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Review

The Roles of Long Noncoding RNA in Depression

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Abstract

Depression is a common psychiatric disorder that brings great pain and burden to patients and their families. However, the pathogenesis underlying the development of depression remains unclear, limiting the development of diagnostic and therapeutic approaches for the disease. Recently, an increasing number of studies have shown that long noncoding RNAs (lncRNAs) play modulatory roles in depression. Here, we summarize the general mechanism of action and their roles in depression. LncRNAs are suggested to exert regulatory functions in depression in various ways, including competing endogenous RNA (ceRNA) networks, interacting with epigenetic modifications, interacting with single-nucleotide polymorphisms (SNPs), acting in *cis* or *trans* on target genes and regulating the immune system. A total of 13 lncRNAs (involving 16 ceRNA regulatory axes) have been revealed to have regulatory mechanisms. The potential relationship between methylation modification and lncRNA was also analyzed through lncRNA expression profile data. Functional annotation analysis showed that methylation-related lncRNAs were mainly enriched in postsynaptic specialization, neuron-to-neuron synapses, asymmetric synapses, and postsynaptic density. This indicates that methylation-related lncRNAs may have an impact on the synaptic microenvironment and may thus contribute to the development of depression. Moreover, we predicted potential interactions between SNP sites and lncRNAs in depression by querying the database. Through this review, we hope to deepen the understanding of the regulatory landscape of lncRNAs in depression and propose that future efforts should focus on establishing comprehensive and robust diagnostic models and further revealing the exact mechanism of lncRNA action in depression by experimental evidence.

Keywords: lncRNA; depression; regulatory mechanism; depression diagnosis and therapy

1. Introduction

Depression is a severe affective mental disorder with typical clinical manifestations of depressed mood, reduced volitional activity, and slowed thinking and may be accompanied by somatic discomforts, such as abdominal distention, chest tightness, and pain [1]. More than 300 million people suffer from severe depression, with a lifetime prevalence rate of 17% [2]. In 2010, depression accounted for 8.2% (5.9%–10.8%) of global years lived with disability and 2.5% (1.9%–3.2%) of global disability-adjusted life years [3]. Depression causes great losses to human health and property. By the end of 2030, depression is expected to impose the world's leading disease burden. This is because individuals with early onset depression are less likely to complete secondary education (2–3 times), and this population has a higher unemployment rate (29% at age 40) than that of the general population [4,5]. Although the exact pathogenesis of depression has not been determined, it is generally believed that genetic factors are one of the causes of depression [6,7]. Based on different pathogenesis hypotheses, genes related to neurotrophic factors, monoamine neurotransmitters, and neuroendocrine factors have received attention; these genes include *BDNF* [8], *COMT* [9], and *NET* [10]. In a large genome-wide association meta-analysis study involving 135,458 cases and 344,901 controls, 44 variants were identified as genetic risk factors for depression. However, these findings are still insufficient to provide us with a comprehensive understanding of the pathogenesis of depression and to find corresponding strategies.

Recent studies have confirmed that in different biological lineages, the protein coding sequence of the genome remains relatively stable, while the noncoding sequence shows a significant correlation with the heterogeneity and complexity of the organism [11,12]. Long noncoding RNAs (lncRNAs), which account for 80%–90% of all noncoding RNAs (ncRNAs), are RNAs with a length of more than 200 nucleotides but no protein coding activity [13]. Compared with microRNAs (miRNAs), circular RNAs (circRNAs), and other ncRNAs, lncRNAs have long sequences and complex spatial structures and can bind to many diverse proteins. Thus, they carry more information and perform more diverse functions. LncRNAs can act at multiple levels, including the pretranscriptional, posttranscriptional, translational, and posttranslational levels. The primary mechanisms include the following: (1) acting as a

"sponge" for miRNA, competitively blocking its binding to target mRNAs; (2) interfering with the expression of genes through *cis* or *trans* regulation; (3) participating in epigenetic modifications of DNA and chromatin remodeling; (4) regulating transcription factor activity and affecting their binding to gene promoter regions; (5) affecting covalent modifications of RNAs; (6) influencing alternative splicing of RNAs; (7) altering the subcellular localization of RNAs; and (8) altering the stability of RNAs [14,15].

With the development of high-throughput technologies and various genomics approaches, we are now better equipped to comprehend the biological characteristics and disease expression profile of depression on a genome-wide scale and to construct the global expression network. To date, 21,183 lncRNAs from *Homo sapiens* have been included in the National Center for Biotechnology Information database (https://www.ncbi.nlm.nih.gov/). Databases for querying and analyzing lncRNAs are constantly emerging. Examples include, LNCipedia (https://lncipedia.org/), RNAcentral (https://rnacentral.org/), and LncRNADisease (http://www.cuilab.cn/lncrnadisease). An increasing number of studies have reported altered lncRNA expression profiles in both brain regions and the blood of patients with depression [16–19]. In this article, we focus on a systematic review of the role of lncRNAs in depression, and aim to generate novel insights for objective diagnostic marker identification, efficacy prediction, and antidepressant therapy development [15]. Through PubMed and the Web of Science Library, we conducted an online search for all research published up to March 2023. The databases were searched by using the terms "lncRNA", "long noncoding RNA", and their combinations with "major depression", "major depressive disorder", and "depression". The language was limited to English.

2. LncRNAs Involved in Competing Endogenous RNA (ceRNA) Networks

The ceRNA hypothesis was proposed in 2011 [20]. MiRNAs are negative regulators of gene expression since they can diminish the stability of target RNAs or repress their translation via complementary pairing with the 3′ untranslated region (3′UTR) of mRNAs [21,22]. If a lncRNA and a mRNA have high sequence homology, i.e., a lncRNA and mRNA have the same miRNA response element, then the lncRNA can competitively bind the miRNA and reduce its intracellular content, thereby reducing the repressive effect of the miRNA on its target gene.

