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REVIEW PAPER

The Potential of Targeting Autophagy-Related Non-coding RNAs in the Treatment of Alzheimer's and Parkinson's Diseases

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Abstract

Clearance of accumulated protein aggregates is one of the functions of autophagy. Recently, a clearer understanding of non-coding RNAs (ncRNAs) functions documented that ncRNAs have important roles in several biological processes associated with the development and progression of neurodegenerative disorders. Subtypes of ncRNA, including microRNA (miRNA), long noncoding RNA (lncRNA), and circular RNA (circRNA), are commonly dysregulated in neurodegenerative disorders such as Alzheimer and Parkinson diseases. Dysregulation of these non-coding RNAs has been associated with inhibition or stimulation of autophagy. Decreased miR-124 led to decreased/increased autophagy in experimental model of Alzheimer and Parkinson diseases. Increased BACE1-AS showed enhanced autophagy in Alzheimer disease by targeting miR-214-3p, Beclin-1, LC3-I/LC3-II, p62, and ATG5. A significant increase in NEAT1led to stimulated autophagy in experimental model of PD by targeting PINK1, LC3-I, LC3-II, p62 and miR-374c-5p. In addition, increased BDNF-AS and SNHG1 decreased autophagy in MPTP-induced PD by targeting miR-125b-5p and miR-221/222, respectively. The upregulation of circNF1-419 and circSAMD4A resulted in an increased autophagy by regulating Dynamin-1 and miR-29c 3p, respectively. A detailed discussion of miRNAs, circRNAs, and lncRNAs in relation to their autophagy-related signaling pathways is presented in this study.

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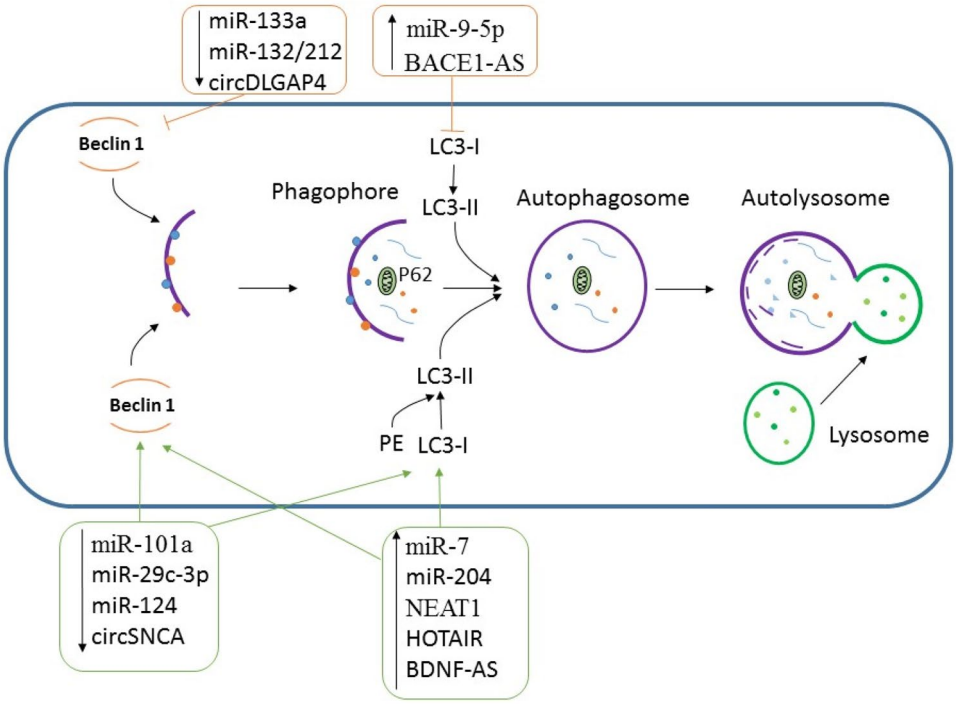
Graphical Abstract

Autophagy-related non-coding RNAs in neurodegenerative diseases.



Keywords Neurodegenerative disorders · Non-coding RNAs · Autophagy · microRNA · Long non-coding (lnc) RNA

Introduction

The term "neurodegenerative disease (ND)" describes the progressive loss of specific populations of neurons by toxic or metabolic processes. There are several means to classify neurodegenerative diseases by their primary clinical features, anatomic distributions of neurodegeneration, or molecular abnormalities (Dugger and Dickson 2017). Alzheimer's disease (AD) and Parkinson's disease (PD) are two major NDs (Checkoway et al. 2011). As the ability of the central nervous system (CNS) for regeneration is limited, it is essential to limit injury within this organ (Kuhn et al. 2001).

A cell's autophagy process involves the transport of cytosolic components, macromolecules, viruses, bacteria, and organelles to lysosomes for destruction (Patergnani and Pinton 2015). Physiological and pathological conditions are impacted by autophagy and its specialized forms. The function of autophagy in normal conditions is to remove unnecessary material, regulate organelle turnover, and meet energy demands. Autophagy can have both beneficial and harmful effects on pathological conditions (Patergnani et al. 2020; Xue et al. 2020). The clearance of accumulated protein aggregates is one of the functions of autophagy that contributes to neuronal function and neurodegenerative disorders (Nah et al. 2015). A wide range of neurodegenerative diseases is characterized by the accumulation of proteins (Menzies et al. 2015; Ravikumar et al. 2002), with autophagy contributing to disease progression (Menzies et al. 2015) and neuronal loss (Hara et al. 2006; Komatsu et al. 2006; Levine and Kroemer 2008; Nikoletopoulou et al. 2013).

