Autophagy-regulating miRNAs: Novel therapeutic targets for Parkinson's disease (Review)

ZHENWANG MA[1*], HAO LIANG[1*], BINGCHENG HU[1], SHAOJIE CAI[2] and DONG YAN[3]

[1]Department of Encephalopathy, Heilongjiang Academy of Traditional Chinese Medicine, Harbin, Heilongjiang 150036; [2]Graduate School of Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150040; [3]Department of Endocrinology, Heilongjiang Academy of Traditional Chinese Medicine, Harbin, Heilongjiang 150036, P.R. China

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Abstract. Parkinson's disease (PD) is a neurodegenerative disorder that has a high incidence during the aging process and is characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor dysfunctions and non-motor symptoms. Impaired clearance and excessive accumulation of aberrantly modified proteins or damaged organelles, such as aggregated α-synuclein and dysfunctional mitochondria, are regarded as the main causes of nigrostriatal neurodegeneration. As one of the major degradation pathways, autophagy can recycle these useless or toxic substances to maintain cellular homeostasis and it plays a crucial role in PD progression. MicroRNAs (miRNAs) are a group of small non-coding RNA molecules that regulate gene expression by silencing targeted mRNAs. Recent studies have illustrated that autophagy-regulating miRNA has been implicated in pathological processes of PD, including α-synuclein accumulation, mitochondrial damage, neuroinflammation and neuronal apoptosis, which suggests that targeting autophagy-regulating miRNAs may provide novel therapeutic strategies for this disease. The present review summarizes the role of autophagy in PD and emphasizes the role of miRNA-mediated autophagy in PD, for the development of promising interventions in this disease.

Contents

Correspondence to: Professor Dong Yan, Department of Endocrinology, Heilongjiang Academy of Traditional Chinese Medicine, 72 Xiang'an Street, Harbin, Heilongjiang 150036, P.R. China
E-mail: yandong5453@163.com

*Contributed equally

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease with a high morbidity that affects nearly 2% of the elderly (1). PD is neuropathologically characterized by progressive loss of dopaminergic neurons in the substantia nigra (SN), accompanied by accumulation of Lewy bodies (LBs) and neurites, whose main component are aggregated α-synuclein (encoded by the SNCA gene) leading to nigrostriatal neurodegeneration and clinical manifestations, including motor dysfunctions and non-motor symptoms, such as cognitive deficits and sleep disorders (1). Several cytotoxic stimuli, like 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 1-methyl-4-phenylpyridinium iodide (MPP^+), 6-hydroxydopamine (6-OHDA) and rotenone are employed to simulate the pathogenesis of PD *in vivo* and *in vitro* (2). Current treatments alleviate symptoms in patients with early-stage PD but fail to halt disease progression or reverse existing disabilities. Thus, elucidation of the pathogenesis is crucial for developing novel and promising therapeutic modalities in PD. Autophagy is an evolutionarily conserved self-digesting process that functions as a cytoprotective cellular machinery to recycle misfolded proteins and damaged organelles to produce energy for cell survival under stressful conditions, such as nutrient deficiency and hypoxia (3). Aggregation of α-synuclein in PD brains has been suggested to be attributed to impaired autophagic-lysosomal degradation (4). In addition, dopaminergic neurons are susceptible to deficient clearance of damaged mitochondria due to their hypermetabolism with high mitochondrial energy demand (5). Accumulation of damaged mitochondria owing to autophagy impairment leads to reactive oxygen species (ROS) overproduction, which further augments mitochondrial dysfunction and causes oxidative damage to neurons, facilitating PD progression in a vicious cycle (6,7). Autophagy dysfunction has been implicated in the pathological processes of PD, including aberrant protein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation and neuronal

apoptosis (6,8). Thus, autophagy mainly acts as a protective factor in PD. Understanding the role of autophagy in PD progression is of great significance, and the regulation of autophagy provides a novel potential therapeutic target for this disease.

Non-coding RNAs (ncRNAs) mainly comprise microRNA (miRNA), long ncRNA (lncRNA) and circular RNA (circRNA). miRNAs are a group of small endogenous, single-stranded molecules with lengths of 21-25 nucleotides that regulate gene expression by binding to the 3'-untranslated region of a target gene mRNA, thus suppressing its translation or promoting its degradation (9). The miRNA-mediated gene regulation can be also modulated by lncRNA and circRNA, which act as competing endogenous RNAs to sponge miRNAs (10). Abnormal expression of miRNAs in PD has been found to regulate autophagy via affecting the expression of autophagy-related genes (ATGs) and autophagy-related signaling molecules, and miRNA-mediated autophagy is involved in pathological processes, such as α-synuclein and mitochondrial dysfunction, implicated in the pathogenesis of PD (11,12). Hence, targeting miRNAs to modulate the functional status of autophagy may provide promising therapeutic strategies for this disease. The present review summarizes the autophagy process and autophagy-related signaling pathways in PD and discusses the role of autophagy in the pathogenesis of this disease. It emphasizes the paradoxical effects of miRNAs through regulation of autophagy, and concludes the potential of targeting autophagy-regulating miRNAs as promising interventions for patients with PD.

2. Autophagy in PD

Autophagic process. Autophagy generally contains macro-autophagy, micro-autophagy and chaperone-mediated autophagy (13). Macro-autophagy is simply referred to as autophagy due to the extensive research in this area. Specific conditions such as starvation, hypoxia and inflammation, are responsible for autophagy induction (14). The autophagic process consists of initiation, elongation, maturation, fusion and degradation, all of which are finely regulated by various ATGs and autophagy-related signaling pathways (Fig. 1). The inactivation of mammalian target of rapamycin (mTOR) induces the formation of the unc-51-like kinase 1 (ULK1) complex, containing ULK1-ATG13-ATG101-FIP200, which initiates autophagy (15). The complex containing Beclin-1-AMBRA 1-ATG14L-VPS15-VPS34 recruits the PI3K-ATG2-ATG18 complex to facilitate lipid transport through the transmembrane protein, ATG9, as well as recruit the ATG5-ATG12-ATG16L1 complex to trigger autophagic membrane elongation (15). The ATG5-ATG12-ATG16L1 complex also interacts with the ATG3-ATG7 complex to promote the binding of microtubule associated protein light chain 3 (LC3)-II. LC3-II is derived from the cleavage of LC3 by cysteine protease ATG4, and combines with phosphatidylethanolamine (PE) to produce PE-conjugated LC3-II, which forms a mature autophagosome and further combines with cargo receptors, such as p62, to anchor autophagic substrates (16). Finally, the autophagosome fuses with the lysosome to form the autolysosome, where substances are degraded and recycled for cellular metabolism and growth. In addition, the autophagy of mitochondria, also known as mitophagy, is mainly responsible for the clearance of aging and damaged mitochondria ensuring the metabolic equilibrium of mitochondrial energy.

