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Review

Unraveling the role of miRNAs in the diagnosis, progression, and therapeutic intervention of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a debilitating neurological disorder characterized by the impairment of the motor system, resulting in symptoms such as resting tremor, cogwheel rigidity, bradykinesia, difficulty with gait, and postural instability. The occurrence of striatal dopamine insufficiency can be attributed to a notable decline in dopaminergic neurons inside the substantia nigra pars compacta. Additionally, the development of Lewy bodies serves as a pathological hallmark of PD. While current therapy approaches for PD aim to preserve dopaminergic

Abbreviations: AAV, Adeno-associated virus; AD, Alzheimer's disease; ASK1, apoptosis signal-regulating kinase1; ATP13A2, ATPase Cation Transporting 13A2; BBB, blood-brain barrier; CNS, central nervous system; DA, dopamine; DAPK1, death-associated protein kinase 1; DFO, deferoxamine; DJ1, parkinsonism-associated deglycase; DJ-1, Parkinson's disease protein; ER, endoplasmic reticulum; ETC, electron transport chain; FBXO7, F-box only protein 7; HNE, 4-Hydroxynonenal; IP3R, inositol trisphosphate receptors; iPSC, induced pluripotent stem cell; LNP, lipid nanoparticle; LRRK2, leucine-rich repeat kinase 2; MAO-B, monoamine oxidase-B; MHC, major histocompatibility complex; miRNA, microRNA; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; ncRNAs, non-coding RNAs; NF-kB, nuclear factor kappa B; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NPs, nanoparticles; PARP, poly ADP-ribose polymerase; PD, Parkinson's disease; PINK1, phosphatase and tensin homologue-induced kinase 1; PPD, Parkin/PINK1/DJ-1; pre-miRNA, precursor miRNA; pri-miRNA, primary miRNA; PRKN, parkin RBR E3 ubiquitin protein ligase; RNS, reactive nitrogen species; ROS, reactive oxygen species; RyR, ryanodine receptors; SN, substantia nigra; SNCA, Alpha-synuclein" or SNCA, Synuclein Alpha Non-A4 component of amyloid precursor; SNP, single nucleotide polymorphism; α-Syn, alpha-synuclein.

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neurons or replenish dopamine levels in the brain, it is important to acknowledge that achieving complete remission of the condition remains elusive. MicroRNAs (miRNAs, miR) are a class of small, non-coding ribonucleic acids involved in regulating gene expression at the post-transcriptional level. The miRNAs play a crucial part in the underlying pathogenic mechanisms of several neurodegenerative illnesses, including PD. The aim of this review is to explore the role of miRNAs in regulating genes associated with the onset and progression of PD, investigate the potential of miRNAs as a diagnostic tool, assess the effectiveness of targeting specific miRNAs as an alternative therapeutic strategy to impede disease advancement, and discuss the utilization of newly developed nanoparticles for delivering miRNAs as neurodegenerative therapies.

1. Introduction

Parkinson's disease (PD) is a neurological ailment that impacts a significant global population of over 6 million individuals. Its prevalence is expected to increase due to the growing elderly population [1]. PD is commonly categorized as a movement condition characterized by a combination of three primary symptoms: bradykinesia, rigidity, and tremor [2]. The primary pathological factor responsible for the manifestation of these motor symptoms is the progressive deterioration of the dopaminergic nigrostriatal pathway [3].

Dopamine replacement treatment has served as the fundamental approach for symptomatic therapy for over 50 years. Nevertheless, the advantages of symptomatic therapy are constrained by the occurrence of adverse effects and the decline in effectiveness with time, as well as their unequal efficacy in addressing all symptoms of PD [4]. These limits arise partially due to neuroplastic changes in brain circuits resulting from prolonged treatment, partially due to the gradual advancement of the underlying disease, and partly because not all symptoms of PD are solely caused by malfunction in the nigrostriatal pathway [5]. Regarding the latter, aside from the motor symptoms discussed earlier, PD is associated with a wide range of non-motor symptoms. Remarkably, the majority of these non-motor symptoms still pose major obstacles to medical intervention and treatment [6]. Non-motor symptoms encompass a range of cognitive and behavioral issues, such as executive dysfunction, psychosis, apathy, and mood disorders. Additionally, autonomic failure, including urinary bladder disturbances, as well as constipation, loss of sense of smell, sleep disturbance, and pain, are also observed [7].

Regardless of the underlying cause, whether it is genetic or sporadic in nature, the majority of PD cases exhibit pathology associated with alpha-synuclein (α-Syn). This pathology is characterized by Lewy bodies and Lewy neurites [8]. The accumulation of α-Syn in the nigrostriatal pathway is associated with the degenerative process. However, this synucleinopathy is not limited to this pathway but is also present in various brain and peripheral nervous system regions. These regions are believed to contribute to non-motor symptoms, such as the enteric plexus, dorsal nucleus of the vagal nerve, locus coeruleus, dorsal raphe nucleus, and eventually the cerebral cortex, particularly in the later stages of the disease [8].

The observation that α-Syn pathology is a distinguishing characteristic of PD, regardless of its cause, implies that although the initial events triggering the disease may vary, there is a shared subsequent progression that results in the participation of α-Syn as a central contributor to the development of the disease [7]. Numerous disease mechanisms have been postulated, and several targets have been discovered for potentially manipulating these pathways [9]. These targets have been verified to different extents in cell-based systems, animal models, and post-mortem material from individuals with PD. The targets under consideration encompass α-Syn and a diverse range of mechanisms that could affect α-Syn in various subsets or the entire population of individuals with PD [7]. These mechanisms comprise oxidative stress [10], LRRK2 [11], apoptosis [12], neuroinflammation [13], misfolding proteins [14], age [2], melanin [15], and iron accumulation [16]. The targets that are considered particularly appealing in this context are also substantiated by genetic investigations. These targets encompass LRRK2 [17], parkin, PINK1 [18], and GBA [19].

The microRNAs (miRNAs) have garnered growing interest as new targets in the field of neurodegenerative illnesses, such as PD [20]. The miRNAs have significant functions in regulating the cell transcriptome through RNA interference. However, their abnormal expression can also contribute to the development of diseases including cancer [21–55], liver diseases [56], bone diseases [57], multiple myeloma [58,59], multiple sclerosis [60], cardiovascular diseases [61,62], metabolic syndrome [63–65], toxoplasma [66], rheumatoid arthritis [67,68], diabetes [69–72], and coronavirus disease 2019 (COVID-19) infection [73–76], and Alzheimer's [77–79].

To complete this review, we searched the following phrases in the online medical databases NCBI and PUBMED: Studies on Parkinson's disease diagnosis, pathogenesis, therapeutic intervention, mental health, and miRNA were finalized as of June 20, 2023. Clinical guidelines, randomized clinical studies, meta-analyses, systematic reviews, narrative reviews, and original papers were prioritized to present a unified picture of the current understanding of the role of major miRNAs in Parkinson's disease development, progression, and therapeutic intervention.

In this context, the dysregulated production of a particular miRNA can be restored to its physiological level using synthetic oligos, which can disrupt crucial pathways involved in the etiology of diseases [80,81]. In this review, the role of miRNAs in the underlying mechanisms of PD is looked at. New technologies have been developed to improve the effectiveness and delivery of small RNAs, which opens the door to a miRNA-based neuroprotective treatment.

2. Pathogenesis of PD

Concerning PD, it is often unobservable if only the frontal cortex shows mild atrophy. The typical change in brain morphology starts when there is a loss of darkly pigmented areas in the single nucleotide polymorphism (SNP) and locus coeruleus in the transverse section of the brain stream (Fig. 1). Moreover, the death of dopamine (DA) neuromelanin-containing neurons in SNP and adrenergic neurons in locus coeruleus are the main reasons for that loss. There is a noticeable loss of the ventrolateral tier of neurons of pars compacta (A9) in the substantia nigra (SN), while less loss was observed in the dorsal and medial neuronal cells [82].

Tissue cues including hypoxia trigger their migration, tumor formation, and endothelial cell differentiation [83–87]. The formation of new blood vessels is encouraged by vascular endothelial growth factor (VEGF) [88–98]. The VEGF, is a putative target for miRNA regulation that has been linked to PD. Numerous investigations have emphasized the deregulation of VEGF-related miRNAs in PD. For example, one of the most important upstream regulators of dysregulated miRNAs in PD serum was shown to be VEGF in a study published in 2021 [99].

Further investigation of PD brains revealed changes in mitochondrial function, increased oxidative stress, lysosomal dysfunction, protein aggregation, impaired degradation, iron deposition, inflammation, environmental risks, age, and glial activation (Fig. 2) [100].

2.1. Reactive oxidative stress molecules

The brain uses around 20% of the oxygen that is supplied to the body

in its entirety. In neurons and glial cells, a substantial percentage of this oxygen transforms into reactive oxygen species (ROS) from several sources. The primary generator of ROS at the mitochondrial level is the electron transport chain; further sources include nitric oxide (NO), monoamine oxidase, NADPH oxidase, and other flavoenzymes [101] I, which is inhibited because of respiratory chain degradation brought on by oxidative damage to mitochondrial DNA. Similarly, different biological components are affected by reactive nitrogen species (RNS), like nitrosyl radicals, peroxynitrite (ONOO−), and NO, which can lead to lipid peroxidation, protein oxidation, and DNA damage, ultimately compromising cellular function.

2.1.1. Death of dopaminergic neuron cell

The substantia nigra's dopaminergic neurons, in contrast to most other brain neurons, use L-type Ca^{2+} channels (which have an unusual Cav 1.3 pore-forming subunit, Cacna1d) to set the pace, which increases ATP consumption and Ca^{2+} input. Through a smooth endoplasmic reticulum (ER) Ca^{2+} pump with high affinity, Ca^{2+} enters the ER. A high-concentration Ca^{2+} zone develops adjacent to mitochondria as Ca^{2+} enters the cytoplasm via ryanodine receptors (RyR) and inositol trisphosphate receptors (IP3R). The Na^{+}/Ca^{2+} exchanger (Na^{+}) promotes the Ca^{2+} efflux through mitochondria in dopaminergic neurons. In contrast, the mitochondrial Ca^{2+} uniporter enhances Ca^{2+} uptake as 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) [102]. MPTP has been used to create animal models of PD because it explicitly destroys dopaminergic neurons by inhibiting mitochondrial complex I from engaging. Numerous cellular death cascades, including caspase-dependent and caspase-independent pathways, stress, neuronal nitric oxide synthase (nNOS) activation, DNA damage, poly ADP-ribose polymerase (PARP) activation, and GAPDH modification, end up resulting in the death of the dopaminergic neuron. Furthermore, microglial activation plays a role in dopaminergic neuron degeneration [102].

2.1.2. Iron molecules

Iron is required for neurotransmitter synthesis as a cofactor of tyrosine hydroxylase, which converts tyrosine to DA and norepinephrine. Catechol is a chemical molecule that can bind iron [103]. An overabundance of iron can induce a massive increase in free radical generation, which overwhelms the body's natural defense mechanisms and causes damage at multiple cellular levels. The SN of PD patients had higher iron levels in both the pars compacta and the pars reticulata [104]. Reduced ferritin expression and neurodegeneration of nigral melatonin neurons increase the reactive Fe^{2+} iron pool. Reduced Fe^{2+} interacts quickly with H_2O_2 to produce OH radicals. Age-related iron accumulation and a leaky blood-brain barrier (BBB) also contribute to increased iron accumulation. The ratio of reduced to oxidized iron in a healthy SN is 1:1; however, in PD patients, the ratio increases to 1:3. This increase is hazardous and is not found in other brain parts with decreased glutathione and DA autoxidation; free radical levels increase, provoking several harmful events such as protein misfolding, lipid peroxidation, glial cell activation, mitochondrial dysfunction, and α-Syn aggregation [105].

2.1.3. Lipids

The 4-Hydroxynonenal (HNE) is formed because of lipid peroxidation. Immunocytochemistry shows that HNE levels in dopaminergic cells increase in PD and cerebrospinal fluid (CSF) [105]. Furthermore, lower polyunsaturated fatty acid levels and increased malondialdehyde levels in SN suggest improved lipid peroxidation [106]. HNE is a highly reactive lipophilic beta alkenyl that forms persistent adducts with protein nucleophiles such as thiols and amines. HNE can also trigger apoptosis by activating caspases 8, − 9, and − 3 and fragmenting DNA. It also inhibits the nuclear factor kappa B (NF-kB) signaling pathway, decreases glutathione levels due to fast consumption by glutathione peroxidase, inhibits complexes I and II of the mitochondrial respiratory chain, and produces PARP cleavage [107].