Studies have focused on evaluating specific biomarkers related to genes that encode autophagy pathways-related proteins in neurodegenerative diseases. In this regard, through their ability to adjust the translation of other RNAs, non-coding RNAs (ncRNAs) contribute to the generation of functional proteins through the effect on the expression of protein-coding transcripts (Esteller 2011). A series of cleavage events produce mature microRNAs after RNA polymerases II and III transcribe microRNA precursors. lncRNAs also contain a poly (A) terminus at 3′ and a 5′ methyl-cytosine cap which is transcribed by RNA polymerase II (Pol II). lncRNAs biogenesis is similar to that

of mRNA with a few variations in the process. RNA circular molecules (circRNAs) are endogenous non-coding RNAs generated by the back-splicing process. Some circRNAs consisting of introns originate in the nucleus, while others have one or more exons with major locations in the cytoplasm. A circular RNA does not have a polyadenylated tail or a 5–3′ direction. These characteristics render ncRNAs more stable in plasma and tissues as they possess a continuous loop of covalent bonds. ncRNAs can be useful in diagnostic and prognostic goals and have roles in regulating autophagy pathways in neurodegenerative diseases (Shah et al. 2018; Xu et al. 2020).

Herein, we highlight the role of several ncRNAs associated with autophagy in AD and PD as neurodegenerative diseases. miRNAs, circRNAs, and lncRNAs will be discussed in detail. Due to the importance of RNAs for neurodegenerative diseases, multiple studies have been conducted on ncRNAs; however, in the present review, the effects of these ncRNAs on autophagy-related genes and pathways in AD and PD are discussed, distinguishing this review from others.

Autophagy and Neurodegenerative Diseases

The biochemist Christian de Duve introduced the term autophagy in late 1963, referring to cellular degradation and recycling via a self-degradative pathway (Duve and Wattiaux, 1966). In mammalian cells, macroautophagy is the best-characterized and most prevalent mode of autophagy. Macroautophagy occurs when the expanding phagophore sequesters random cytoplasm and dysfunctional organelles, leading to autophagosome formation. Following autophagosome fusion with the vacuole membrane, the autophagic body enters the vacuole lumen. Vacuolar hydrolases eventually degrade or process the sequestered cargo (Feng et al. 2014).

Autophagy initiates when two protein complexes are triggered at phagophore assembly sites, UN51-like Ser/Thr kinase (ULK) and phosphatidylinositol-3-kinase (PI3K) (Agarwal et al. 2015; Ohsumi and Mizushima 2004). ULK complexes consist of the ULK1/2 and FAK family interacted proteins, and autophagy-related gene 13 (ATG13) (Jung et al. 2009). The PI3K complex comprises Vps34, Vps15, Beclin1, and ATG14 (Fan et al. 2011). It is noteworthy that anti-apoptotic dimers BCL-XL and BCL-2 regulate Beclin1 localized on endoplasmic reticulum (ER) membranes. Beclin1 is dissociated from BCL-2. Next, it coordinates with Vps34 after autophagy is triggered (Marquez and Xu 2012; Martyniszyn et al. 2011; Pattingre et al. 2005). As a result, phosphatidylinositol 3-phosphate (PI3P) will concentrate on the phagophore's surface (Obara and Ohsumi 2008; Puri et al. 2013). Autophagosome expansion and closure are mediated via two ubiquitin-like complexes. Initially, upon the interaction of Atg7, Atg5 covalently attaches to Atg12 (Shao et al. 2007). The complex then binds to Atg16 for Atg5-Atg12-Atg16 complex formation, which is accountable for phagophore elongation. Atg4B cleaves microtubule-associated protein 1 light chain 3 (LC3) to form LC3-I, in another ubiquitin-like complex (Fujita et al. 2008). Next, LC3-I is converted to phosphatidylethanolamine (PE)-conjugated LC3-II with assistance of the Atg5-Atg12-Atg16 complex. LC3-II is considered an important marker for autophagosomes (Kabeya et al. 2000). Subsequently, mature autophagosomes move along microtubules to fuse with lysosomes (Ravikumar et al. 2005). This involves the recruitment of multiple membrane protein complexes such as soluble NSF attachment protein receptors (SNAREs) (Itakura et al. 2012). A proteolytic reaction occurs after autolysosomes are formed to degrade the cargoes they carry (Guo et al. 2018b).

The pathophysiology of AD includes two abnormal structures: Neurofibrillary tangles (NTs) and senile plaques. Altered cleavage of amyloid precursor protein (APP) has been implicated in increased β-amyloid tangles, constituting senile plaques (Querfurth and LaFerla 2010). NTs, which are hyperphosphorylated tau proteins associated with microtubules, are pathological, insoluble aggregates. In normal conditions, microtubule stabilization and vesicle transport in neurons are controlled by tau's interaction with tubulin (Wang et al. 2013). AD brains with autophagic vacuoles (AVs) are indicative of altered autophagy in this disease. Disruption of retrograde transport of autophagosomes along axons results in the repletion of naive AVs and Aβ-producing AVs (Ułamek-Kozioł et al. 2013; Yu et al. 2005), leading to increased production of Aβ. Autophagy contributes to clearance of soluble as well as insoluble tau aggregates in conjunction with the ubiquitin-proteasome system. Chloroquine, causes tau clearance to be delayed and tau aggregates to accumulate by inhibiting autophagosome–lysosome fusion (Hamano et al. 2008). Phosphorylated tau is more affected by autophagic failure than other forms of tau (Rodríguez-Martín et al. 2013).

Another common neurodegenerative disorder is PD, characterized by accumulation of α-synuclein and degeneration of dopaminergic neurons, and presence of ubiquitin in Lewy bodies, which are intracytoplasmic inclusions (Tan et al. 2014).

