Long Non-coding RNAs in Pathogenesis of Neurodegenerative Diseases

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Emerging evidence addresses the link between the aberrant epigenetic regulation of gene expression and numerous diseases including neurological disorders, such as Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington’s disease (HD). lncRNAs, a class of ncRNAs, have length of 200 nt or more, some of which crucially regulate a variety of biological processes such as epigenetic-mediated chromatin remodeling, mRNA stability, X-chromosome inactivation and imprinting. Aberrant regulation of the lncRNAs contributes to pathogenesis of many diseases, such as the neurological disorders at the transcriptional and post-transcriptional levels. In this review, we highlight the latest research progress on the contributions of some lncRNAs to the pathogenesis of neurodegenerative diseases via varied mechanisms, such as autophagy regulation, Aβ deposition, neuroinflammation, Tau phosphorylation and α-synuclein aggregation. Meanwhile, we also address the potential challenges on the lncRNAs-mediated epigenetic study to further understand the molecular mechanism of the neurodegenerative diseases.

Keywords: long non-coding RNAs, neurodegenerative diseases, Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis

INTRODUCTION

Epigenetics literally refers to regulation of gene expression due to external modifications to DNA and histones without altering DNA sequence. Caused by a variety of factors inside / outside of organisms, such as hormones, metabolism, diet, temperature, light, drugs, air pollution, age and so on, epigenetic changes could alter growth, development, reproduction and aging, and even contribute to pathogenesis of diseases such as neurological disorders. Significant efforts have been made in study of the epigenetic basis of neurodegenerative diseases (Thompson et al., 2020), such as Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), Huntington’s disease (HD), and so on.

Epigenetic modifications could be classified into three main categories including DNA modifications, histone modifications, and non-coding RNAs (ncRNAs)-mediated modifications (Hwang et al., 2017; Thompson et al., 2020). Of the DNA methylation modifications, 5-methylcytosine (5-mC), 5-hydroxymethylcytosine (5-hmC), and N6-methyladenosine (m6A) have been identified and characterized as important epigenetic markers involved in regulation of gene
expression in complicated mechanisms (Dermentzaki and Lotti, 2020; Pizzorusso and Tognini, 2020). In a broad sense, the ncRNAs are widely defined as all types of RNAs that are not translated into proteins due to the lack of an open reading frame (ORF).

Based on the length with 200 nt as cutoff value (Elling et al., 2016), ncRNAs could be classified into small ncRNAs (sncRNAs) and long ncRNAs (lncRNAs). Typical sncRNAs include microRNAs (miRNAs), piwi interacting RNAs (piRNAs), endogenous small interference RNAs (esiRNAs), micronucleus RNAs (snRNAs), small nucleolar RNAs (snoRNAs) and so on (Sosinska et al., 2015; Elling et al., 2016; Wu and Kuo, 2020).

It has been estimated that there are more than 50,000 of lncRNAs in the human genome (Managadze et al., 2013). Based on the genomic location of lncRNAs relative to protein coding genes, lncRNAs could be classified into five categories (Figure 1): (1) long intergenic non-coding RNAs (LincRNAs), consisting of independent transcriptional units located between but not overlapped with protein codes; (2) intron transcripts located in the intron region of protein coding genes (sense or antisense); (3) Sense lncRNAs are transcribed by the sense chain of the protein-coding gene, which overlaps with at least one exon of the protein-coding gene on the same chain and has the same transcriptional direction. The sense lncRNAs may partially overlap with the protein coding gene, or it may cover the entire sequence of the protein coding gene; (4) Antisense lncRNAs are transcribed by a complementary DNA chain of protein-encoded genes, they are transcribed in the opposite direction and overlap with at least one exon of the positive gene; (5) bidirectional lncRNAs (bilncRNAs) transcribed from different bidirectional promoters (Quan et al., 2017; Liu et al., 2021).

Structurally, majority lncRNAs are very similar to but different from mRNAs. In terms of the similarity, they are transcribed from RNA polymerase II (POLII) from genomic sites in a chromatin-like state; usually 5-capped, spliced, and polyglandular. However, there is still a general trend to distinguish lncRNAs from mRNAs: lncRNAs tends to be shorter than mRNAs, with fewer but longer exons, failing to translate due to lacking in open reading frame, relatively low expression level and poor conservation of primary sequences (Quinn and Chang, 2015).

LncRNA could regulate expression of genes located in other genomic loci on different chromosomes at the transcriptional and posttranscriptional levels, such as RNA processing and translation (Elling et al., 2016). Most lncRNAs are located in the nucleus, thereby acting as scaffolds for chromatin modifiers by interacting with chromatin modification complexes or performing their regulatory functions as transcription co-regulators via binding to transcription factors (Ulitisky and Bartel, 2013). For example, LncRNA-XIST is a well-studied cis-acting LncRNA, which performs the critical developmental process of dosage compensation in females (Cerase et al., 2015). It suppresses the expression of the entire chromosome by inhibition the deposition of chromatin markers and relocating this inactive X chromosome to the periphery of the nucleus (Cerase et al., 2015). In the cytoplasm, lncRNAs usually act as regulators of RNA processing, such as RNA editing, splicing, and miRNA-mediated mRNA expression. LncRNAs also bind to other coding or ncRNAs to regulate transcription as competing endogenous RNAs (ceRNAs) (Salmena et al., 2011). LncRNAs can be used as a molecular sponge of miRNAs and titrate their levels, thereby increasing the expression of mRNAs targeted by these miRNAs (Salmena et al., 2011).