CeRNA regulatory networks, which are mediated by lncRNA–miRNA–mRNA, play an important role in the gene regulatory network of depression (Table 1, Ref. [23–41]) and have become a potential treatment target for depression. One of the most extensively researched neurotrophic factors, *BDNF*, is substantially expressed in human brain tissues, including the hippocampus, amygdala, neocortex, and cerebellum. *BDNF* is crucial in multiple neuropsychiatric conditions [42–44]. To date, approximately 20% of lncRNAs involved in ceRNA networks in depression have been found to be related to the regulation of *BDNF* expression [23–25]. For example, the regulatory role of the lncRNA *GAS5* in depression implicates the lncRNA *GAS5*-miR-10b/*BDNF* axis. The lncRNA *GAS5* was found to act as a miR-10b sponge in a rat model of post-stroke depression (PSD). By upregulating *GAS5*, curcumin inhibits miR-10b, thus activating the BDNF/Trkβ pathway, promoting the expression of synapse-associated proteins, and improving PSD [24]. Huan *et al*. [23] documented that the lncRNA *MIR155HG* regulates the miR-155/*BDNF* axis to alleviate depressive-like behavior in mice. Table 1 lists more mechanisms by which lncRNAs control *BDNF* expression through their activity as ceRNAs.

LncRNAs also have multiple targets, and a single lncRNA molecule may inhibit multiple target miRNAs. In addition to the miR-10b/*BDNF* pathway previously mentioned, the lncRNA *GAS5*, for instance, may also be implicated in the regulation of gene expression in depression through the microRNA-26a/*EGR1* axis [26]. MiR-26a targets *EGR1*, while the lncRNA *GAS5* can specifically bind miR-26a. In mice with depressive-like behavior, EGR1 suppresses the activation of the PI3K/AKT pathway to induce the release of inflammatory substances and the apoptosis of hippocampal neurons. Therefore, lncRNA *GAS5* reduces the inhibitory effect of miR-26a on *EGR1* by acting as a ceRNA, inhibiting PI3K/AKT pathway activation and protecting hippocampal neurons from damage in mice with depressive-like behavior. This relationship between one lncRNA and multiple miRNA targets was also predicted by bioinformatics analysis [27]. For example, Chen *et al*. [27] identified that seven miRNAs (miR-425, miR-486, miR-28-5p, miR-29b, miR-100, miR-125b and miR-320) showed potential matching sequences with the lncRNA *Gm26917*.

In depression, the targets regulated by lncRNAs through their ceRNA activity are involved in several processes, including neurotrophic processes [23], immunoinflammatory processes [26], glutamatergic processes [28], and methylation modifications [29]. In the prefrontal cortex of chronic unpredictable mild stress (CUMS) rats, miR-29b-3p expression was elevated after ketamine treatment, leading to a decrease in the expression of the glutamate metabotropic receptor *GRM4* [28]. Based on the inhibition of miR-29b-3p by lncRNA *Gm26917*, lncRNA *Gm26917* is a crucial regulator of fluoxetine and ketamine and a potential target for depression treatment [30]. Ding X *et al*. [29] found that *lncXR_351665*, as a miR-152-3p sponge, upregulated the DNA methyltransferase DNMT1 to promote the development of chronic pain-induced depression. In summary, miRNAs and their target genes, as downstream targets of lncRNA regulation, establish a complex ceRNA regulatory network together with lncRNAs. LncRNAs are involved in the progression of depression through multiple

Table 1. LncRNAs involved in depression by mediating the ceRNA network.

LncRNA	Target miRNAs	Regulatory mechanisms	Reference
GAS5	miR-26a	*GAS5*-miR-26a → *EGR1*↑ → PI3K/AKT pathway↓ → the release of inflammatory factors and the apoptosis of hippocampal neuron of mice with depression-like behaviors.	[26]
	miR-10b	*GAS5*-miR-10b → *BDNF*↑ → remission of poststroke depression in rats	[24]
MIR155HG	miR-155	*MIR155HG*-miR-155 → *BDNF*↑ → alleviation of depression-like behaviors in mice	[23]
Gm26917	miR-29b-3p	*Gm26917*-miR-29b-3p → *GRM4*↑ → aggravation of the depressive behaviors in CUMS rats	[27,28,30]
XR_351665	miR-152-3p	*XR_351665*-miR-152-3p → *DNMT1*↑ → inducing the depression-like behaviors	[29]
LINC01108	hsa-miR-1202	hsa-miR-1202 is a primate specific and brain abundant microRNA involved in major depressive disorder and antidepressant treatment.	[31,32]
LINC00998	miR-16	miR-16 targets serotonin transporters and contributes to the therapeutic effects of antidepressants.	[31,33]
	miR-30e	miR-30e may be a susceptibility factor for MDD.	[31,34]
LINC00473	miR-497-5p	*LINC00473*-miR-497-5p → *BDNF*↑ → alleviation of depression-like behaviors in mice	[25]
LncRNA-84277	miR-128-3p	*LncRNA-84277*-miR-128-3p → *SIRT1*↑ → improvement of chronic pain-related depression-like behavior	[35]
NEAT1	miRNA-320-3p	*NEAT1*-miR-320-3p → *CRHR1*↑ → promoting pathological damage and apoptosis in the hippocampus in depressed rats.	[36]
	miRNA-144-3p	*NEAT1*-miRNA-144-3p → VGAT ↑ → GABA↑ → ameliorating the SST-positive neuron deficits	[37]
2210408F21Rik	miR-1968-5p	*2210408F21Rik*-miR-1968-5p → Hras↓ → thereby affecting neuronal excitation in CUMS mice	[38]
BDNF-AS	miR-124	*BDNF-AS*-miR-124-BDNF↑ → increased BDNF-TrkB signaling in the VTA-NAc pathway	[39,40]
BACE1-AS	miR-485-5p	*BACE1-AS*-miR-485-5p → BACE1↓ → leads to BACE1 cleaving amyloid precursor protein decreasing	[41]
Malat1	miRNA-15b-5p	*Malat1*-miRNA-15b-5p → GAT-3↑ → GABA↑ → ameliorating the SST-positive neuron deficits	[37]