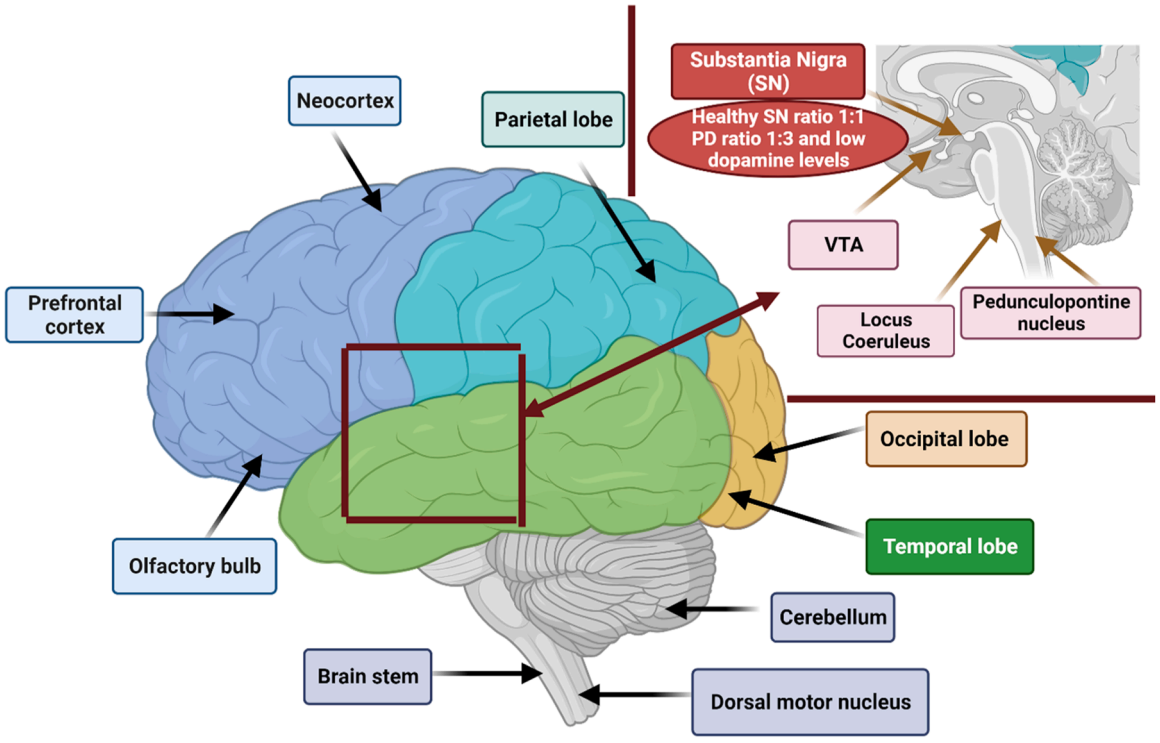

Fig. 1. Schematic diagram of the human brain. Several areas of the brain are adversely affected by Parkinson's disease. For example, the substantia nigra shows a significant loss of dopaminergic neurons as well as altered levels of reduced iron, most likely because of increased oxidative stress. As the disease progresses, other brain areas develop lesions, including the dorsal motor nucleus, neocortex, prefrontal cortex, locus coeruleus, amygdala, and others.

2.2. Mitochondrial dysfunction

The first evidence that mitochondria play a role in PD development came when a person ingested a medicine contaminated with the toxin MPTP. Mitochondria are essential for energy metabolism and oxidative phosphorylation. Complex I (NADH dehydrogenase-ubiquinone oxidoreductase), Complex II (succinate dehydrogenase-ubiquinone oxidoreductase), Complex III (ubiquinone-cytochrome c oxidoreductase), Complex IV (cytochrome c oxidase), and Complex V (ATP synthase) comprise the oxidative phosphorylation system [108]. Electrons are transferred from the matrix to the intermembranous space via a sequence of protein complexes in the inner mitochondrial membrane. Some protons are translocated from the matrix to the intermembranous space, generating a proton gradient [109]. Following the gradient, protons flow back to the matrix, generating energy for ATP synthase to phosphorylate ADP. The first evidence that mitochondria play a role in PD development came when a person ingested a medicine contaminated with the toxin MPTP. Research indicates that monoamine oxidase-B (MAO-B) oxidizes MPTP, resulting in 1-methyl-4-phenylpyridinium (MPP+), which reaches DA neurons in the SN via the DA reuptake system. MPP+ then inhibits the mitochondrial electron transport chain (ETC) Complex I enzyme and the NADH ubiquinone oxidoreductase, leading to electron leakage and the production of ROS. Similarly, rotenone (insecticide and a herbicide), pyridazine (antifungal), trichloroethylene (industrial degreasing solvent), and fenpyroximate (acaricide/insecticide) are complex I inhibitors that cause PD [110].

Furthermore, PD-related genes, including phosphatase and tensin homolog-induced kinase 1 (PINK1), PARK2 (Parkin), Parkinson's disease protein (DJ-1), and leucine-rich repeat kinase 1 (LRRKS), encode proteins that regulate mitochondrial and ROS homeostasis. In healthy mitochondria, PINK1 is promptly degraded. Nevertheless, in those with misfolded proteins, severe oxidative stress, or diminished membrane potential, PINK1 degradation is slowed, resulting in PINK1 buildup on the outer mitochondrial membrane. PINK1 recruits Parkin and activates the E3 ubiquitin ligase. Parkin attaches ubiquitin chains to mitochondrial membrane proteins, signaling autophagy. Mitophagy is a type of autophagy that results in the engulfment and degradation of mitochondria [110]. DJ-1 translocates to the outer membrane during oxidative stress and blocks MPP+ -induced cell death. Nevertheless, the mechanism is unknown.

2.3. PD genes and molecular pathogenesis

2.3.1. Autosomal-dominant PD genes

Alpha-Synuclein, a presynaptic neuronal protein, is a 140 amino acid-long peptide abundantly produced. Seven highly conserved 11 amino acids repeat sequences form an amphipathic helix, allowing it to bind to membranes. The amyloidogenic component (61−95) is responsible for protein aggregation. The C terminal (96−140) is polar, consisting of charged amino acid residues responsible for post-translational modification and mediating the interaction of α-Syn with other proteins, ligands, and metal ions. α-Syn resides in a state of balance between its soluble, naturally unstructured form and its membrane-bound, alpha-helical structure [111]. The unusual structure of α-Syn allows it to easily interact with anionic lipids, resulting in conformational alterations, aggregation, and toxicity. These aggregate-prone soluble forms of α-synuclein, in turn, can interfere with lysosomes. The typical proteinaceous cytoplasmic inclusions, LB, and LNs include filamentous phosphorylated and ubiquitinated α-Syn aggregates, causing misfolding and aggregation. Oligomers are formed as a non-fibrillar off-pathway and soluble transitory pre-fibrillar intermediate. Oligomers degrade to generate insoluble fibrillar aggregates with a unique cross beta-sheet shape. Several animal and cellular models show that α-Syn overexpression causes cytotoxicity. (1) Lag phase, known to be rate limiting, leads to the creation of an aggregation-competent nucleus; (2) elongation phase, where the nucleus converts into protofibrils and higher-order aggregating species; and (3) stationary phase, where the bulk of soluble protein converts. A dynamic equilibrium exists between fibrils and monomers, resulting in amyloid fibrils [111]. The pace of α-Syn synthesis and clearance maintains the protein level in the CNS, which occurs via direct proteolysis, chaperones, autophagy, and proteasome-mediated degradation. Failure in these pathways results in α-Syn buildup [105].

The failure of the lysosomal degradation system to eliminate

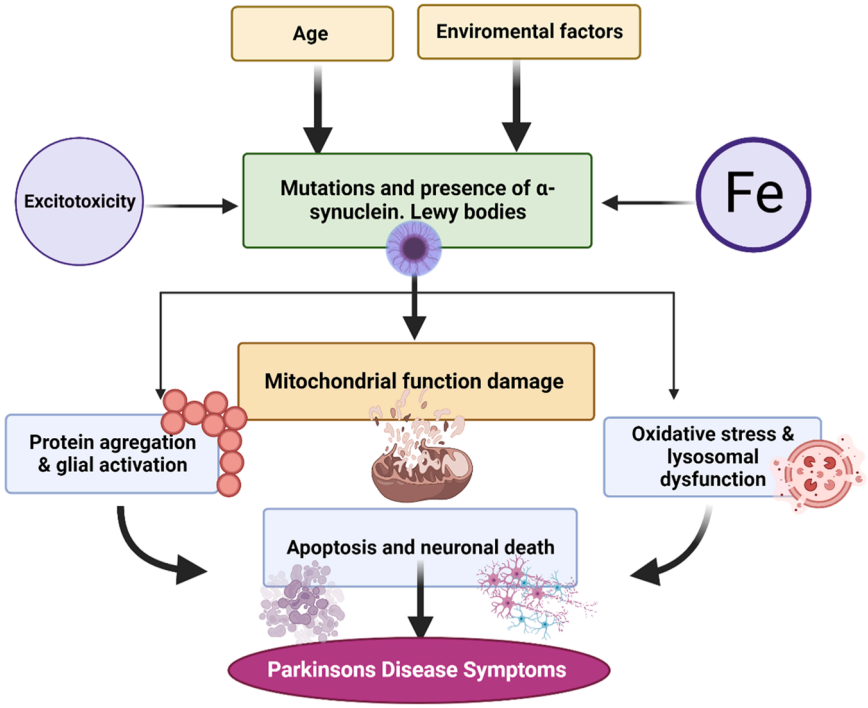

Fig. 2. Overview of the pathology of Parkinson's disease.

aberrant proteins promotes inclusion development in cells. Individuals with a heterozygous GBA1 mutation have a 7% probability of developing sporadic PD. GBA1 mutation decreases glucocerebrosidase, which can enhance the generation of insoluble α-Syn clumps [112]. Post-translational alterations to α-Syn include phosphorylation, nitration, and DA modification. In healthy brains, only around 4% of the total α-Syn is phosphorylated at Serine-129, whereas in PD brains harboring LB, about 90% of phosphorylation at Serine-129 is found [14]. This type of phosphorylation at serine-129 promotes the aggregation of oligomeric α-Syn. Protein kinases, such as casein and polo-like kinase 2 regulate α-Syn phosphorylation and phosphoprotein phosphatase dephosphorylation, such as phosphoprotein phosphatase 2 A, respectively [112].

Autosomal PD is caused by altered α-Syn Non-A4 component of amyloid precursor (SNCA) genes caused by point mutations (p.A53T, p. A30P, and p.e46K) or entire locus multiplication. Furthermore, missense SNCA mutation produces LB illness, and SNCA duplication or triplication exacerbates the formation of misfolded α-Syn [113]. Neuronal death occurs by the overexpression of α-Syn from the mutant form in primary dopaminergic neurons. Additionally, PD toxins increase α-Syn mutant overexpression sensitivity to apoptosis-mediated cell death. Twenty-two distinct genes with causing mutations are linked to PD or risk factors. A53T, E46K, and H50Q mutations accelerate α-Syn fibrillation, whereas A30p, A53E, and G51D mutations slow it down. A53V enhances initial oligomerization and increases α-Syn aggregation [112]. α-Syn is a chaperone that regulates SNARE's degradation, distribution, and maintenance, directly implicated in dopamine release [114]. α-Syn oligomers and amyloids are neurotoxic. Exogenously supplied α-Syn might internalize and seed endogenous monomeric α-Syn into LB, spreading PD from one cell to the next [14].

LRRK2 comprises a leucine-rich repeat, a Roc GTPase domain, a COR (C-terminal of Ras), a kinase domain, and a WD40-repeat. LRRK2 is found in the cytoplasm and relates to membrane structures such as mitochondria, the endoplasmic reticulum, and α -synaptic vesicles. LRRK2 familial mutations have a kinase-dependent gain of function and neuronal toxicity regulated by the chaperones CHIP and HSP90. Through the ubiquitin-proteasome system, these chaperones regulate LRRK2 levels [115]. Moesin is thought to be an LRRK2 substrate. According to functional investigations, LRRK2 is involved in neurite outgrowth and α -synaptic vesicle endocytosis. 4E-BP is a possible LRRK2 substrate, implying that LRRK2 plays a role in translation. According to the data, LRRK2 could influence mitochondrial function. LRRK2 mutations that cause disease [116].

2.3.2. Autosomal-recessive PD genes

The function of PINK1 is unknown. Nevertheless, it is thought to be a mitochondrial kinase that operates upstream of Parkin in the PD pathogenesis cascade. Mutations in PINK1 that cause disease can lead to a loss of function. The mitochondrial chaperone TRAP1 and the serine protease HtrA2 are suspected PINK1 substrates that regulate mitochondrial activity and mitochondrial-dependent cell death pathways. PINK1 may also control Ca^{2+} outflow from the mitochondria via NCK [117].

The DJ-1 is a multifunctional molecular chaperone. DJ-1 mutations that cause disease may result in a loss of function. DJ-1 affects RNA metabolism and gene transcription and regulates ROS levels by acting as an atypical peroxiredoxin-like peroxidase. DJ-1 may also bind to Daxx/apoptosis signal-regulating kinase1 (ASK1), inhibiting ASK1 activity and cell death. DJ-1 is also a component of the Parkin/PINK1/DJ-1 (PPD) complex, which promotes unfolded protein degradation [117].

Parkin's capacity to serve as an E3 ubiquitin ligase is reduced by mutations in the parkin gene and post-translational changes to the protein, such as phosphorylation or S-nitrosylation by ROS/RNS [117]. This causes an accumulation of its substrates, such as AIMP2, FBP-1, and others, all involved in mitochondrial dysfunction and neurotoxicity. Parkin promotes substrate breakdown by using poly-K48 ubiquitin bonds. Parkin also regulates intracellular signaling, receptor trafficking, and inclusion formation via poly-K63 ubiquitin bonds or mono-ubiquitination. Parkin plays a role in the clearance of mitochondria via autophagy (mitophagy) in genetic models [116].