**PHYSIOLOGICAL FUNCTION OF LncRNAs IN THE CENTRAL NERVOUS SYSTEM**

It is estimated that about 40% of LncRNAs are specifically expressed in brain tissue, and their number far exceeds that of protein-coding genes (Derrien et al., 2012). And compared with other tissues, LncRNAs are more conservative in brain tissue. In addition, in brain tissue, LncRNAs show stronger temporal and spatial specificity than mRNAs (Ponjavic et al., 2009). For example, LncRNAs have significant differences in different brain tissues (brain cortex, hippocampus, etc.) and in different age groups (Kadakkuzha et al., 2015). For example, human acceleration region 1 (HAR1), which is part of the overlapping lncRNA gene HARIF (HARIA). The gene is specifically expressed in Cajal–Retzius neurons in the developing human cerebral cortex (Pollard et al., 2006). LncRNAs are related to neural differentiation. In proliferative stem cells / progenitor cells, LncRNAs control the sequential activation of cell type-specific gene regulatory programs, thus promoting the development from pluripotent cells in early embryos to the terminal cell types evident in the brain of mature mammals (Zimmer-Bensch, 2019). LncRNA_DALI promotes neural differentiation by driving the expression of necessary neuronal differentiation genes in neuroblastoma cells through a variety of mechanisms. It promotes the expression of Pou3f3 in cis, forms a trans-acting regulatory complex with DALI, and regulates the expression of neural differentiation genes (Chalei et al., 2014). LncRNAs are related to neurite outgrowth, synaptogenesis and synaptic plasticity (Yang et al., 2021). Neurite outgrowth, synaptogenesis and synaptic plasticity all require complex gene expression regulation and signal transduction, in which lncRNA plays an important role (Modarresi et al., 2012; Mateos-Aparicio and Rodriguez-Moreno, 2019). Brain-derived neurotrophic factor (BDNF) is related to synaptogenesis and neurite outgrowth (Modarresi et al., 2012). BDNF-AS, the antisense LncRNA of BDNF, suppresses the BDNF growth factor gene by recruiting PRC2 to the BDNF site, thus affecting BDNF-mediated axonal growth, proliferation and apoptosis (Modarresi et al., 2012).

**LncRNAs AND AD**

Alzheimer’s disease is the most common, irreversible, and progressive neurodegenerative disorder, accounting for 60% of all dementia cases (Ryan et al., 2018), particularly the people over 65 years old. Among the more than 50 million cases of dementia patients worldwide in 2018, AD patients accounted for 50.75%. Statistically, the global cost of dementia reached United States $957.56 billion in 2015 and will continue increasing.
to United States $9.12 trillion in 2050 as estimated. The main pathological features of AD include β-amyloid plaque deposition, neurofibrillary tangles caused by hyperphosphorylated tau protein, and neuronal loss in specific areas of the brain (Lashley et al., 2018). Despite the high prevalence of AD, the etiology of AD remains to be unclear.

Emerging data have correlated the imbalance of lncRNA expression with a variety of human diseases, such as cardiovascular diseases, cerebrovascular diseases, malignant tumors and neurodegenerative diseases. Indeed, expression disorder of many lncRNAs has been detected in AD (Luo and Chen, 2016), mainly involved in Aβ deposition, Tau protein hyperphosphorylation, oxidative stress, neuroinflammation, mitochondrial dysfunction, autophagy regulation and other pathological processes (Table 1).

Aβ Plaque Formation

Previous studies have proven the contribution of lncRNAs to formation of the Aβ plaques derived from the proteolytic cleavage of Aβ precursor protein (APP) by β-position APP cleaving enzyme 1 (BACE1) and γ secretase. Indeed, dysregulation of BACE1 leads to overproduction of Aβ, contributing to pathogenesis of AD (Modarresi et al., 2011). Basically, lncRNA BACE1-AS is transcribed by RNA polymerase II from the antisense strand of the BACE1 locus located on chromosome 11. It was clear that BACE1-AS is highly expressed in brains of the AD patients and APP transgenic mice, regulates the expression of BACE1 mRNA and increases the production of Aβ (Cortini et al., 2019). The loss of BACE1 in animal models led to physical and behavioral defects, such as decreased learning ability, memory and emotional loss (Ma et al., 2007). The siRNA-based silencing of BACE1-AS in mouse brains significantly decreased the BACE1 mRNA levels in cortex, central and dorsal hippocampal regions (Faghihi et al., 2008). Mechanistically, high level expression of BACE1-AS could promote the stability of BACE1mRNA, which in turn enhances the processing ability of APP and consequently promotes Aβ deposition.

### Table 1: Main dysregulated long non-coding RNAs in Alzheimer’s disease.

| lncRNA | Target mRNA | AD-related process | Biological function | References |
|--------|-------------|--------------------|---------------------|------------|
| BACE1-AS | BACE1 | Aβ deposition | Upregulating BACE1 mRNA stability | Faghihi et al., 2008; Shah et al., 2012; Cortini et al., 2019 |
| XIST | BACE1 | Aβ deposition | Upregulating BACE1 mRNA stability | Zhu et al., 2018; Yue et al., 2019 |
| 51A | SORL1 | Aβ deposition | Downregulating SORL1 mRNA stability | Ciarlo et al., 2013 |
| Linc00507 | MAPT / TTBK1 | Tau hyperphosphorylation | Regulating the expression of MAPT and TTBK1 | Yan et al., 2020 |
| NEAT1 | FZD3 | Tau hyperphosphorylation | Impairing the FZD3/GSK3β/ρ-tau signaling pathway | Zhao et al., 2020 |
| MALAT1 | IL-10 / SOC1 | Neuroinflammation | Regulating the expression of IL-10 and SOC1 | Masourni et al., 2019; Ma et al., 2019 |
| EBF3-AS | EBF3 | Neuronal apoptosis | Promoting neuronal apoptosis in AD | Magistri et al., 2015; Gu et al., 2018 |
| SNHG1 | KRENEN1 | Neuronal apoptosis | Target miR-137 to inhibit KRENEN1 | Causeret et al., 2016; Wang et al., 2019 |
(Faghihi et al., 2008). Some epigenetic factors could regulate the expression of BACE1-AS. For example, stress response stimulates the expression of the BACE1-AS, accelerating development of AD (Shah et al., 2012).

Another important lncRNA essentially involved in the pathogenesis of AD is XIST, one of the most extensively characterized lncRNAs, which plays important roles in cancer and cardiovascular diseases as well (Sun et al., 2017; Kong et al., 2018; Zhou et al., 2019). Expression of the XIST was upregulated in AD model mice and N2a cells in response to \( \text{H}_2\text{O}_2 \) oxidative stress. Bioinformatic analysis predicted a binding site between miR-124 and XIST as well as between miR-124 and BACE1. Expression of XIST was negatively correlated with miR-124 but positively with BACE1. Consistently, knockdown of XIST upregulated expression of miR-124 but downregulated the expression of BACE1 in N2a cells. The direct interactions between XIST and miR-124, as well as BACE1 and miR-124 were further confirmed by using luciferase reporter assay (Zhu et al., 2018). Altogether, it could be concluded that silencing of XIST could attenuate alteration of the AD-related BACE1 via the miR-124 / BACE1 signaling pathway (Yue et al., 2019).