↑, up-regulation; ↓, down-regulation. *GAS5*, growth arrest specific 5; *EGR1*, early growth response 1; PI3K, phosphoinositide-3-kinase; AKT, serine/threonine kinase; *BDNF*, brain-derived neurotrophic factor; *MIR155HG*, micro RNA 155 host gene; *GRM4*, glutamate metabotropic receptor 4; *DNMT1*, DNA methyltransferase 1; *LINC*, long intergenic non-coding RNA; MDD, major depressive disorder; *SIRT1*, sirtuin 1; NEAT1, nuclear paraspeckle assembly transcript 1; *CRHR1*, corticotropin releasing hormone receptor 1; GABA, γ-aminobutyric acid; VGAT, GABA vesicular transporter; SST, Somatostatin; Hras, Harvey rat sarcoma virus oncogene; CUMS, chronic unpredictable mild stress; BDNF-AS, BDNF- antisense lncRNAs; TrkB, Tyrosine Kinase receptor B; VTA-NAc, Ventral tegmental area-nucleus accumbens; *BACE1-AS*, beta-secretase 1- antisense lncRNAs; *Malat1*, metastasis associated lung adenocarcinoma transcript 1; GAT-3, GABA transporter-3.

targets and multiple pathways. A total of 13 lncRNAs (involving 16 ceRNA regulatory axes) are summarized in Table 1.

3. LncRNAs Participate in Depression through Epigenetic Modifications

3.1 Interaction and Cooperation between LncRNAs and Epigenetic Modifications

Epigenetic modifications, primarily in the form of DNA methylation, histone modification, and chromatin remodeling, lead to heritable changes in genetic phenotypes and gene expression that do not involve changes in DNA sequences [45]. DNA methylation modifications occur mainly on cytosines in CpG islands [46]. Another important type of epigenetic change is histone modification. In general, histones can undergo different types of covalent modifications (e.g., methylation and acetylation) catalyzed by various histone-modifying enzymes [46]. It is commonly accepted that methylation represses gene transcription, whereas acetylation relaxes the chromatin structure by charge neutralization and enhances transcription. LncRNAs can function as molecular scaffolds, molecular decoys, molecular guides, etc., either to regulate epigenetic processes or as targets for epigenetic modifications [47,48].

Changes in epigenetic modifications (including the addition and removal of groups) interact and coregulate lncRNAs in complex disorders in at least three different ways. First, the alterations of covalent modification in the lncRNA locus result in changes in the biochemical properties or chromatin structure of the DNA sequence. This affects the binding of RNA polII or other transcription factors and alters lncRNA transcription. For example, DNA hypermethylation occurs in a CpG island of a specific gene, and the addition of methyl groups to histones in the promoter region leads to chromatin remodeling [49]. This not only decreases the expression of the protein coding gene

but also inhibits the transcription of antisense lncRNAs of the encoding gene [49]. In addition to antisense lncRNAs, intergenic lncRNAs may also be affected by methylation. If the CpG island in the protein-coding gene is embedded in the promoter of the lncRNA, the transcription of the lncRNA decreases. Second, lncRNAs can mediate covalent modification-related enzymes to change the epigenetic modification of target genes, thus affecting gene expression [50]. LncRNAs can recruit or activate methyltransferases to increase the DNA methylation level of their target genes [51]. They can also mediate histone-modifying enzymes to covalently modify histones in the promoter regions of the genes [52], change the biochemical properties or chromatin conformation of the genes, affect the binding of transcription factors to the genes and switch the expression of the genes on or off. In mice, the lncRNA *BDNF-AS* was identified to block *BDNF* transcription by recruiting the histone methylation transferase EZH2 [53]. By recruiting PRC2, the lncRNA *Xist* can initiate chromosomal CpG island methylation. This, in turn, suppresses the expression of genes on the X chromosome [54] and leads to gender-specific differences in susceptibility to neurological and psychiatric disorders [55]. Third, lncRNAs themselves serve as targets for methylation. m6A is one of the most common types of methylation on lncRNAs, and this modification is formed by the addition of a methyl group to an adenosine base through a reaction catalyzed by the methylases METTL3 and METTL14. m6A-modified lncRNAs are recognized by reader proteins, such as the YTH family, which induce RNA binding proteins to form RNA–protein complexes, thus regulating mRNA expression [49]. Clearly, in the first two regulatory mechanisms, epigenetic modifications occur on DNA or histones, causing changes in mRNA transcription levels. However, in the third mechanism, modifications occur on RNA and are posttranscriptionally regulated.

3.2 LncRNAs Associated with m6A Modification in Depression and Prediction of Their Functions

Although an increasing number of studies have noted the effects of altered methylation modifications and lncRNAs on depression, their interactions and mechanisms of action in depression are still unclear. Due to the availability of data, we focused on the mechanisms of lncRNA regulation associated with m6A modifications in depression. We identified the lncRNAs associated with m6A modifications and further explored the potential biological functions of these lncRNAs by using the transcription profile GSE217811 [containing data for 10 patients with major depressive disorder (MDD) and 10 healthy control individuals] from the Gene Expression Omnibus (GEO, online: http://www.ncbi.nlm.nih.gov/geo/) database.

Via the limma package of R software, 14137 differentially expressed lncRNAs were identified from the dataset ($p < 0.05$). Generally, genes with similar expression profiles are considered to be potentially involved in parallel biological processes; thus we further screened 206 lncRNAs with a coexpression relationship with m6A modification-related genes from the set of differentially expressed lncRNAs (Table 2). Finally, mRNAs were screened by the similarity matrix of the mRNA–lncRNA expression profile ($p < 0.05$), and the biological significance of the lncRNAs was recognized by the functional annotation of the mRNA.

Table 2. Summary of genes related to m6A modification and the number of lncRNAs coexpressed with them in GSE217811.

