a diversity of tissue samples from brain, a highly heterogeneous organ, with different drug exposure history. Despite these complexities in the samples analyzed, it is notable that several genes have been found as differentially expressed in two or more studies (Fig. **1**). Most interestingly, these genes also show, like genome-wide association genes mentioned above, significant enrichment for immune and inflammation related processes, besides others, in gene ontology analysis. Examples of the enriched processes with numerous differentially expressed genes are tabulated here (Table **3**). It is notable that a majority of these processes were also identified in genome-wide association (Table **1**) analysis in human depression. Additional overrepresented processes include cytokine production involved in immune response, innate immune response activating cell surface receptor signaling pathway, mast cell mediated immunity etc. Although gene expression studies in depression have also been conducted on peripheral

Table 2. Transcriptomic studies reported in human depression.

Tissue	Method	Reported Genes*	Refs.
BA 21	Affymetrix HG-U95A arrays	30	[23]
Anterior cingulate cortex	Affymetrix HG-U95Av2 arrays	5	[24]
Dorsolateral prefrontal cortex	Affymetrix HG-U95Av2 arrays	10	[24]
BA 4, 8/9 & 11	Affymetrix HG-U133 set arrays	50#	[25]
Dorsolateral prefrontal cortex	Agilent Human 1A Oligo chip arrays	250	[26]
Amygdala, hippocampus, BA 24 & BA 29	Affymetrix HG-U133 set arrays	35#	[27]
BA 10	Affymetrix HU-95Av2 arrays	100	[28]
Mediodorsal nucleus	Affymetrix HG-U133 Plus 2.0 arrays	30	[29]
BA 8/9, 11 & 47	Affymetrix HG-U133 set arrays	10#	[30]
Locus coeruleus	Affymetrix HG-U133 Plus 2.0 arrays	20	[31]
BA 10	Affymetrix Exon 1.0 ST arrays	30	[32]
Dorsal raphe	Affymetrix HG-U133 Plus 2.0 arrays	250	[33]
Dentate gyrus	Microarray Inc. HEEBO arrays	15	[34]
CA1 pyramidal cell layer	Microarray Inc. HEEBO arrays	15	[34]
Hippocampus	RNA-Sequencing	3	[35]

BA, Broadman Area; *approximate number of differentially expressed genes; #commonly altered genes in the indicated regions.

Fig. (1). Transcriptomic analyses in human depression. Clustering of genes showing differential expression in at least two studies listed in Table **2**. Black, dark grey and light grey indicate no differential expression, upregulation and downregulation, in that order. Numbers indicate references in Table **2**.

blood, these are not reviewed here as the present objective is to specifically examine direct pathophysiological evidence obtained from studies on brain samples. These studies are nonetheless discussed later in the article.

PROTEOMIC ANALYSES IN HUMAN DEPRESSION

Proteomic profiling of brain samples has also been reported in depression (Table **4**). Notably, in a small set of proteins that show differential expression in more than one study (Fig. **2**), there is one, *APOE*, that is categorized under negative regulation of inflammatory response in gene ontology [21]. In enrichment analysis mentioned above, this process is found to be significantly overrepresented in the set of differentially expressed proteins. Cumulatively, genetic association, and mRNA and protein expression analyses, though diverse, together support immune and inflammation hypothesis of depression. Although protemic profiling of peripheral blood has also been reported in depression, the same is not reviewed here because, as mentioned above, the present focus is to examine direct pathophysiological evidence resulting from the analysis of brain samples. Nevertheless, these proteomic studies are discussed in the later section of the article.

Table 3. Differentially expressed genes in two or more depression studies overrepresenting immune and inflammation related processes.

Immune Response	Innate Immune Response	Immune System Process	Immune System Development	Inflammatory Response
FGFR3 (26, 31)	*FGFR3*	*ANLN* (29, 33)	*ANLN*	*PIK3C2A*
AQP4 (28, 31)	*AQP4*	*AQP4*	*BCL6*	*BCL6*
BCL6 (28, 33)	*CHGA*	*BCL6*	*SMPD3*	*CNR2*
CHGA (28, 33)	*ITPR1*	*CHGA*	*THRA*	
CNR2 (26, 27)	*LGALS3*	*CNR2*		
ITPR1 (27, 33)	*PIK3C2A*	*FGFR3*		
LGALS3 (28, 29)	*PSMD4*	*GPM6B* (26, 29)		
NFIL3 (26, 33)		*ITPR1*		
PIK3C2A(27, 30)		*LGALS3*		
PSMD4 (26, 33)		*NFIL3*		
		PIK3C2A		
		PSMD4		
		SMPD3 (26, 33)		
		THRA (28, 33)		

Numbers in the parentheses indicate references in Table **2**, provided for genes at their first column-wise occurrence.