A variety of signaling pathways are involved in the regulation of autophagy. The inactivation of the mTOR signaling pathway is the key step to stimulate autophagy, which can be further regulated by various signaling pathways, such as PI3K/AKT, adenosine monophosphate-activated protein kinase (AMPK), mitogen activated kinase-like protein (MAPK), and phosphatase and tensin homolog (PTEN) pathways (17). PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate to generate phosphatidylinositol 3-phosphate, which induces AKT phosphorylation, and subsequently mTOR is activated to suppress autophagy (18). Under stress conditions, such as cellular energy deficiency, the expression level of AMPK is elevated to phosphorylate ULK1 for the activation of autophagy, and to inactivate mTOR for the indirect induction of autophagy (19). As a crucial regulator of the autophagic process, BCL2 interacts with Beclin-1 and further abrogates the formation of the autophagosome (20). c-Jun N-terminal kinase (JNK), a subtype of MAPK, phosphorylates BCL2, leading to the dissociation of Beclin-1 from BCL2, thus eliciting autophagy (20). However, extracellular signal-regulated kinase (ERK), another subtype of MAPK, is activated to inhibit the formation of Tuberous sclerosis complex 1 and 2 (TSC1-TSC2) complex and subsequently contributes to the activation of mTOR, which causes the suppression of autophagy (19). In addition, PTEN has been demonstrated to inactivate the PI3K/AKT signaling pathway (21). Consequently, the PTEN-mediated suppression of the AKT signaling pathway enhances autophagy activity. Furthermore, mitophagy is regulated by several signaling pathways, including the PTEN-induced putative kinase protein 1 (PINK1)/Parkin, BCL2/adenovirus E1B 19kDa interacting protein 3/NIP3-like protein X (BNIP3/NIX) and FUN14 domain containing 1 (FUNDC1) pathways (6). PINK1 is located in the mitochondrial outer membrane and mediates E3 ubiquitin ligase Parkin to initiate mitophagy. The BNIP3/NIX signaling pathway accelerates mitophagy by dissociating BCL2-Beclin-1, which recruits Parkin to the mitochondrial outer membrane and participates in the transportation of LC3 to the mitochondria (6). FUNDC1, a mitophagy-related protein, can be activated under hypoxic conditions and thus triggers mitophagy by binding to LC3-II and regulating the mitochondrial dynamics (22).

Autophagy is an intracellular self-digesting process by which misfolded proteins and damaged organelles are recycled to sustain cell metabolism. Dysfunction of autophagy is accompanied by abnormal activation of autophagy-related signaling pathways, which further affects the expression of ATGs. Thus, clarifying autophagy-related signaling pathways and the roles of autophagy in the pathogenesis of PD may provide potential therapeutic targets to tackle this disease.

Autophagy-related signaling pathways in PD. As aforementioned, signaling pathways, including PI3K/AKT/mTOR, MAPK, AMPK and PINK1/Parkin, can regulate autophagy. Indeed, these pathways are related to various cellular processes, such as proliferation and apoptosis, affecting the occurrence and progression of PD. In the early stage of rotenone-induced PD in rats, hydrogen-saturated saline

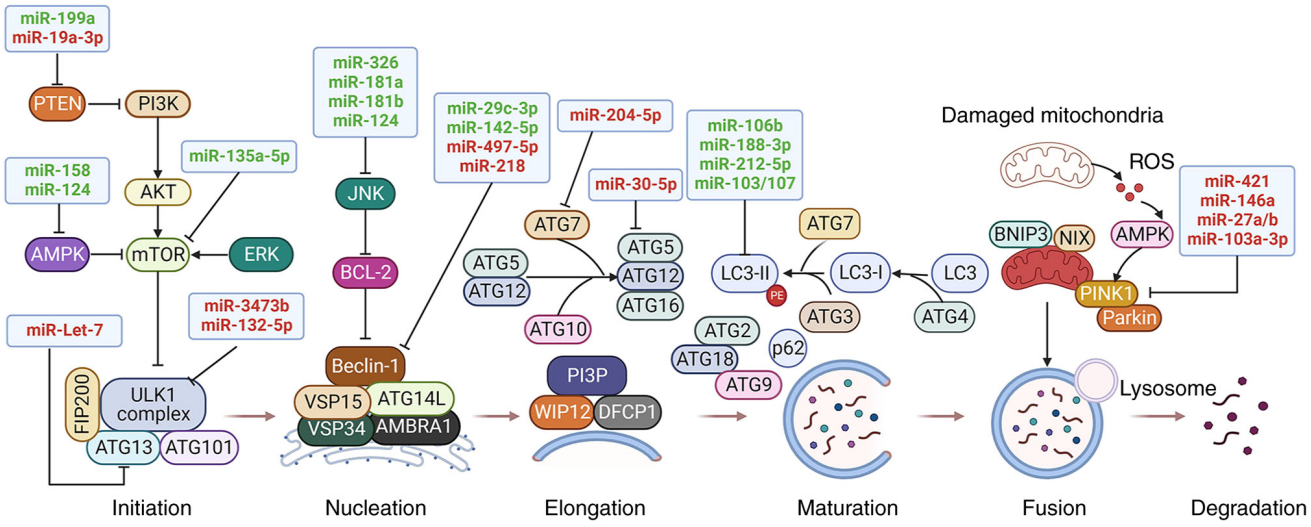

Figure 1. The regulatory role of miRNAs on the autophagy process in PD. Autophagy-related proteins and signaling pathways are regulated by miRNAs during each stage of autophagy, including initiation and nucleation, elongation, maturation, fusion and degradation. Both neuroprotective miRNAs (green) and neurotoxic miRNAs (red) are involved in the regulation of autophagy by targeting autophagy-related proteins and signaling pathways, thus affecting the pathogenesis of PD. → indicates a promoting effect and ⊥ indicates an inhibitory effect. AMPK, adenosine monophosphate-activated protein kinase; ATG, autophagy-related gene; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; miR, microRNA; miRNA, microRNA; mTOR, mammalian target of rapamycin; PD, Parkinson's disease; PINK1, PTEN-induced putative kinase protein 1; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; ULK1, unc-51-like kinase 1.

postpones motor impairments as it alleviates the damage of catecholaminergic and nigral dopamine neurons, and decreases the expression of ROS and α-synuclein by activating the autophagy machinery through the inactivation of the PI3K/AKT/mTOR pathway (18). This signaling pathway is also suppressed in neuroendocrine cells treated with sodium butyrate, and autophagy is subsequently promoted, mediating α-synuclein degradation in PD (23). Further investigation demonstrated that inhibiting the PI3K/AKT/mTOR pathway with a natural compound, astragalus polysaccharide, enhances the expression of autophagy-related proteins and formation of the autophagosome, thus increasing cell viability and exerting anti-Parkinson effects (24). However, when autophagy is overactivated in MPP^+-treated SH-SY5Y cells, the addition of IGF-1 decreases autophagic neuron death through the PI3K/AKT/mTOR pathway (25). Thus, the PI3K/AKT/mTOR pathway improves neuronal survival by modulating autophagy in PD. In addition, several common subtypes of MAPK, including p38 and JNK, can regulate autophagy via interaction with the mTOR and BCL2 pathways in PD. In zebrafish and PC12 cells exposed to pyrethroid, the p38 MAPK pathway is activated to inhibit mTOR, which induces excessive autophagy and thus overproduces the LBs in neurons that lead to the PD-like symptoms, suggesting the neurotoxicity of p38 MAPK-mediated autophagy, which is contrary to the pattern of the effect of autophagy on PD generally reported (26). The stimulation of autophagy induced by the JNK/BCL2 pathway after caffeic acid administration mitigates α-synuclein generation and loss of dopaminergic neurons in the SN, and improves behavioral abnormalities in a A53T α-synuclein-induced PD mouse model (27). By contrast, by administering β-asarone to 6-OHDA-treated rats, JNK signaling is blocked, which suppresses autophagy but upregulates the expression of BCL2 (an anti-apoptotic protein), which alleviates the α-synuclein accumulation and behavioral impairments (20). These findings indicate that the bi-directional regulation of autophagy by the JNK/BCL2 axis exerts neuroprotective effects in PD. Besides, AMPK-mediated autophagy is also associated with the progression of PD. In both MPTP and rotenone-induced mouse models of PD, it has been discovered that the activation of AMPK-mediated autophagy by several compounds, including mitochonic acid 5 and α-mangostin, ameliorate α-synuclein aggregation, oxidative stress, neuroinflammation, neuronal degeneration and motor deficits (28,29). Moreover, inhibitors of AMPK and autophagy counteract these effects, indicating the neuroprotection of AMPK-activated autophagy in PD (28,29). Targeting the AMPK/mTOR signaling pathway to inhibit excessive autophagy induced by 6-OHDA alleviates neuronal death, exerting a neuroprotective effect on PD (30). Furthermore, restoring rotenone-induced autophagy impairment via activation of the AMPK/mTOR/ULK1 signaling cascade attenuates neuronal apoptosis, α-synuclein accumulation and ROS production, and improves the cell viability and antioxidant capacity of SH-SY5Y cells (31,32). Therefore, modulating AMPK-induced autophagy may be a potential therapeutic strategy for PD. Furthermore, in response to mitochondrial damage, mitophagy activated by the PINK1/Parkin pathway recycles dysfunctional mitochondria and improves energy sources (33). Mitophagy induced by salidroside diminishes DA neuron degeneration and motor deficits by enhancing the expression of PINK1 and Parkin, conferring neuroprotective effects in MPP^+/MPTP-induced PD models (34); albeit, amplifying the PINK1/Parkin-mediated mitophagy pathway by mono-2-ethylhexyl phthalate exacerbates mitochondrial damage accompanied by enhanced mitochondrial fragmentation and ROS production (35). Hence, the selective autophagic elimination of damaged mitochondria by PINK1/Parkin-induced mitophagy is essential for the maintenance of mitochondrial integrity.