Function	Gene name	Number of associated lncRNAs
m6A writer	*METTL3*	205
	METTL14	184
	METTL16	20
	RBM15	202
	VIRMA	22
	WTAP	58
	ZC3H13	206
m6A eraser	*ALKBH5*	183
m6A reader	*HNRNPA2B1*	103
	HNRNPC	64
	YTHDC1	205
	YTHDC2	1
	YTHDF1	45
	YTHDF2	84
	YTHDF3	175

lncRNA, Long noncoding RNA; m6A, N6-methyladenosine; *METTL3*, methyltransferase 3; *METTL14*, methyltransferase 14; *METTL16*, methyltransferase 16; *RBM15*, RNA binding motif protein 15; *VIRMA*, vir like m6A methyltransferase associated; *WTAP*, WT1 associated protein; *ZC3H13*, zinc finger CCCH-type containing 13; *ALKBH5*, alkB homolog 5; *HNRNPA2B1*, heterogeneous nuclear ribonucleoprotein A2/B1; *HNRNPC*, heterogeneous nuclear ribonucleoprotein C; *YTHDC1*, YTH N6-methyladenosine RNA binding protein C1; *YTHDC2*, YTH N6-methyladenosine RNA binding protein C2; *YTHDF1*, YTH N6-methyladenosine RNA binding protein F1; *YTHDF2*, YTH N6-methyladenosine RNA binding protein F2; *YTHDF3*, YTH N6-methyladenosine RNA binding protein F3.

Functional annotation analysis showed that these mRNAs with similar expression profiles to those of lncRNAs were mainly enriched in 116 Gene Ontology (GO) terms and 35 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways ($p < 0.05$) (Fig. 1). Altered neuronal synapse number and function and impaired synaptic plasticity are common features of depression [44,56]. The m6A modification-related lncRNAs were shown to act at targets associated with the synaptic microenvironment, with enrichment in terms such as postsynaptic specialization, neuron-to-neuron synapses, asymmetric synapses, and postsynaptic density, according to functional annotation

analysis (Fig. 1b). This suggests that alterations in lncRNAs and their m6A modifications may have an impact on the synaptic microenvironment and thus contribute to the development of depression. The lncRNAs were also enriched in molecular functions or biological processes, such as the regulation of I-κB kinase/NF-κB signaling, anion transport, dephosphorylation, and ubiquitin-like protein ligase activity (Fig. 1a,c). Numerous studies have demonstrated the involvement of these molecular functions or biological processes in neurological disorders, even providing direct evidence of their association with depression [56–61]. The functional annotation analysis of lncRNAs in this paper shows the relationship between lncRNAs and m6A modifications and the abovementioned molecular functions or biological processes, reiterating their roles in depression.

According to KEGG pathway analysis, m6A modification-associated lncRNAs may be related to the pathways of endocytosis, tight junctions, Salmonella infection, activation of chemoattractant receptors, Wnt signaling pathway, and PPAR signaling pathway (Fig. 1d). Among these pathways, the PPAR signaling pathway has received attention in the study of neurological diseases. PPARs have three subtypes, PPARα, PPARβ, and PPARγ. Drug molecules can induce a neuroprotective microglial phenotype in the hippocampus via the PPAR-γ pathway, resulting in the amelioration of chronic mild stress (CMS)-induced depression-like behavior [62].

4. The Effect of SNPs on LncRNAs in Depression

Single nucleotide polymorphisms (SNPs) are DNA sequence polymorphisms resulting from single nucleotide variations at the genomic level. More than 90% of all known polymorphisms are SNPs, making it the most prevalent heritable variation in humans [63]. SNP loci have been used in genome-wide association studies (GWAS) and have become the major route for the discovery of complex genetic mechanisms of disease. Depression has complex genetic variations, with numerous SNPs identified across the genome.

4.1 The Effects of SNPs on LncRNAs and Their Cooperation in Diseases

There are at least two effects of SNPs on lncRNAs: SNPs in nonlncRNA loci that indirectly affect lncRNA transcription and SNPs in lncRNAs that directly regulate lncRNA expression. First, SNPs in genes encoding proteins (e.g., transcription factors) may lead to functional changes in the structure of the encoded protein and enhance or weaken its capacity to bind target lncRNAs. These alterations may either improve disease phenotypes or contribute to disease progression by mediating changes in lncRNA expression levels [64,65]. Second, SNPs in lncRNAs can become switches for lncRNA gene expression. Mutations in the lncRNA regulatory region change the binding ability of nucleic acid sequences to transcription factors or other protein factors, thus activating/enhancing or blocking/decreasing the expression of the lncRNA [66].

4.2 SNPs in LncRNAs Involved in Depression

The results from clinical cohort studies have shown that polymorphisms in depression risk genes are significantly related to the pathogenesis of depression and the efficacy of antidepressants. In a cohort study that consisted of people with MDD who attempted suicide, people who did not attempt suicide, and healthy subjects, Zheng *et al*. [67] identified 83 SNP loci in *EPHX2* and *P2X2*. *EPHX2* and *P2X2* may mediate the antidepressant-like effects of ATP. Among these SNP loci, rs9331949 is located in lncRNA *NONHSAT215593.1* (Table 3, Ref. [67–77], querying the lncRNASNP v3 database, http://gong_lab.hzau.edu.cn/lncRNASNP3/#!/) [78]. Namvar A *et al*. [68] fully discussed the relationship between the SNP sites on lncRNA ANRIL and the risk of MDD were in different inheritance models. Two SNPs, rs1333045 and rs1333048, were verified as risk loci [68]. SNP loci associated with major depression in Europeans individuals were first reported in a study by Hyde CL *et al*. [69]. This study investigated a combined cohort of 130,620 lifetime major depression cases and 347,620 controls and established 17 genome-wide SNPs in 15 independent gene regions, including rs1475120 in the intron of *LIN28B* (aka NONHSAT251362.1, etc.). Retrieval of SNPs in the lncRNASNP2 database revealed that rs1475120 is located in the linkage disequilibrium (LD) region and affects the binding of a lncRNA (NONHSAT207767.1) to miRNAs (Table 3).