Besides BACE1-AS and XIST, lnc-51A has been acknowledged as an important factor for Aβ deposition. Upregulation of the lnc-51A was detected in plasma of sporadic AD patients. Furthermore, expression of lnc-51A was negatively correlated with disease progression assessed by MMSE score most probably because the upregulation of lnc-51A altered splicing mode of SORL1, thereby causing damage to APP processing and leading to promotion of the Aβ deposition (Ciarlo et al., 2013). These results suggest that the lnc-51A may serve as a stable diagnostic biomarker of AD as well.

**Tau Hyperphosphorylation**

As another important possible pathogenesis of AD, Tau plays an important role in inducing Aβ deposition. Hyperphosphorylation of Tau leads to tau aggregation, exerting neurotoxicity that destroys neuronal function and thereby inducing AD (Clavaguera et al., 2009; Zempel and Mandelkow, 2015). So far, several lncRNAs have been identified to be involved in Tau hyperphosphorylation, such as linc-00507, lncRNA SOX21-AS1, and NEAT1. Expression of linc-00507 was significantly upregulated in hippocampus, cerebral cortex, and AD SH-SY5Y-like cells of APP/PS transgenic mice. The linc-00507 could regulate the expression of microtubule-associated proteins Tau (MAPT) and tau-tubulin protein kinase 1 (TTBK1) via two mechanisms: as competitive endogenous RNA (ceRNA) to bind miR181c-5p, as enhancer of hyperphosphorylation of tau protein by activating P25/P35 /GSK3β signaling pathway (Yan et al., 2020).

Upregulation of SOX21-AS1 was also observed in SH-SY5Y and SK-N-SH cells treated with Aβ 1-42. Essentially, the SOX21-AS1 functions as a sponge for miR-107 in SH-SY5Y and SK-N-SH cells. Silencing of SOX21-AS1 could attenuate the level of Tau phosphorylation mediated by Aβ 1-42 in SHSY5Y and SK-N-SH cells. Consistently, the SOX21-AS1 knockdown reversed the level of p-Tau mediated by miR107 inhibition (Xu et al., 2020a). More importantly, SOX21-AS1 silencing could inhibit hippocampal neuronal apoptosis and enhance memory and learning ability in AD mice (Zhang et al., 2019a), suggesting that SOX21-AS1 could serve as a potential biomarker for AD patient.

Similarly, NEAT1 was upregulated in SH-SY5Y cells and primary neurons of the AD model, and downregulation of NEAT1 promoted Tau protein phosphorylation through FZD3/GSK3β / p-tau pathway (Zhao et al., 2020).

**Neuroinflammation**

The neuroinflammation has been acknowledged as one of the key features in AD with a primary role in exacerbation of Aβ plaques and tau hyperphosphorylation, contributing to AD pathology. So far, some lncRNAs have been identified to be involved in the neuroinflammation, such as MALAT1.

Downregulation of MALAT1 promotes the polarization of macrophages to M1 phenotype and induces the proliferation of T cells in multiple sclerosis (MS), indicating the potential anti-inflammatory effect of MALAT1 on MS (Masoumi et al., 2019). Stimulation of SD rat embryonic PC12 cells and primary cortical neurons with nerve growth factor (NGF) inhibited apoptosis of neurons in PC12 AD model and primary neuronal AD model mediated by lncMALAT1 and promoted growth of neurites in primary neuronal AD model. To further explain the mechanism of MALAT1 on neuroinflammation in AD, it was found that MALAT1 downregulated expression of IL-6 and TNF-α in PC12 AD model and primary neuronal AD model, but enhanced expression of IL-10. These results suggest that MALAT1 contributes to the pathogenesis of AD by regulating inflammation response. Further study demonstrated that MALAT1 may inhibit several inflammation-related miRNAs, such as miR-125b and miR-155. These miRNAs targets to the genes involved in many signaling pathways, such as JAK signal transduction and activator of transcription (STAT) pathway, nuclear factor- kB (NF-kB) signaling pathway, JNK pathway and p38 signaling pathway, thereby inhibiting neuroinflammation of AD (Ma et al., 2019).

LncRNA MEG3 (maternally expressed gene 3) plays important roles in cell proliferation, learning, and memory (Guo et al., 2016; Zhang et al., 2016a). The expression of MEG3 was downregulated in the hippocampus of rats with AD. It has been found that MEG3 upregulation could improve the spatial learning and memory ability of AD rats. MEG3 can reduce the deposition of Aβ 25–35 and oxidative stress in the hippocampus of rats with AD, and reduce the inflammatory injury by downregulating IL-1 β, IL-6 and TNF- α. In addition, the overexpression of MEG3 inhibits the activation of astrocytes in the hippocampus of patients with AD by inhibiting PI3K/Akt signal pathway (Yi et al., 2019).

**Neuronal Apoptosis**

LncRNA-mediated neuronal apoptosis has been linked to pathogenesis of AD. Knockout of SNHG1 could increase cell viability and inhibit apoptosis in SH-SY5Y and HPN cells treated with Aβ 25–35. The SNHG1 could protect SH-SY5Y and HPN cells treated with Aβ 25–35 from neuronal apoptosis via...
Molecular mechanism of lncRNAs and miRNAs mediated accumulation of A\beta plaques and pTAU, neuronal apoptosis and neuroinflammation in AD.

(A) Dysregulation of BACE1-AS, XIST, and lnc-51A leads to overproduction of A\beta, contributing to pathogenesis of AD. BACE1-AS, XIST, and lnc-51A are highly expressed in brains of the AD patients and APP transgenic mice, regulates the expression of BACE1 mRNA and increases the production of A\beta. Enhanced expression of lnc-51A in AD patient altered splicing mode of SORL1, thereby causing damage to APP processing and leading to promotion of the A\beta deposition. XIST and BACE1 are targets of miR-124 because there is a binding site in these two targets. The XIST-miR-124-BACE1 axis regulates the expression of BACE1 in AD, determining the formation of A\beta.