Autophagic dysfunction in the substantia nigra is inherent to PD (Alcalay et al. 2010). Autophagy pathway can be regulated by proteins encoded by PD-relevant genes. LRRK2, one of the genes whose mutation is associated with PD, may regulate macroautophagy (Bonifati 2006). Knockdown of LRRK2 stimulates autophagy and inhibits LRRK2 kinase activity, thus increasing macroautophagy, absent changes in TORC1 levels (Alegre-Abarrategui et al. 2009; Manzoni

et al. 2013). Mitophagy also mediates the function of autosomal recessive genes associated with PD. Parkin, an E3-like ligase, mostly localizes to the cytosol, but once a mitochondrial uncoupler (CCCP) is applied, it is translocated to damaged mitochondria for removal (Narendra et al. 2008). As a result, Parkin mutations block the ability of mitophagy to clear damaged mitochondria in PD. In addition, studies have shown that depolarization of mitochondria recruits Parkin by accumulating PINK1 on its external membrane (Scarffe et al. 2014). Nonetheless, the link between mitophagy and the etiology of PD has yet to be fully characterized. Moreover, oxidative stress has been shown to trigger PD. In this regard, autophagy, which reduces oxidative stress, may be an effective treatment for PD (Surendran and Rajasankar 2010). The PD SNCA model of the BECN1 gene showed attenuation in neurodegenerative pathology (Spencer et al. 2009). Overexpressing RAB1A, which controls cell membrane transfer and autophagosome construct, alleviates deficiencies in dopaminergic neurons expressing SNCA (Coune et al. 2011). Dopaminergic neurodegeneration by SNCA in *Drosophila* has been shown to be inhibited by histone deacetylase 6, an enzyme controlling autophagosomal maturation (Du et al. 2010). Enhanced expression of transcription factor EB leads to clearance of SNCA from dopaminergic neurons through autophagy (Decressac et al. 2013). PD patients' brains have lower expression of LAMP2A and HSC70, the constituents of CMA (Sala et al. 2014). Taken together, these studies show that autophagy has an important function in the pathogenesis of PD (Fig. 1).

Microglia, the brain's resident macrophages with an inherent ability to respond to CNS injury, play a crucial role in promoting repair and ensuring proper brain function. While studies examining the impact of autophagy on neurodegenerative disorders has concentrated on neurons, recent findings suggest that autophagy might also play a role in the functioning of glial cells (Dello Russo et al. 2013; Yamamoto and Yue 2014). Increased evidence purports that autophagy is regulated by both innate and adaptive responses in the peripheral immune system (Shibutani et al. 2015) and the process of phagocytosis (Green et al. 2016). Microglia are the brain's phagocytes (Sierra et al. 2013). Autophagy and phagocytosis share striking morphological and mechanistic similarities, as both processes rely on the formation of transient vesicular structures (autophagosomes and phagosomes, respectively) that engulf and deliver cargo to the lysosomes for digestion. Interestingly, a functional cross-talk exists between autophagy and phagocytosis during the innate immune response in peripheral macrophages. The modulation of autophagy in microglia could affect both microglial phagocytosis and inflammation, potentially playing a role in the progression of neurodegeneration (Plaza-Zabala et al. 2017). Microglial autophagy has the potential to affect the activation and inflammatory responses in microglia (Su et al. 2016). In one study, the inhibition of autophagy was shown to decrease Aβ phagocytosis (Lucin et al. 2013). Microglial autophagy increased Aβ degradation and NLRP3 inflammasome in AD (Cho et al. 2014). Furthermore, the disruption of microglia autophagy exacerbated neuroinflammation and dopaminergic neuron loss via targeting NLRP3 inflammasome in animal model of PD induced by MPTP (Cheng et al. 2020; Qin et al. 2021b). Therefore, microglia autophagy plays a neuroprotective role in the progression of AD and PD.

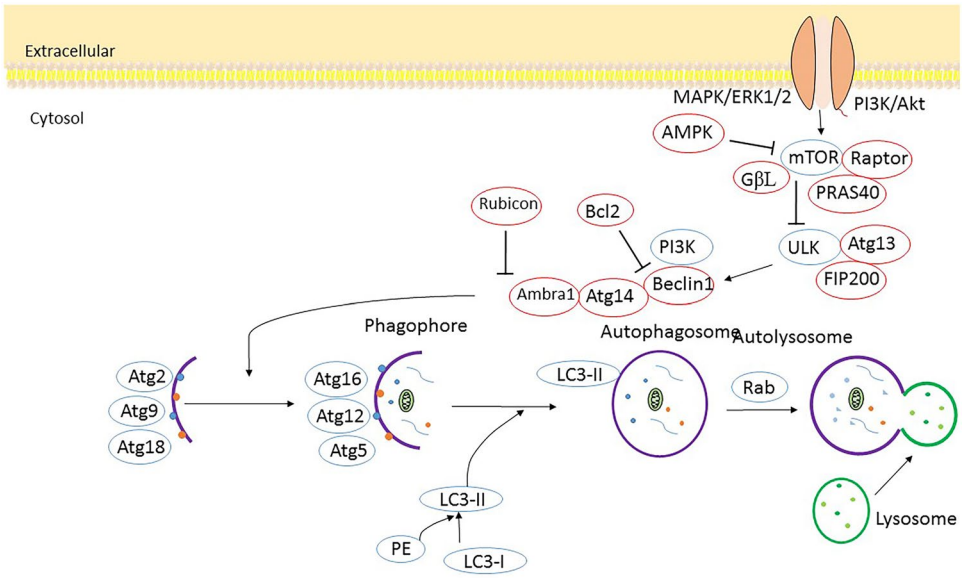


Fig. 1 A schematic representation of the autophagy pathway. This figure adapted from (Riebisch et al. 2021)

Non-coding RNAs

A series of cleavage events produce mature microRNAs after RNA polymerases II and III transcribe microRNA precursors (Annese et al. 2020). In the canonical pathway of biogenesis, they are processed into pre-miRNAs by the microprocessor complex, including a ribonuclease III enzyme, Drosha, and an RNA binding protein DiGeorge Syndrome Critical Region 8 (DGCR8) (Gregory et al. 2004). In addition, there are two main non-canonical miRNA biogenesis pathways: Dicer-independent and Drosha/DGCR8-independent (Felekkis et al. 2010).