Collectively, autophagy activation can be modulated by a variety of signaling pathways in PD. As the autophagy-regulating signaling hub, mTOR interacts with other pathways such as PI3K/AKT, MAPK and AMPK to indirectly regulate autophagy, while the PINK1/Parkin pathway plays an essential role in mitophagy. Further exploring the regulatory mechanisms of autophagy-related pathways is key to clarifying the pathogenesis of PD. It should be noted that α-synuclein-activated p38 MAPK is required for the phosphorylation of Parkin and thus contributes to mitochondrial dysfunction and neuronal apoptosis in PD (36). Activating AMPK to stimulate PINK1/Parkin-mediated mitophagy in MPTP-induced PD mice maintains mitochondrial homeostasis and neuronal survival (37). Thereby, the interplay among autophagy-related signaling pathways in PD progression is complex and more detailed studies are needed. In addition, autophagy-regulating pathways also participate in the induction of other cell death processes, such as apoptosis, necroptosis and ferroptosis (38,39). However, the intrinsic crosstalk between autophagy and these processes, which is simultaneously regulated by shared upstream pathways, has not been fully elucidated. Moreover, it is reported that AMPK inhibition in response to mitochondrial oxidative stress promotes autophagy, which maintains mitochondrial integrity and survival of SH-SY5Y cells exposed to MPP^+ (40). Thus, the interaction between autophagy-related signaling pathways and autophagic processes deserves further investigation for the development of potential strategies of PD treatment.

Effects of autophagy in PD. Aberrant expression of autophagy-related proteins in the brain is observed in patients with PD and various cellular and animal models of PD. Previous studies reported that dysregulated autophagy occurs in the dopaminergic neurons of the SN in patients with PD, in which LBs colocalize with upregulated LC3, an autophagy-related protein that is responsible for autophagosome formation (41,42). Autophagic impairment, attributed to the defective removal and excessive accumulation of undegraded autophagosomes in LBs, causes lysosomal breakdown and the release of proteases into the cytosol, leading to dopaminergic cell death in the brain of patients with PD and MPTP-induced mice (43). The ectopic protein signals of chaperone-mediated autophagy and mitophagy, such as LAMP2A, HSC70 and p-S65-Ub, are also present in PD brain tissues, where they colocalize with α-synuclein, LBs and tangle aggregations (44,45). Recent studies have discovered a downregulation of autophagic components, including LC3, Beclin-1, p62 and ATG5, in peripheral blood cells of patients with PD (46,47). Abnormal expression of these autophagy-related proteins in the SN of PD-related mice is accompanied by both upregulated α-synuclein and clinical symptoms, such as constipation, olfactory impairment and depression-like behaviors (48). Therefore, these findings indicate that autophagy is involved in the pathological process of PD.

Autophagy is considered to exert a neuroprotective role in PD, since it can clear neuronal protein aggregates and impaired mitochondria (3,8). As the major component of LBs, fibrillar α-synuclein aggregation initiates the propagation of α-synuclein pathology, which causes intracellular organelle dysfunction and dopaminergic neuronal death (1). Moreover, these effects are aggravated via the chloroquine-mediated blockade of autophagy but are alleviated by rapamycin-induced activation of autophagy (49). Dopaminergic neurons are metabolically very active with high mitochondrial energy demand, and are therefore particularly vulnerable to mitochondrial dysfunction (5). Mitophagy is required for maintaining the timely turnover of defective mitochondria, and its impairment contributes to ROS overproduction and oxidative stress, accelerating disease progression in PD (6,7). The accumulation of α-synuclein and damaged mitochondria is a consequence of the impaired autophagic-lysosomal degradation system. Upregulation of α-synuclein compromises autophagy degradation by restraining the fusion of autophagosomes with lysosomes, which in turn further facilitates the aggregation and toxicity of α-synuclein (50,51). Excessive α-synuclein expression has also been demonstrated to interfere with mitophagy and mitochondrial functions. For instance, α-synuclein upregulates the expression of Miro protein, an adaptor on the outer mitochondrial membrane that mediates mitochondrial motility, which contributes to abnormal accumulation of Miro in damaged mitochondria, deferring mitochondrial clearance via mitophagy (52). Mutant α-synuclein disturbs mitochondrial dynamics and fusion, and causes pathological changes in mitochondrial morphology (53). Additionally, multiple protein products encoded from PD-related genes are related to autophagy regulation. The leucine-rich repeat kinase 2 (LRRK2) gene mutations, which are linked to familial and sporadic PD, enhance the accumulation of large autophagic vacuoles and perturb autophagic clearance of protein aggregates along with the induction of dysfunctional expression of autophagic receptors p62 and optineurin, leading to impairment of mitophagy, chaperone-mediated autophagy and lysosomal function (54,55). Mutations in the PRKN and PINK1 genes (encoding parkin and PINK1, respectively) also impair the autophagic process and are related to autosomal recessive PD (56,57). The downregulation of PINK1 decreases both starvation-induced autophagy and mitophagy (56,57). Mutation of the GBA gene that encodes β-glucocerebrosidase, which shuttles between the endoplasmic reticulum and the lysosomal lumen, promotes lysosomal dysfunction and α-synuclein pathology in PD through blockade of chaperone-mediated autophagy (4,58). Furthermore, microglia-mediated neuroinflammation has been implicated in autophagy abnormality. Deficiency of DJ-1 in microglia impairs the autophagy-dependent degradation of p62 and LC3 proteins, which decreases the phagocytosis of α-synuclein by microglia (59). Excessive α-synuclein expression, in turn, represses microglial autophagy activity and further exacerbates inflammatory responses, dopaminergic neuron losses and locomotor deficits (60), resulting from NLRP3 inflammasome activation induced by microglial autophagy sabotage (61).

In summary, as an essential degradation process, autophagy is responsible for the elimination of aggregated α-synuclein and damaged mitochondria, thus conferring a neuroprotective role in PD. The excessive accumulation of α-synuclein and mutations in PD-related genes (LRRK2, PINK1, PRKN and GBA) impair the process of autophagy, which in turn enhances aggregation of α-synuclein and other pathogenic proteins in the PD brain, exacerbating neuronal inflammation and degeneration and forming a vicious circle in the pathogenesis of PD.