Table 4. Proteomic studies reported in depression.

Tissue	Method	No. of Reported Proteins*	Refs.
Anterior cingulate cortex	MALDI-TOF-MS, LC-MS/MS	15	[36]
Cerebrospinal fluid	MALDI-TOF-MS	35	[37]
BA 9	Shotgun LC-MS#	85	[38]
BA 9	Shotgun LC-MS	40	[39]

BA, Broadman Area; *approximate number of differentially expressed proteins reported; #phosphoproteomic analysis

TRANSCRIPTOMIC ANALYSES OF ANTI-DEPRESSANT EFFECTS IN ANIMAL MODELS

Transcriptomic effects of antidepressant drugs in rats and mice have also been investigated by several groups (Table **5**). Although these studies differ with respect to animal model, antidepressant drug and brain region investigated, a combined analysis is presented here because the number of published studies is not sufficient to support individual model, drug and region specific examination of transcriptomic convergence. Interestingly, genes showing differential expression in two or more studies (Fig. **3**) are found to overrepresent, immune and inflammation related in gene ontology based enrichment analysis mentioned above. Some of the overrepresented processes with several differentially expressed genes are listed here (Table **6**). It is interesting to note that a majority of these processes, or all of them, were also identified in genome-wide association (Table **1**) and transcriptomic (Table **3**) analysis in human depression. Other enriched processes include adaptive immune response, regulation of acute inflammatory response, regulation of innate immune response etc.

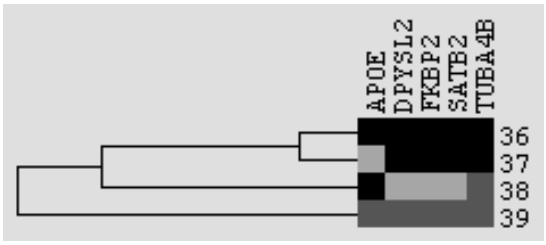

Fig. (2). Proteomic analyses in human depression. Clustering of genes showing differential expression in at least two studies listed in Table **4**. Black, dark grey and light grey indicate no differential expression, upregulation and downregulation, in that order. Numbers indicate references in Table **4**.

Table 5. Transcriptomic studies reporting antidepressant action in animal models.

Drug	Tissue	Treatment Conditions	Animal Models	Reported Genes*	Refs.
Amitriptyline	Nucleus accumbens	15 mg/kg i.p., 28 days	Male C57Bl/6 mice	95	[40]
Imipramine	Hippocampus	10 mg/kg i.p., 1, 3 or 7 days	Male Sprague-Dawley rats	25	[41]
Fluoxetine	Hippocampus	10 mg/kg i.p., 1, 3 or 7 days	Male Sprague-Dawley rats	30	[41]
Phenelzine	Hippocampus	7 mg/kg i.p., 1, 3 or 7 days	Male Sprague-Dawley rats	30	[41]
Despiramine	Hippocampus	7.5 mg/kg i.p., 21 days	Male Swiss-Webster mice, high-swim stress	70	[42]
Despiramine	Hippocampus	7.5 mg/kg i.p., 21 days	Male Swiss-Webster mice, low-swim stress	40	[42]
Imipramine	Fronto-temporal cortex	10 mg/kg i.p., 96 h	Sprague-Dawley rats	3	[43]
Imipramine	Fronto-temporal cortex	10 mg/kg i.p., 4 wk	Sprague-Dawley rats	5	[43]
Citalopram	Fronto-temporal cortex	10 mg/kg i.p., 96 h	Sprague-Dawley rats	10	[43]
Citalopram	Fronto-temporal cortex	10 mg/kg i.p., 4 wk	Sprague-Dawley rats	10	[43]
Paroxetine	Hippocampus	10 mg/kg oral, 28 days	Male DBA/2OlaHsd mice	55	[44]
Imipramine	Frontal cortex	10 mg/kg s.c., 7 days	Male Wistar rats, olfactory bulbectomized	230	[45]

*approximate number of differentially expressed genes reported in microarray analysis.