miRNAs expression in neurodegenerative diseases is altered, providing further evidence for their putative function in neurodegeneration. For instance, transfection of miR-7 suppresses microglial NLRP3 inflammasome activation and decreased dopaminergic neuron degeneration by decreasing microglial activation in the PD model induced by MPTP (Titze-de-Almeida and Titze-de-Almeida 2018). miR-7 inhibited neuronal apoptosis in PD cell lines model via targeting Sirt2 and Bax (Li et al. 2016). However, the upregulation of miR-7 promoted the production of extracellular Aβ in nerve cells (Fernández-de Frutos et al. 2019). miR-106b enhanced levels of secreted Aβ by regulating ABCA1 (Kim et al. 2012). miR-106b affected TGF-β signaling, thereby contributing to the pathogenesis of AD (Wang et al. 2010). Zhang et al. (2022) demonstrated that miRNA-mediated autophagy might be a putative therapeutic strategy AD.

lncRNAs also contain a poly (A) terminus at 3′ and a 5′ methyl-cytosine cap (Zhang et al. 2019), which are transcribed by RNA polymerase II (Pol II) (Nojima and Proudfoot 2022). lncRNAs biogenesis is analogous to that of mRNA with few variations. There is strong evidence that lncRNAs are capped and polyadenylated by canonical splicing in the vast majority of cases (Gourvest et al. 2019).

Information on LncRNAs target genes and signaling pathways in neurodegenerative diseases has been recently addressed. lnc-ANRIL knockdown inhibits cell inflammation via the binding of miR-125a in vitro model of AD (Zhou et al. 2020a). LncRNA H19 decreases apoptosis in neurons of MPTP-induced PD mice via regulating miR-585-3p/PIK3R3 (Zhang et al. 2020b). LncRNA-mediated autophagy may be a strategy for the treatment of neurodegenerative diseases (Jiang and Xu 2023; Xu et al. 2020).

RNA circular molecules (circRNAs) are endogenous non-coding RNA generated by the back-splicing process. Some circRNAs consisting of introns originate in the nucleus, while others have one or more exons with major locations in the cytoplasm (Guo et al. 2014). A circular RNA does not have a polyadenylated tail or a 5–3′ direction, rendering them more stable in plasma and tissues as they have a continuous loop of covalent bonds (Guo et al. 2014; Suzuki and Tsukahara 2014). For instance, circDLGAP4 has neuroprotective effects in animal models of PD by targeting the miR-134-5p and CREB (Feng et al. 2020). Circular RNA Cwc27 participates in the pathogenesis of AD by repressing Pur-α activity (Song et al. 2022).

Non-coding RNAs and Autophagy in AD and PD

miRNAs and Autophagy in AD and PD

miR-7 and miR-153

An in vitro study showed that miR-7 or miR-153 overexpression protected cortical neurons against MPP+. A small amount of miR-153 debilitated MPP+-induced initiation of p38MAPK, while miR-7 preserved that of mTOR, JNK , and SAPK protein expressions. Rapamycin co-administered with MPP+ ameliorated the neuroprotective influence of miR-7 and miR-153 (Fragkouli and Doxakis 2014). An in vitro study showed that miR-7 reduced α-Syn expression and degraded α-Syn without targeting the 3′-UTR of the α-Syn mRNA. Its function is applied by increasing autophagy via the conversion of LC3-I to LC3-II and autophagosome formation (Choi et al. 2018).

miR-9-5p

miR-9-5p exacerbates MPP+—induced neurotoxicity by targeting SIRT1 (Wang et al. 2019). miR-9-5p antagomirs increased Aβ clearance and improved cognition in APPswe/PS1dE9 mice by targeting autophagy via autophagy receptor Optineurin (Optn) (Chen et al. 2021).

miR-29c

A PD mouse model has shown enhanced autophagy and down-regulation of miR-29c-3p in dopamine neurons. In a PD mice and in vitro models, increased miR-29c-3p reduced autophagy by decreasing LC3-II/I and Beclin-1 and increasing p62 expression via targeting of TET2 (Wang et al. 2021a).

miR-101

miR-101 is implicated in normal cognitive function. It has a vital role in the pathology of aging-related

neurodegenerative diseases (Barbato et al. 2020). MiR-101 decreased APP in AD (Long and Lahiri 2011). Increased miR-101 led to α-syn accumulation (Valera et al. 2017). miR-101 mimic inhibited cell death in PD (Omura et al. 2021). miRNA-101a markedly down-regulated in AD patients and mouse. miRNA-101a transfection decreased autophagy in in vitro model of AD by targeting MAPK1 pathway, beclin-1 (Li et al. 2019).

miR-124

miR-124 is known as a neuron-specific miR (Lagos-Quintana et al. 2002; Mishima et al. 2007). The increased miR-124 level may be effective in decreasing neuroinflammation (Han et al. 2020). Exosomal miR-124-3p transferring into hippocampal neurons decreased neuronal injury by regulating the Rela and ApoE expressions (Ge et al. 2020). Translation of miR-124 in APP/PS1 transgenic mice showed improvements in their AD pathology and learning ability. As a consequence, the expression of p62/SQSTMl, Atg5, and LC3II was down-regulated, while Beclin-1 levels were increased (Du et al. 2017). Upon targeting LC3II/I expression, overexpression of miR-124 increased autophagy in PD induced by MPTP (Yao et al. 2019). Moreover, miR-124 was suppressed in SK-N-SH cell line treated with MPTP, resulting in enhanced autophagy by increased LC3-II/I and Beclin-1. In addition, p-AMPK levels increased in neurons upon miR-124 suppression, while p-mTOR levels decreased (Gong et al. 2016). Increased miR-124 led to decreased loss of dopamine by regulating apoptosis and autophagy in animal model of PD induced by MPTP. miR-124 decreased autophagosome accumulation and lysosomal depletion in PD (Wang et al. 2016).