Thus, induction of protective autophagy has been regarded as a promising strategy for PD treatment. However, studies have suggested that overactivation of autophagy causes autophagic neuronal death owing to the overwhelmed lysosomal and mitochondrial clearance that may stress the cells (62,63). Future investigations should be performed to estimate the level of autophagy that is within a safe and efficacious range. Rather, deficient elimination of toxic α-synuclein suppresses autophagy, and further aggravates α-synuclein accumulation, leading to a pathological feedforward loop in PD (51,52). Therefore, identifying the molecular mechanism by which α-synuclein affects autophagy may provide strategies for autophagy restoration. It has been suggested that increased autophagy may also act as a cellular compensatory mechanism to other blocked degradation pathways (64). In fact, impairment of the autophagy-lysosomal pathway can be alleviated by the inhibition of the ubiquitin-proteasome system in neurotoxin-induced dopaminergic cell death (64). Further dissecting the dynamic interplay between autophagy and other protein degradation pathways is crucial for the progression of PD.

3. Roles of autophagy-regulating miRNAs in PD

According to previous studies (65-68), miRNAs play a vital role in the regulation of autophagy-related genes and signaling pathways, thus the abnormal expression of miRNAs can affect the pathological process of PD by modulating autophagy (Fig. 1).

Neuroprotection of miRNAs by regulating autophagy. miRNAs have been demonstrated to participate in the pathological process of PD by activating autophagy (65-71). For instance, the expression of miR-326 decreases in the absence of PINK1, a PD-related gene (65). Administration of a miR-326 mimic to MPTP-treated mice diminishes the levels of α-synuclein and inducible nitric oxide synthase, and mitigates the locomotory impairment of the mice by promoting autophagy of dopaminergic neurons through the activation of JNK signaling by inhibiting XBP1 (66). Clearance of aggregated α-synuclein is also mediated by miR-4813-3p. miR-4813-3p is downregulated in a transgenic Caenorhabditis elegans model of PD, where excessive α-synuclein contributes to oxidative neuronal damage (67). miR-4813-3p generally mobilizes protein quality control machinery, including the autophagosome-lysosomal-pathway and the ubiquitin-proteasomal-system, for the clearance of misfolded and aggregated proteins, suggesting the potential of targeting miR-4813-3p in PD treatment (67). Besides, delivery of miR-106b by mesenchymal stem cells-derived extracellular vesicles rescues the neuronal apoptosis induced by MPTP, and enhances autophagy by downregulating CDKN2B, a gene encoding a protein that promotes G1-phase cell cycle arrest, which is accompanied by the increased BCL2 but decreased BAX expression (68). Sun *et al* (69) demonstrated that miR-212-5p is expressed at a low level in SH-SY5Y cells and the midbrain of PD animal models, and stereotactic injection of miR-212-5p mimics into the midbrain alleviates the loss of dopaminergic neurons by inhibiting sirtuin2 and further activating autophagy via decreasing cytoplasmic p53 expression. In addition, in the MPP^+-treated SH-SY5Y cells and MPTP-treated mice, there existed a decreased expression of miR-124, autophagosome accumulation and lysosomal depletion. Upregulating miR-124 by using its agonists and mimics decreases the loss of dopaminergic neurons and elevates the level of striatal dopamine via restoring the impaired autophagy process, simultaneous suppressing BIM expression and thus BAX translocation to the mitochondria (70). Further investigation on the protective mechanism of miR-124 revealed that exogenous transferring of miR-124 into the SN of MPTP-treated mice inhibits the release of proinflammatory cytokines from activated microglia by suppressing the expression of p62 and p38 (71). These findings indicate that downregulated expression of miRNAs in the brain of animal PD models is associated with α-synuclein aggregation, oxidative stress, neuronal apoptosis and neuroinflammation, and upregulation of these miRNAs alleviates these effects by inducing autophagy. Therefore, regulating autophagy by miRNAs could become a promising therapeutic strategy for PD.

It is reported that miR-142-5p is downregulated in 6-OHDA-treated SH-SY5Y cells, and its upregulation enhances neuronal vitality by suppressing Beclin-1-dependent autophagy, implying a neuroprotective role of miR-142-5p in the progression of PD (72). In addition to targeting ATGs, miRNAs have been implicated in the regulation of autophagy-related signaling pathways in PD. For example, miR-199a level is decreased in MPP^+-treated PC12 cells, and transfection of miR-199a mimics improves neuronal viability and survival via activating the PTEN/AKT/mTOR signaling pathway (21). This signaling pathway is also activated after overexpressing miR-181b in the same experimental settings, and autophagy is subsequently suppressed, which alleviates the cytotoxicity of MPP^+ (73). The mTOR/ULK1/S6K1 signal transduction cascade is also blocked by miR-135a-5p in MPP^+-treated SH-SY5Y and CHP-212 cells, thus attenuating MPP^+-induced neuronal autophagy and apoptosis (74). Analogously, miR-185 is downregulated in SH-SY5Y cells cultured with MPP^+, and its upregulation impedes cell apoptosis and autophagy by inactivating the AMPK/mTOR signaling pathway (75). Likewise, the expression of miR-181a is decreased by MPP^+ in SK-N-SH cells, and overexpression of miR-181a decreases the rate of cell apoptosis via abrogating activation of the p38MAPK/JNK pathway (76). These results suggest that miRNAs play a protective role in PD progression through inactivation of autophagy by targeting various autophagy-related signaling pathways. It is also worth noting that miRNAs can affect end-stage autophagy by regulating the cyclin-dependent kinase 5 (CDK5) signaling pathway, which has been demonstrated to induce MPTP-induced neuronal death (77). Li *et al* (78) demonstrated that in both MPP^+-treated MN9D cells and MPTP-treated mice, autophagy is blocked by downregulating miR-103/107 and further activating the CDKR5 signaling pathway, while HMGA1 is elevated to sustain the expression of miR-103/107, forming a negative feedback loop between HMGA1 and miR-103/107, which drives neuroprotection through autophagy modulation. Moreover, CDK5-mediated autophagy is suppressed by the injection of miR-188-3p-enriched exosomes, derived from adipose-derived stem cells, into MPTP-induced mice, which abrogates α-synuclein aggregation, NLRP3-induced inflammasomes and neuronal damage in SN (79). These findings

indicate that CDK5-mediated autophagy might be an enlightening target in PD treatment. Moreover, miR-29c-3p has been demonstrated to repress microglial NLRP3 inflammasome activation and neuronal apoptosis in PD models (80). Further mechanistic evaluation has indicated that upregulation of miR-29c-3p inhibits autophagy by decreasing the expression of ten-eleven translocation 2, thus alleviating MPTP-mediated loss of dopaminergic neurons in SN (81).

In conclusion, neuroprotective miRNAs are downregulated in various cellular and animal PD models, and upregulation of these miRNAs can alleviate α-synuclein pathology, neuroinflammation, neuronal oxidative damage and apoptosis, accompanied by increased or decreased levels of autophagy, by targeting ATGs and autophagy-related signaling pathways (Table I). As aforementioned, it is generally acknowledged that enhanced autophagy delays PD progression in most cases owing to its neuroprotective feature. However, some neuroprotective miRNAs are associated with low levels of autophagy. Notably, the same miRNA appear to exert neuroprotective effects on the PD progression with different autophagy levels. By taking miR-124 as an example, several studies have demonstrated that miR-124 elicits autophagy to inhibit microglial activation and neuronal death *in vivo* and *in vitro* (70,71), whereas in another study, it is demonstrated that miR-124 suppress both autophagy and neuronal apoptosis (82). The exact mechanisms of these phenomenon remain elusive. It should be noted that PD stimuli, such as MPP^+, are known to induce autophagy in a concentration-dependent manner, and excessive autophagy attributed to high concentration or prolonged activation of PD toxins may trigger autophagic neuronal death (21,73). Thus, one explanation may be that upregulation of these miRNAs acts as an adaptive response to block autophagic neuronal death. In this regard, future experimental settings should take the concentration of PD-related stimulus and the different models of PD into consideration as the dose of PD stimulus treatment could affect the regulation of miRNAs on autophagy during disease progression. Hence, future experimental designs should estimate the concentration gradient of PD stimulus, for selecting the optimal concentration to simulate PD pathology. Moreover, administering these neuroprotective miRNAs in patients with PD may provide a potential therapeutic strategy by modulating autophagy. Currently, the locked-nucleic-acids-modified oligonucleotides targeting miR-122 method is being employed in Phase I clinical trials for hepatitis C virus infection (83). Further exploring miRNA-based therapeutic approaches, such as miRNA-coated nanoparticles and miRNA microinjection, are expected to treat PD.