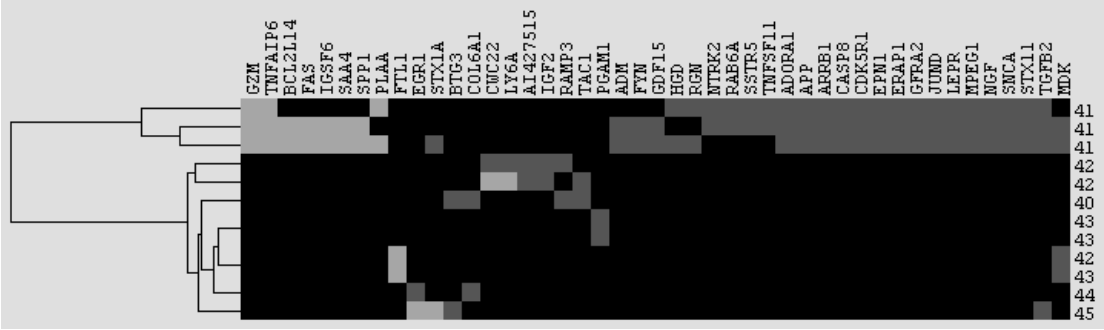

Fig. (3). Transcriptomic analyses in animal models of antidepressant treatment. Clustering of genes showing differential expression in at least two analyses listed in Table **5**. Black, dark grey and light grey indicate no differential expression, upregulation and downregulation, in that order. Numbers indicate references in Table **5**.

TRANSCRIPTOMIC ANALYSES IN A RODENT MODEL OF DEPRESSION

Finally, transcriptomic analyses in chronic social defeat stress in rodents, an established model of depression, is considered. A review of findings reported in this model (Table **7**) shows several genes that are differentially expressed in two or more studies (Fig. **4**). Notably, two of these genes, *APOD* and *JUN*, are related to immunity and inflammation. Whereas the former is categorized under negative regulation of cytokine production involved in inflammatory response, and negative regulation of T cell migration, the latter is under innate immune response, response to cytokine, and toll-like receptor signaling pathway. Together, animal model studies, despite their diversity, seem consistent with the immune and inflammation hypothesis of depression. Besides chronic social defeat stress, other animal models of depression also exist. It will be interesting to review gene expression evidence obtained in these models in future.

GENE LEVEL CONVERGENCE AMONG REVIEWED STUDIES

It is interesting to note that the lone common gene between genome-wide association (Table **1**) and transcriptomic (Fig. **1**) analysis in human depression, *ITPR1*, which encodes an intracellular receptor for inositol 1,4,5-trisphosphate, is related to, besides immunity and inflammation, several brain development and function related pathways relevant to depression. For example, the brain development related pathways include signaling by FGFR3, the gene encoding which, interestingly, is found to be differentially expressed in human depression (Fig. **1**), and NGF signaling *via* TRKA from the plasma membrane [50]. The brain function related pathways include, besides others, dopaminergic synapse and serotonergic synapse which are involved in learning and memory, motivation and reward, emotion, sleep and pain, and in pathological states like abnormal mood and cognition [50]. Remarkably, it has been

Table 6. Differentially expressed genes in two or more analyses of antidepressant effects in animal models overrepresenting immune and inflammation related processes.

Immune response	Innate Immune Response	Immune System Process	Immune System Development	Inflammatory Response
ADM (41 F, 41 P)	*APP*	*ADM*	*CASP8*	*ADORA1* (41 F, 41 P)
APP (41 F, 41 I, 41 P)	*CASP8*	*APP*	*EGR1*	*PLAA* (41 I, 41 P)
CASP8 (41 F, 41 I, 41 P)	*EGR1*	*CASP8*	*FAS*	*SAA4* (41 F, 41 P)
EGR1 (44, 45)	*FYN*	*EGR1*	*TGFB2*	*SPP1*
ERAP1 (41 F, 41 I, 41 P)	*SNCA*	*ERAP1*	*TNFSF11*	*TAC1* (40, 42)
FAS (41 F, 41 P)	*STX11*	*FAS*		*TNFAIP6* (41 F, 41 I, 41 P)
FYN (41 F, 41 P)		*IGSF6*		
IGSF6 (41 F, 41 P, 42)		*RAB6A* (41 F, 41 I)		
SNCA (41 F, 41 I, 41 P)		*SNCA*		
STX11 (41 F, 41 I, 41 P)		*SPP1* (41 F, 41 P)		
TNFSF11 (41 F, 41 I)		*STX11*		
		TGFB2 (41 F, 41 I, 41 P, 45)		
		TNFSF11		

Numbers in the parentheses indicate analyses referred in Table **5**, provided for genes at their first column-wise occurrence. F, fluoxetine; I, imipramine, P, phenelzine.