(B) LncRNAs regulate pTAU accumulation. Linc-00507, SOX21-AS1, and NEAT1 have been characterized to be involved in Tau hyperphosphorylation. Significantly upregulated expression of linc-00507 downregulates miR181c-5p, thereby elevating the levels of MAPT and TTBK1 and consequently enhancing hyperphosphorylation of tau protein by activating P25/P35 /GSK3\beta signaling pathway. On the other hand, silencing of SOX21-AS1 could attenuate the level of Tau phosphorylation mediated by miR107 inhibition. Similarly, downregulation of NEAT1 promoted Tau protein phosphorylation via FZD3/GSK3\beta/p-tau pathway.

(C) LncRNAs regulate neuronal apoptosis. LncRNA-SNHG1, lnc-EBF3-AS, and MEG3 have been identified to be involved in neuronal apoptosis, linking to pathogenesis of AD. SNHG1 silencing inhibited miR-137, therefore repressing KRENEN1 expression and increasing cell viability and inhibiting apoptosis. Lnc-EBF3-AS was maladjusted in late-onset AD patients (Magistri et al., 2015), its upregulation was detected to stimulate the expression of EBF3 in the hippocampus of the AD transgenic mouse model, thus promoting the apoptosis of neurons in AD.

(D) LncRNAs regulate neuroinflammation. Some lncRNAs, and miRNAs such as MALAT1 and MEG3, have been identified to be involved in the neuroinflammation. Upregulation of MALAT1 downregulated expression several inflammation-related miRNAs, such as miR-125b and miR-155. These miRNAs target to the genes involved in many signaling pathways, such as JAK signal transduction and activator of transcription (STAT) pathway, nuclear factor –kB (NF-kB) signaling pathway, JNK pathway and p38 signaling pathway, thereby inhibiting neuroinflammation of AD. downregulated expression of MEG3 promoting the occurrence of inflammation.

Inhibiting miR-137. KRENEN1 belongs to the dickkopf (Dkk) family of Wnt antagonists. Wnt-independent way plays a role in promoting apoptosis in cells (Causeret et al., 2016). Further study showed that knockdown of SNHG1 exerts its neuronal protective effect through the inhibition of KRENEN1 by ceRNA miR-137 (Wang et al., 2019).

Lnc-EBF3-AS was maladjusted in late-onset AD patients (Magistri et al., 2015), its upregulation was detected to stimulate the expression of EBF3 in the hippocampus of the AD transgenic mouse model, thus promoting the apoptosis of neurons in AD (Gu et al., 2018). This study suggests the potential role of lnc-EBF3-AS in the pathogenesis of AD (Figure 2).
LncRNAs AND PD

Parkinson’s disease is an age-related progressive neurodegenerative disease, affecting 1% of people mainly over the age of 65. Compared with effect on memory, thinking and cognition in AD, PD mainly affects the motor system. The two typical features of PD include loss of dopaminergic neurons in the substantia nigra and accumulation of α-synuclein (Calabresi et al., 2013; Bose and Beal, 2016). Despite decades of research, our understanding to the pathophysiology and diagnosis of PD is still at infancy stage. Accordingly, so far, there is no efficient strategy for therapy of the disease albeit the current dopamine replacement strategies and surgical interventions can provide symptom relief, still failing to prevent or reverse the underlying pathology (Hegarty et al., 2020; Table 2).

Dopaminergic Neuron Loss

Efforts have been made to elucidate the mechanisms of the lncRNA-mediated dopaminergic neuron loss in AD (Jiang et al., 2020). H19, among the first lncRNAs identified, has been considered as one of the major players in embryonic development, cancer, and PD via regulating proliferation, differentiation and cell motility through controlling DNA methylation and intracellular miRNA pattern being both a sponge for miRNAs and miRNA reservoir.

H19 is located in the imprinted gene cluster H19-IGF2 (Li et al., 2016), whereas the IGF2- proinsulin precursor (INS)-TH gene cluster located at the telomere end of chromosome 11 has been reported to encode various proteins important for homeostasis in dopamine neurons (Sutherland et al., 2008). Therefore, this gene cluster is associated with the risk of PD (Sutherland et al., 2008). Level of the H19 significantly decreased in the 6-hydroxydopa (6-OHDA)-induced PD mouse model as well. Therefore, silencing of SNHG14 reduces the damage induced by rotenone. Binding affinity of the transcription factor SP-1 to SNHG14 promoter was enhanced, leading to upregulation of SNHG14 expression in the rotenone induced PD model of M99D cells. Consistently, knockdown of SNHG14 expression in M99D cells could alleviate the damage induced by rotenone in dopaminergic neurons through activation of the miR-133b inhibited by SNHG14, whereas miR-133b targets to 3′UTR of α-synuclein that contributes to PD pathogenesis. Similarly, the silencing of SNHG14 reduced the neuronal damage in the PD mouse model as well. Therefore, silencing of SNHG14 reduces the damage of dopaminergic neurons by downregulating α-synuclein via miR-133b, improving the symptoms of PD (Zhang et al., 2019).

Table 2: Main dysregulated long non-coding RNAs in Parkinson’s disease

| LncRNA | Target mRNA | AD-related process | Biological function | References |
|--------|-------------|--------------------|---------------------|------------|
| H19    | HPRT1       | Dopaminergic neuron loss | Upregulating HPRT1 mRNA stability | Li et al., 2016; Jiang et al., 2020 |
| NEAT1  | LRRK2       | Dopaminergic neuron loss | Regulation of oxidative stress in dopaminergic neurons | Bastias-Candia et al., 2019; Simchovitz et al., 2019 |
| SNHG1  | SIAH1       | α-synuclein aggregation | Promoting the ubiquitination of α-synuclein | Lee et al., 2008; Chen et al., 2018 |
| LncRNA-p21 | α-Synuclein | α-synuclein aggregation | Transcription repressor | Xu et al., 2018 |
| GASS   | NLPR3       | Neuron inflammation  | Promoting inflammation of microglia | Xu et al., 2020b |
| HAGLROS | PISK       | Autophagy            | Regulating the PI3K/AKT/mTOR signaling pathway | Peng et al., 2019 |

α-Synuclein Aggregation

The α-synuclein, a presynaptic neuron protein, is a major component of Lewy bodies and has been linked to several neurodegenerative diseases (Bennett, 2005). Mutations in the α-synuclein gene are associated with the pathophysiology of PD. The abnormally soluble oligomeric conformation of α-synuclein is considered to be a toxic, leading to neuronal death and disruption of cell homeostasis. Targeting α-synuclein is generally considered as a potential strategy for PD therapy (Dehay et al., 2015).

