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Review article

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MicroRNAs regulation in Parkinson's disease, and their potential role as diagnostic and therapeutic targets

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MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression by binding to target messenger RNA (mRNA) molecules and promoting their degradation or blocking their translation. Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons in the substantia nigra. There is increasing evidence to suggest that miRNAs play a role in the pathogenesis of PD. Studies have identified several miRNAs that are dysregulated in the brains of PD patients, and animal models of the disease. MiRNA expression dysregulation contributes to the onset and progression of PD by modulating neuroinflammation, oxidative stress, and protein aggregation genes. Moreover, miRNAs have emerged as potential therapeutic targets for PD. This review elucidates the changes in miRNA expression profiles associated with PD, emphasising their potential as diagnostic biomarkers and therapeutic targets, and detailing specific miRNAs implicated in PD and their downstream targets.

Parkinson's disease (PD) is a prevalent movement disorder that affects the ageing population, with an estimated prevalence of 1% in individuals over 60 years old. It is characterised by a gradual loss of neurons in the brain, particularly the dopamine-producing neurons in the Substantia Nigra Pars Compacta (SNpc) region. This results in a decrease in dopamine neurotransmitter production and signalling, leading to motor dysfunction symptoms like tremors, slow movements, stiffness, and instability in posture[1,2]. The fundamental mechanism behind PD is linked to disruptions in protein balance due to the misfolding and clustering of alpha-synuclein (α-Syn) proteins. This leads to the development of Lewy bodies and Lewy neurites, which are intracellular aggregates[3].

Presently, the clinical treatments for PD primarily aim to alleviate symptoms and include both pharmacological options like Levodopa, dopamine agonists, catechol-O-methyl transferase inhibitors, and monoamine oxidase B inhibitors, as well as non-pharmacological interventions like deep brain stimulation[4,5]. While these treatments help to relieve the motor symptoms of PD, they do not provide neuroprotection, cannot halt or slow disease progression nor reverse neurodegeneration[6]. Both environmental and genetic factors, such as mutations in the *alpha-synuclein (SNCA)* and leucine-rich repeat kinase 2 (LRRK2) genes, have been implicated in the development of PD through their regulation of mitochondrial function in dopamine-producing neurons[7,8]. The blood-brain barrier (BBB) compromise and infiltration of peripheral immune components have also been reported in PD patients. Immune components that infiltrate the brain can interact with dopamine neurons, leading to their decline[9,10]. The pathological hallmarks of PD include widespread α-synuclein aggregation and the gradual degeneration of the nigrostriatal pathway, resulting in the death of dopamine neurons in the SNpc. This process ultimately manifests in both motor and non-motor symptoms associated with PD[11–13].

Recent groundbreaking discoveries have shed light upon the pivotal role of miRNAs, dynamically governed by genes implicated in PD susceptibility, in shaping the pathogenesis of this debilitating disorder. Remarkably, accumulating evidence indicates that miRNAs exert their profound impact on PD pathophysiology by assuming a direct regulatory role in key cellular processes, specifically within mitochondrial and immune pathways[9,10]. Recent discoveries show that miRNAs, which are regulated by genes associated with PD risk, can contribute to the disease by directly regulating mitochondrial and immune pathways[9,10].

Several studies indicate that dysregulated miRNA expression is involved in the onset and progression of PD[14–22]. Patients with PD have

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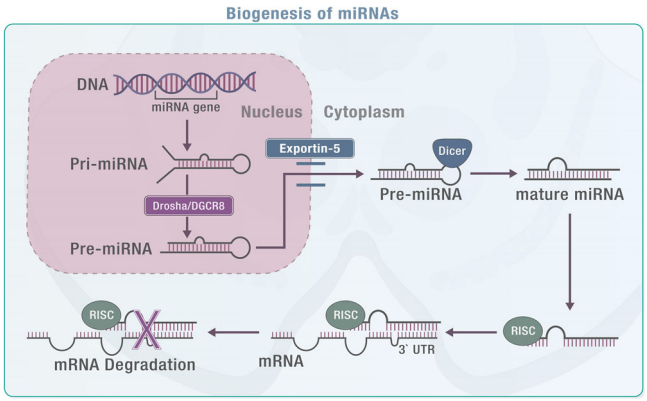

Fig. 1 | The process of generating mature miRNAs from their genes. Note: this figure is an original figure created by the authors.

aberrant miRNA levels in both their brain tissue and peripheral blood[16,17,19,22,23]. Of particular interest are several miRNAs that target genes involved in dopaminergic neurotransmission, mitochondrial function, immune response, and SNCA aggregation through several pathways[9,10,17,18].