Table 7. Transcriptomic studies in rodent models of chronic social defeat stress.

Tissue	Animal Model	Reported Genes*	Refs.
Posterior cortex	Male Long-Evans rats, 6 h#	20@	[46]
Dorsal raphe	Male Wistar rats	2@	[47]
Frontal cortex	Male Wistar rats	35@	[47]
Nucleus accumbens	Male C57BL/6J mice, 24 h#	315@	[48]
Nucleus accumbens	Male C57BL/6J mice, 4 wk#	135@	[48]
Medial prefrontal cortex	Male C57BL/6J mice	20$	[49]
Amygdala	Male C57BL/6J mice	70$	[49]
Ventral hippocampus	Male C57BL/6J mice	55$	[49]

*approximate number of differentially expressed genes reported; **indicates reported brain harvestinf time after the end of stress procedure; @indicates microarray analysis; $indicates RNA sequencing.

reported that mice carrying cerebral knockdown of ITPR1 show an antidepressant behaviour [51].

DISCUSSION

The present review of genomic, transcriptomic and proteomic studies shows that human depression associated genetic variations, and differentially expressed mRNAs and proteins in general represent development and functioning of immune and inflammation system more than expected by chance. Animal studies on the transcriptomic effects of antidepressant treatment, and on chronic social defeat stress, a model of depression, further support the hypothesis that altered immune and inflammatory pathways underlie the etiology and pathophysiology of the disease. Notably, several of the previous meta-analyses or reviews of genomic, transcriptomic and proteomic studies in depression are consistent with this hypothesis. For example, a pathway enrichment analysis of available genome-wide association data on MDD implicated immune system and inflammatory response, besides neurotransmitter and neuronal systems, in the pathophysiological mechanisms underlying depression [16]. Similarly, another pathway based analysis of existing genome-wide association findings revealed that a significant proportion of disease candidate genes are related to inflammatory or immune response [52]. In a separate study of association data on six major neuropsychiatric disorders including MDD, it was found that several of the highly

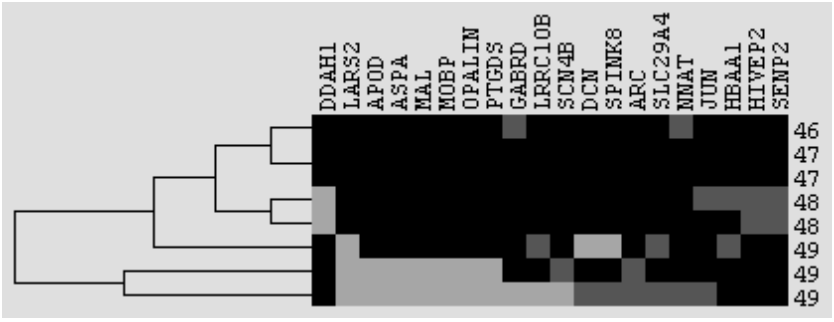

Fig. (4). Transcriptomic analyses in chronic social defeat stress model of depression in rodents. Clustering of genes showing differential expression in at least two studies listed in Table **7**. Black, dark grey and light grey indicate no differential expression, upregulation and downregulation, in that order. Numbers indicate references in Table **7**.

shared genes across disorders are expressed in immune tissues, besides being co-expressed in developing human brain, and implicated in the postsynaptic density [53]. Further, a gene ontology based analysis of available expression profiling data in MDD reported enrichment of innate immune response related processes in genes showing differential expression in hippocampus, not prefrontal cortex and striatum [54]. Although only brain associated transcriptomic and proteomic changes have been reviewed here, it is interesting to note that a recent large scale analysis of gene expression alterations in peripheral blood cells in MDD has identified genes that overrepresent immune pathways previously associated with the disease etiology, clearly supporting the immune hypothesis of depression [55]. Another circulating blood cell transcriptomic study recently provided gene set enrichment based evidence that long-standing depressive symptoms are associated with activated immune-inflammatory pathways [56]. Similarly, proteomic profiling of serum or plasma samples has also revealed altered expression of proteins associated with immunity and inflammation, besides others, in patients with MDD [57-60]. These findings are consistent with immunological and neurobiological studies on human patients and animal models that increasingly suggest the role of peripheral and central inflammation in depression [61-63]. Given the emerging interest in anti-inflammatory agents as potential antidepressants [62, 63], gene expression analysis in animal models of depression may provide a valuable drug discovery approach for identifying small molecules that modulate immune and inflammatory pathways in the desired direction.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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