2.4. Neuroinflammation

Neuronal cell death occurs via two mechanisms: cell-autonomous, in which neuronal degeneration occurs through pathological interaction with glial cells (microglia, astrocytes) or infiltration of peripheral immune cells (macrophages, lymphocytes) [118]. In the presence of pathogens or tissue damage, microglia, innate immune cells in the brain, induce complex immune responses via increased expression of toll-like receptors, pro-inflammatory mediators, and activation of peripheral immune cells, as well as initiating oxidative stress to restore tissue homeostasis [119]. Activated microglia undergo morphological alterations and phenotypic changes in gene expression and signaling molecule activation. These activated microglia play a dual role in neuroinflammation in that they can both mediate the inflammatory response by producing mediators that function to clear the source of the inflammatory stimuli and regulate the inflammatory response by perpetuating the pro-inflammatory response through the continued release of inflammatory mediators of inflammatory chemicals, which operate to stimulate and regulate microglia and astrocyte responses. When inflammatory stimuli are removed, microglia can stimulate neurogenesis by producing neurotrophins and anti-inflammatory cytokines, potentially leading to neurodegeneration and wound healing within the SN and striatum [120].

Microglia are the primary major histocompatibility complex (MHC) class II-expressing antigen-presenting cells in brain parenchyma with neuronal injury [121]. T- cell infiltration is also elevated in PD patients' postmortem brain tissue [122]. According to one study, CD4 + T lymphocytes from PD patients react exclusively with α-Syn-generated MHC class II epitopes [123]. Microglial stimulation increases additional α-Syn disease by increasing NO generation, which can trigger nitration of α-Syn in adjacent neurons and result in cell death [124]. On the other hand, α-Syn disease and monocyte dysregulation can cause exaggerated inflammatory responses to α-Syn [125]. NM also causes microgliosis, chemotaxis, and activation of microglia. NM stimulates NF-κB by phosphorylating and degrading inhibitor protein B, increasing TNF-alpha and NO [126].

Although the precise mechanisms of the pathogenesis of PD are still being studied, various environmental factors work in tandem with hereditary risk factors. The functions of proteins are outlined in this SnapShot. Some of the most common and unique pathways of PD pathogenesis are encoded by PD-associated genes (Fig. 3).

2.5. Risk factors

2.5.1. Genetic risk factors

Both autosomal dominant and recessive transmission are types of Mendelian genetic transmission. The *SNCA* gene, which has six-point mutations (53 T, E46P, A30P, H50Q, G51D, and A53E), is associated with a higher tendency for α-Syn to form oligomers or fibrils in autosomal transmission. Similarly, *LRRKS* links autophagy, mitochondrial function, and vesicle trafficking. A change in the *VPS35* gene is linked to cathepsin D trafficking and retrograde vesicle transfer to the breakdown of α-Syn. Furthermore, there is a connection between the mitochondrial respiratory intricate [127]. Parkin interacts with *PINK1* and F-box only protein 7 (*FBXO7*) to decay dysfunctional mitochondria in recessive transmission. *PINK1* also collaborates with Parkin to recruit mitochondria. These genes are engaged in mitophagy pathways, and activation of wild-type PINK1 inhibits stress-induced apoptosis. DJ1 is a chaperone protein that promotes PINK1-Parkin translocation to mitochondria and avoids α-Syn aggregation. Mutation alters the structure of mitochondria and raises ROS levels. ATPase Cation Transporting 13A2 (ATP13A2) is

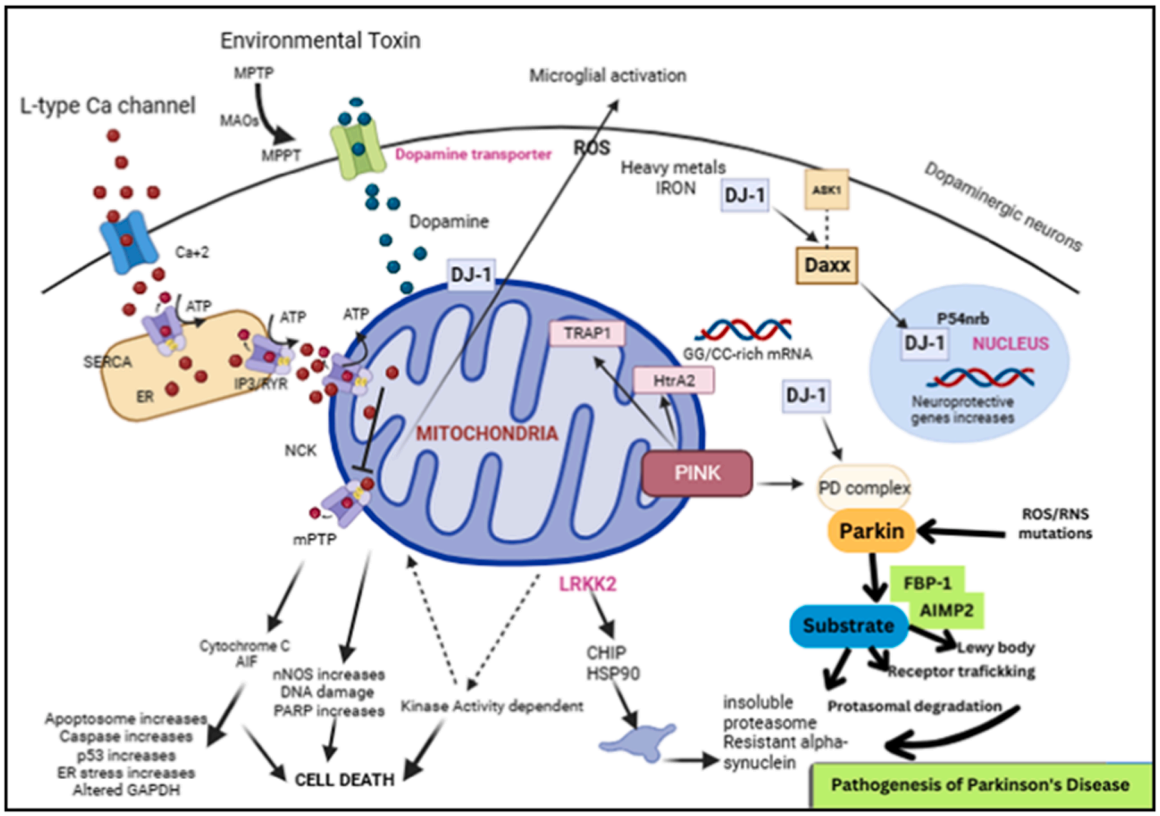

Fig. 3. Pathogenesis of Parkinson's disease. AD: autosomal-dominant; AIMP2: aminoacyl tRNA synthetase complex interacting multifunctional protein 2; ATP: adenosine triphosphate; CC: cell cycle genes; Chip: clonal hematopoiesis of indeterminate potential; Daxx: death domain-associated protein; Dj-1: Parkinson disease protein 7; ER: endoplasmic reticulum; FBP-1: fructose-bisphosphates 1; GG: GG-genotype; HSP90: heat shock protein 90; HtrA2: high-temperature-required protein A2; IP3: inositol triphosphate; LRKK2: leucine-rich repeat kinase 2; MPPT: methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PAAR: peroxisome proliferator-activated receptors; RYR: ryanodine receptor; SERC: sarcoendoplasmic reticulum calcium; TRAP: triiodothyronine receptor auxiliary protein.

responsible for juvenile-onset syndrome characterized by parkinsonism, dystonia, and supranuclear palsy. PLA2G6 has been linked to neurodegeneration and iron buildup in the brain. FBXO7 straight Parkin and PINK1 interact with it for mitophagy, and when mutant, it is mislocalized to the cytosol. *NAJC6*, which codes for auxilian, is involved in clathrinid uncoating and synaptic vesicle production [126].

2.5.2. Environmental risk factors

Neurotoxins in the brain induce oxidative stress and neurotransmission disruption, harming the basal ganglia. Several chemical elements, including iron and copper, cause oxidative stress. Copper acts through the Fenton-Haber-Weiss reaction and the 6-OHDA redox system [127]. Cycle forces a decline in dopamine, α-Syn aggregation, and a reduction in superoxide dismutase 1 [128]. Manganese (Mn) exposure can affect oxidative parameters such as glutathione levels, lipid peroxidation, and protein oxidation [129]. Lead (Pb) enters the brain by mimicking calcium through calcium channels, producing swelling and cell death in the CNS and peripheral nervous system. Also, Pb decreases voluntary muscle movements [130]. Additionally, Pb may aggravate PD-related neuronal dysfunction and reduce cognition [130]. Mercury (Hg) can diminish the number of neurons in the brain, leading to tremors and voluntary muscle loss [130].

Pesticides could also be used to target the SN. Dieldrin, an organochlorine insecticide, induces dopaminergic system neurotoxicity [131]. The organophosphate rotenone increases α-Syn aggregation while inhibiting mitochondrial complex I [132]. Various illegal substances can lead to a rise in ROS, which can lead to neurotoxicity. Methamphetamine degrades the integrity of DA neuron terminals in the basal ganglia and causes them to rupture. Reduces the expression of DA and dopamine transporters. Amphetamine in high dosages can harm the body. The human brain has dopaminergic neurons and axon terminals. Cocaine interacts with DA transporters. Short-term DA inhibition is caused by cocaine addiction, and iron dysregulation is caused by cocaine addiction [133]. Melanin-containing neurons of SN degenerate and die, and Lewy pathology is one of the main pathological features of PD. The development of intracytoplasmic Lewy bodies (LB) with inclusions primarily containing α-Syn, ubiquitin, and Lewy neurites (LN) is known as Lewy pathology, represents comparable inclusions' neural projections [116]. The loss of dopaminergic neurons in the substantia nigra pars compacta is the hallmark of PD, the most prevalent movement disorder. Several PD-associated genes, including those encoding α-Syn, Parkin, PINK1, DJ-1, LRRK2, and ATP13A2, have been identified by sophisticated genetic research (Table 1).

3. miRNAs biogenic pathways and function

3.1. Canonical and non-canonical miRNA biogenesis pathways

Non-coding RNAs (ncRNAs), like miRNAs, play an important function in gene regulation across all eukaryotic species. Recent years have seen a spike in research into these little but mighty regulators, revealing their remarkable versatility, complex regulatory networks, and far-reaching impact on various biological processes [143–147]. The transcription of miRNA genes by RNA polymerase II results in the first stage of the canonical pathway, primary miRNA (pri-miRNA). The microprocessor complex converts the pri-miRNA into the precursor (pre--miRNA). Exportin 5 brings miRNA into the cytoplasm, where Dicer might metabolize it (Fig. 4) [148–151]. Some miRNAs go through non-canonical processing that doesn't require Dicer. As well as others, like tRNase Z and Mirtrons, have contributed to the most common

Table 1
The role of causative genes in PD pathogenesis and their implications in astrocytes.

Gene	Protein Model used	Main findings	Ref.
Park 7/ DJ-1	DJ-1 KO mice	• Alteration in cholesterol levels • Alterations in membrane fluidity and lipid raft-dependent endocytosis • Altered glutamate uptake capacity.	[134]
Park 7/ DJ-1	DJ-1 KO mice	• Regulates anti-inflammatory role of astrocytes through Prostaglandin D2 synthase expression	[134]
PARK2/ Parkin	Parkin KO mice	• KO astrocytes exhibit exaggerated ER stress, JNK activation cytokine release, and reduced neurotrophic factors.	[135]
PINK1/ PINK1	PINK1 KO mice	• Reduced astrocyte differentiation, increased p38 activation	[136]
SNCA/ α-syn	Human SNCA, over-expressing primary fetal astrocytes α-syn changed expression of GF production and secretion, e.g., EGF, PDGF,	• VEGF and their receptors • α-syn changed expression of IGF-related proteins	[137]
SNCA/ α-syn	A53T WT α-syn in mouse astrocytes	• Disrupted glutamate uptake • Increased neuronal cell death by overexpressing astrocytes.	[138]
LRRK2/ LRRK2	G2019S- LRRK2-Tg het mice, astrocytes + α-syn	• Increased ER stress proteins • Increased cell death with α-syn • Mitochondrial dysfunction with α-syn	[139]
GBA1/ GCase	Mice GBA1 D409V knockin Astrocytes	• Defects in lysosomes • Defects in TLR4-dependent cytokine release	[138]
LRRK2/ LRRK2	Human iPSC LRRK2-G2019S-astrocytes and neurons	• Impaired autophagy in astrocytes • PD astrocytes accumulate and transfer α-syn to healthy dopamine neurons.	[140]
LRRK2/ LRRK2	Human Ipsc LRRK2-G2019S—MB astrocytes	• Downregulation of MMP2 and TGFβ	[141]
GBA1/ GCase	Human iPSC-derived astrocytes from GD1 with genotype N370S/N370S or N370S/c.84insG	• Abnormal α-syn accumulation due to Impaired lysosomal cathepsin activity • Increased inflammatory response.	[142]

LRRK2: leucine-rich repeat kinase 2; GC: GC: β-Glucocerebrosidase; α-syn: alpha-synuclein; Ipsc: pluripotent stem cells; MMP2: matrix metalloproteinase 2; PINK1: PTEN-induced putative kinase-1; iNOS: inducible nitric oxide synthase; MB: midbrain; GF: growth factor; EGF: epidermal growth factor; PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor; IGF: Insulin-like growth factor; GD: Gaucher disease.

non-canonical biogenic pathways [152–154].