Genes related to neurodevelopment, neuroplasticity, and neurotransmission, such as *DISC1*, *TSNAX*, and *DAOA*, have attracted considerable attention in depression research. Allelic variations in these genes are more likely to be identified as risk SNPs and potential antidepressant targets. Arias B *et al*. [70] investigated the relationship of 13 polymorphic loci in *DISC1-TSNAX* and *DAOA* with MDD and citalopram efficacy. The results revealed associations between MDD and rs3738401 in *DISC1* and rs1615409 and rs766288 in *TSNAX* ($p = 0.004$, $p = 0.0019$, and $p = 0.008$, respectively). Among them, rs3738401 is located in a lncRNA (*NONHSAT150722.1*) (Table 3). Another depression susceptibility gene of long-standing interest, BDNF, also has multiple SNPs. Multiple novel SNP loci in the *BDNF* sequence were identified by a deep sequencing effort [71]. The association analysis of MDD patients and control individuals revealed that six SNPs were associated with MDD (rs12273539, rs11030103, rs6265, rs28722151 rs41282918, and rs11030101). Among them, three SNPs, rs6265, rs28722151, and rs11030101, are located in lncRNAs. Whether these allelic variants regulate *BDNF* expression by mediating lncRNAs needs further verification (Table 3).

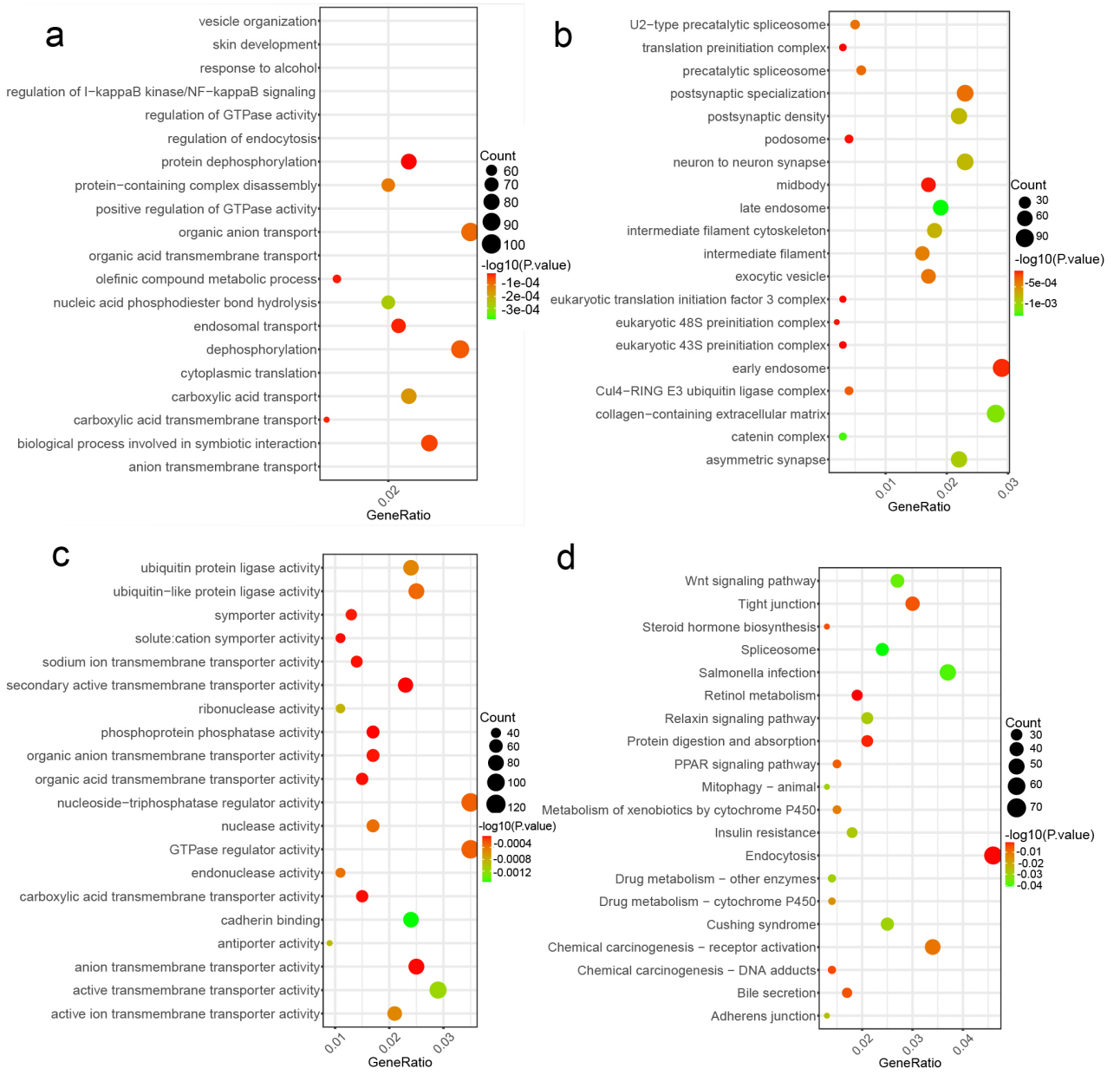

Fig. 1. The top 20 molecular functions and pathways in GO and KEGG analyses of lncRNAs related to m6A from the transcriptional profile of GSE217811. (a) Biological processes in which m6A-related lncRNAs are involved. (b) Cell components in which m6A-related lncRNAs are involved. (c) Molecular functions in which m6A-related lncRNAs are involved. (d) Biological signaling pathways in which m6A-related lncRNAs are involved. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

5. *Cis* or *trans* Regulation of LncRNAs is Involved in Depression

LncRNAs can not only interact with nucleic acid sequences by base complementary pairing to form RNA–DNA complexes but also form relatively complex and variable spatial structures (compared to those formed by other small ncRNAs) to recruit or act as scaffolds to bind other proteins to form RNA–protein complexes. Thus, lncRNAs have flexible and diverse mechanisms of controlling gene expression. Numerous studies have indicated this feature and regulatory mechanism of lncRNAs. Using RNA pull-down, chromatin immunoprecipitation, and RNA immunoprecipitation approaches, these studies have shown that lncRNAs bind to biomolecules such as transcription factors, proteins, mRNAs and DNA and form gene regulatory networks, revealing the biological functions and mechanisms of lncRNAs. According to the position of lncRNAs relative to the target genes, the regulation mode of lncRNAs with respect to the target genes can generally be classified into two categories: *cis* and *trans* regulation [79]. Next, we discuss the mechanism of lncRNAs in depression from two perspectives, *cis* and *trans* regulation.