As mentioned above, MALAT1 confers neuroinflammation in AD. However, in PD, instead of leading to neuroinflammation, MALAT1 was related to the aggregation of α-synuclein. The expression of MALAT1 is upregulated in the midbrain of MALAT1 -induced PD mouse model and in SH-SY5Y cells exposed to MPP+, suggesting that MALAT1 may play an
important role in the pathogenesis of PD. MALAT1 binds to α-synuclein to enhance its stability, resulting in high abundance of α-synuclein. It is well known that β-asarone plays a neuroprotective role by mediating the downregulation of α-synuclein and MALAT1. In a in vivo PD model, β-asarone could increase the number of TH+ cells and downregulate expression of α-synuclein, while the overexpression of MALAT1 could reverse its effect (Zhang et al., 2016b). To understand the pathophysiology of PD models induced by MPP+ and MPTP, miRNA profiling was conducted and found that miR-15b-5p expression was downregulated in response to MPP+ and MPTP accompanied by upregulation of SNHG1 expression.

On another hand, it has been reported that SIAH1 interacts with the brain-rich E2 ubiquitin-binding enzyme UbcH8 to promote the ubiquitination of α-synuclein, thereby promoting the aggregation and toxicity of α-synuclein (Lee et al., 2008) in neurons. Interestingly, SIAH1 serves as one of the downstream targets of miR-15b5p, and upregulation of miR-15b-5p repressed the accumulation of α-synuclein and inhibited apoptosis induced by α-synuclein in SH-SY5Y cells. In contrast, overexpression of SIAH1 or downregulation of miR-15b-5p reversed the protective effect of siSNHG1 on SH-SY5Y cells due to α-synuclein aggregation. Therefore, it is further concluded that SNHG1 promotes the aggregation and toxicity of α-synuclein through activating SIAH1 in SH-SY5Y cells via downregulating miR-15b-5p (Chen et al., 2018). In addition to SNHG1, a long intergenic non-coding RNA-p21 (lincRNA-p21) with a length of 3,100 nt located on chromosome 6, also play a part in cell proliferation, metabolism and reprogramming, and lincRNA-p21 is considered as a potential diagnostic marker for many diseases (Chen et al., 2017). The lincRNA-p21 is a p53-dependent transcriptional target gene that functions as a transcriptional inhibitor and triggers apoptosis (Huart et al., 2010). In the MPTP-induced PD mice and the MPP+ -treated SH-SY5Y cells, lincRNA-p21 expression was significantly upregulated, in accordance with inhibition of cell viability and induction of apoptosis associated with downregulation of miR-1277-5p and upregulation of α-synuclein protein (Xu et al., 2018). Altogether addresses the regulation of α-synuclein aggregation and toxicity by axis of SNHG1-miR15b-5p- SIAH1-linc-p21- miR-1277-5p-α-synuclein aggregation.

**Neuroinflammation**

Neuroinflammation is considered to promote the development of PD (Kaur et al., 2017). As the main immune cells of CNS, microglia are activated in PD models in response to MPTP or lipopolysaccharide (LPS) (More and Choi, 2017), mediating the immune response in the brain and triggering the release of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα), IL-1β and IL-6, and consequently leading to apoptosis and death of DA neurons in the midbrain (Tang and Le, 2016).

Some lncRNAs are involved in activation of microglia such as SNHG1 and Inc-GAS5. Upregulation of SNHG1 has been observed in both LPS-stimulated BV2 microglia and MPTP-induced PD mice, suggesting that this lncRNA is related to LPS-induced activation and inflammation of BV2 microglia. In the MCS metastasis model, downregulation of SNHG1 could prevent the apoptosis of activated microglia and reduce the activation of microglia and the loss of dopaminergic neurons in PD mice induced by MPTP. Moreover, SNHG1 as the ceRNA of miR-7, regulates the expression of NLRP3, leading to the activation of NLRP3 inflammatory bodies (Cao et al., 2018). More data showed that by spongifying miR223-3p, the GAS5 could also promote microglial inflammation in PD via regulation of NLRP3 pathway (Xu et al., 2020b).

**Autophagy**

Increasingly emerged evidence supports the view that autophagy dysfunction contributes to occurrence or development of PD (Ghavami et al., 2014). For example, overexpression of transcription factor EB (TFEB), a key autophagy regulator, helps to clean the α-synuclein aggregation and to prevent neuronal loss in PD (Decressac et al., 2013).

After death autopsy showed significant upregulation of the SNHG1 in PD patient brain samples (Kraus et al., 2017). Consistent with PD patients, substantial increase of SNHG1 expression in vivo and in vitro were detected the MPP+-treated MN9D cells. Bioinformatic analysis confirmed a common miR-221/222 response element specifically for SNHG1. Interestingly, overexpression of miR-221/222 promoted the level of LC3-II and reduced the neurotoxicity induced by MPP+, in consistency with the increased the level of LC3-II in MN9D cells under SNHG1 silencing, thereby preventing cytotoxicity and suggesting the regulation of SNHG1 through miR-221/222. In MPP+-treated MN9D cells, miR221 or miR-222 inhibitors reversed siRNA-SNHG1-induced p-mTOR inhibition, which was consistent with the effect of silencing p27. This experiment finally confirmed that lncRNA-SNHG1 regulates the expression of p27/mTOR through competitive interaction with miR-221/222 members in MPP+-treated MN9D cells (Qian et al., 2019).