3.2. Function of miRNA

The miRNAs play an essential role in the development and adult brain activities of neurons and are expressed extensively and in a tissue-specific manner throughout CNS. Due to their role in modulating neuronal signaling, neuronal excitability, dendritogenesis, local translation in dendritic spines, and neurotransmitter release can all be influenced by miRNAs. As a result, adult neurons' survival, function, and connection can be altered by a disruption in the miRNA biogenesis pathway [155,156]. Cell differentiation, angiogenesis, and inflammation are just a few of the many essential biological processes that have been identified to benefit from miRNAs. Complex disorders have been linked to inadequate control of ncRNAs. If the processing of these tiny yet powerful regulators is messed up, it might disrupt cellular function. [157–159]. Studies of complex diseases like cancer, cardiovascular disease, and diabetes mellitus are bolstered by growing data on miRNA-PD interactions.

In the early pathophysiology and development of PD, numerous miRNAs targeting vulnerable PD-related genes and pathways were found to play a significant role [160–163]. In particular, the activities of the parkinsonism-related genes parkinsonism-associated deglycase (DJ1), parkin RBR E3 ubiquitin-protein ligase (PRKN), and α-Syn are modulated by miRNAs that are dysregulated in several PD cellular and animal models. In particular, α-Syn significantly impacts the underlying genetics of PD. Epigenetics studies how gene regulation affects non-genetic characteristics. Epigenetic alterations include DNA methylation, histone modification, and miRNA-mediated silencing. The miRNAs are crucial gene expression regulators in the complex gene regulatory system [164,165].

4. miRNA Dysregulation in PD

4.1. miRNAs related to the regulation of PD-associated genes

CNS is recognized as the richest source of miRNAs in the body. These miRNAs are involved in modulating several essential physiological processes in maintaining cellular homeostasis. Any alterations in these miRNAs could predispose to several pathological conditions, such as neurodegenerative disorders that are characterized by their multi-genetic origin [166].

Various miRNAs are significantly linked with neuronal proliferation, synaptic plasticity, memory formation, and neurodegenerative diseases by influencing the expression of specific genes. Importantly, particular genes have been extensively linked with PD pathogenesis. These PD-associated genes include SNCA, LRRK2, PRKN, PINK1, and DJ-1 (PARK7). Furthermore, a growing body of evidence suggests that the development and progression of PD are closely linked to the deregulation of these genes and their corresponding proteins, which are regulated by diverse miRNAs that ultimately promote inflammation, oxidative stress, and apoptosis [167–172].

4.1.1. PINK1-targeting miRNAs

The link between mitochondrial mechanics and PD and the biological roles of the mitochondrial kinase PINK1 are intricate processes. PINK1 protein is a potential serine/threonine kinase in the mitochondria that shields cells from oxidative stress-induced cell death [173]. Aberrations of PINK1 lead to electron transport chain alterations accompanied by reduced ATP production. PINK1 gene deregulations in cases of familial PD have aroused interest in the biology of mitochondria in PD [174].

Despite the clear involvement of PINK1 in the mechanisms of the disease, it remains debated. After reaching the mitochondria, the PINK1 protein is split into two parts. There is currently doubt whether these cleavage products are exported or released from mitochondria. Realizing its vital functions in neurological protection and mitochondrial stability, the PINK1 regulation mechanism has been the focus of much research. Despite much work on the post-translational stabilization of PINK1 following mitochondrial injury, little is known about the transcriptional or translational regulatory mechanisms of PINK1 [173,174].

The upregulated miR-1976, located on chromosome 1p36.11, was associated with a high risk of PD by targeting the PINK1 gene. Introduction of the miR-1976 molecule into the substantia nigra neurons of mice induced neuronal apoptosis both in vitro and in vivo. This suggests that miR-1976 can trigger neuronal apoptosis, leading to the underlying mechanism of PD. Upregulated levels of miR-1976 foster apoptosis and mitochondrial insults in the dopaminergic neurons by targeting the PINK1 gene. Knockdown of PINK1 promoted mitochondrial malfunction

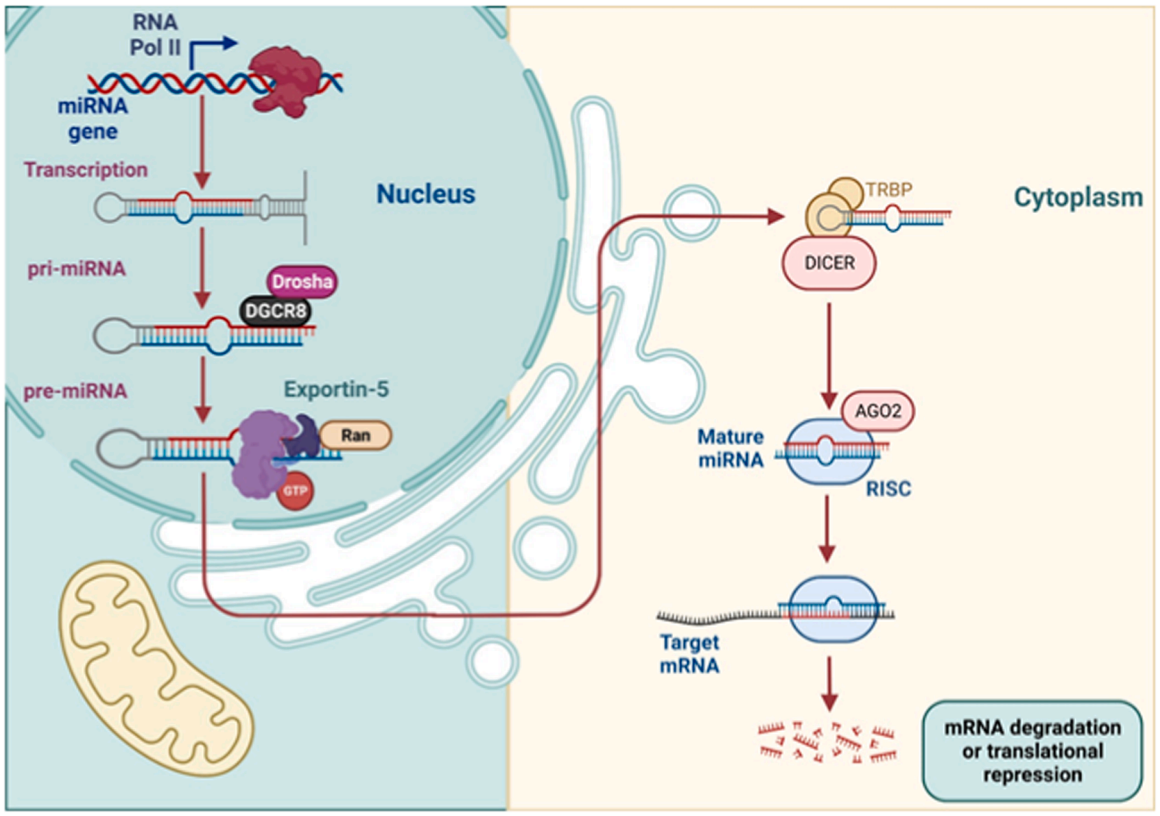

Fig. 4. Canonical pathway of miRNA biogenesis. Ago: argonaute1; DGCR8: DiGeorge Critical Region 8; Dicer: an endoribonuclease enzyme that in humans is encoded by the DICER1 gene; Drosha: double-stranded RNA-specific endoribonuclease; Ran: RAS-related nuclear protein; RISC: RNA-induced silencing complex; RNA Pol II: RNA polymerase II; TRBP: transactivation response element RNA-binding protein.

and death in the dopaminergic neurons; such aberrations were observed in the PD mice model [175].

In addition, Kim *et al.* reported that the level of PINK1 protein and the autophagic clearance of defective mitochondria are influenced by miR-27a and miR-27b. Under normal conditions, reducing miR-27a and miR-27b markedly raised the levels of PINK1 protein. Accordingly, endogenous miR-27a/b plays a vital role in preserving PINK1 protein levels optimum for mitophagic activation, which may protect cells from the unwanted loss of mitochondria [176].

Interestingly, earlier research has suggested the potential relationship between neurodegenerative disorders and miR-326, miR-330, and miR-3099 [177–179]. Moreover, another study rationalized the link between PD and PINK1 via influencing the expression of miR-326, miR-330, and miR-3099. High levels of miR-326 modulate dopamine D2 receptor expression [178]. The miR-330 stimulates cell growth and hampers apoptosis through modulating phosphoinositide 3-kinase (PI3K)/AKT cascades [179]. The miR-3099 influences embryogenesis and neuronal development [180]. In PD, Choi *et al.* demonstrated that PINK1 protein loss may lead to the downregulation of these three miRNAs, which subsequently causes a significant decline in glial fibrillary acidic protein (GFAP) and aberrant formation of astrocytes [181].

4.1.2. PRKN-targeting miRNAs

In addition to PINK1, the PRKN gene and its protein product parkin are other key modulators in mitophagy. In conditions of mitophagy activation, parkin protein is translocated to the mitochondria and enhanced autophagy to eliminate the mitochondrial debris. Patients with PRKN gene mutations showed various architectural and functional alterations in mitochondria, such as reduced mitochondrial membrane potential and abnormality in the autophagic process. Thus, upregulated PRKN expression is essential in preventing and treating PD [182–184].

A battery of miRNAs participates in the modulation of PRKN. Xhou *et al.* addressed that the miR- 103a-3p influences mitophagy via modulating parkin/Ambra1 (Activating molecule in Beclin 1-regulated autophagy) cascade [185], whereas miR-103a-3p can modulate PRKN gene, by binding to the 3-UTR of the PRKN mRNA. In the case of mitophagy promotion, parkin works with Ambra1, leading to autophagic activation to eliminate the defective mitochondria. Thus, Ambra1 is essential in the parkin-mediated mitophagy axis [186,187]. The miR- 103a-3p is extensively expressed in the human brain and is essential in neurodegenerative disorders such as Alzheimer's disease (AD) [188].

Another study on PD revealed that the stimulated NF-κβ attached to the miR-146a promoter region leads to the enhancement of its expression, which finally depresses parkin release. Thus, low levels of miR-146a elevate parkin levels in the rotenone-treated SH-SY5Y cells. PRKN loss causes a deposition of damaged and malfunctioning mitochondria, which induces ROS release leading to further deterioration of neurons [189]. It is noteworthy that the miR-146a was previously reported in modulating motor dysfunction and axonal demyelination [190].

In the same context, miR-181a was reported in preceding studies as an apoptosis modulator [191]. Cheng *et al.* reported that the miR-181a suppresses mitophagy induced by mitochondrial uncoupling agents. On the other hand, silencing of miR-181a fosters the autophagic degradation of the deteriorated mitochondria via modulating the parkin level. These data show a significant connection between microRNA and PRKN-mediated mitophagy [192]. Moreover, another study addressed that the dysregulations of miR-181a influence the signaling pathways crucial for neuronal development. Suppression of neuronal *miR-181a* leads to Smad signaling activating and enhancing neuronal development [193].

Similarly, upregulated levels of miR-218 suppress PRKN expression, as well as deregulate the E3 ubiquitin ligase action. Indeed, parkin phosphorylation is needed to recruit and stimulate the E3 ubiquitin

ligase action in malfunctioned mitochondria. Consequently, parkin conjugates ubiquitin chains on outer mitochondrial membrane proteins, leading to the phosphorylation of ubiquitins. Collectively, mitochondrial clearance is reduced by miR-218 via affecting PRKN E3 ubiquitin ligase [194].

Nevertheless, it was detected that the level of miR-218 was downregulated in other clinical and experimental studies [195,196]. In the same scenario, another modulatory mechanism of PINK1 and PRKN by miR-421, where the suppression of the miR-421 stimulates the release of PINK1 and parkin, boosts the mitochondrial role [197]. Likewise, the suppression of miR24–3p mitigates the damage of neurons in PD via stimulating PINK1-PRKN-controlled mitophagy [198]. BCL2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3) is implicated in autophagy and exerts a protective effect on PD. Additionally, BNIP3 suppresses PINK1 proteolytic effect, thus enhancing the effect of PINK1/PRKN controlling cellular mitophagy [199]. Interestingly, the knockdown of the miR-96 stimulates BNIP3-induced mitophagy via modulating the PINK1/PRKN trajectory in PD [200].

4.1.3. SNCA-targeting miRNAs

Agglomeration of PD-associated misfolded proteins is a hallmark of PD. Several factors disrupt the regular function of α-Syn [184]. α-Syn is one of the proteins secreted at the presynaptic terminals in the CNS. Indeed, α-Syn malfunctioned proteins, also known as Lewy bodies, are considered major contributors to dopaminergic neuron apoptosis. α-Syn encouraged oxidative insults within the dopaminergic neurons, leading to PD progression[201]. The progression of neuronal cell toxicity by α-Syn may occur through many mechanisms, including aggregation or interaction with other chemicals and proteins. Studies have revealed that several miRNAs target α-Syn and inhibit its release by binding to the 3'UTR of the SNCA gene and prohibiting its translation [202].

McMillan *et al.* revealed that the modulation of α-Syn and dopamine biological function are significantly influenced by miR-7. Downregulated levels of miR-7 were detected in the Substantia Nigra Pars Compacta of PD patients, whereas elevated expression of miR-7 results in a substantial decrease in α-Syn expression [203]. The miR-203–3p, which possesses tumor suppressor activity, was downregulated in the PD cell model. The miR-203–3p had binding sites for SNCA through which it negatively regulates the levels of α–Syn, p53, and cleaved caspase-3 proteins [204]. Another study revealed that the miR-214 downregulated in the midbrain of PD mice and MPP+ treated SH-SY5Y cells concurrently with elevated gene and protein expression of α-Syn. On the other side, exogenous induction of miR-214 levels in experimental models resulted in a marked reduction of α-Syn expression [205].