miR-132/212

Tauopathies such as AD are associated with reduced microRNA (miRNA) cluster expression, miR-132/212 (Wang et al. 2017b). Decreased miR-132/212 expressions led to AD pathogenesis (Wang et al. 2017b). An in vivo study showed that a deficiency of miR-132/212 results in increased tau, along with increased tau aggregation. miR-132 directly regulated tau expression. Induction of tau aggregation by miR-132/212 deletion was associated with dysfunctional autophagy via targeting Beclin-1, ATG5–12, 9a, P62 and TMEM106b. On the other hand, miR-132 mimics were shown to restore in part cognition and tau expression in AD mice treated with miR-132 mimics. Finally, miR-132 and miR-212 were shown to be associated with cognitive dysfunction and insoluble tau in humans (Smith et al. 2015).

miR-133a

In cells treated with MPP+, a model for PD, miR-133a expression levels decreased. MiR-133a overexpression enhanced cell proliferation and autophagy (LC3II/I and Beclin-1 expression declined, while p62 expression increased), but inhibited apoptosis. The inhibition of PC12 cell autophagy and apoptosis by miR-133a was attenuated by RACY upregulation by miR-133a targeting RAC1 (Lu et al. 2020).

miR-181

Dysregulation of miR-181a is inherent to neurodegenerative diseases (Hegarty et al. 2018). miR-181a is upregulated in patients with MCI. It is involved in AD pathogenesis (Ansari et al. 2019). The inhibition of miR-181a improved synapse and cognitive function in 3xTg-AD animals (Rodriguez-Ortiz et al. 2020). However, miR-181a was decreased in vitro model of PD (Liu et al. 2017). miR-181a/b suppressed synaptic transmission, mitochondrial respiration, and neurite outgrowth-related gene expression in MPP+-treated SK-N-SH cells (Stein et al. 2022). The upregulation of miR-181a inhibited autophagy by targeting Beclin-1, LC3II/I, p-p38, and p-JNK (Liu et al. 2017). In addition, miR-181b inhibited MPP+-induced cytotoxicity in PC12 cells via the inhibition of autophagy by targeting PTEN, Akt and mTOR expression (Li et al. 2018).

miR-185

The protective function of miR-185 was shown in controlling PD progression (Rahimmi et al. 2019). miR-185 decreased cell death in dopaminergic neuron by activating PI3K/AKT signaling in PD (Qin et al. 2021a). Increased miR-185 suppressed autophagy in cells treated with MPTP by targeting the AMPK and mTOR (Wen et al. 2018).

miR-204

miR-204 is upregulated in neurodegenerative diseases (Talepoor Ardakani et al. 2019). Enhancement in miR-204 expression was observed in AD (Zhang et al. 2021a). The upregulation of miR-204-5p induced dopaminergic cell death by targeting ER stress-mediated by DYRK1A and apoptosis (Chiu et al. 2019). Overexpression of TRPML1 led to downregulation of miR-204 and activation of STAT3, while mitochondrial autophagy was attenuated. miR-204 silencing suppressed mitochondrial autophagy by inhibiting Parkin, PINK1,,LC3II, and Beclin1 through STAT3 pathway and up-regulating TRPML1 expression in APP/

PS1 transgenic AD mice and a cell model of AD induced by Aβ1-42 (Zhang et al. 2021a).

miR-214

Decreased miR-214 contributes to the neuronal injury induced by Aβ (Yu and Zhang 2013). MiR-214–5p expression decreased in AD mice. Dexmedetomidine has a neuroprotective effect on AD via targeting miR-214–5p (Hu et al. 2022). miR-214-3p inhibited autophagy by inhibiting Atg12 in SAMP8 mice (Zhang et al. 2016a).

miR-221/222

In MN9D cells treated with MPP+, miR-221/222 was targeted and bound to p27/mTOR. By downregulating p27 levels, inhibiting the mTOR pathway. Thus, miR-221/222 facilitates autophagy and protects cells from death (Qian et al. 2019). MiR-212-5p protected against cell death in dopaminergic neuron by targeting p53, SIRT2, LC3 B and p62 expression in an animal model of PD induced by MPTP (Sun et al. 2018).

The number of miRNAs associated with autophagy in AD and PD is also continually expanding as shown in Table 1.

lncRNAs and Apoptosis in AD and PD

BACE1-AS

Increased BACE1-AS expression is inherent to AD (Zhou et al. 2021). BACE1-AS downregulation was related to decreased synuclein, iNOS and glutamate (Li et al. 2020). ATG5 expression was indirectly regulated by BACE1-AS through the interaction with miR-214-3p. Neuronal damage secondary to inhibition of autophagy is relieved by suppression of BACE1-AS in vivo (Zhou et al. 2021). In AD, it has been shown both in vitro and in vivo that BACE1-AS and miR-214-3p are overexpressed and suppressed, respectively. BACE1-AS reduction as well as miR-214-3p overexpression promote the acceleration of autophagy by targeting LC3 I/II, p62 and Beclin-1 (He et al. 2020).

NEAT1

Increased NEAT1 expression was noted in SH-SY5Y cells upon MPP+ treatment. NEAT1 silencing restored the MPP+-induced effects on SH-SY5Y cells, including inflammation, cell viability, and stimulated apoptosis. NEAT1 targets miR-124 and targeting miR-124 with anti-miR-124 reversed its inhibition effects (Xie et al. 2019). NEAT1 level was elevated in vitro AD experimental model, while its depletion reversed Aβ-induced increase in apoptosis and p-Tau levels. MiR-107 is targeted by NEAT1. miR-107 expression decreased in Aβ-treated cells, and its upregulation reversed Aβ-induced damage. Neuronal injury in Aβ-treated cells was suppressed by NEAT1 knockdown and reversed by miR-107 (Ke et al. 2019). Animal models of AD have shown upregulation of NEAT1 lncRNA. Inhibition of PINK1-dependent autophagy by ubiquitinating and degrading PINK1 has been posited as a potential sequela of NEAT1 interaction with NEDD4L (Huang et al. 2020). A significant increase in NEAT1 was observed in MPTP-treated mice and PD patients, as well as in SH-SY5Y cells treated with MPP+ (Dong et al. 2021; Liu et al. 2020; Xie et al. 2019). SH-SY5Y cells treated with MPP+ increased proliferation upon NEAT1 inhibition, whereas apoptosis and autophagy were inhibited. MPTP-treated mice with NEAT1 inhibition showed enhanced MIR-374c-5p expression, increased cell viability, and repressed autophagy and apoptosis by targeting miR-374c-5p, LC3 II/LC3 I, P62 (Dong et al. 2021). Autophagy was suppressed in in vitro and in vivo model of MPTP- induced PD by NEAT1 knockdown via targeting PINK1, LC3-II, and LC3-I protein, decreasing dopaminergic neuronal damage (Yan et al. 2018).