Table 3. Depression risk SNPs and their related lncRNAs (obtained by querying the lncRNASNP v3 database. http://gong_lab.hzau.edu.cn/lncRNASNP3/#!/).

SNP ID	Position	Related lncRNA ID	Located in LD regions	Impact lncRNA: miRNA	Reference
rs9331942	chr8:27597597	NONHSAT215593.1	×	×	[67]
rs1475120	chr6:104942078	NONHSAT251362.1	√	√	[69,72]
rs1333045	chr9:22119196	NONHSAT130429.2	√	√	[68]
rs3738401	chr1:231694549	NONHSAT150722.1	√	√	[70]
rs778294	chr13:105489886	NONHSAT035043.2	×	√	[70]
		NONHSAT167180.1			
rs6675281	chr1:231818355	NONHSAT010191.2	×	√	[70]
		NONHSAT227747.1			
		NONHSAT010195.2			
rs6265	chr11:27658369	NONHSAT018519.2	√	×	[71,73]
		NONHSAT018511.2			
		NONHSAT018510.2			
		NONHSAT018491.2			
		NONHSAT018493.2			
		NONHSAT018494.2			
		NONHSAT018495.2			
		NONHSAT018496.2			
		NONHSAT018497.2			
		NONHSAT018498.2			
		NONHSAT018500.2			
rs28722151	chr11:27659629	NONHSAT018518.2	√	√	[71]
rs11030101	chr11:27659197	NONHSAT018524.2	√	×	[71]
		NONHSAT018525.2			
		NONHSAT018491.2			
		NONHSAT018493.2			
		NONHSAT018494.2			
		NONHSAT018495.2			
		NONHSAT018496.2			
		NONHSAT018497.2			
		NONHSAT018498.2			
		NONHSAT018511.2			
		NONHSAT018519.2			
		NONHSAT018518.2			
rs1800947	chr1:159713648	NONHSAT149924.1	√	×	[74]
rs2253206	chr2:207527254	NONHSAT242930.1	√	×	[75]
		NONHSAT242907.1			
		NONHSAT242915.1			
		NONHSAT242916.1			
rs885861	chr7:159028856	NONHSAT124557.2	√	×	[76]
		NONHSAT124557.2			
rs3810950	chr10:49616573	NONHSAT013314.2	√	×	[77]
		NONHSAT013315.2			

√: Yes. ×: No.

5.1 Cis and trans Regulation of LncRNA

Cis regulation by lncRNAs is typically based on the observation that lncRNAs have close physical proximity to their target genes. First, lncRNAs have the ability to bind directly to the 5′-UTRs of adjacent genes and inhibit or promote the expression of the genes by blocking or recruiting transcription factors, such as RNA polII [80–82] (Fig. 2a). LncRNAs can also contribute to looping cross-talk with chromatin in adjacent genes to regulate gene expression. In some cases, lncRNAs do not directly participate in the reg-

ulation of gene expression but share the same transcription factors, including RNA polII, with adjacent genes. When transcribed, lncRNAs can compete with adjacent gene promoters to bind RNA polII or affect the local chromatin state and transcription factor binding to the promoter and enhancer regions [83–85] (Fig. 2b). There is another species of lncRNAs whose sequences contain DNA regulatory elements, such as enhancers. These DNA regulatory elements regulate the expression of the adjacent genes independent of lncRNA transcription [83]. That is, the RNA transcripts of the lncRNA genes have no effect on the adjacent genes, but mutations in the DNA sequence of the lncRNA genes or elimination of this sequence alters the expression of the adjacent target genes [83] (Fig. 2c). In summary, it is clear that *cis* regulation by lncRNAs has two distinct features. First, the lncRNA and the target gene are in close proximity; second, the lncRNA directly or indirectly affects the regulatory regions of the target gene, which regulates its transcription.

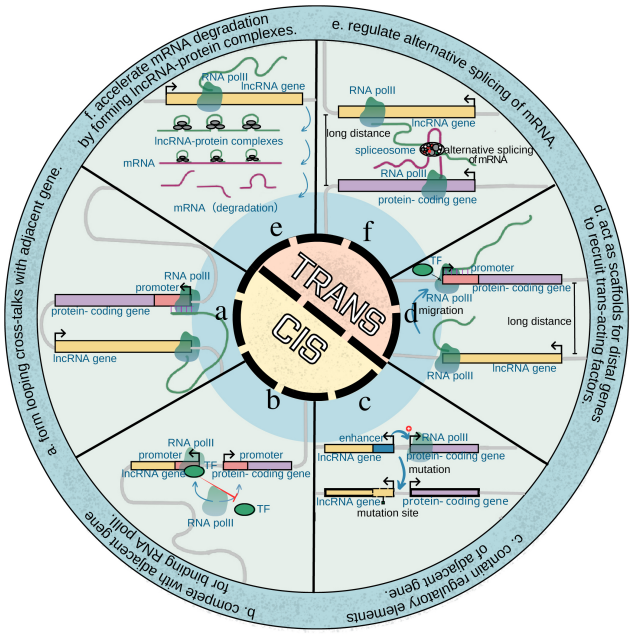

Fig. 2. The *cis* and *trans* regulation modes of lncRNAs. (a–c) The *cis* regulation modes. (d–f) The *trans* regulation modes. (a) LncRNA binds directly to the 5′-UTR of adjacent genes and forms looping crosstalk to regulate gene expression. (b) LncRNA loci share RNA polII with adjacent genes. Thus, lncRNAs compete with gene promoters and inhibit their expression. (c) LncRNA loci contain the regulatory elements of adjacent genes, such as enhancers, in which the mutations alter gene expression. (d) LncRNA leaves the locus to combine with the distant gene and act as scaffolds to recruit proteins to synergistically regulate gene expression. (e) LncRNA in the nucleus is recruited into nuclear speckles to form spliceosomes and regulate the alternative splicing of RNA. (f) LncRNA combines with the 3′UTR binding proteins of the distal gene mRNA, thereby accelerating mRNA degradation. TF, transcription factor.