In this review, we are going to focus on miRNA expression in PD, their biomarker and therapeutic potential, specific miRNAs and targets, and the challenges of using miRNAs therapeutically.

Biogenesis of miRNAs

MiRNAs were first discovered in 1993 and research has shown them to be crucial biological molecules that play a role in maintaining normal cellular functions[24–26]. MiRNAs are non-coding RNA molecules that come from miRNA genes and intronic sequences. They are initially transcribed as primary miRNAs (pri-miRNAs) and stem-loop precursor miRNAs (pre-miRNAs) in the nucleus. The Drosha/DGCR8 complex processes pri-miRNAs into pre-miRNAs, which are then transported out of the nucleus by Exportin-5. In the cytosol, Dicer cleaves pre-miRNAs to create double-stranded mature miRNAs. The single-stranded mature miRNA, which is usually around 20-22 nucleotides long, is then loaded onto Argonaute proteins to form the RNA-induced silencing complex (RISC). The mature miRNA attaches to complementary sequences, typically located at the 3′-UTR of the mRNA and works as a potent gene expression regulator. The targeting specificity is determined by the seed sequence located at the miRNA's 5′-end, spanning bases 2-8[27–29] (Fig. 1)[30,31].

Emerging research presents an intriguing perspective, suggesting that miRNAs within exosomes may be relatively scarce. Instead, the majority of circulating miRNAs are associated with non-vesicular extracellular particles (EPs) and extracellular vesicles such as circulating lipoproteins and other protein complexes[30,31]. This notion challenges the prevalent concept of positing exosomes as the primary source of miRNAs for intercellular signalling and biomarker discovery[32]. However, countervailing studies have furnished compelling evidence demonstrating the presence of copious and functionally active miRNAs within exosomes, capable of modulating the gene expression and phenotypic traits of recipient cells[33,34]. Consequently, discerning the relative contribution and biological significance of miRNAs hosted in exosomes versus Eps, the setting of PD, entails a multifaceted consideration of factors such as particle origin, isolation methods, comprehensive particle characterisation, cell type, physiological and pathological context, among others[30].

Exosomal miRNAs: key players in neurodegenerative disease pathogenesis and therapeutics

Exosomes carry an array of materials like proteins, lipids, and noncoding RNAs, such as miRNA, long noncoding RNA (lncRNA), and messenger RNA (mRNA)[35,36]. Upon release, exosomes navigate to specific destinations, like immune cells in the central nervous system (CNS), where they exert varied effects. These vesicles are pivotal in intercellular communication, influencing disease development in immunological disorders, tumorigenesis, and neurodegenerative disorders[37]. They stem from sources like human mesenchymal stem cells, immune cells, and microglia, significantly impacting the progression of neurodegenerative diseases by influencing gene expression and cellular processes[38–40]. Exosomal miRNAs play a role in managing oxidative stress, a significant aspect of neurodegenerative events. Their ability to breach the BBB and concentrate in brain tissue suggests their potential as drug carriers and biomarkers for neurodegenerative diseases[41,42]. Additionally, their effectiveness as non-invasive biomarkers for disease progression is noteworthy[15–20]. Present methods for isolating exosomes encompass various techniques like ultracentrifugation, density gradient centrifugation, size exclusion chromatography, exosome precipitation, and immunoaffinity capture. Exosome characterisation involves approaches like western blotting and ELISA. These diverse methods possess distinct merits and drawbacks in terms of efficiency, purity, yield, cost, and time requirements. However, a consensus agreement on the optimal technique for both isolation and characterisation of exosomes remains elusive[43–46].