Neurotoxicity of miRNAs by regulating autophagy. Although miRNAs have been shown to be neuroprotective in PD, increasing the level of miRNAs have been implicated in disease exacerbation through suppression of autophagy. It has been demonstrated that miR-204-5p is highly expressed in both the serum and brain tissues of an MPTP-induced animal model of PD, and it augments the levels of α-synuclein and tau in SN, and further causes autophagy impairment and cell death by disturbing ATG7-regulated autophagy process and JNK-mediated apoptotic cascade in dopaminergic cells (84). The miR-30c-5p/ATG5 axis, playing a detrimental role in PD progression, contributes to a decrease in antioxidants (malondialdehyde, catalase and superoxide dismutase), dopamine and its metabolites, and neuronal apoptosis, which aggravates motor deficits in MPTP-treated mice (85). Likewise, knockdown of miR-let-7, which is upregulated in a *C. elegans* model of PD, decreases α-synuclein expression, ROS-mediated oxidative stress and motor function via suppressing the ATG13-related autophagy (11). Evidence also demonstrates that silencing of miR-497-5p, which is expressed at high level in PD models, plays a protective role in MPP^+-treated SH-SY5Y cells by inhibiting cell apoptosis and promoting autophagy via upregulation of fibroblast growth factor-2, a neurotrophic factor that serves as a regulator of p62 in an AKT pathway-dependent manner (86,87). These findings demonstrate that upregulated miRNAs in PD exacerbate the disease progression through inhibition of neuronal autophagy via targeting various ATGs. Nevertheless, miRNAs can affect microglial autophagy and thus participate in inflammation in PD. Lv *et al* (88) demonstrated that the expression of miR-3473b is elevated in brain tissues of MPTP-treated mice and increases the inflammatory reaction. Transfection with a miR-3473b mimic promotes the microglial secretion of inflammatory factors TNF-α and IL-1β by downregulating the TREM2/ULK1 expression and thus inhibiting autophagy (88). Similarly, the increased level of miR-19a-3p in the exosomes of SH-SY5Y cells transfected with the α-synuclein gene, has been demonstrated to represses microglial autophagy by targeting the PTEN/AKT/mTOR signaling pathway, possibly affecting α-synuclein phagocytosis and inflammation activation in microglia, suggesting an autophagy-related neurotoxicity of miR-19a-3p in PD (89).

Furthermore, aberrant expression of miRNAs is linked to the pathogenesis of PD by targeting mitophagy-related signaling pathways. Under chronic mitochondrial stress, miR-27a/b are upregulated as an adaptive response to prevent the induction of mitophagy by suppressing the expression of PINK1, which hinders lysosomal degradation of damaged mitochondria (90). PINK1-mediated mitophagy is also inhibited by miR-421 in both PD cells and animal models, and mitochondrial autophagy is disrupted, leading to ROS-mediated oxidative damage to neurons (12). In addition, in rotenone-treated SH-SY5Y cells, miR-146a is increased by NF-kB-mediated transcriptional activation, and further decreases the level of mitophagy by inhibiting Parkin, resulting in accumulation of dysfunctional mitochondria and ROS overproduction in degenerating neurons (91). Consistently, depletion of miR-103a-3p, which is a highly expressed in MPTP-induced PD models, alleviates the loss of dopaminergic neurons in SN and improves gait disorders via activating the Parkin/Ambra1-mediated mitophagy (92). Thus, these results reveal that miRNA-induced dysfunction of mitophagy is a critical pathogenic mechanism in PD. Besides, increased miR-320a level in PD brains has been demonstrated to suppress chaperone-mediated autophagy by targeting heat shock protein 70, facilitating α-synuclein intracellular accumulation (93,94).

It can be concluded that almost all reported miRNAs in this review are upregulated in PD models and exert neurotoxic effects through participation in various pathological process, including α-synuclein accumulation, mitochondrial dysfunction and microglial activation by inhibiting autophagy (Table II). However, a contradictory study demonstrates that inhibition

Table I. Neuroprotective effects of autophagy-regulating miRNAs in Parkinson's disease.

First author, year	miRNA	Expression	Autophagy-related target	Autophagy	Outcome	Experimental model	(Refs.)
Qin, 2022	miR-135a-5p	Down	mTOR/ULK1/S6K1	Inhibition	Protecting MPP+-induced neuronal cell death	MPP^+-treated SH-SY5Y and CHP 212 cells	(74)
Bai, 2021	miR-106b	Down	CDKN2B, LC3-II	Activation	Alleviating neuronal apoptosis	MPTP-treated mice and mouse primary hippocampal neurons	(68)
Wang, 2021	miR-29c-3p	Down	TET2, Beclin-1, LC3-II, p62	Inhibition	Protecting inflammation-mediated neuronal damage	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(81)
Li, 2021	miR-188-3p	Down	CDK5, LC3-II, p62	Inhibition	Increasing cell proliferation	MPTP-treated mice and MPP^+-treated MN9D cells	(79)
Li, 2021	miR-103/107	Down	CDKR51/CDK5, LC3-II	Inhibition	Reducing neuronal cell death	MPTP-treated mice and MPP^+-treated MN9D cells	(78)
Ba, 2020	miR-199a	Down	PTEN/AKT/mTOR, LC3-II, Beclin-1	Inhibition	Elevating cell viability and survival	MPP^+-treated PC12 cells	(21)
Chen, 2020	miR-142-5p	Down	Beclin-1, LC3-II, p62	Inhibition	Enhancing cell vitality	6-OHDA-treated SH-SY5Y cells	(72)
Zhao, 2019	miR-326	Down	XBP1/JNK, LC3-II	Activation	Improving the behavioral symptoms in mice and the clearance of α-synuclein	MPTP-treated mice	(66)
Sun, 2018	miR-212-5p	Down	SIRT2, p53, LC3-II, p62	Activation	Ameliorating neuronal apoptosis and degeneration	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(69)
Li, 2018	miR-181b	Down	PTEN/AKT/mTOR	Inhibition	Increased cell viability	MPP^+-treated PC12 cells	(73)
Wen, 2018	miR-185	Down	AMPK/mTOR, Beclin-1, LC3-II	Inhibition	Inhibit dopaminergic cell apoptosis	MPP^+-treated SH-SY5Y cells	(75)
Liu, 2017	miR-181a	Down	p38 MAPK/JNK, Beclin-1, LC3-II	Inhibition	Reducing neuronal cell apoptosis	MPP^+-treated SK-N-SH cells	(76)
Yao, 2019	miR-124	Down	p62, p38	Activation	Attenuating the activation of microglia and neuronal apoptosis	MPTP-treated mice and LPS-treated BV2 cells	(71)
Wang, 2016	miR-124	Down	LC3-II	Activation	Attenuating mitochondria-dependent apoptotic cell death and neurodegeneration	MPP^+-treated SH-SY5Y cells and MPTP-treated mice	(70)
Gong, 2016	miR-124	Down	AMPK/mTOR, Beclin-1, LC3-II	Inhibition	Decreasing cell apoptosis	MPP^+-treated SH-SY5Y and SK-N-SH cells	(82)

6-OHDA, 6-hydroxydopamine; AMPK, adenosine monophosphate-activated protein kinase; JNK, c-Jun N-terminal kinase; miR, microRNA; miRNA, microRNA; MPP^+, 1-methyl-4-phenylpyridinium iodide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTOR, mammalian target of rapamycin; PTEN, phosphatase and tensin homolog; ULK1, unc-51-like kinase 1; TET2, ten-eleven translocation 2.