Another lncRNA HAGLROS is considered to be involved in occurrence and development of PD. Upregulated expression of HAGLROS in PD mouse model induced by MPTP and SH-SY5Y cells poisoned by MPP, is in consistency with the reduction of apoptosis and autophagy in response to silencing of Inc-HAGLROS. Further in vitro studies showed that HAGLROS negatively regulated the expression of miR-100, and that HAGLROS enhanced apoptosis and autophagy of SH-SY5Y cells exposed to MPP through downregulation of sponge-like miR-100. These findings indicated that the inhibition of HAGLROS could alleviate the MPP induced damage of SH-SY5Y cells by activating PI3K/AKT/mTOR pathway, suggesting the essential role of Inc-HAGLROS in PD (Peng et al., 2019).

Instead of promoting MPP+-induced apoptosis as did the HAGLROS, upregulation of NORAD could protect the apoptosis and mitochondrial dysfunction, while the downregulation of NORAD could reverse the protection (Tatton et al., 2003). To further understand the protection mechanism of the NORAD, in vitro cytotoxicity assays were conducted by generating stable SHSY5Y cell lines that silence or overexpress NORAD mediated by lentivirus in the SHSY5Y cells. Overexpression of NORAD could significantly protect SH-SY5Y cells from the MPP+-induced cytotoxicity, while the down-regulation enhanced the cytotoxicity in a MPP+ dose and time dependent manner (Song et al., 2019) (Figure 3).
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FIGURE 3 | Molecular mechanism of lncRNAs and miRNAs mediated accumulation of dopaminergic neuron loss, α-synuclein aggregation and autophagy in PD. (A) LncRNAs regulate α-synuclein aggregation and autophagy. SNHG1 and lnc-MALAE1 are highly expressed in AD, promotes the α-synuclein aggregation. SNHG1 also can inhibit autophagy by reducing the expression of mTOR. Linc-P21 is down-expressed in PD and promotes aggregation through upexpression of miR-1277-5P. (B) LncRNAs regulate dopaminergic neuron loss. Overexpression of the H19 could prevent dopaminergic neuron loss in the 6-OHDA-induced PD model by activating HPRT1-mediated Wnt/β-catenin signaling pathway via impairing miR-301b-3p-targeted repression of HPRT1 transcription. NEAT1 upregulation in dopaminergic neurons of PD may protect dopaminergic neurons from LRRK2-mediated damage under oxidative stress. Overexpression of the ln_SNHG14 could promote dopaminergic neuron loss.

LncRNAs AND ALS

As a common and serious adult-onset neuromuscular disease, ALS affects motor neurons in the spinal cord, brainstem and motor cortex. Sporadic ALS (SALS) accounts for up to 90% of ALS cases and the other 10% have a strong genetic component also called as familial ALS (FALS). Mutations in more than 20 genes contribute to FALS (Renton et al., 2014). TDP-43, a multifunctional RNA binding protein encoded by TARDBP gene, is considered to be the main component involved in ALS. TDP-43 mutations contribute to about 95% of SALS cases, while FALS cases are caused by C9ORF72 gene mutations. However, the pathological boundary is not that clear between SALS and FALS. For example, dozens of TARDBP mutations have been found in both FALS and SALS patients. Further characterization of all these TDP-43 mutation cases via loss of TDP-43 from the nucleus and cytoplasmic and gain of TDP-43 function suggests that this protein is related to ALS (Shelkovnikova et al., 2018; Table 3).

LncRNAs Interactive With TDP-43

Transcriptomic profiling conducted in 30 patients with SALS and 30 matched normal persons, led to identification of 293 of lncRNAs differentially expressed (DE) in the SALS patients. Of the DE lnc-RNAs, 183 out of 293 (62.5%) were upregulated, while 184 out of 293 (62.8%) belong to antisense RNAs and 81 out of 293 (27.7%) were reported as real DE lincRNAs (Gagliardi et al., 2018), suggesting the lncRNAs mediated regulation of ALS.

NEAT1 containing a sequence rich in GpCs, mainly expressed in spinal motoneurons at the early stage of ALS and contributed to pathogenesis of ALS. The NEAT1 mainly binds to TDP43 in the brain tissue of ALS patients and cultured cells (HeLa and SH-SY5Y) (Tollervey et al., 2011). Both TDP-43 and fused in sarcoma/translocated in liposarcoma (FUS/TLS) are considered to be necessary components for the formation of normal accessory spots via direct protein-protein interactions (Hutchinson et al., 2007). The frequency of accessory spot formation increased dramatically at the early stage of ALS. Therefore, NEAT1 was considered to be the scaffold of RNA binding proteins in the motor neuron nuclei of ALS patients. As a component of Paraspeckles, FUS significantly promotes their stability by regulating the steady-state level of NEAT1 and maintaining the structure of the nucleosome (Naganuma et al., 2012). More detailed analysis showed that NEAT1 was highly enriched in neurons of the anterior horn of the spinal cord and in the cortex of ALS patients (Tollervey et al., 2011; Shelkovnikova et al., 2018). Given that the formation of accessory spots in the spinal cord of SALS and FALS patients is much more than that in the healthy people, it is plausible to speculate that the accessory spot formation might be a common feature of ALS patient (Shelkovnikova et al., 2018).

Other lncRNAs are involved in ALS mostly via interaction with proteins related to ALS pathogenesis, such as TDP-43 or FUS. The expression of the MALAT1 was significantly upregulated in the cortex of sporadic FTD patients and binds to...
TDP-43 that interacts with several other lncRNAs, including lnc-BDNFOS and lnc-TFEB α (in SHSY5Y cells) and lnc-Myolinc (in muscle cells) (Militello et al., 2018). The expression of heat shock RNA ω (hsr ω) in lncRNA is positively regulated by TDP-43 via direct interaction with hsr ω. Upregulated expression of hsr ω is detected in both human FTD patients and cellular model of TDP-43 overexpression (Chung et al., 2018). The ALS-related mutations in FUS affect expression of several lncRNAs in mESC- MN. For example, relative to wild-type FUS/- MNS, mutation FUSP517L/517L could upregulate lnc-Lhx1os specifically, while both lnc-MN-1 (2610316D01Rik) and lnc-MN2 (5330434G04Rik) were downregulated, indicating that the loss of FUS function altered the expression of several lncRNAs.