In an attempt to recognize the possible connection between PD, altered miRNA expression, and manganese exposure, Tarale *et al.* revealed that manganese exposure elevates α–Syn by diminishing miR-7 and miR-433 levels, leading to neurotoxicity symptoms clinically identical to idiopathic PD [206]. In the MPP(+)-induced PD model, the miR-30b was significantly decreased, leading to the elevation of α -Syn levels.

The miR-30b is attached to the 3′-UTR region of α-Syn and downregulates its expression. In other words, the α-Syn level was significantly reduced by miR-30b, which subsequently attenuated the levels of Bax and elevated Bcl-2, thus inhibiting apoptosis [207]. In line with this notion, miRNA-7 and miR-153 can inhibit MPP+ -mediated neuronal death by significantly regulating α-Syn translation. Increasing the mitochondrial ROS may underscore the regulation of α-Syn by miR-7 and miR-153 [208]. Clinically, Wu *et al.* revealed high plasma levels of miR-153 and miR-223 in PD patients [209]. A preceding study revealed that let-7 miRNA was highly expressed in PD and elevated α-Syn, promoting autophagy and oxidative stress [210].

4.1.4. LRRK2-targeting miRNAs

Much research has documented that the gain-of-function mutations in LRRK2 lead to degeneration of dopaminergic neurons, essential characteristics in familial and sporadic PD. The interplay between LRRK2 and diverse miRNAs influences the level of different proteins [211]. Cho *et al.* revealed that reducing the miR-205 stimulates the excessive production of LRRK2 within the brain of sporadic PD, while upregulated miR-205 may reduce the elevated levels of LRRK2 in PD [212]. Moreover, the highly expressed *LRRK2 gene* enhanced α-Syn--mediated neuronal damage, while the reduced expression of LRRK2 suppressed α-Syn-induced neurodegeneration [213]. Relatedly, the miR-599 was significantly downregulated in different PD models, which sequentially elevates the LRRK2 protein [214].

4.1.5. DJ-1-targeting miRNAs

The multifunctional DJ-1 protein, also known as PARK7 involved in the various levels of cell growth and development, including transcriptional regulation, cell transformation, antioxidant stress reaction, molecular chaperoning, and mitochondrial regulation. Particularly, oxidative stress is proposed as one of the triggers of PD. DJ-1 is known as an oxidative sensor that shields cells from oxidative stress. DJ-1believed to be an oxidative sensor and molecular chaperone that contributes to familial and sporadic PD [215,216]. Additionally, DJ-1 inhibits microtubule-associated protein 1B (MAP1B) aggregation that predisposes to endoplasmic reticulum stress, triggering neuronal apoptosis [217].

It was postulated that diverse miRNAs could modulate the regulation of the DJ-1 expression. Xiong *et al.* and his colleagues documented that the miR-494 modulates DJ-1 gene expression through binding to its 3′UTR. Thus, upregulated miR-494 markedly reduces the level of DJ-1 leaving the cells exposed to oxidative stress [218]. Another study by Chen *et al.* revealed that the highly expressed miR-4639–5p results in reduced levels of DJ-1 protein, which finally triggers oxidative stress and neuronal apoptosis in MPP+ - and rotenone-treated SH-SY5Y cells [219].

In the same context, miR-874 and miR-145–3p were highly expressed in the saliva of PD patients that regulate DJ-1 gene expression [220]. Deletion of DJ-1 in human neuroblastoma cells leads to low expression of miR-221, one of the important miRNAs in the CNS. miR-221 participates in neuron growth and differentiation. Oh, and his colleagues suggest that DJ-1 stimulates the release of miR-221, inhibiting pro-apoptotic genes such as bcl-2-like protein 11, oxidative stress, and neurite retraction [221].

Both miR-34b and miR-34c were downregulated in the amygdala, substantia nigra, frontal cortex, and cerebellum of PD patients. Inhibition of miR-34b and miR-34c resulted in mitochondrial disruption and stimulated ROS production. Loss of miR-34b and miR-34c caused a significant reduction in PRKN and DJ-1, whereas elevation of α-Syn [222–224]. Also, the miR-155 was investigated in diverse diseases [225]. Thome *et al.* addressed that the loss of miR-155 attenuates α-Syn release, which sequentially mitigates microgliosis [226]. Concurrently, low levels of DJ-1 elevated the expression of miR-155 in microglia and astrocytes, which reduces the suppressor of cytokine signaling 1 (SOCS1) expression [227]. Collection of miRNAs involved in PD-associated gene regulation are gathered in (Table 2).

4.2. The role of miRNAs in the regulation of dopaminergic neurons

It has been shown that dopaminergic neurons depend critically on a functional miRNA network in cultured and in vivo settings. When mature miRNAs were removed from a mouse ES cell line by deleting Dicer, a type III ribonuclease necessary for the initial stages of miRNA synthesis, the dopaminergic neuronal phenotype under the right differentiation signals was almost entirely lost, in contrast to ES cells of the wild-type. According to Kim *et al.*, this was caused by decreased neurogenesis and increased apoptosis. Dopamine neuron loss and climbing deficits were observed in Drosophila when Dicer1 was knocked down by RNA interference in a dicer1 heterozygous background [228]. miRNAs may have a role in the formation of DA neurons since it has been

Table 2
miRNAs related to the regulation of PD-associated genes.

miRNAs	Up/downregulation in PD	PD-associated genes	The regulated proteins	Effects in PD	Ref.
miR-1976	Up	Down-regulation of PINK1 gene	Reduction of PINK1	Induction of neuronal apoptosis and mitochondrial insults in the dopaminergic neurons	[175]
miR-27a miR-27b	Up			Modulation of mitophagy activation	[176]
miR-326 miR-330 miR-3099	Down			Decline in GFAP and aberrant formation of astrocytes.	[181]
miR-103a-3p	Up	Down-regulation of PRKN gene	Reduction of parkin protein	Inhibition of mitophagy	[185]
miR-146a	UP			Stimulation by NF-κβ, deposition of damaged and malfunctioning mitochondria, which induces the release of ROS	[189].
miR-181a	Up			Suppression of mitophagy produced by mitochondrial uncoupling agents. Inhibition of Smad signaling and enhanced neuronal development	[192,193]
miR-218	Up			Deregulating the E3 ubiquitin ligase action Suppression of mitochondrial clearance	[194]
miR-421	Up	Down-regulation of PINK1 and PRKN gene	Reduction of PINK1 & parkin proteins	Inhibition of mitophagy	[197]
miR24–3p	Up				[198]
miR-96	Up			Modulation of BNIP3-induced mitophagy controlling the PINK1/Parkin trajectory	[200]
miR-7	Down	Upregulation of the SNCA gene	Aggregation of α -Syn	Alteration in synaptic transmission and apoptosis. Dopaminergic neuron death, and a reduction in striatal dopamine.	[203]
miR-203a-3p	Down			Elevation of p53 and cleavage of caspase-3 proteins. Promotion of apoptosis	[204]
miR-214	Down			Enhancement of apoptosis	[205]
miR-7 miR-433	Down			Regulation of synaptic transmission and apoptosis.	[206]
miR-30b	Down			Elevation of Bax and reduction of Bcl-2, thus enhancing apoptosis	[207]
miR-7 miR-153	Down			Regulation of mitochondrial ROS	[208]
Let-7	Up			Promotion of autophagy and oxidative stress	[210]
miR-205	Down	Upregulation of the LRRK2 gene	Elevated LRRK2	Enhancement of α-Syn-mediated neuronal damage	[212]
miR-599	Down			-	[214]
miR-494	Up	Downregulation of DJ-1	Loss of DJ-1 (PARK7)	Trigger of oxidative stress and neuronal apoptosis	[218]
miR-4639–5p	Up				[219]
miR-874 miR-145–3p	Up				[220]
miR-221	Down				[221]
miR-34b miR-34c	Down	Down-regulation of PINK1and PRKN gene and upregulation of α-Syn	Loss of PRKN and DJ-1 Enhance α-Syn	Mitochondrial disruption and stimulated ROS production	[222–224]
miR-155	Up	Down-regulation of DJ-1 gene and upregulation of α-Syn	Elevates α-Syn and loss of DJ-1	Reduction of suppressor of cytokine signaling 1 (SOCS1) expression. Trigger oxidative stress and neuronal apoptosis	[226,227]

α-Syn: α- Synuclein, Ambra1: Activating molecule in Beclin 1-regulated autophagy, BNIP3: BCL2/adenovirus E1B 19 kDa interacting protein 3, GFAB: glial fibrillary acidic protein, MAP1B: microtubule-associated protein 1B, LRRK2: leucine-rich repeat kinase 2, PI3K: Phosphoinositide 3-kinase, PINK1: Phosphatase, and tensin homolog-induced kinase 1, SNCA: Synuclein Alpha Non-A4 component of amyloid precursor.

demonstrated that deleting particular miRNAs causes a progressive loss of mesencephalic DA neurons. According to several studies, miRNAs are further involved in DA neuron development and PD [229].

MiRNAs play a critical role in several biological processes, including neurogenesis, neuronal maturation, synaptic formation, axon guidance, neurite outgrowth, and neuronal plasticity. They are widely expressed within the nervous system and exhibit tissue-specific expression patterns. The pathogenic pathways of neurodegenerative disorders, such as PD, are influenced by modifications in miRNAs. The critical function of miRNAs in neurodegenerative illnesses has been shown using Dicer knock-out mice.

The cytoplasmic ribonuclease III, or dicer, is necessary to produce mature miRNA. Several studies have suggested a crucial role for miRNAs in the development, survival, and function of mDA neurons, showing that cell type-specific deletion of miRNAs produced in mDA neurons causes these cells to disappear gradually. Recent years have seen a significant amount of research on the connection between miRNAs and mDA neuron differentiation, as well as between miRNA dysregulation and mDA system malfunction, including PD. Therefore, identifying miRNAs expressed in mDA neurons may provide new and potentially useful pharmacological techniques and intriguing information for the early diagnosis and prognosis of Parkinson's disease [230].

MiRNA overexpression has surfaced as a prospective supplementary tactic to enhance DA survival to impede the gradual loss of neurons in PD and associated illnesses. Furthermore, this method offers an appealing substitute for boosting dopaminergic differentiation in vitro by reprogramming human fibroblasts or beginning with undifferentiated ES cells. Two miRNAs, miR-34b/c and miR-218, have shown great promise in this regard because they can raise the total number of functioning DA neurons when expressed in conjunction with particular DA-related transcription factors. Together with the transcription factors Ascl1 and Nurr1, overexpression of miR-34b/c decreases Wnt1 expression and facilitates the maturation of DA neurons into functional neurons that exhibit the characteristic electrophysiological characteristics

of DA neurons, such as an action potential firing pattern punctuated by bursts [231].

Through post-transcriptional regulation, Death-associated protein kinase 1 (DAPK1) overexpression is induced by a reduction in miR-26a in the PD model [232]. The DAPK1 mRNA levels in the acute and chronic MPTP mouse models did not alter, indicating that increased gene transcription does not cause DAPK1 overexpression in PD mice [233]. It was postulated that the loss of certain miRNAs mediates DAPK1 overexpression [234]. Neuronal synucleinopathy is strongly linked with DAPK1 overexpression in PD mice. In wild-type mice, silencing miR-26a or upregulating DAPK1 causes synucleinopathy, DA neuron cell death, and motor impairments [235].

Similarly, in MPTP animals, motor problems, synucleinopathy, and dopaminergic neuron loss are prevented by a cell-permeable competitive peptide that inhibits α-syn 's phosphorylation. In vivo, DA neurons experienced synucleinopathy and cell death due to downregulation of miR-26a and overexpression of DAPK1. Through direct phosphorylation of α-syn at the Ser129 location, DAPK1 causes synucleinopathy. Furthermore, in mice receiving chronic MPTP treatment, DAPK1 deletion can similarly repair the loss of DA neurons and locomotor impairments. Eventually, the clinical and behavioral defects in the MPTP mice were ameliorated by the synthesis of a membrane-permeable peptide that directly disrupted the connection between DAPK1 and α-Syn [236, 237].

Early B cell factor (Ebf3) was selectively increased in the midbrain of the Dicer knockout mice, indicating that miRNA may be involved in regulating this gene [238]. Due to its dynamic expression throughout the formation of midbrain DA neurons, the Ebf3 gene in the midbrain was initially discovered. Here, we demonstrated how Ebf3 controls the specification and maturation of DA neurons during their development. It was also shown that miR-218 controls the dynamic expression of Ebf3 during the formation of DA neurons and is crucial for tumor growth and metastasis during cancer development [239].

4.3. *Neuroinflammation-related miRNAs*

Neuroinflammation, the inflammatory response within CNS, is an adaptive response to tissue damage or infection. Although this response may be beneficial, uncontrolled neuroinflammation often causes and even worsens and exacerbates neurological pathology [240]. It is commonly known that many neurodegenerative diseases, such as PD, AD, and multiple sclerosis, are pathogenetically linked to neuroinflammation [241]. Numerous important proinflammatory cytokines (IL-1β, IL-6, and TNF-α), chemokines (CCL2, CCL3, CCL5, and CXCL1), secondary messengers (NO and prostaglandins), and ROS, which are released by activated resident CNS cells like microglia and astrocytes, mediate neuroinflammatory responses (Fig. 5) [242]. Endothelial cells and immune cells coming from the periphery play a significant role in the propagation of these inflammatory signals [243].