The interaction between exosomal miRNAs and oxidative stress in the context of PD

The brain needs a substantial oxygen supply, and a considerable portion of this is converted into (ROS)[47]. Normal cellular processes, including oxidative phosphorylation in mitochondria, produce ROS like hydrogen peroxide (H_2O_2), superoxide anion (O_2-), and nitric oxide. While these ROS are crucial for redox signalling and other cellular functions, they can also cause oxidative damage. This damage includes lipid peroxidation in cell and organelle membranes, protein oxidation through cross-linking, fragmentation, and carbonyl group formation, as well as oxidation of DNA and RNA within cells[48]. Antioxidative mechanisms increase the production of several antioxidants to mitigate these radicals. However, in PD, the endogenous antioxidants needed are inadequate, leading to unchecked ROS generation. This can result in the excessive accumulation of non-physiological and toxic levels of ROS, leading to oxidative stress[49].

One proposed explanation posits those neurodegenerative diseases manifest through the distinct processes of apoptosis/necrosis and neuronal cell dysfunction, leading to compromised motor or cognitive functions. The CNS, due to its elevated metabolic rate and significant lipid content, is notably susceptible to oxidative stress. Elevated levels of oxidative stress are frequently observed in the brains of patients afflicted with neurodegenerative conditions[50–52].

In PD patients, excessive ROS production elevates oxidative stress. Evidence indicates that dopamine metabolism, elevated levels of iron and calcium in the substantia nigra (SN), mitochondrial dysfunction, and neuroinflammation all contribute to the heightened oxidative stress and loss of dopaminergic neurons observed in the brains of PD patients[49].

Neurodegenerative diseases are closely linked with both oxidative stress and exosome-derived miRNAs[42]. Interestingly, oxidative stress can influence the expression of various miRNAs, while miRNAs can also regulate many genes that are involved in the response to oxidative stress. Therefore, the relationship between oxidative stress and miRNA networks is complex and interconnected during the process of neurodegeneration[42]. Oxidative stress exerts a substantial impact on the expression levels of numerous miRNAs, and reciprocally, miRNAs play a pivotal role in the regulation of a multitude of genes associated with the oxidative stress response[53]. The interplay between oxidative stress and miRNA networks extends its influence beyond the primary regulatory axis, influencing critical processes implicated in neurodegeneration. Notably, these interconnected pathways contribute to mitochondrial dysfunction, disruption of proteostasis, and heightened neuroinflammation, collectively culminating in the outcome of neuronal death[53]. This intricate web of interactions underscores the comprehensive involvement of oxidative stress and miRNA networks in the multifaceted landscape of neurodegenerative processes[53].

Recent research indicates that miR-34a plays a significant role in the neurotoxic pathways associated with neurotoxins like paraquat, rotenone, and 6-hydroxydopamine (6-OHDA) in PD[54]. However, lithium chloride,

which is a mood-stabilising medication, can safeguard SH-SY5Y cells from paraquat-induced neurotoxicity by inhibiting miR-34a and activating the antioxidant protein expression regulator nuclear factor 2-related factor 2 (NRF2)[55]. The significance of miRNA is highlighted by the fact that Schisandrin B, an antioxidant found in dibenzo cyclooctadiene lignin, was able to reverse the inhibition of NRF2 and the increase in miR-34a expression caused by 6-OHDA in cells. This effect was observed by Ba et al.[56] who also found that the behavioural improvement caused by Schisandrin B was hindered by miR-34a overexpression in a 6-OHDA PD-mouse model. Additionally, astrocytes may secrete more miR-34a under stressful conditions. In the context of PD, the function of miRNA (miR-34a) was observed through its transmission from astrocytes to dopaminergic neurons via exosomes. This transmission resulted in an increased susceptibility of the neurons to neurotoxins by regulating the Bcl-2 gene[57]. A recent investigation has demonstrated that increasing the expression of miR-34a may help to reduce neuronal apoptosis caused by oxidative stress. This finding underscores the importance of miRNA in this process[58]. Currently, our understanding of the impact of this effect on the development of PD is limited. However, based on studies conducted on cellular and animal models, it appears that miR-34a may have a pathophysiological function in PD[58].

MiR-137 is a miRNA that is highly conserved. It is mainly present in the brain of Drosophila and has been observed to increase in the early stages of PD in flies. Similar results have been found in the plasma of PD patients. In a recent study, Jiang and colleagues demonstrated that reducing the levels of miR-137 in exosomes led to an increase in the expression of oxidation resistance 1 (OXR1), which provided neuroprotective effects against oxidative stress in a PD-mouse model[59–61].