Evolutionarily, lnc-Lhx1os, lnc-MN-1 and lnc-MN2 are conserved between mice and humans, and their expressions levels are elevated during the differentiation of human MN in vitro (Biscarini et al., 2018). The homologous gene dFU in Drosophila and human FUS both interact with hsr ω, and its deletion could lead to cytoplasmic dislocation and loss of nuclear dFU function. In addition, knockout of MN-specific hsr ω impaired the movement of larvae and adults of Drosophila melanogaster, and also led to the anatomical defects of MN presynaptic terminals. In view of the different interactions between TDP-43 / FUS and lncRNAs, the cytoplasmic mislocalization and dysfunction of TDP-43 and FUS in ALS may affect the distribution, expression and / or function of lncRNAs, thereby leading to degeneration and ALS of MN (Lo Piccolo and Yamaguchi, 2017).

### LncRNAs Derived From C9ORF72 Antisense Transcript

Expansion of (GGGGCC)n (G4C2) repeats in 5′ UTR of the C9orf72 gene has been acknowledged as one of the most common genetic factors in ALS (Shelkovnikova et al., 2018). Three transcript variants were detected in the expansion of the (G4C2)n repeats in C9ORF72, including variants 1 and 2 located in intron 1, and variant 2 in the promoter region (Balenda and Isaacs, 2018). The (G4C2)n repeats in C9ORF72 were observed in nearly 40% of FALS and FTD cases and in up to 8% of SALS, respectively (Majounie et al., 2012; Dejesus-Hernandez et al., 2017). As for the (G4C2)n repeat number, healthy persons carry as many as 20–30 repeats, while the repeat number was expanded to hundreds even thousands in ALS (DeJesus-Hernandez et al., 2017). The C9orf72-associated ALS cases (C9-ALS) are associated with loss of C9orf72 function and acquisition of toxic function mediated by expansion of (G4C2)n repeats. C9orf72 antisense transcript (C9orf72-AS) is a kind of lncRNA named as Inc-C9orf72-AS transcribed from intron 1 of the C9orf72 gene (Mori et al., 2013). Although C9orf72 and its corresponding proteins have been extensively investigated, the functional correlation of Inc-C9orf72-AS remains poorly understood. C9orf72-S can form a G-quadruplex known to regulate gene expression (Reddy et al., 2013; Haeusler et al., 2014). Theoretically, C-rich C9orf72-AS repeats may not form a similar structure. On the contrary, the expansion of (G2C4)n repeats in Inc-C9orf72-AS may form a C-rich sequence (Kovanda et al., 2013), thereby potentially affecting the stability and transcription of the genome. Furthermore, it was found that these could rescue disease-specific transcriptional changes in iPSC-derived neurons by using antisense oligodeoxynucleotides (ASO) against C9orf72 in Drosophila model (Sareen et al., 2013; Zhang et al., 2015).

### LncRNAs AND HUNTINGTON’S DISEASE

Huntington’s disease is a neurodegenerative disease characterized by autosomal dominant inheritance, cognitive impairment, dance motor disorder and mental disorder. Selective loss of intermediate spinous neurons in caudate nucleus and putamen is a typical pathological feature of HD (Labbadia and Morimoto, 2013). The abnormal expansion of (CAG)n in HT protein gene leads to the formation of mutant HT proteins containing the expanded polyglutamine region. The mutant HT protein induces neurodegeneration through a variety of mechanisms such as transcriptional disorders, clearance of misfolded proteins, toxic N-terminal fragments, mitochondrial dysfunction and oxidative stress (Ross and Tabbri, 2011; Sunwoo et al., 2017). Given that HT protein is widely expressed in different cell types at all developmental stages of the body, the pathogenesis of HD may begin early and last for a lifelong process (Bassi et al., 2017; Table 3).

Previous studies have confirmed the contribution of ncRNAs to HD pathogenesis. 12 of ncRNAs were identified and characterized in the brains of HD mice, eight of which are human homologs. Of the identified ncRNAs, MEG3, NEAT1 and XIST...
showed a sustained and significant increase in HD cells and animal models. Knockdown of MEG3 and NEAT1 in HD cell model resulted in a significant decrease in the aggregation of mutant HT protein and a downregulation of endogenous Tp53 expression (Chanda et al., 2018). Upregulation of MEG3 was observed at the early stage (6 weeks) and lasted to late stage (8 weeks) in R6/2 mice as well as in other HD cell models. However, downregulation of MEG3 was also reported in the brains of HD patients (Johnson, 2012).

Previous studies reported elevation of the NEAT1 levels in both GEO data mining, HD models, and autopsy samples of HD patients (Brochier et al., 2008; Makhlouf et al., 2014). However, no information is available for the alteration of XIST levels in HD (Chanda et al., 2018). Other studies have shown that NEAT1 physically interact with loci of other genes located on the active chromatin sites near the Tp53 gene (Yang et al., 2013). Tp53 directly regulates the transcription of NEAT1 by binding to the promoter region of the gene (West et al., 2014; Sunwoo et al., 2017). Therefore, the level of NEAT1 and Tp53 is controlled by the feedback loop. Given that inhibition of proteasome degradation could increase levels of NEAT1, cytoplasmic and nuclear polymers containing ubiquitin proteins are expected to be identified as well (Idogawa et al., 2017). In view of the fact that proteasome degradation is affected in HD (Hirose et al., 2014; Hyrskyluoto et al., 2014) and that NEAT1 level is elevated in HD (Makhlouf et al., 2014), it could be inferred that Neat1 may affect proteasome degradation in HD. Aberrant expression of lncRNAs was observed in the postmortem brain of human HD and the brain of R6/Unx2 mice, such as upregulation of NEAT1. Transfection of the short isomser of NEAT1 into N2a cells significantly reduced cell death caused by H2O2 oxidative stress, revealing the functional correlation of NEAT1 and neuroprotective mechanism in the pathogenesis of HD (Sunwoo et al., 2017).

MEG3, NEAT1, and XIST may interact with many miRNAs through sequence complementarity, potentially reducing the efficiency of binding to their target miRNAs by acting as “sponges” or competitors. Reduced levels of miR-9, miR-125b, miR-132, miR-146a and miR-150, miR-221, and miR-222 have been reported in various HD cells, HD models as well as in postmortem HD tissues (Sinha et al., 2012; Blume et al., 2015). Therefore, it is reasonable to speculate that the interaction of lncRNAs and miRNAs may contribute to the reduced levels of these miRNAs, thereby promoting the occurrence and development of HD.