There is growing evidence that miRNAs play a major role as regulators in neuroinflammation. The miRNAs like miR-155 can stimulate inflammatory processes (pro-inflammatory), while miRNAs like miR-146a, miR-124, and miR-21 can inhibit them (anti-inflammatory). Certain miRNAs, including those in the let-7 family, can either stimulate or prevent the inflammatory response from being induced. Many neurodegenerative and neurobehavioral illnesses have been linked to dysregulation of miRNAs [244].

The miR-155 is a crucial modulator of neuroinflammation by directly

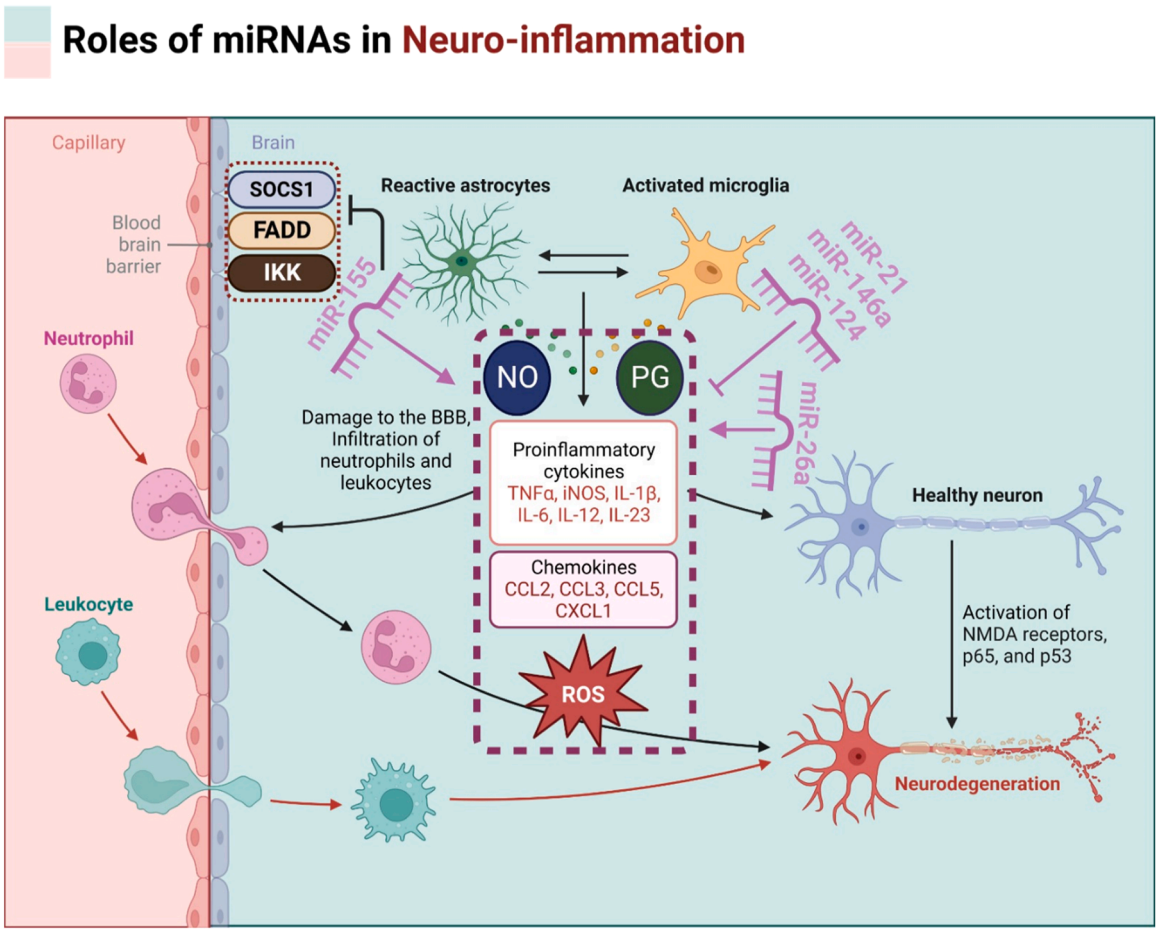

Fig. 5. Role of miRNAs in neuroinflammation.

inhibiting the suppressor of cytokine signaling 1 (SOCS1), Fas-associated protein with death domain (FADD), IkB kinase (IKK), and interleukin 13 receptor alpha 1 (IL13Rα1), among other pro-inflammatory signaling cascades and effector functions. This miRNA contributes to an increase in these proinflammatory molecules. It is regarded as a key inflammatory mediator that is frequently elevated in neurodegenerative diseases, including PD [245]. In PD mice models, it has been demonstrated that miR-155 also controlled α-Syn-induced inflammatory responses [246].

It was demonstrated that the neocortex in AD has significantly higher levels of seven inflammatory miRNAs, including miR-155, miR-7, miR-9, miR-23a/miR-27a, miR-34a, miR-125b, and miR-146a [247].

Their significance in altered neuroinflammatory signaling, which leads to the progressive degeneration of human brain cells and tissues, has also been well-documented [248]. Moreover, it has been demonstrated that miR-142–3p controls IL-1β-dependent synaptic defects that transpired during neuroinflammatory episodes [249]. In contrast, miRNAs may significantly impact the subsequent inflammatory response by directly targeting mRNAs that encode particular proinflammatory mediators.

A clinical condition's underlying inflammatory response may be dysregulated due to the downregulated expression of anti-inflammatory miRNAs, which could increase the synthesis of pro-inflammatory molecules [250]. MiR-21 was found to have a significant role in the negative feedback of inflammatory pathways, which helps to resolve inflammation. By focusing on programmed cell death 4, this anti-inflammatory miRNA functions as a negative modulator of TLR4 signaling. This results in decreased secretion of the pro-inflammatory cytokine IL-6 and increased synthesis of the anti-inflammatory cytokine IL-10 [251].

The miR-124 levels have been shown in several studies to have an anti-inflammatory function in neuropathology. It was found to suppress neuroinflammation during PD progression by controlling the MEKK3/NF-B signaling pathways [252] and focusing on p62, p38, and autophagy [253]. The function of miR-26a in controlling the inflammatory response in microglia has been studied. It was found that while miR-26a knockdown significantly raised the expression of TNF-α and IL-6, it significantly reduced the production of these inflammatory cytokines in microglia [254,255]. It was also found that patients with PD had downregulated levels of MiR-26a-5p in their peripheral blood [256]. Also, in a PD mouse model, overexpression of miR-190 decreased the expression of iNOS, IL-6, and TNF-α but increased the expression of transforming growth factor β1 (TGF-β1) and IL-10. Furthermore, miR-190 targeted nod-like receptor protein 3, one of the most prevalent immune complexes implicated in the etiology of numerous infectious and immunological disorders as well as the development and progression of Parkinson's disease, and it reduced neuronal damage and reduced neuroinflammation in PD mouse model [257].

Another negative regulator of inflammation, miR-146a, is expressed in microglia, astrocytes, and neurons. TLR signaling via NF-kB also induces miR-146a [258]. MiR-146a functions as a negative feedback regulator of NF-kB signaling by focusing on IL-1 receptor-associated kinase 1 (IRAK1) and TNF receptor-associated factor 6 (TRAF6), two members of the myeloid-differentiation primary response (MyD88) signaling complex [259].

However, it has been discovered that miR-146a is elevated in several inflammatory neurodegenerative diseases, indicating that this could be an anti-inflammatory compensatory response aimed at restoring homeostasis in the early stages of the disease [260]. Additionally, the let-7 miRNAs have a significant role in controlling neuroinflammatory processes. Let-7 miRNAs are known to target the C/EBP-δ transcription factor, which polarises macrophages into the anti-inflammatory M2 phenotype. They also can prevent apoptosis and enhance the M2 phenotype in microglia [261] [262]. In addition to the receptor TLR4 [263], Let-7 can regulate inflammation by focusing on the cytokines IL-6 and IL-10 [264].

4.4. The role of miRNA dysregulation in iPSC-based PD modeling

In various neurodegenerative disorders, including PD, induced pluripotent stem cell (iPSC) disease modeling has proven beneficial by offering cellular insight into disorder pathophysiology [265]. For instance, extensive DNA hypermethylation alterations were seen in iPSC-derived dopaminergic neurons from individuals with genetic LRRK2-linked PD and idiopathic PD [266]. In the frontal cortex of cases with idiopathic PD, LRRK2 protein levels rose. In contrast, its mRNA levels did not significantly change, indicating that miRNAs are involved in suppressing the post-transcriptional control of LRRK2 [267].

In iPSC-derived dopaminergic neurons from PD cases, an experimental genome-wide analysis of miRNA expression revealed that miR-135a-5p, miR-135b-5p, miR-9–5p, miR-449b-5p, and miR-449a were found to be up-regulated. On the other hand, miR-519a-3p, miR-518e-3p, miR-141–3p, miR-299–5p, and miR-199a-5p were found to be downregulated [268]. Although miR-449b-5p and miR-449a are connected to disease in other research employing PD models, dysregulations of miR-135b-5p, miR-135a-5p, and miR-9–5p expression were already linked to PD in studies utilizing specimens from PD cases. Blood samples from Parkinson's disease cases were shown to have elevated levels of miR-9–5p [269].

In a study employing laser micro-dissected midbrain dopaminergic neurons from the substantia nigra pars compacta of eight idiopathic PD cases and eight healthy control subjects, miR-135a-5p was found to be increased [270]. Remarkably, miR-135a-5p targets LIM-homeobox transcription factor 1 beta (LMX1B) and other Wingless-related integration site (Wnt) signaling cascade genes throughout midbrain growth, thereby reducing the dorsoventral expansion and recruitment of dopaminergic neuron progenitors [271].

Besides, it has been demonstrated that miR-135a-5p provides adaptive protection in adult dopaminergic neurons of a subacute in vivo model of Parkinson's disorder [272]. The CSF of cases with Alzheimer's disorder and the substantia nigra pars compacta of PD were shown to have dysregulated expression levels of the biologically closely associated miR-135b-5p [273,274]. Furthermore, suppressed production of glial cell line-derived neurotrophic factor, a crucial neurotrophin that raises the quantity of adult dopaminergic neurons in the substantia nigra pars compacta and supports dopaminergic neuron survival in vivo and in vitro, was linked to elevation of miR-9 [275].

According to a study by Heman-Ackah *et al.*, miR-449a and miR-449b are anticipated to target a-synuclein, the main aggregating protein in Lewy bodies in PD cases [276]. Indeed, they are also crucial for healthy brain growth and microtubule behavior [277]. In putamen and CSF from PD cases, Hesse and Arenz's research revealed the dysregulation of miR-449b and miR-9 [278].

While deregulation of miR-519a-3p and miR-518e-3p was never earlier linked to PD, downregulation of miR-199a-5p, miR-141–3p, and miR-299–5p was found in biological specimens from PD patients. Hence, at early Hoehn and Yahr motor stages, miR-141 serum expression levels were markedly reduced in PD cases [279]. Using a systems biology technique, Chatterjee *et al.* established miR-141–3p as the hub miRNA implicated in PD, and they hypothesized that this miRNA may be introduced as a diagnostic indicator and treatment option for the disorder [280]. According to a study by Martins *et al.*, peripheral blood mononuclear cells from PD cases have been reported to have reduced miR-199a-5p expression [256], which was anticipated to target a-synuclein [276].

Moreover, it has been revealed that PD patients' substantia nigra pars compacta have decreased miR-299–5p expression [273]. Targeting genes important in modulating axonal transport, cytoskeleton movements, cell growth, and cell adhesion comprise a canonical cascade previously demonstrated to be disrupted in PD [281,282]. Notably, Rho GTPases, essential for neurite development through actin cytoskeleton remodeling, rely on LRRK2 activity [283]. As a compensatory strategy, miR-135a-5p inhibits Rho-associated factor kinase 2's mRNA

translation, accelerating neurodegeneration in neuronal cells during PD [272].

Interestingly, it has been revealed that in early 30-day dopaminergic neuron cultures, PD differentially expressed miRNA dysregulations coincide with significant PD-linked DNA methylation modifications, including an enhancer element hypermethylation in the DNA structure [268]. This is linked to a deficiency of a set of PD transcription factors, including forkhead box A1, FOS Like 2 transcription factor, and hepatocyte nuclear factor-4 alpha [266]. According to a study by Tolosa *et al.*, iPSC-derived dopaminergic neurons from PD cases have the potential to be a helpful humanized cell model that can mimic molecular changes that occur in PD while maintaining the patient's genetic makeup, offering a special way for simulating the disorder at the cellular level [268].

5. Role of miRNAs in PD diagnosis

Unraveling the patterns by which circulating miRNAs are dysregulated in various disorders is a primary target of studies. miRNA dysregulation pattern was proven to be disease-specific, where signature patterns were attributed to diseases and promoted to newer fields of diagnostics and therapy. Moreover, miRNAs fulfill the criteria of excellent biomarkers as the stability in biological fluids [284], and they offer versatility in disease staging, treatment monitoring, and predicting prognosis [285]. Regarding PD, as with all neurodegenerative diseases, they lack specific diagnostic biomarkers, and their diagnosis is almost impossible before irreversible damage and the appearance of symptoms; thus, the provision of sensitive and specific biomarkers will incrementally improve the disease outcomes [286–288].