As a highly conserved miRNA, Let-7 has been extensively studied for its involvement in various physiological processes and diseases. Its dysregulation can have significant implications for human health. Specifically, Let-7 is upregulated in the PD-mouse model, suggesting a potential therapeutic target for this debilitating condition[62,63]. A previous study indicated that an increased level of Let-7, which is carried by exosomes, can be detected in the cerebrospinal fluid(CSF) of individuals with PD. This suggests that these miRNAs can be transported via exosomes. If neurons absorb Let-7 that is carried by exosomes, it can trigger neurodegeneration by activating toll-like receptor 7 (TLR7)[64]. The Let-7 group has been found to have a positive impact on the effects of functional mutations of leucine-rich repeat kinase 2 (LRRK2), which plays a role in the development of PD. In a PD-mouse model using C. elegans, the inhibition of Let-7 leads to a slight rise in ROS levels, which promotes neuronal autophagy and decreases the buildup of α-synuclein protein. This, in turn, lessens the progression of PD. These findings emphasise the significance of miRNA in the development of PD[65,66].

Dysregulation of miRNAs in neurodegenerative diseases

The multifaceted involvement of miRNAs in neurodegenerative diseases stems from various mechanisms, each impacting distinct facets of neuronal function and disease progression. Firstly, miRNAs exert influence by targeting mRNA transcripts of regulatory-related genes, impeding protein translation or inducing protein degradation. This regulation significantly affects crucial aspects of neuronal biology, including survival, differentiation, synaptic plasticity, and axonal guidance. Notable instances include miR-9's targeting of REST, a repressor of neuronal genes, fostering neuronal differentiation[67]. Similarly, miR-124's interaction with PTBP1, a splicing factor inhibiting neuronal gene expression, enhances neuronal identity[68]. Furthermore, miR-29's action on BACE1, an enzyme involved in amyloid beta production, mitigates amyloid beta levels[69].

Secondly, miRNAs play a pivotal role in modulating neuroinflammation by directly engaging toll-like receptors or regulating their mRNA expression. This regulatory process influences the innate immune response and the production of pro-inflammatory cytokines within the brain. For instance, miR-146a's binding to TLR4 and TLR2 curtails NF-kappaB activation, consequently dampening the expression of inflammatory genes and mitigating neuroinflammation[70]. Conversely, miR-155's targeting of SOCS1, a negative regulator of cytokine signalling, amplifies the inflammatory response[71].

Finally, disruptions in miRNA biogenesis contribute significantly to disease pathogenesis. Mutations or dysregulation in key enzymes involved in miRNA processing, such as Dicer, Drosha, and RISC components, disrupt miRNA formation. For instance, mutations in TARDBP, encoding TDP-43—a constituent of RISC—disrupt miRNA processing, contributing to amyotrophic lateral sclerosis[68]. Dysregulation of Dicer expression alters miRNA profiles, impacting neuronal function and survival in AD and PD. These multifaceted mechanisms underscore the intricate and diverse roles of miRNAs in neurodegenerative diseases, offering potential avenues for targeted therapeutic interventions.

Dysregulation of miRNAs in PD

Dysregulation of miRNAs has been linked to the development of diseases, including brain disorders and cancers[72–75]. In PD, research has indicated that the expression profile of miRNAs is dysregulated and may contribute to the pathogenesis of the disease[76].

Numerous miRNA molecules have been discovered in immune cells, exceeding 100, which regulate the development and operation of innate and adaptive immune responses. For instance, certain miRNAs like miR-9, miR-21, miR-29b, and miR-34a are responsible for regulating MG during the innate immune response. MiRNAs, being small molecules with biologically active functions, can easily pass through the BBB[77–80]. This leads to the hypothesis that miRNAs could form a significant component in the construction of the secondary network within the central-peripheral inflammatory network, thus serving as a key pathway for communication between the central and peripheral inflammatory states.

In patients with PD, research indicates that miRNA expression profiles are disrupted in striatal brain tissue and dopamine neurons in the substantia nigra pars compacta (SNpc)[20,81]. Examining post-mortem prefrontal cortex samples from miRNA profiles of PD patients has shown significant changes in 125 miRNA molecules compared to neurologically normal controls. This suggests that miRNA dysregulation may play a role in PD pathogenesis by influencing various genes and proteins linked to the disease[82] (Table 1).