Via *trans* regulatory mechanisms, lncRNAs have a variety of potential effects on the spatial conformation of distal genes. Transcribed lncRNAs can leave the locus to bind to target genes and act as scaffolds or decoys to recruit proteins to synergistically regulate gene expression [86,87] (Fig. 2d). The way a lncRNA functions is to some extent influenced by its cellular localization. LncRNAs can affect the structure of the nucleus. The lncRNAs in the nucleus can be recruited into nuclear speckles to form spliceosomes with numerous cleavable proteins to regulate alternative splicing of RNA and maintain the normal function of organelles in the nucleus [88,89] (Fig. 2e). The last species of lncRNAs can also perform *trans* regulatory functions by influencing *trans* acting factors or other RNA molecules with regulatory functions (Fig. 2f). In conclusion, the above three types of lncRNA *trans* regulatory modes share the same regulatory characteristics. The first is, the ability to affect genes that are distant from their own loci, and the second is the ability to regulate target genes at the transcriptional or posttranscriptional level.

5.2 Cis or trans Regulation of LncRNAs in Depression

Cis or *trans* regulation of lncRNAs is widespread in the nervous system. For example, the KALRN gene encodes several protein isoforms that play key roles in dendritic arbors and spine remodeling and synaptic plasticity. Dysregulation of the KALRN gene has been implicated in various neurological disorders. LncRNA Kalnc2, arising from the 5′ end of the KALRN locus, *cis* regulates KALRN transcripts in mouse neuronal cells [90]. Important strategies for treating depression include boosting neurotrophic factor expression and promoting neural regeneration [91]. Perry *et al.* [92] documented that the lncRNA *Silc1* is highly expressed in regenerated neurons and activates dormant RNA pol on the promotor of the transcription factor *Sox11* by acting in *cis*. Then, Sox11 is activated to promote neuronal regeneration [92]. The prefrontal cortex and hippocampus tend to exhibit dysfunction and aberrant gene expression in depression. Zhang *et al.* [93] found that the expression of the lncRNA *GM16638-201* in the hippocampus and prefrontal cortex of CUMS mice was high and inhibited the 14-3-3Ɛ pathway. Nine genes were predicted to be regulated by *GM16638-201*. Seven of these genes (*Elmo2*, *Satb1*, *Hnrnpul1*, *Sipa1l3*, *Mapt*, *Tada3*, and *Sgip1*) were regulated in *trans* by the lncRNA *GM16638-201*, and two genes (*StarD5* and *IL-16*) were regulated in *cis* (Table 4, Ref. [93,94]). In depression, lncRNAs also regulate interferon expression in *cis*. We clarify the mechanisms and provide specific instances in the following section.

6. LncRNAs Regulate the Immune System in Depression

The immune-inflammatory hypothesis is one of the explanatory hypotheses for the pathogenesis of depression. This hypothesis proposes that inflammation is crucially in-

Table 4. Summary of the *cis* and *trans* regulation of lncRNAs in depression.

LncRNA	Target	Type	Mechanism	Reference
GM16638-201	*Elmo2*	*trans*	*GM16638-201* inhibits the 14-3-3Ɛ pathway in mouse prefrontal cortex, thereby inducing depressive behavior. However, the relationship between the predicted target genes of *GM16638-201* and 14-3-3Ɛ pathway remain unclear.	[93]
	Satb1	*trans*		
	Hnrnpul1	*trans*		
	Sipa1l3	*trans*		
	Mapt	*trans*		
	Tada3	*trans*		
	Sgip1	*trans*		
	StarD5	*cis*		
	IL-16	*cis*		
RP11-326I11.3	*IRF2*	*cis*	*RP11-326I11.3* mediated depression by *cis* regulating *IRF2*, which encodes a transcription factor involved in interferon signaling.	[94]
RP11-273G15	*G15LY6E*	*cis*	*RP11-273* mediated depression by *cis* regulating *G15LY6E*, which is an interferon-stimulated gene.	[94]
CTD-2647L4.4	*HMBOX*	*cis*	*CTD-2647L4.4* mediated depression by *cis* regulating *HMBOX*, which encodes a transcription factor involved in transcriptional repression, including the interferon gene.	[94]

Elmo2, engulfment and cell motility 2; *Satb1*, special AT-rich sequence binding protein 1; *Hnrnpul1*, heterogeneous nuclear ribonucleoprotein U like 1; *Sipa1l3*, signal-induced proliferation-associated 1 like 3; *Mapt*, microtubule-associated protein tau; *Tada3*, transcriptional adaptor 3; *Sgip1*, SH3-domain GRB2-like (endophilin) interacting protein 1; *StarD5*, StAR-related lipid transfer (START) domain containing 5; *IL-16*, interleukin 16; *IRF2*, interferon regulatory factor 2; *G15LY6E*, lymphocyte antigen 6 family member E; *HMBOX*, Homeobox Containing.

volved in the onset of depression or that depression is an immune system-mediated warning to the body.