Interestingly, miRNAs are detectable in all body tissues (Fig. 6), including the CSF, which is in direct contact with brain cells, offering precise insights into the disease mechanism [289,290].

Among the upregulated miRNAs in plasma is miR-155–5p, whose levels were restored to normal in response to treatment and were suggested to be used for follow-up and assessment of disease progression [291]. In addition, four miRNAs were consistently elevated in exosomes from CSF, namely let-7 g-3p, miR-10a-5p, miR-153, and miR-409–3p [292]. Examining the profile of miRNAs in the peripheral leukocytes could also be used for diagnosis, where the miR-30 family was dysregulated [293]. While the downregulated miRNAs included miR-146a-5p [291], miR-1 and miR-19b-3p [292], miR-133b characteristic of neuronal loss [294], also, miR-34b and miR-34c were under-expressed in early stages of PD. Their modulation is a suggested strategy for delaying and treating PD [295]. Moreover, miR-7 was found to be depleted in PD, particularly in diseased areas [296]. Yet, the field of diagnostic markers remains to have great gaps and areas requiring further investigation to promote earlier disease detection and better-prospected outcomes.

6. miRNA and therapeutic intervention in PD

The miRNAs have shown promise in therapeutic interventions for PD. Research suggests that miRNAs regulate genes associated with PD and can serve as promising biomarkers or potential therapeutic tools. Here are some examples of miRNAs associated with PD treatment. The miR-124 is abundantly expressed in the brain and plays various roles related to neurogenesis, synapse morphology, neurotransmission, and inflammation, making it an essential microRNA in the brain's function and development [297]. Because of its pro-neurogenic and neuroprotective properties, it has been considered a promising therapeutic agent for regulating the inflammatory response in patients with PD. The miR-124 has been revealed to target p38, p62, and autophagy to prevent inflammation during PD development [253]. Additionally, miR-124 can regulate the expression of MEKK3, a protein linked to cell signaling and inflammation that may have consequences for PD and neuroinflammation [252]. In PD mice, miR-124 has been reported to inhibit

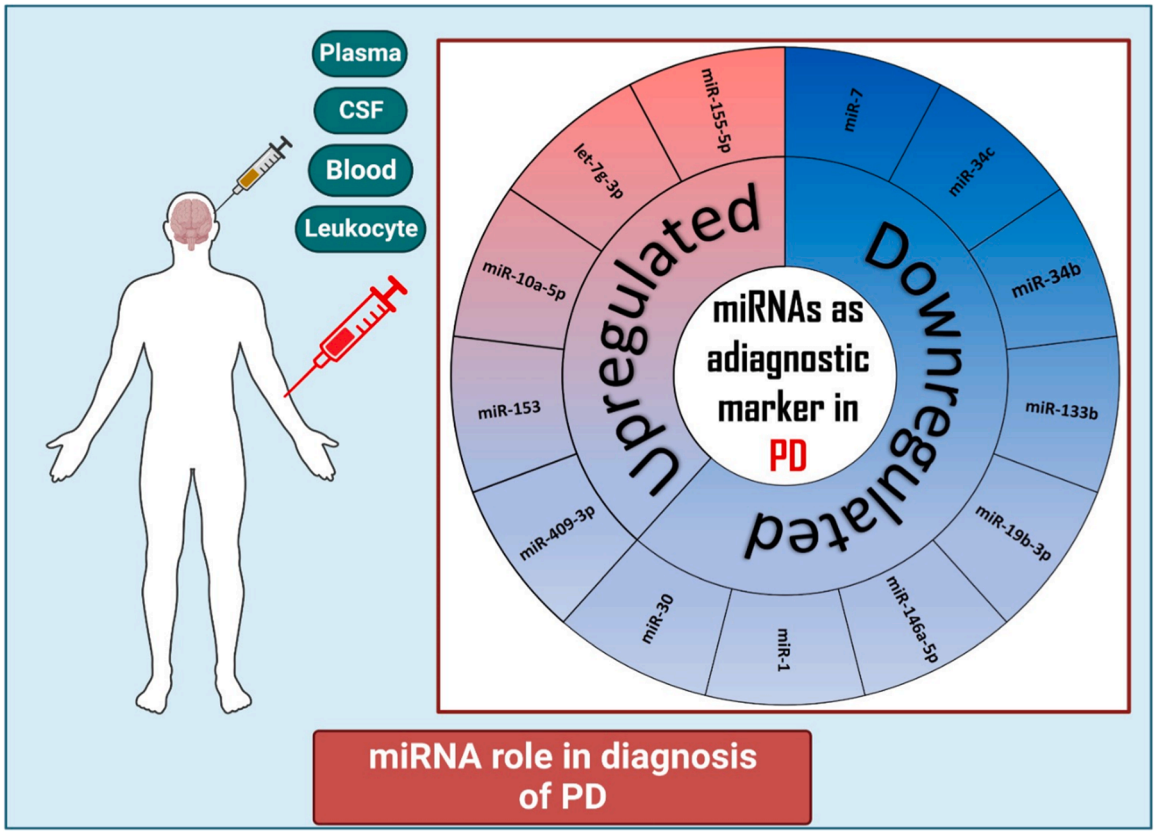

Fig. 6. Role of miRNAs in the diagnosis of Parkinson's disease.

Axin1 and trigger the Wnt/β-catenin signaling pathways, which are critical for neuroprotection (Fig. 7) [298].

The miRNA-195 has been demonstrated to lessen neuroinflammation by inhibiting the release of pro-inflammatory cytokines such as inducible nitric oxide synthase (iNOS), interleukin-6 (IL-6), and tumor necrosis factor-α while increasing the release of anti-inflammatory cytokines such as IL-4 and IL-10. Additionally, Rho-associated kinase 1 (ROCK1) has been stated to be negatively regulated by miRNA-195, where its low expression can prevent neuroinflammation in PD. Since miR-195 has a variety of roles in PD pathogenesis, research is still being done to pinpoint the precise mechanisms. Microglia-mediated neuroinflammation plays a major role in the pathophysiology of neurodegenerative diseases such as PD. Research suggests that miR-let-7a, a member of the let-7 family of microRNAs, may have a role in PD progression. miR-let-7 has been connected to the translational control of some PD-related genes, including leucine-rich repeat kinase 2 (LRRK2)-mediated pathways [299]. Moreover, by targeting the signal transducer and activator of transcription-3 (STAT3), miR-let-7a can control the activity of microglia (Fig. 7) [300].

In the context of PD, miR-150 behaves as a significant biomarker and regulatory molecule. Specifically, miR-150 inhibits neuroinflammation by reducing apoptosis, autophagy, and inflammatory cytokine release through targeting AKT3 [301]. Simultaneously, targeting miR-150–5p may result in downregulation of the lncRNA rhabdomyosarcoma 2-associated transcript (RMST), which inhibits inflammatory cytokine release, as well as neuronal cell death and, thereby, regulates the onset and progression of PD [302]. Further investigation is needed to clarify the role of miR-150 in the neuroinflammatory pathophysiology of PD. MiR-155 is an important regulator of neuroinflammation, a process associated with PD. Microglia expresses miR-155, which promotes inflammation and is essential for the immune response to proceed. MiR-155 can down-regulate the suppressor of cytokine signaling 1 (SOCS-1) protein, a key inhibitor of the inflammatory process, and thus, encourages the production of cytokines and nitric oxide. In addition, lowering miR155–5p expression has been reported to suppress NF-κB activity and upregulate SH-2 containing inositol 5' polyphosphatase 1 (SHIP1), preventing inflammation and microglial activation [303].

It has been demonstrated that one of miR-433 targets is fibroblast growth factor 20 (FGF20), whose expression is linked to α-syn, which aggregates in PD. People with PD have been found to exhibit lower miR-433 levels in their blood, which may indicate a connection between this microRNA and the illness [304]. Indeed, miR-433 can affect cell autophagy, preventing neuronal growth and impacting neurodegenerative diseases like PD [305]. Notably, miR-7116–5p has drawn attention in PD research because of its possible functions in controlling important molecular pathways involved in the etiology and development of the illness [306]. In particular, it has been shown that miR-7116–5p—rather than miR-7116–5b—plays a crucial role in microglia-related inflammation. According to prior research, downregulation of miR-7116–5p in microglia increased the production of TNF-α, a key molecule linked to neuroinflammatory responses and, thus, may be responsible for PD development [307].

The miR-425 deficiency has been documented to promote necroptosis activation, which is a programmed form of cell death that can contribute to dopaminergic neurodegeneration in PD, emphasizing the importance of these microRNAs in regulating gene expression and promoting therapy of this neurological disorder [308]. The miR-7 is considered a potential intervention target for neuroinflammation in PD because of its direct link with NLRP3 inflammasome-mediated neuroinflammation [309]. Interestingly, it has been observed that downregulation of long noncoding RNA small nucleolar RNA host gene 1 (SNHG1), a protein that promotes neuroinflammation in PD pathophysiology, increases miR-7expression to inhibit NLRP3 inflammasome and microglial activation and subsequently lessen the loss of dopaminergic neurons in the substantia nigra region [310]. The miR-7 has also been previously investigated for its role in inhibiting neuronal apoptosis and reducing neurotoxicity via targeting Bax and Sirt2, thereby controlling PD [311]. Research suggests that miR-7 replacement therapy

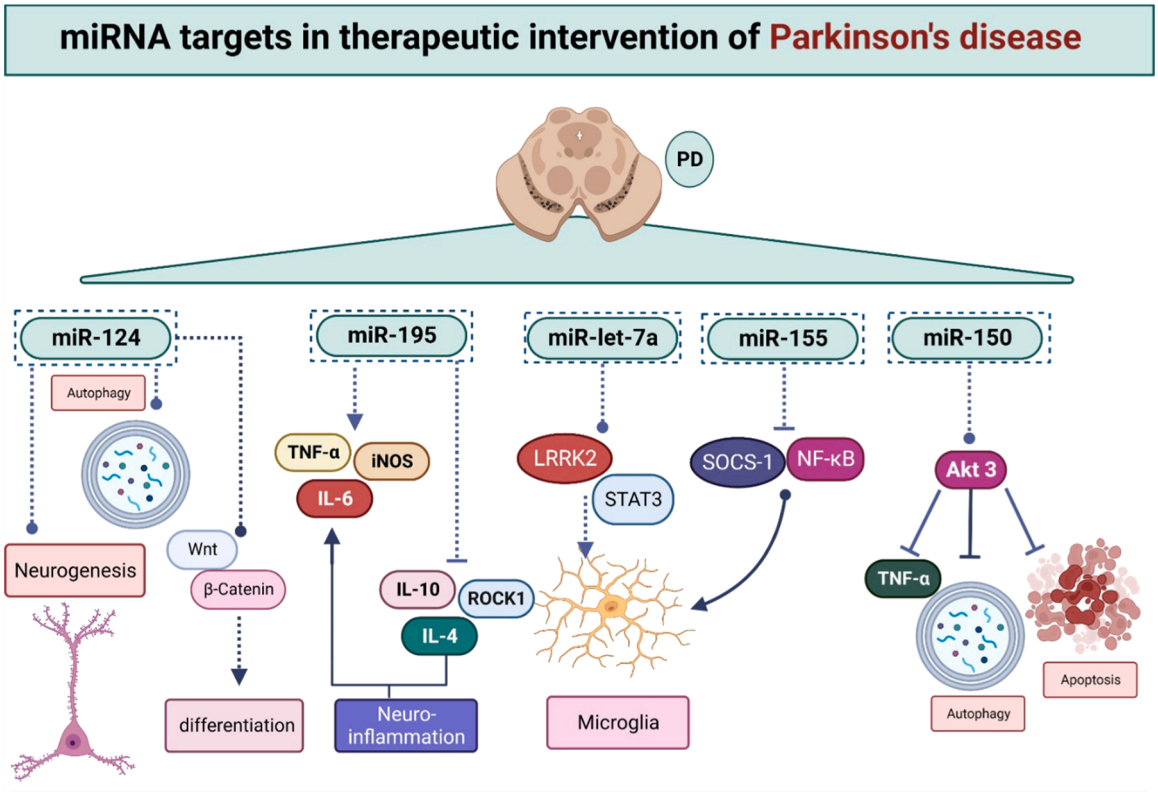

Fig. 7. Role of miRNAs as therapeutic intervention tools in Parkinson's disease.

may benefit PD by downregulating α-Syn, a key protein associated with PD [312].

MiR-190 may protect neurons by reducing neuronal damage and inhibiting neuroinflammation through the NLRP3 inflammasome, suggesting it could be a potential PD treatment [257]. To guard against PD's neuroinflammatory and apoptotic reactions, miR-29c may directly focus on the specificity protein 1 (SP1), offering a potential biomarker for PD diagnosis and treatment [313]. Furthermore, miR-29c-3p has been found to target the expression of nuclear factor of activated T cells 5 (NFAT5), a promising therapeutic target for PD, by modulating the NLRP3 inflammasome to reduce microglial inflammatory responses [314]. In a particular investigation, it was discovered that miR-29c-3p can also control the expression of the PD-related gene ten-eleven translocation 2 (TET2), making it a potential target for further research into PD therapy [315]. Previous research has shown that miR-30e inhibits the expression of the α-syn protein and decreases the rise in inflammatory cytokines like COX-2, TNF-α, and iNOS. When combined, miR-30e reduced the activity of the NlRP3 inflammasome, thereby reducing neuroinflammation, a pathological hallmark of PD, suggesting its potential therapeutic significance in this disease [316].