Table II. Neurotoxic effects of autophagy-regulating miRNAs in Parkinson's disease.

First author, year	miRNA	Expression	Autophagy-related target	Autophagy	Outcome	Experimental model	(Refs.)
Dong, 2022	miR-421	Up	PINK1/Parkin, LC3-II	Inhibition	Promoting ROS overproduction and neuronal death	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(12)
Zhu, 2021	miR-497-5p	Up	FGF2, Beclin-1, LC3-II, p62	Inhibition	Inducing cell apoptosis and mice bradykinesia	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(86)
Zhang, 2019	miR-30c-5p	Up	ATG5, LC3-II	Inhibition	Aggregating cell apoptosis and behavioral symptoms in mice	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(97)
Lv, 2021	miR-3473b	Up	TREM2, ULK1, LC3-II	Inhibition	Promoting the microglia-mediated inflammatory responses	MPTP-treated mice and LPS-treated BV2 cells	(88)
Zhou, 2020	miR-103a-3p	Up	Parkin/Ambra1, LC3-II	Inhibition	Reducing cell viability and exacerbating neurodegeneration in mice	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(92)
Zhao, 2020	miR-132-5p	Up	ULK1, Beclin-1	Activation	Decreasing cell survival ability and increasing apoptosis	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(95)
Jauhari, 2020	miR-146a	Up	Parkin	Inhibition	Causing accumulation of mitochondria and overproduction of ROS	Rotenone-treated SH-SY5Y cells	(91)
Zhou, 2019	miR-19a-3p	Up	PTEN/AKT/mTOR, LC3-II, p62	Inhibition	Impairing the phagocytosis and degradation of α-synuclein in microglia	SH-SY5Y cells overexpressing the α-synuclein gene	(89)
Chiu, 2019	miR-204-5p	Up	DYRK1A, Beclin-1, ATG7, ATG16L1, LC3-II	Inhibition	Inducing the death of dopaminergic cells	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(84)
Shamsuzzama, 2017	miR-Let-7	Up	ATG13	Inhibition	Increasing α-synuclein expression	The transgenic *C. elegans* model	(11)
Kim, 2016	miR-27a/b	Up	PINK1	Inhibition	Suppressing lysosomal degradation of the damaged mitochondria	HeLa and M17 cells	(90)
Li, 2014	miR-320a	Up	Hsc70	Inhibition	Inhibiting α-synuclein degradation	SH-SY5Y cell line overexpressing α-synuclein	(93)
Decressac, 2013	miR-128	Down	TFEB, Beclin-1, p62	Inhibition	Aggravating α-synuclein accumulation and toxicity	α-synuclein-transfected HEK 293 cells and α-synuclein-injected rats	(99)

miR, microRNA, miRNA, microRNA; PINK1, PTEN-induced putative kinase protein 1; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP^+, 1-methyl-4-phenylpyridinium iodide; ATG, autophagy-related gene; FGF2, fibroblast growth factor-2; TREM2, triggering receptor expressed on myeloid cells 2; ULK1, unc-51-like kinase 1; PTEN, phosphatase and tensin homolog; mTOR, mammalian target of rapamycin; TFEB, transcription factor EB.

of miR-132-5p, which is upregulated in MPTP-induced PD models, decreases neuronal apoptosis and autophagy via direct targeting of ULK1, suggesting the enhancement of autophagy in miR-132-5p-mediated neurotoxicity in PD (95). One explanation for this may be that miR-132-5p is involved in MPTP-stimulated overactivation of autophagy in neurons, ultimately leading to autophagic cell death. In addition, miRNAs regulate autophagy by crosstalk with apoptotic cell death pathways. For example, Beclin-1 upregulation induced by miRNAs has been demonstrated to enhance the activity of autophagy and simultaneously prevent apoptosis (3). Thus, further clarifying the role of miRNA-regulating autophagy is vital for understanding the pathogenesis of PD. Besides, these neurotoxic miRNAs may affect PD progression through many targets. By taking miR-30c-5p as an example, it is reported that miR-30c-5p antagomir decreases neuronal apoptosis and induces autophagy in brain tissues of MPTP-treated mice (85), while certain studies demonstrate that both immune reactions and pyroptosis, which are associated with the development of PD, can also be modulated by miR-30c-5p (96,97). Therefore, further investigation is needed to fully determine the main target of miRNAs in PD. Otherwise, miRNAs confer paradoxical effects in PD. For instance, the expression of miR-128 is downregulated in PD mice and its upregulation rescues neurons from apoptosis, thereby playing a protective role in PD (98). However, miR-128 also acts as a negative regulator of transcription factor EB, which is a major transcriptional regulator of the autophagy-lysosome pathway, and thus fails to clear α-synuclein oligomers, aggravating the α-synuclein toxicity in PD (99). It can be assumed that the neurotoxic miRNA regulation of autophagy in PD progression is intricate due to its interaction with various pathological processes. The interplay between miRNA-regulated autophagy and PD pathogenesis has not yet been fully elucidated.

4. Regulating miRNA-mediated autophagy as therapeutic strategies for PD

As aforementioned, it is widely believed that miRNAs play a regulatory role in autophagy during PD progression. Therefore, targeting miRNAs to modulate autophagy could offer a promising therapeutic strategy to this disease. However, miRNA-based therapies pose many unsolved challenges due to their unstable structures, non-specific functions, potential toxicities and inefficient deliveries to the brain. Emerging studies have found that miRNA-mediated autophagy can be further modulated by other ncRNAs, including lncRNAs and circRNAs, as well as natural agents (100-115). These findings provide great potential for the prevention and treatment of PD in the future. Whether using ncRNA or natural products to target miRNAs regulating autophagy, further investigations should be performed to clarify how to modulate the level of miRNAs to maintain a desired autophagy level since controlling the level of autophagy within a safe and efficacious range is crucial for the prevention and treatment of PD.

ncRNA. Both lncRNAs and circRNAs can act as competing endogenous RNAs to sponge miRNAs, and thus participate in miRNA-mediated gene regulation and cellular processes, including proliferation, apoptosis and autophagy. With the development of PD, aberrant expression of ncRNAs affect the pathological process of this disease through modulation of miRNA-mediated autophagy (100-109). For instance, lncRNA OIP5-AS1 is decreased in MPP^+-treated SH-SY5Y cells, which is associated with miR-137-mediated suppression of mitophagy (100). Moreover, overexpression of OIP5-AS1 alleviates mitochondrial damage and ROS accumulation via inhibiting miR-137 activity and further restoring mitochondrial autophagy (100). Consistent with these findings, circDLGAP4 has been demonstrated to function as a decoy of miR-134-5p to decrease mitochondrial damage and apoptosis in neurons treated with MPP^+, by targeting the miR-134-5p/CREB axis and further enhancing autophagy (101). It can be concluded that elevating the expression of downregulated ncRNAs in PD exerts neuroprotective effects via restoring the miRNA-induced autophagy impairment. However, several ncRNAs, such as lncRNA SNHG1, lncRNA SNHG14 and lncRNA BDNF-AS, are overexpressed in PD and aggravate neuronal damage through modulating miRNA-mediated autophagy (102-104). Qian *et al* (102) demonstrated that downregulating lncRNA SNHG1 facilitates autophagy and attenuates MPP^+-induced cytotoxicity in neurons through the miR-221/222/p27/mTOR axis, implying an inhibitory effect of SNHG1 on protective autophagy. Besides, other upregulated ncRNAs are reported to exacerbate PD progression by inducing autophagic cell death. It has been demonstrated that lncRNA SNHG14 targets miR-519a-3p to upregulate ATG10 expression in MPP^+-treated SK-N-SH cells, thus accelerating neuronal cell damage by activating autophagy (103). Likewise, overexpressed lncRNA BDNF-AS mediates MPP^+-triggered death and loss of dopaminergic neurons in MPTP-treated mice and promotes autophagy through sponging miR-125b-5p (104). It should be noted that ncRNAs can modulate autophagy in PD through targeting different miRNAs. New evidence demonstrates that lncRNA NEAT1 strengthens neuronal death in PD mice by enhancing autophagy through competitively biding to both miR-107-5p and miR-374c-5p, indicating a potential therapeutic role of NEAT1 in treating PD (105,106). Analogously, lncRNA HOTAIR depletion decreases neuronal apoptosis in MPP^+-treated SK-N-SH and MN9D cells, along with an inhibition of autophagy (107,108). Further molecular investigations demonstrated that HOTAIR functions as a sponge for both miR-874-5p and miR-221-3p, further promoting the expression of ATG10 and NPTX2, which contributes to the neurotoxic role of HOTAIR by upregulating autophagy (107,108). These results indicate that upregulation of lncRNAs during PD progression deteriorate neuronal apoptosis by promoting autophagy by acting as a sponge for miRNAs. Besides, downregulation of circSAMD4A attenuates neuronal damage and motor deficits in PD models, since circSAMD4A modulates disease progression by sponging miR-29c-3p to activate the AMPK/mTOR signaling pathway and further induces autophagy (109). Thus, this previous study demonstrates that circRNAs play a pernicious role in PD by inducing autophagy through targeting miRNAs.