MiRNAs and microglia in PD

MiRNAs play roles in PD pathogenesis by modulating inflammatory responses. Dysregulation and downstream targets of specific miRNAs, such as miR-124, miR-195, miR-let-7a, miR-150, miR-330, miR-7116-5p, miR-7, miR-190, miR-29c, and miR-30e, have potential therapeutic targets in attenuating neuroinflammation and microglial activation in PD.

MiR-124

According to Yao et al.[83], miR-124, brain-specific miRNA, was significantly reduced in the MPTP-induced PD-mouse model and could suppress neuroinflammation during PD development. The researchers aimed to understand the mechanisms underlying the ability of miR-124 to inhibit neuroinflammation and discovered that the expression of p62 and p-p38 was considerably increased in the MPTP-induced PD-mouse model and BV2 cells induced with LPS. Therefore, miR-124 targets p62 and p38 to reduce MG inflammation in PD. Knocking out p62 in BV2 cells has been shown to prevent cell apoptosis and death in the SH-SY5Y human neuroblastoma cell line following MG activation. Additionally, providing miR-124 exogenously can decrease p62 and p-p38 expression and reduce MG activation in the SNpc of MPTP-induced PD-mouse model, implying that miR-124 suppresses neuroinflammation in PD development through targeting p62 and p38[84]. In addition, the introduction of miR-124 from an outside source can impede the production of mitogen-activated protein kinase 3 (MEKK3) and p-p65 in the SNpc of the MPTP-induced PD-mouse model. This also helps to diminish the activity of microglia, leading to the proposal that miR-124 may have the potential as a target for therapy in regulating the inflammatory response associated with PD[84].

Table 1 | presents information on how specific genes (SNCA, PRKN, PINK1, LRRK2, PARK7) are influenced by miRNAs, detailing how these miRNAs regulate their expression, the mechanisms involved, and the experimental proof supporting their involvement in PD pathogenesis

Target	miRNA	Expression regulation	Mechanism	Experimental evidence
SNCA	miR-7[117,129–131]	Downregulation	Inhibits translation	Patients with PD have reduced expression in SNpc of Over-expression of miR-7 reduces SNCA mRNA and protein levels
	miR-153[129–132]	Upregulation	Degrades mRNA	Over-expression of miR-153 reduces SNCA mRNA and protein levels
	miR-203a-3p[133]	Downregulation	Treatment with MMP + -treated SH-SY5Y cells resulted in decreased cell proliferation and triggered apoptosis in the SH-SY5Y cells.	Downregulation in MMP + -treated SH-SY5Y cells Leading to expression of SNCA, p53, and cleaved Caspase-3 proteins
PRKN	miR-103a-3p[134]	Upregulation	Binds to 3′-UTR of Parkin mRNA	Over-expression decreases Parkin protein expression
	miR-146a[135]	Upregulation	Downregulates Parkin	Upregulation leads to Parkin downregulation
	miR-181a[136]	Upregulation	Downregulates Parkin	Over-expression decreases Parkin mRNA and protein levels
	miR-218[137]	Downregulation	Downregulates Parkin	Over-expression decreases Parkin's expression
PINK1	miR-27a/b[138–140]	Upregulation	Downregulates PINK1	Inhibits PINK1 expression by binding to 3′ UTR
LRRK2	miR-205[131,141]	Downregulation	Downregulates LRRK2	Reduced expression in PD patients Over-expression decreases LRRK2
	miR-599[142]	Downregulation	Downregulates LRRK2	Reduced expression in PD models; Over-expression decreases LRRK2
PARK7	miR-494[143,144]	Upregulation	Downregulates DJ-1	Binds to 3′ UTR, decreases DJ-1 expression
	miR-4639-5p[145]	Upregulation	Downregulates DJ-1	Negatively regulates DJ-1 post-transcriptionally

SNCA Alpha-synuclein gene, *miRNA* MicroRNA, *PRKN* Parkin gene, *PINK1* PTEN-induced putative kinase 1 gene, *LRRK2* Leucine-rich repeat kinase 2 gene, *PARK7* Protein deglycase DJ-1 gene, *MMP* + 1-methyl-4-phenylpyridinium, *SH-SY5Y* Human dopaminergic neuroblastoma cell line, *NF-κB* Nuclear factor kappa-light-chain-enhancer of activated B cells.