7. Role of nanoparticles (NPs)-based therapy in PD

Nanotechnology-enabled drug delivery systems present a promising approach to circumvent the pharmacokinetic limitations associated with conventional medications due to their minute size range of 1–100 nm. Furthermore, nanoparticles can directly modify biological entities such as DNA, RNA, and proteins, as well as their role as medicine delivery carriers. Drug stabilization, extended-release capabilities, enhanced blood-brain barrier permeability, and targeted intracellular route delivery are potential benefits of these systems [317,318].

The NPs possess continually diminished dimensions, notable interface-to-volume ratios, and modifiable surface functionalization attributes concerning their structure. This particular attribute offers a more consistent distribution across biological systems, improves the encapsulation of a broader spectrum of pharmaceuticals and genetic materials, and facilitates accurate control over the release of medications and efficient transportation into cells [319–322].

The scope of potential applications for integrating gene therapy with nanoparticles is continuously broadening [323,324]. It assists in bypassing the cellular barrier and promoting the release of the payload from the drug delivery mechanism, enabling subsequent translation without provoking any immune response. Emerging research indicates that a wide array of NPs exists for mRNA transportation. The above-mentioned NPs encompass many substances, including lipids and lipid derivatives, polymers, proteins, inorganic compounds, and hybrid particles [325,326].

Using exosome-secreting cells has been suggested as a potential method for local in situ implantation subcutaneously inside a PD model in mice with 6-hydroxydopamine (6-OHDA) lesions. The cells independently produce and encapsulate catalase mRNA within exosomes within a living organism. The exosomes were coated with ligands that facilitated penetration over the BBB and absorption by neurons, thereby enabling mRNA translation into catalase. This study demonstrated that the delivery of mRNA-loaded exosomes through designer cell implantation reduced neuroinflammation in mice induced with 6-OHDA. These findings offer promising prospects for developing future treatment strategies [327].

Restoring the normal function and amount of regulatory T cells presents a distinctive therapeutic strategy for addressing neurodegenerative disorders. The robust anti-inflammatory and neuronal-sparing response can be achieved through several means, such as adoptive cell migration, immunological modulators, or medicines that enhance Treg function. To induce the production of regulatory T cells and provide therapeutic intervention for mice with clinical PD, a newly developed lipid nanoparticle (LNP) was engineered. This LNP was designed to encapsulate mRNA that expresses granulocyte-macrophage colony-stimulating factor (Gm-csf mRNA). In a study conducted on rats and mice that were treated with MPTP and exhibited overexpression of alpha-synuclein, the administration of Gm-csf mRNA resulted in a dose-dependent rise in both plasma GM-CSF levels and peripheral populations of CD4 +CD25 +FoxP3 + Treg cells.

The observed increase in altitude resulted in a decrease in microglial cell activation and was associated with the preservation of neurons in the nigrostriatal pathway. Additionally, it elicited an upregulation of mRNAs associated with immunosuppression, hence facilitating the identification of a specific population of CD4 + T cells generated by the therapy [328].

Enhanced brain regeneration through manipulation of the subventricular zone (SVZ) neurogenic niche can benefit individuals with Parkinson's disease and other similar conditions. To study the intricate miR-124, a crucial element in neuronal fate determination, biocompatible and traceable polymeric Poly(lactic-co-glycolic acid) (PLGA) NPs were utilized. These nanoparticles were coated with protamine sulfate and included perfluoro-1,5-crown ether (PFCE).

This study aimed to evaluate the potential of neural progenitor cells to efficiently deliver miR-124 and promote neurogenesis in the subventricular zone (SVZ) to facilitate brain repair in individuals with PD. In vitro, neural stem/progenitor cells and neuroblasts demonstrate efficient internalization of miR-124 nanoparticles, which contributes to their neuronal attachment and developmental processes. After the administration of miR-124 NPs, the expression levels of two specific targets of miR-124, namely Sox9 and Jagged1, as well as genes associated with stemness, were downregulated. In healthy mice and a mouse model for PD induced by 6-OHDA, the intracerebral administration of miR-124 nanoparticles increased the number of migrating neuroblasts. These neuroblasts successfully reached the granule cell layer of the olfactory bulb in vivo. In the experimental group of mice subjected to 6-OHDA treatment, the administration of miR-124 NPs resulted in neuronal migration toward the damaged striatum. Significantly, the apomorphine-induced rotation test proved that the administration of miR-124 nanoparticles enhanced motor function in rats with 6-OHDA-induced motor symptoms. In the context of neurodegeneration, substantial evidence supports the utilization of miR-124 neural progenitor cells as an innovative therapeutic approach to augment the inherent regenerative mechanisms of the brain [329].

The PD is thought to be primarily characterized by Lewy bodies. Lewy bodies primarily consist of α-Syn. The application of gene therapy specifically targets and blocks α-Syn expression in neurons has drawn much interest. Oleic acid-coated magnetic Fe3O4 nanoparticles were employed as a nano-carrier. Following photo immobilization of the N-isopropyl acrylamide derivative (NIPAm-AA) onto the oleic acid molecules, shRNA (short hairpin RNA) was absorbed. Nerve growth factor (NGF) was absorbed into NIPAm-AA using the same technique, specifically stimulating neuronal uptake through NGF receptor-facilitated endocytosis.

Furthermore, the temperature and pH sensitivity of NIPAm-AA interference with α-Syn formation may release the shRNA genome into neurons. Both in vitro and in vivo apoptotic neurons with disrupted α-Syn expression were studied. The outcomes showed that shRNA for α-Syn carried by multifunctional superparamagnetic nanoparticles could effectively repair a PD model [330].

In an alternative investigation, a synthetic gene delivery system employing mRNA was administered via intracerebroventricular injection into the murine brain. The carrier employed in this study consists of LNPs composed of SS-cleavable proton-activated lipid-like components, which exhibit environmental sensitivity. The apolipoprotein E-mediated cellular absorption of lipid nanoparticles significantly contributes to their enhanced and consistent transfection efficacy, surpassing that of commercially available transfection reagents in both in vitro and in vivo settings.

The utilization of antibodies to stain brain specimens has facilitated

the observation that astrocytes and neuronal cells have the potential to encounter foreign proteins via mRNA-based gene carriers. DNA-based artificial gene carriers are incapable of accomplishing this task. The findings suggest that the combination of mRNA and a lipid-based delivery method holds significant promise for the therapeutic management of PD [331].

Various synthetic polymer carriers have been effectively utilized for the transportation of miRNAs. Poly (ethyleneamine)-based polymers (PEIs) have been found to have effective encapsulation properties and have shown promise in the delivery of miR-145 and miR-33a molecules. Despite the potential drawbacks of positive charges and non-biodegradability in polymeric carriers, numerous studies have demonstrated their effectiveness in PD.

Therefore, a study conducted in live animals utilizing PEI/siRNA complexes resulted in a reduction of approximately 50% in the expression of α-syn mRNA and protein in the striatum without inducing any observable deleterious effects [332]. The combination of PLGA particles with the rabies virus glycoprotein RVG29 also has been found to augment the transfection efficiency of miR-124 into substantia nigra cells when administered via the intraventricular method. The observed neuroprotective effects of this particular miRNA were attributed to its ability to downregulate the expression of pro-inflammatory cytokines and inhibit cellular death [333].

The activation of caspase-3 is a significant characteristic in the pathogenesis of PD. The potential effects of this phenomenon include the initiation of neuronal apoptosis and the activation of microglia through inflammatory processes. Consequently, suppressing caspase-3 activation would manifest a synergistic dual effect within the brain, impeding the progression of PD. The inhibition of caspase-3 activation can be achieved by employing RNA interference to silence caspase-3 genes. A brain-targeted gene delivery method was developed utilizing dendrigraft poly-L-lysines, a non-viral gene vector.

The conjugation of a 29-amino acid peptide derived from the glycoprotein of the rabies virus to dendrigraft poly-L-lysines has been shown to confer gene vectors with the capacity to traverse the BBB via receptor-mediated transcytosis. The NPs were generated by complexing the brain-targeted vector with plasmid DNA encoding caspase-3 short hairpin RNA. The investigation of in vivo imaging revealed that the targeted NPs exhibited a higher efficiency in accumulating within the brain than the non-targeted NPs. The injection of NPs by a weekly IV dosing regimen can decrease activated caspase-3 levels, enhance locomotor activity, and mitigate the loss of dopaminergic neurons in the brains of rats with PD. The findings of this study suggest that brain-targeted nanoparticles, which have been modified with a peptide derived from the rabies virus glycoprotein, show promise as a gene delivery system for RNA interference. This approach can potentially provide synergistic therapeutic benefits by down-regulating the expression and activation of caspase-3, hence exerting anti-apoptotic and anti-inflammatory effects [334].

The conversion of CD4 + T cell effector cells into regulatory (Teff to Treg) cells has been demonstrated to mitigate the advancement of neurodegenerative illnesses by reinstating immunological equilibrium throughout their initiation and progression. The viable and efficient approach to reestablishing this equilibrium by reinstating the quantities and functionality of regulatory T cells through the regular administration of the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) and its feasibility and validity in preclinical models of PD as well as in the initial phase I clinical trials has been investigated.

In both cases, they functioned to improve the indications and symptoms associated with the condition. Nevertheless, despite the documented effectiveness, the cytokine's limited duration of action, inadequate absorption into the bloodstream, and adverse effects at the injection site have been identified as constraints that hinder its widespread application. To address these constraints, researchers devised mRNA lipid nanoparticles that encode a fusion protein of albumin-GM-CSF with an extended half-life. These nanoparticles were specifically designed for use in mice (Msa-GM-CSF) and rats (Rsa-GM-CSF). The efficacy of these formulations was evaluated in preclinical models of PD utilizing MPTP and human wild-type α-Syn overexpression.

The evaluation focused on their immunomodulatory and neuroprotective properties. The administration of a solitary dose of lipid nanoparticles containing prolonged half-life mouse and rat mRNA resulted in the detection of quantifiable quantities of GM-CSF plasma cytokines for up to four days. This study's findings indicate a correlation between an elevated frequency and enhanced functionality of regulatory T cells and a state of microglial quiescence. This association is further linked to protecting the nigrostriatal system and re-establishing immunological homeostasis within the brain tissue. The results of this study far exceeded the documented effectiveness of daily administration of recombinant wild-type GM-CSF, which has a recorded half-life of six hours.

A mechanistic assessment of transcriptional profiles in the neuropathologically afflicted nigral brain region revealed an increase in the expression of neuroprotective CREB and synaptogenesis signals and neurovascular coupling pathways. The findings above underscore the significance of the alteration involving the fusion of mRNA-encoded albumin and GM-CSF, as it is associated with notable enhancements in treatment effectiveness. The enhancements seen were correlated with the heightened bioavailability of the medication. Collectively, mRNA LNP carrying the genetic code for an extended half-life albumin-GM-CSF fusion protein can be used as a standard for evaluating immune-based treatments targeting the pathophysiology of PD [335].

The accumulation of excessive iron in the brain frequently leads to the occurrence of oxidative stress-induced harm and death of dopaminergic neurons in the substantia nigra. This phenomenon has been identified as a significant susceptibility factor in the development of PD. The utilization of deferoxamine (DFO) in iron chelation therapy can impede the degeneration of the nigrostriatal system and halt the progression of PD.

Nevertheless, it has been observed that DFO exhibits a notably brief half-life within living organisms and possesses little ability to traverse the BBB. A novel polymeric nanoparticle platform engineered with the brain-targeting peptide rabies virus glycoprotein (RVG) 29 for developing DFO formulations that can facilitate the safe and effective transport of drugs into the brain. This modified nanoparticle system can effectively carry the compound DFO directly into the brain. The mechanism by which the nanoparticle system can traverse BBB is hypothesized to involve receptor-mediated endocytosis, which the RVG29 peptide may facilitate. The nanoparticles were administered, resulting in a notable reduction in iron content and oxidative stress levels in the substantia nigra and striatum of mice with PD.

The nanoparticles effectively mitigated damage to dopaminergic neurons and reversed neurobehavioral deficits in these mice. No evident adverse effects were observed in the brain or other organs following nanoparticle administration. The nanoformulation based on DFO exhibits significant potential for facilitating the transport of DFO across the blood-brain barrier and effectively implementing iron chelation therapy in the treatment of PD [336].

8. Conclusion

This review suggests that dysregulation of multiple miRNAs is a crucial factor in the pathogenesis of PD. The α-syn-induced neurodegeneration, the control of PD-associated genes, and the preservation of dopamine neuronal health are the two roles of miRNAs. Gaining knowledge about the functions of miRNAs may offer valuable insights into the pathogenesis of PD and develop into potential therapeutic targets, given that the regulation of specific miRNAs has yielded favorable outcomes in both in vitro and in vivo models. Additional research is required to determine the further functions of these miRNAs and others in the pathogenesis PD.

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Authorship statement

Conception and design: A.I.A, A.E.E., M.A.E., Y.N., A.S.D., and H.M. E. Collection and/or assembly of data: M.A.A., S.S.A., E.G.K., O.A.M., M. S.E., and M.M.A-R. Manuscript writing: A.M.A.M, H.M.I., W.A.E., O.E., S.S., A.A.E., and M.M.E. All authors have read and approved the published version of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors have declared that no competing interests exist.

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