Many other lncRNAs, such as BACE1-AS, TUG1, and HAR1, were also involved in the occurrence and development of HD although no evidence to show that they interact with miRNAs. For example, BACE1 antisense transcripts (BACE1-AS) positively regulate BACE1 mRNA levels in the brain of HD patients. It is worth of noting that knocking down of BACE1-AS, could reduce the stable mRNA level of the justice gene (Johnson, 2012). Another up-regulated TUG1 has been reported to target p53 target (Khalil et al., 2009), a known transcriptional regulatory pathway in HD driven by the pathological activation of P53 tumor suppressor proteins. Different from BACE1-AS and TUG1, the HAR1 expression was downregulated in two brain regions cortex (Brodmann region 7/9) and striatum comparing the HD autopsy to the control persons. More specifically, significant reductions in the levels of both HAR1F and HAR1R were observed in the striatum of HD patients, but not in the cortex compared with the Brodmann 7/9 region. Furthermore, HAR1 was considered as the target of REST, but no evidence could support this thought in a way that disruption of REST failed to downregulate HAR1 level in mice (Johnson et al., 2010).

CONCLUSION

Although significant efforts have been made in dissection of pathology for the neurodegenerative disorders such as AD, PD, HD, and ALS, our understanding is still very limited. Excitingly, dramatic breakthroughs in high throughput sequencing technologies in recent years significantly speeds up our understanding on epigenetic contribution to pathogenesis of neurodegenerative disorders. Accumulated evidence has enabled us to acknowledge that lncRNAs could suppress or promote the neurodegenerative disorders via epigenetically regulating expression of genes crucially involved in the pathogenesis at both transcriptional and posttranscriptional levels. In the nucleus, lncRNAs can inhibit or promote gene expression through a cis or in trans (Wang et al., 2011). XIST is the most extensively investigated cis-acting lncRNA, which inactivate the whole X chromosome by inhibiting the deposition of chromatin markers and relocating this chromosome to the periphery of the nucleus (Cerase et al., 2015). LncRNA HOTAIR interacts with polycomb repressive complex2 (PRC2), leading to H3K27me3-mediated gene silencing at HOXD locus in trans (Rinn et al., 2007). However, the exact mechanisms of how these lncRNAs affect the onset and progression of neurodegenerative diseases remains largely unknown. On one hand, some studies on lncRNAs lack biological repeats or conducted only in vitro, without confirmation in vivo. On the other hand, although some lncRNAs are differentially expressed in in the patients and normal persons, they lack tissue specificity. For example, MEG3 has been demonstrated to be differently expressed in AD, ALS, HD and some malignant tumors. This poses a great challenge for identification of the CNS-specific lncRNAs as biomarkers. More importantly, the ceRNA theory has become the main hypothesis of how lncRNAs function as ceRNA in neurodegenerative diseases. However, it is still skeptical about whether the physiological expression level of a single lncRNA is sufficient to alter the expression level of miRNAs, because a single lncRNA represent only a very small fraction of the total miRNA targets (Denzler et al., 2014; Thomson and Dinger, 2016). Besides, since most databases were generated by using a variety of miRNA prediction algorithms, biochemical and gene expression data, hard to determine the reliability of the ceRNA interactions established from these different prediction methods (Thomson et al., 2011). In terms of the experimental strategy, the models were generated via ceRNA overexpression or silencing. Thus, the concern is that overexpression of miRNAs or ceRNAs at the physiological level is experimentally challenging (Liu et al., 2021). As mentioned above, most of the lncRNA studies are conducted
in vitro, failing to mimick the in vivo patients. Therefore, mouse models or human brain organoids should be used as more relevant physiological model.

It is well known that a plurality of lncRNAs can target a miRNA and a single lncRNA targets multiple miRNAs simultaneously, making the interplay of miRNAs and lncRNAs extremely complicated. In this context, it is essential for the future study to investigate all the genes crucially involved in the pathogenesis as well as their regulation elements such as ncRNAs (miRNAs and lncRNAs) genetically, epigenetically, molecularly, and biochemically. Understanding the interaction networks and orchestration of all the ncRNAs and target genes could help us identify the biomarkers for diagnosis and therapy.

Antisense oligonucleotides (ASOs) have been confirmed to target lncRNAs in the nucleus more effectively than siRNAs. Furthermore, ASOs based study in disease animal models as well as the clinical trials have been conducted for some disease such as cancer. For example, specific ASO can act on specific lncRNA to alleviate the production of A β in the AD animal model (Massone et al., 2012). Moreover, Clinical trials using ASO to treat malignant tumors (Adams et al., 2017) and intrathecal injection of ASO for the therapy of ASL (Chiriboga et al., 2016) have been carried out. These studies shed light on the expectation that lncRNAs could potentially become new biomarkers for diagnosis and clinical therapy of ND, meanwhile the promising results inspire the scientists to make greater efforts to reach this goal. However, there is distance to go to identify and characterize the specific lncRNAs that contribute to the pathogenesis of neurodegenerative diseases. To this end, the animal ND models, the cell-based assays, the human brain organoids derived from ND patients and normal persons, the patients’ samples (brain tissues and blood) should be employed for analysis and validation of the specific ncRNAs. The cell-based assays and animal models such as mouse could be employed for fast and primary screening. It is worthy of noting that the large evolutionary distance between mouse and human lead to a discrepancy in genetic, anatomic, and physiological basis between animal models and humans. In addition, human brain organoids are a miniaturized and simplified version of brain organ generated in vitro but could recapitulate key features brain development. Thus, candidate lncRNAs identified in animal models should be further validated in human organoids even human tissues.

To sum up, further study on lncRNAs in CNSNDs will contribute to further understanding of brain function and the pathogenesis as well as the development of the promising therapeutic strategies for the CNSNDs.

AUTHOR CONTRIBUTIONS
SX designed the topic and conceived the structure of the manuscript. SZ, XY, YM, DS, HY, and DW collected the articles, and made the tables and figures. SZ wrote the manuscript. SX, MW, and JB revised the manuscript. All authors contributed to the manuscript.

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