Significantly elevated expression levels of different types of proinflammatory cytokines in cerebrospinal fluid and peripheral blood are common in patients with depression [95,96]. The reason for this may be that the HPA axis, which secretes a number of hormones and neurotransmitters to regulate peripheral immunity, becomes more active in response to stress [97]. The immune system responds quickly and increases the levels of inflammatory mediators, including cytokines. Immune messages are transmitted between the peripheral and central neural systems by inflammatory cytokines, altering the central nervous system or causing corresponding behavior changes [98]. Since Smith first proposed in 1991 that cytokines could be involved in depression [99], inflammatory cytokines have been found to induce depression-like behavior [95,100]. For example, proinflammatory cytokines, such as IL-2 and IL-16, affect the function of serotonergic neurons by inducing dioxygenases, resulting in a depressive state in the body [101]. Clinical studies have found that patients develop MDD symptoms during interferon treatment, and the risk of depression after interferon treatment is 30%–70% regardless of the treatment indication [102]. In a study by Zhou *et al.* [94], several lncRNAs were identified, and the overlapping or antisense genes of these lncRNAs, such as *IRF2*, *LY6E*, and *HMBOX1*, were shown to be associated with interferon transcription, activation, and signal transduction (Table 4). *IRF2* is antisense to the lncRNA *RP11-326I11.3* and encodes a transcription factor (TF) involved in interferon signal transduction. *LY6E* is antisense to the lncRNA *RP11-273G15.2* and is an interferon-stimulated gene with immunomodulatory function. The lncRNA *CTD-2647L4.4* is a sense intron of *HMBOX1*, which encodes a TF involved in transcriptional repression, including inhibition of interferon genes [103–107]. Therefore, these overlapping protein-coding genes or antisense genes of these differentially expressed lncRNAs were predicted to be potential targets of lncRNA *cis* regulation by Zhou *et al.* [94]. In short, lncRNAs may be involved in depression by *cis* regulating the expression of these interferon-related genes. Recent research has revealed that lncRNAs may regulate proinflammatory cytokines to lessen the symptoms of depression [108,109]. Sun *et al.* [110] showed that lncRNA *MSTRG.81401* significantly reduced the expression of the cytokines TNF-α and IL-1β in animal models and alleviated diabetic neuropathic pain and depressive behavior in rats. Although there is no direct evidence yet that lncRNAs are involved in depression mediated by immune factors, an increasing number of studies have shown a potential regulatory relationship between lncRNAs and inflammatory factors in this disease. For example, in macrophages, the lncRNA *THRIL* can activate the transcription of *TNF*α by binding to its promoter [111], and TNFα mediates depression like behavior caused by stress induced GSK3 activation in a learned helplessness mouse model [112]. Therefore, it was suggested that there

may be a potential *THRIL*-TNFα axis in depression, but this requires further experimental verification. We have summarized more potential lncRNA-cytokine regulatory axes in **Supplementary Table 1**.

Inflammasomes are polymeric protein complexes that resemble apoptotic bodies and have the ability to cause inflammation in the cytoplasm [113]. LncRNAs may also be involved in MDD by interfering with the formation of inflammasomes. The role of lncRNA *Gm14205* in postpartum depression (PPD) was described by Zhu *et al*. [114]. The lncRNA *Gm14205* may palliate PPD by inhibiting oxytocin receptor activation and inducing activation of NLRP3 inflammatory vesicles in astrocytes.

The gut-brain axis affects the nervous system through the interaction between the vagal nervous system and the intestinal immune system [115]. Evidence of crosstalk between the gut-brain axis and the HPA axis was demonstrated by Misiak B *et al*. [116]. Dyshomoeostasis of the gut flora severely interferes with central nervous system neurotransmission through the HPA axis and vagal afferent nerve fibers, accompanied by local inflammation that exacerbates anxiety or depressive behavior [117,118]. There is no direct experimental evidence to confirm the interactions between lncRNAs and the gene regulatory network of the gut-brain axis in depression. However, recent artificial intelligence-mediated biological analysis has shown that multiple lncRNAs, including *HOTAIR*, *MEG3*, *GAS5*, and *TUG1*, may be hub factors in the lncRNA regulatory network and are influenced by improvements in the gut environment in animal models of depression [119].

7. Conclusion

The current state of depression treatment is characterized by the lack of knowledge of the pathophysiology and objective diagnostic indicators of depression, as well as the limited availability of drugs, the slow onset or even ineffectiveness of drugs, the high relapse rate, and the harmful side effects of drugs [120,121]. It is crucial to understand the pathogenesis of depression and develop new diagnostic biomarkers and therapeutic targets. The abundant lncRNA expression profile data provide us with new tools. Considering the high heterogeneity of complex diseases such as depression, future research may need to build a good framework with multiple dimensions. Since alterations in gene expression lead to the remodeling of central nervous system structure, immunoregulation, and neurotransmission, the establishment of multidimensional and efficient diagnostic models by combining lncRNAs with other indicators, such as imaging features, protein profiles, and metabolite profiles is a promising strategy [12]. Constructing a diagnostic classifier by the nomothetic network psychiatry (NNP) approach may be a useful attempt. Maes *et al*. [122] integrated and ensembled multiple factors into a cause-to-outcome model by means of NNP in a study of MDD. Factors integrated in this study included genome and environmentome features (psychosocial aspects, context-centered hermeneutic data), brainome features, cognitome features, symptomatome features (different symptom domains or clinical phenotypes) and descriptive psychopathological assessments. According to the NNP, the diagnostic gold standard DSM/ICD has been challenged, and multiple false dogmas are thought to exist in mood disorder research. NNP has been attempted in studies of MDD, bipolar disorder, schizophrenia, and other disorders [122–125]. However, to date, no study has provided both lncRNA expression profiles and abundant other information for modeling NNP. This is one of the future endeavors to look forward to. Furthermore, as we have reviewed before, lncRNAs may be involved in the development of depression through various mechanisms, such as ceRNA activity, epigenetic regulation, inflammation and immunity, and single nucleotide polymorphisms. The bioinformatics analysis performed in this review also suggests potential relationships between lncRNAs and methylation modifications and SNPs in depression. However, research on the mechanisms of action of lncRNAs in depression is still in its infancy. Additionally, most studies only show their correlation with the occurrence of depression by statistical analysis of differentially expressed lncRNAs and predict the regulatory mechanism by bioinformatics tools. Therefore, providing clear and powerful evidence to explain the role of lncRNAs in depression through molecular biology experimental approaches should be one of the future directions of subsequent work.

Author Contributions

SW and LT performed the data analysis and wrote the original manuscript. NH collected and organized the literatures, and visualized the data. HW conceived and revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors revised and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.fbl2811321.

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