SNHG1

MPP+ enhanced expression of SNHG1 (Zhang et al. 2020a; Zhao et al. 2020a). Furthermore, silencing SNHG1 improved the behavior in MPTP-treated mice in vivo (Xiao et al. 2021). In addition to promoting autophagy and preventing MPP+-induced cell death, SNHG1 indirectly affects the expression of p27/mTOR by binding to the miR-221/222 cluster (Qian et al. 2019).

HOTAIR

SH-SY5Y cells treated with MPP+ showed enhanced expression of lncRNA HOTAIR. PD-like symptoms were significantly alleviated in vivo when HOTAIR was knocked down. As a result of the downregulation of HOTAIR in the presence of MPP+, SH-SY5Y cells increased their viability and NLRP3-mediated pyroptotic cell death was suppressed. By targeting miR-326, HOTAIR regulates ELAVL1 expression. Downregulation of HOTAIR or ELAVL1 significantly reduced the pyroptosis-promoting effects of miR-326 inhibitor through activation of NLRP3 inflammasomes (Zhang et al. 2021c). In SK-N-SH cells treated with MPP+, increased expression of HOTAIR and ATG10 was noted (Zhao et al. 2020b). MPP+-induced neurodegeneration was decreased by the knockdown of HOTAIR. HOTAIR aggravates MPP+-mediated neuronal

Table 1 Autophagy-related microRNAs in AD and PD

Neurodegenerative disease	Model	miRNAs	Expression status	Targets	Main targets	References
Alzheimer disease	In vitro/SH-SY5Y cells treated by H_2O_2	miR-101a	Downregulated	MAPK1 pathway, beclin-1, LC3-II	Stimulate autophagy	Li et al. (2019)
Alzheimer disease	In vitro/PC12 and SK-N-SH cells	let-7	Upregulated	Atg-5, -7, LC3 II/I, beclin-1, PI3K/Akt/mTOR	Stimulate autophagy	Gu et al. (2017)
Alzheimer disease	In vitro/cycloheximide-treated SH-SY5Y cells In vivo/E64D + PEPA-treated *Tau-BiFC* mice	miR-9a	Upregulated	*UBE4A* and *UBE4B*	Stimulate autophagy	Subramanian et al. (2021)
Alzheimer disease	in vivo/SAMP8 mice	miR-214-3p	Downregulated	Atg12, 3′-UTR, LC3βII and Beclin1	Inhibit autophagy	Zhang et al. (2016a)
Alzheimer disease	In vivo/APPswe/PS1dE9 mice In vitro/N2a/SH-SY5Y cells	miR-299-5p	Downregulated	LC3βII, p62 and Atg5	Inhibit autophagy	Zhang et al. (2016b)
Alzheimer disease	In vivo/SH-SY5Y cell APPswe/PS1dE9 mouse	miR-9-5p and miR-331-3p	Downregulated	Aβ clearance, *Sqstm1, Optn*, *LC3b* and *Becn1*	Stimulate autophagy	Chen et al. (2021)
Alzheimer disease	In vivo/APP/PS1 transgenic mice	miR-124	Downregulated	BACE1, LC3II, Atg5, p62/SQSTMl, Beclin-1	Stimulate autophagy	Du et al. (2017)
Alzheimer disease	In vivo/3xTg-AD^{WT} mice	miR-132/212	Downregulated	tau mRNA, ATG5–12, ATG9a, Beclin1, P62, TMEM106b	Inhibit autophagy	Smith et al. (2015)
Alzheimer disease	In vivo/Aβ1-42 and APP/presenilin-1 AD modeled mice	miR-204	Upregulated	TRPML1 -activated STAT3 pathway	Inhibit autophagy	Zhang et al. (2021a)
Parkinson disease	In vitro/SK-N-SH neuroblastoma cells treated by MPP	miR-181a	downregulated	LC3II/LC3I, Beclin 1, p-p38, p-JNK	Stimulate autophagy	Liu et al. (2017)
Parkinson disease	In vivo/SH-SY5Y cells, BV2 cells MPTP-treated, treated with VX702	miR-124	downregulated	p62, p-p38	Inhibit autophagy	Yao et al. (2019)
Parkinson disease	in vitro/mouse microglia cell line (BV2) treated by MPTP	miR-3473b	upregulated	TNF-α, IL-1β, TREM2 and ULK1	Inhibit autophagy	Lv et al. (2021)
Parkinson disease	in vivo/C57BL/6 mice model treated by MPTP	miR-3473b	upregulated	substantia nigra pars compacta (SNpc), TREM2, ULK1	Inhibit autophagy	Lv et al. (2021)

Table 1 (continued)