Collectively, aberrant expression of ncRNAs affects the pathological processes of PD, including neuronal apoptosis, oxidative stress and mitochondrial dysfunction by modulating miRNA-mediated autophagy (Table III). lncRNA

Table III. Regulatory roles of ncRNAs on miRNA-mediated autophagy in PD.

First author, year	NcRNA	Expression	Effect on miRNA	Autophagy	Mechanism of alleviating PD	Experimental model	(Refs.)
Dong, 2022	lncRNA NEAT1	Up	miR-107-5p ↓	Activation	Interfering with NEAT1 increases neuron viability and suppresses apoptosis	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(105)
Dong, 2021	lncRNA NEAT1	Up	miR-374c-5p ↓	Activation	Suppression of NEAT1 facilitates cell proliferation and inhibits apoptosis	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(106)
Zhuang, 2022	lncRNA SNHG14	Up	miR-519a-3p ↓	Activation	Silencing SNHG14 and restoring miR-519a-3p reduce neuronal cell death	MPP^+-treated SK-N-SH cells	(103)
Qian, 2019	lncRNA SNHG1	Up	miR-221/222 ↓	Inhibition	Silencing SNHG1 reduces cell death	MPTP-treated mice and MPP^+-treated MN9D cells	(102)
Zhao, 2022	lncRNA OIP5-AS1	Down	miR-137 ↑	Inhibition	Restoring OIP5-AS1 promotes mitophagy and thus protects neurons from degeneration	MPP^+-treated SH-SY5Y cells	(100)
Wang, 2021	circSAMD4A	Up	miR-29c 3p ↓	Activation	Knockdown of circSAMD4A inhibits neuronal cell apoptosis	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(109)
Zhao, 2020	lncRNA HOTAIR	Up	miR-874-5p ↓	Activation	Inhibition of HOTAIR reduces neuronal injury	MPP^+-treated SK-N-SH cells	(107)
Lang, 2020	lncRNA HOTAIR	Up	miR-221-3p ↓	Activation	Downregulation of HOTAIR enhances cell viability	MPTP-treated mice and MPP^+-treated MN9D cells	(108)
Fan, 2020	lncRNA BDNF-AS	Up	miR-125b-5p ↓	Activation	Knockdown of BDNF-AS promotes cell proliferation and suppresses apoptosis	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(104)
Feng, 2020	circDLGAP4	Down	miR-134-5p ↑	Inhibition	Upregulation of circDLGAP4 reduces mitochondrial damage and apoptosis	MPTP-treated mice and MPP^+-treated SH-SY5Y cells	(101)

PD, Parkinson's disease; miR, microRNA; miRNA, microRNA; ncRNA, non-coding RNA; lncRNA, long ncRNA; circ, circular RNA; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP^+, 1-methyl-4-phenylpyridinium iodide.

OIP5-AS1 and circDLGAP4 are downregulated in PD, and their upregulation alleviates neuronal damage by inhibiting neurotoxic miRNAs to activate autophagy (100,101). Thus, administration of these ncRNAs may be beneficial for PD treatment by restoring miRNA-induced autophagy impairment. Furthermore, other upregulated ncRNAs (lncRNA SNHG1, lncRNA SNHG14, lncRNA BDNF-AS, lncRNA NEAT1, lncRNA HOTAIR and circSAMD4A) in PD are linked to excessive autophagy by negatively targeting neuroprotective miRNAs (102-109). Hence, maintaining sufficient levels of neuroprotective miRNAs to alleviate excessive autophagy by silencing these ncRNAs may become a potential therapeutic strategy for PD.

Drugs and natural compounds. In addition to the regulatory role of ncRNAs on miRNA-mediated autophagy, drugs and natural products have also been demonstrated to regulate autophagy by targeting miRNAs for the prevention and treatment of PD. For instance, empagliflozin, a selective sodium-glucose co-transporter-2 inhibitor, can suppress rotenone-induced endoplasmic reticulum stress, α-synuclein accumulation and neuroinflammation in the striatum of PD rats by inhibiting miR-211-5p expression to upregulate Beclin-1-mediated autophagy, executing neuroprotection (110). Pramipexole is a dopamine D2/D3 receptor agonist with proven efficacy in the treatment of motor symptoms in early and advanced PD (111). It has been demonstrated that pramipexole can rescue MPTP-induced neuronal death in mice by activating BNIP3-mediated mitophagy via directly decreasing miR-96 levels (111). Moreover, pramipexole mitigates cell apoptosis and indirectly promotes cell autophagy in PD by downregulating the expression of circSNCA, which serves as a miR-7 sponge, thereby triggering miR-7-induced autophagy (112). In addition, baicalein, a natural compound that is regarded as a novel regulator for cell metabolism, proliferation and apoptosis, can increase dopamine concentration and neuronal viability in 6-OHDA-treated rats by inhibiting miR-30b, and thus inducing mitochondrial autophagy via the activation of the NIX/BNIP3 signaling pathway (113). Similarly, it has been demonstrated that baicalein alleviates neuronal apoptosis and recovers mitochondrial dysfunction by restoring mitophagy via targeting miR-30b-5p and thus inactivating the SIRT1/AMPK/mTOR pathway (114). However, in 6-OHDA-treated PC12 cells, baicalein negatively regulates the expression of miR-192-5p and further decreases cell injury and autophagy through suppression of the PI3K/AKT signaling cascade, indicating that baicalein inhibits excessive autophagy to protect against PD (115).

In summary, some drugs and natural compounds have been implicated in the regulation of miRNA-mediated autophagy and play a positive role in the prevention and treatment of PD (Table IV). Further identification of the mechanisms by which various drugs or natural products regulate miRNA-mediated autophagy is crucial to develop targeted interventions in PD. However, whether various targets acting on miRNA-mediated autophagy exist in these drugs or natural products needs to be confirmed.

Table IV. Regulatory roles of drugs and natural agents on miRNA-mediated autophagy in PD.