MiR-195

The role of miR-195 in modulating inflammation during the development of PD is significant. MiR-195 expression was observed to decrease in BV2 cells induced with LPS, while upregulation of miR-195 led to inhibition of the release of proinflammatory cytokines such as iNOS, TNF-α, and IL-6 while inducing the release of anti-inflammatory cytokines such as IL-4 and IL-10. MiR-195 acts by negatively regulating Rho-associated kinase 1 (ROCK1), which is responsible for inducing MG activation. The decreased expression of ROCK1 also has a similar effect on MG regulation as the overexpression of miR-195. The interaction between miR-195 and ROCK1 is crucial in inducing the activation of MG[24].

MiR-let-7a

MiR-let-7a has been identified as a potential contributor to decreasing PD symptoms by acting as a negative regulator of MG-induced neuroinflammation. Previous research has revealed that the activation of the Signal transducer and activator of transcription-3 (STAT3) occurs simultaneously in the SNpc. Meanwhile, miR-let-7a targets STAT3, and the PD-mouse model showed a decrease in miR-let-7a expression. Increasing miR-let-7a expression has been demonstrated to impede BV-2 MG activation and reduce the production of pro-inflammatory agents instigated by α-syn. However, the influence of miR-let-7a was nullified by reintroducing the STAT3 protein[85].

MiR-150

In the pathogenesis of PD, miR-150 has been linked to neuroinflammatory processes. The AKT signalling pathway is widely recognised for its involvement in various pathophysiological mechanisms, including the advancement of PD. According to Li et al.[85], the level of miR-150 expression in PD patients was lower, and the study demonstrated that overexpressing miR-150 in BV2 cells induced with LPS cells can reduce the release of TNF-α, IL-1β, and IL-6. Moreover, the study showed that AKT3 was directly targeted by miR-150 in BV2 cells, and the overexpression of miR-150 could help treat PD as it suppressed neuroinflammation by targeting AKT3[86].

MiR-330

MiR-330 was found to be upregulated in two animal models, namely an LPS-induced MG chronic neuroinflammatory model and a PD-mouse model. Its overexpression induced the expression of Arg1 and SHIP1, inhibited the translocation of NF-κB, repressed M1 polarisation, and decreased iNOS expression. MiR-330 negatively regulates NF-κB activity through the MG SHIP1 target protein, thereby continuously repressing MG polarization triggered by LPS in vitro and in vivo. This provides a promising neuroprotective approach for PD treatment. SHIP1 is a downstream target molecule of miR155-5p, one of the most crucial miRNAs responsible for a robust inflammatory response. Lowering miR155-5p expression leads to upregulated SHIP1 expression and decreased NF-κB activity, thereby inhibiting inflammation and MG activation[87].

MiR-7116-5p

He et al. [88] illustrated the crucial function of miR-7116-5p in MG-activated inflammation in the MPTP-induced PD mouse model. The study discovered that miR-7116-5p was suppressed and its target was TNF-α. Additionally, the study found that the amplification of miR-7116-5p expression was able to impede the development of TNF-α and the activation of MG, and it could avert the degeneration of dopaminergic neurons[88,89].

MiR-7

A promising approach for treating PD is to understand how miR-7 and the NLRP3 inflammasome are regulated. According to Junn et al.[89] the expression of miR-7 decreases in individuals with PD. MiR-7 has been identified to target α-syn in dopamine neurons, and it is linked to the development of PD. Zhou Y. et al.[90] discovered that NLRP3 is another gene that is targeted by miR-7. In vitro analysis revealed that the transfection of miR-7 inhibits the activation of NLRP3 inflammasomes in MG, whereas the

Table 2 | Summary of miRNAs that are dysregulated in PD and their downstream targets