Neurodegenerative disease	Model	miRNAs	Expression status	Targets	Main targets	References
Parkinson disease	In vivo/SH-SY5Y neuroblastoma cells MPTP-treated In vitro/MPP^+ SH-SY5Y cells	miR-212-5p	downregulated	SIRT2, P53	Stimulate autophagy	Sun et al. (2018)
Parkinson disease	In vivo/C57BL/6 mice HEK-293T MPTP/MPP + -induced	miR-326	upregulated	JNK, XBP1, c-Jun, p–c-Jun, α-Syn, p-α-Syn, iNOS and LC3-II	Stimulate autophagy	Zhao et al. (2019)
Parkinson disease	In vitro/HEK293A cells MPP^+	miR-7 and miR-153	Upregulated	mTOR, SAPK/JNK, P38MAPK, Bcl-2, Caspase-3, LC3-I, LC3-II	Inhibit autophagy	Fragkouli and Doxakis (2014)
Parkinson disease	In vitro/SH-SY5Y cells treated by MPTP	miR-124	Downregulated	Beclin 1, LC3 II/I, AMPK, mTOR	Stimulate autophagy	Gong et al. (2016)
Parkinson disease	In vivo/MPTP-treated mice In vitro/MPP + -challenged MN9D cells	miR-221/222	Upregulated	p27/mTOR, LC3-II, (CDKN1B/p27)	Inhibit autophagy	Qian et al. (2019)
Parkinson disease	In vitro/MPTP-treated SH-SY5Y cells	miR-185	Upregulated	AMPK, mTOR	Inhibit autophagy	Wen et al. (2018)
Parkinson disease	In vivo/Bcl-2 treated 6-OHDA-induced	miR-3557	Upregulated	CaMK2α, CaMKV, Vdac1, PI3K/mTOR and UCH-L1		Liu et al., (2019)
Parkinson disease	In vivo/SH-SY5Y cells were treated with MPP^+	miR-29c-3p	Downregulated	Beclin 1, TET2, LC3	inhibits autophagy	Wang et al. (2021a)
Parkinson disease	In vivo/MPTP-treated mice In vitro/MPP^+-intoxicated SH-SY5Y cells	miR-124	Upregulated	Bim, Bax	Inhibit autophagy	Wang et al. (2016)
Parkinson disease	In vitro/PC12 cells MPP^+	miR-199a	Upregulated	PTEN, GSK3β, Beclin1, LC3II, AKT, mTOR	Inhibit autophagy	Ba et al. (2020)
Parkinson disease	In vitro/MPP^+ treated PC12 cell	miR-181b	Downregulated	LC3II, p-AKT, PTEN, p-mTOR, p-p70S6K	Inhibit autophagy	Li et al. (2018)
Parkinson disease	In vivo/MPTP	miR-106b	Downregulated	Bcl-2 and LC3II/LC3I ratio	Inhibit autophagy	Bai et al. (2021)
Parkinson disease	In vitro/Human neural progenitor cell line ReNcell V	miR-7	Downregulated	LC3-I/LC3-II	Inhibit autophagy	Choi et al. (2018)
Parkinson disease	SH-SY5Y cells treated with MPP^+	MiR-497-5p	Upregulated	LC3-II/I, Beclin1, p62	Inhibit autophagy	Zhu et al. (2021)
Parkinson disease	In vitro/PC-12 treated by MPP^+	miR-133a	Downregulated	LC3II/I, Beclin-1, p62	Stimulate autophagy	Lu et al. (2020)
Parkinson disease	MPP^+- treated SH-SY5Y cells	miR-132-5p	Upregulated	LC3, Beclin 1, ULK1	Stimulate autophagy	Zhao et al. (2020c)

Table 1 (continued)

Neurodegenerative disease	Model	miRNAs	Expression status	Targets	Main targets	References
Parkinson disease	In vitro/SH-SY5Y cells In vivo/MPTP	miR-103a-3p	Upregulated	Parkin,Ambra1, LC3-I/LC3-II	Stimulate autophagy	Zhou et al. (2020b)
Parkinson disease	6-OHDA-treated SH-SY5Y cell model	MiR-142-5p	Downregulated	decreased P62, increased LC3-II, Beclin-1	Stimulate autophagy	Chen et al. (2020)
Parkinson disease	In vivo/rotenone In vitro/MN9D cells	MiR-24	Upregulated	Beclin-1, LC3-II/LC3-I ratio	Inhibit autophagy	Ge et al. (2019)

injury by sponging miR-874-5p (Zhao et al. 2020b). MTPT-treated mice and SH-SY5Y cells pretreated with MPP + showed upregulation of HOTAIR. In SH-SY5Y cells overexpressing HOTAIR, the expression of LRRK2 was enhanced. In SH-SY5Y cells treated by MPP +, HOTAIR knockdown improved cell viability (Kraus et al. 2017; Wang et al. 2017a). HOTAIR inhibited cell viability and stimulated autophagy by attaching to miR-221-3p and targeting LC3-II/-I, LAMP1/2, P62 expressions, and NPTX2 (Lang et al. 2020).

Table 2 Autophagy-related lncRNAs in AD and PD

Neurodegenerative disease	Model	lncRNAs	Expression status	Targets	Main effect	References
Alzheimer disease	In vivo/transgenic mice, In vitro/SH-SY5Y treated by $A\beta_{1-42}$	BACE1-AS	Upregulated	miR-214-3p and ATG5	Stimulate autophagy	Zhou et al. (2021)
Alzheimer disease	In vitro/Aβ-treated SK-N-SH and SK-N-AS cells In vivo	BACE1-AS	Upregulated	miR-214-3p, Bax, Bcl-2, Beclin-1, LC3 I/LC3 II and p62	Stimulate autophagy	He et al. (2020)
Alzheimer disease	In vivo/transgenic mice In vitro/SH-SY5Y cells	lncRNA *RMRP*	Upregulated	*miR-3142/TRIB3* axis	Stimulate autophagy	Tang et al. (2022)
Parkinson disease	MPP^+	lncRNA-SNHG1	Upregulated	miR-221/222 cluster, CDKN1B/p27/mTOR, SNHG1	inhibit autophagy	Qian et al. (2019)
Parkinson disease	In vivo In vitro/MPP + treated-SH-SY5Y cells	NEAT1	Upregulated	PINK1, LC3-I, LC3-II	Stimulate autophagy	Yan et al. (2018)
Parkinson disease	In vitro/MPP +—treated SH-SY5Y cells In vivo/MPTP	NEAT1	Upregulated	miR-374c-5p, LC3 II/LC3 I, P62	Stimulate autophagy	Dong et al. (2021)
Parkinson disease	In vitro/MN9D was treated (MPP^+), In vivo/MPTP	HOTAIR	Downregulated	LC3B-II/LC3B-I, LAMP1/LAMP2, P62, NPTX2	Inhibit autophagy	Lang et al. (2020)
Parkinson disease	In vivo/MPTP In vitro/MPP +	BDNF-AS	Upregulated	miR-125b-5p, LC3II/I and Beclin-1, p62 levels	Inhibit autophagy	Fan et al. (2020)