First author, year	Drug and agent	Effect on miRNA	Autophagy	Mechanism of alleviating PD	Experimental model	(Refs.)
Motawi, 2022	Empagliflozin	miR-211-5p ↓	Activation	Alleviating oxidative stress, glial activation and neuroinflammation	Rotenone-treated rats	(110)
Chen, 2022	Baicalein	miR-30b-5p ↓	Activation	Lessening neuronal injury and recovering mitochondrial dysfunction	6-OHDA-treated rats	(114)
Chen, 2021	Baicalein	miR-30b ↓	Activation	Restoring neuronal activity and alleviating neuron damage	6-OHDA-treated rats	(113)
Kang, 2019	Baicalein	miR-192-5p ↓	Inhibition	Reducing neuronal injury and elevating cell viability	6-OHDA-treated PC12 cells	(115)
Wang, 2021	Pramipexole	miR-96 ↓	Activation	Increasing cell viability and decreasing apoptosis	MPTP-treated mice, MPP^+-treated SH-SY5Y and SK-N-SH cells	(111)
Sang, 2018	Pramipexole	miR-7↑	Activation	Reducing cell apoptosis	MPP^+-treated SH-SY5Y cells	(112)

PD, Parkinson's disease; miR, microRNA; miRNA, microRNA; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP^+, 1-methyl-4-phenylpyridinium iodide; 6-OHDA, 6-hydroxydopamine.

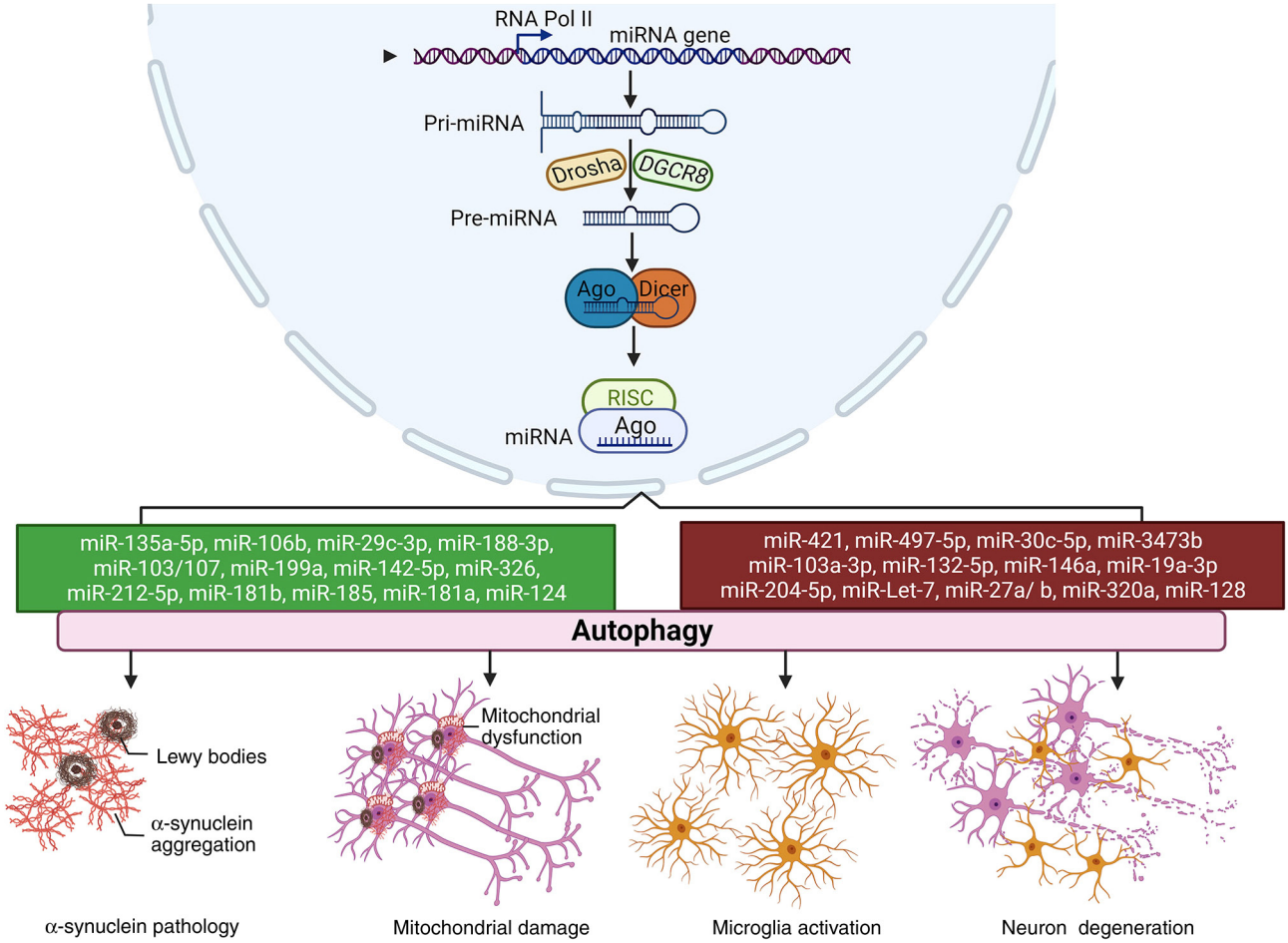

Figure 2. The roles of miRNA-mediated autophagy in PD progression. In the nucleus, a pri-mRNA is transcribed and further cleaved by Drosha and DGCR8 to generate pre-miRNA, which is cleaved into a miRNA duplex by Dicer and then is loaded to the groove of AGO to form the RISC complex. Both neuroprotective miRNAs (green) and neurotoxic miRNAs (red) are involved in the pathological processes of PD, including α-synuclein accumulation, mitochondrial damage, microglial activation and neuronal degeneration by modulating autophagy. AGO, Argonaute; PD, Parkinson's disease; pri-mRNA, primary microRNA; miR, microRNA; miRNA, microRNA; RISC, RNA-induced silencing complex.

5. Conclusions and future perspectives

Autophagy is a crucial biological process that can be regulated through a variety of ATGs and autophagy-related signaling pathways, and its dysfunction is associated with the progression of PD. Although overactivated autophagy causes neuronal damage, the autophagy-lysosomal pathway is responsible for the removal of aggregated α-synuclein and impaired mitochondria, and thus exerts neuroprotective roles in PD. Emerging studies (65-68) have also documented that various miRNAs are involved in the pathological processes of PD, including α-synuclein accumulation, mitochondrial damage, oxidative stress, microglial activation and neuronal apoptosis via regulating autophagy (Fig. 2). Autophagy-regulating miRNAs perform a dual function in the progression PD. By targeting both ATGs and autophagy-related signaling pathways, downregulated miRNAs play neuroprotective roles by activating protective autophagy or decreasing autophagic neuronal cell death, whereas neurotoxic miRNAs are upregulated to induce autophagy impairment. Thus, regulating miRNA-mediated autophagy may be a novel strategy for the treatment of PD. Studies (3,9) have demonstrated that the implementation of miRNA mimics, agonists and antagonists by nanoparticles and microinjection is effective to delay disease progression in PD models. However, the biosafety and reliability of these miRNA-based therapeutic strategies should be fully elucidated before clinical application, owing to multiple gene target and off-target effects of miRNAs. A comprehensive understanding of the regulatory mechanism of miRNAs on autophagy and the crosstalk between miRNA-regulated autophagy and other biological processes in PD, including programmed cell death, protein degradation pathways and pathophysiological mechanisms, can help in developing safe and effective therapeutic targets for this disease. It is worth noting that ncRNAs, including lncRNAs and circRNAs, drugs and natural compounds can restore impaired autophagy via regulating miRNAs, indicating their great potential value in the treatment of PD. However, the identification of these interventions for specifically targeting signaling pathways associated with miRNA-mediated autophagy is needed to fully determine their main target in PD.

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ZM and HL wrote the manuscript, BH and SC revised the manuscript, DY retrieved references and raised the research topic. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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