BDNF-AS

BDNF-AS expression increased in AD patients. The upregulation of BDNF-AS led to cognitive dysfunction in AD mice (Ding et al. 2022). Silencing BDNF-AS inhibited apoptosis and oxidative stress in PC12 cells treated by Aβ25-35 (Guo et al. 2018a). Fan et al. (Fan et al. 2020) was seen the up-regulation of BDNF-AS in both in vitro and in vivo model of PD. BDNF-AS increased autophagy in MPTP-induced PD by targeting microRNA-125b-5p, LC3II/I, and Beclin-1, p62 levels (Fan et al. 2020).

The number of lncRNAs associated with autophagy in AD and PD is also continually expanding as shown in Table 2.

Circular RNAs and Apoptosis in AD and PD

Autophagy is regulated by CircumNF1-419 via Akt-mTOR/PI3K-I and Akt-AMPK-mTOR/PI3K-I signaling pathways. AP2B1 injection into circNF1-419 overexpressing cerebral cortex increased autophagy. Consequently, tau and p-tau were decreased, suggesting a delay in the onset of senile dementia. CirNF1-419 enhanced the activity of several signaling pathways, particularly mediators of transmission in the SAMP8 mouse (Diling et al. 2019). In in vitro model of PD, expression levels of SNCCa and circSNCA were downregulated after PPX treatment, which correlated with apoptotic gene expression, and SNCA expression was increased by CircSNCA through the downregulation of miR-7 in PD as a competitive endogenous RNA (ceRNA). Pro-apoptotic proteins were less expressed in cells with lower circSNCA expression. Downregulation of CircSNCA in PD reduced apoptosis and promoted autophagy (Sang et al. 2018). circDLGAP4 expression decreased in PD mouse model inculcated with MPTP. circDLGAP4 overexpression mitigated mitochondrial impairment, and enhanced cell viability and autophagy, decreased apoptosis and thereby attenuated neurotoxicity. A major function of circDLGAP4 is to regulate miR-134-5p. MiR-134-5p targets the transcription factor CREB, and CREB expression can be affected by the circDLGAP4/miR-134-5p axis. CircDLGAP4/miR-134-5p can also modulate the activity of CREB signaling, PGC-1α, Bcl-2, and BDNF (Feng et al. 2020). circSAMD4A was upregulated in both PD animal and cellular models. Inhibition of MPTP or MPP+-induced apoptosis and autophagy by circSAMD4A knockdown was observed. In MPTP or MPP+-induced PD models, the knockdown of circSAMD4A resulted in a reduction in phosphorylated AMPK expression and a subsequent increase in mTOR expression (Wang et al. 2021b) (Table 3).

Finally, dysregulation of circNF1-419, circSNCA, circHIPK3, circDLGAP4, circSAMD4A, circNF1-419, circSHOC2, circERCC2 has been associated with inhibition or stimulation of autophagy in AD and PD.

Conclusions

Increased evidence suggests that ncRNAs play a key role in autophagic homeostasis and can regulate neurodegeneration in AD and PD. ncRNAs can form complex interactions with other RNAs/DNA/proteins to regulate the autophagic process. For future perspective, the interaction between ncRNAs and autophagy in other neurodegenerative diseases and further clinical studies on the role of ncRNAs in neurodegenerative diseases progression and autophagy are required. In addition, further characterization of ncRNAs in bodily fluids is necessary, in particular, blood and CSF in patients with neurodegenerative diseases. ncRNAs

Table 3 Autophagy-related lncRNAs in AD and PD

Neurodegenerative disease	Model	CircRNAs	Expression status	Targets	Main effect	References
Alzheimer disease	In vivo/SAMP8 mice treated with D-galactose	*circNF1-419*	Upregulated	Dynamin-1, AP2B1, PI3K-I, Akt, AMPK, mTOR, $A\beta_{1-42,}$ Tau, p-Tau, and APOE	Stimulate autophagy	Diling et al. (2019)
Parkinson disease	In vitro/(MPP+) SH-SY5Y cells	CircSNCA	Downregulated	miR-7 sponge to upregulate SNCA	Induce autophagy	Sang et al. (2018)
Parkinson disease	In vivo/MPTP In vitro/SH-SY5Y and MN9D cells treated with MPP^+	circDLGAP4	Downregulated	miR-134-5p/CREB, Beclin-1, LC3 II/I ratio	Inhibit autophagy	Feng et al. (2020)
Parkinson disease	In vitro/SH-SY5Y cells MPTP- or MPP^+	circSAMD4A	Upregulated	AMPK, mTOR, miR-29c-3p	Stimulate autophagy	Wang et al. (2021b)

(miRNAs, lncRNAs, and circRNAs) may serve as putative treatment, prognostic, and diagnostic targets for neurodegenerative diseases**.** The development of reliable for diagnosing early neurodegeneration and its molecular signaling will be pivotal for increased efficiency of therapies. Some studies evaluated targeting and transcriptionally repressing ncRNAs by silencing ncRNAs and RNA interference to inhibit ncRNAs expression in neurodegenerative disorders (Wang et al. 2022; Zhang et al. 2021b). Moreover, CRISPRs could be applied to delete miRNAs/lncRNAs (Ho et al. 2015) and assess the consequences for therapeutic strategies.

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