Study	miRNAs	Dysregulation	Downstream targets	Effect of miRNA regulation on microglia (MG)
Yao et al.[84].	miR-124	Downregulated	p62, p38, p-p65, MEKK3	Reduces inflammation in MG in PD with p62 and p38. In SH-SY5Y human neuroblastoma cells activated with MG, p62 knockdown prevents cell apoptosis and death
Ren et al.[24].	miR-195	Downregulated	ROCK1	RCK1 is responsible for MG activation, by negatively regulating it
Li et al.[85].	miR-let-7a	Downregulated	STAT3	Inhibit BV-2 MG activation and reduce pro-inflammatory agents produced by α-syn
Zhang et al.[86]	miR-150	Downregulated	AKT3	Inhibit the release of proinflammatory cytokines including TNF-α, IL-1β and IL-6
Feng et al.[87].	miR-330	Upregulated	SHIP1	MG SHIP1 target protein negatively controls the activity of NF-κB
Runxiao Lv[146]	miR155-5p	Downregulated	SHIP1	Suppress the activity of NF-κB
He et al.[88]	miR-7116-5p	Downregulated	TNF-α	Inhibition of the production of TNF-α and the activation of MG.
Zhou et al.[90].	miR-7	Downregulated	NLRP3	Inhibits the activation of NLRP3 inflammasomes in MG
Sun et al.[91].	miR-190	Downregulated	NLRP3	Inhibit the release of pro-inflammatory factors, including TNF-α, TGF-β1, iNOS, and IL-6
Wang et al.[92].	miR-29c	Downregulated	NFAT5	Overexpression suppresses pro-inflammatory cytokine release, along with NF-κB and TXNIP/NLRP3 inflammasome activation
Li et al.[93].	miR-30e	Downregulated	NLRP3	Inhibition of NLRP3 mRNA and protein expression

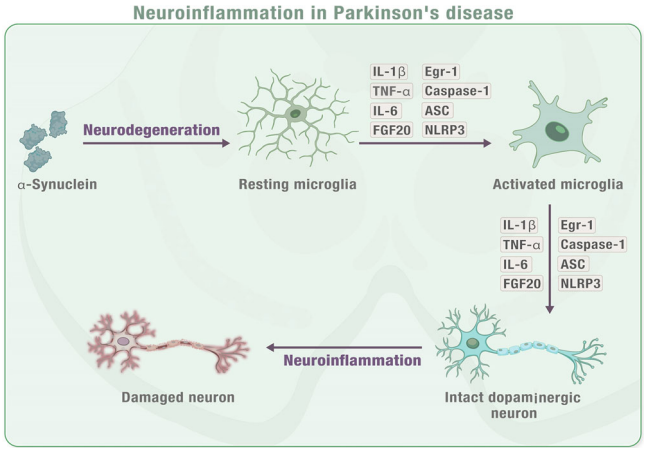

Fig. 2 | illustrates the process by which microglia (MG) become activated during neuroinflammation in PD. When neurons are damaged or dying in PD or toxin-induced models, they release impair-associated molecular patterns (IAMPs) and α-synuclein, which activate microglia through pattern recognition receptors (PRRs). This activation leads to the release of proinflammatory cytokines such as IL-1β, IL-6, TNF-α, and other inflammatory mediators including ASC, IFN2, iNOS, and Caspase-1. The release of these cytokines further activates other resting microglia, which ultimately leads to neuroinflammation or neurodegeneration in the affected area. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), IL-1β (interleukin-1β), IL-6 (interleukin-6), IFN2 (type 2 interferon), iNOS (inducible NOS), TNF-α (tumour necrosis factor-α), and ASC (apoptosis-associated speck-like protein containing a CARD). Note: This figure is an original figure created by the authors.

administration of anti-miR-7 aggravates the activation of inflammasomes. In the MPTP-induced PD-mouse model, the stereotactic injection of miR-7 mimics into the striatum reduced the degeneration of dopaminergic neurons and improved the activation of MG. In the pathogenesis of PD, there is a direct correlation between miR-7 and NLRP3 inflammasome-mediated neuroinflammation[90].

MiR-190

In BV2 cells induced with LPS, miR-190 levels are decreased. However, increasing miR-190 expression has been found to decrease the release of pro-inflammatory factors, such as TNF-α, TGF-β1, iNOS, and IL-6. Research has established a negative regulatory relationship between miR-190 and NLRP3, and in the MPTP-induced PD mouse model, miR-190 was found to decrease neuronal damage and inhibit inflammation by negatively regulating the expression and activation of NLRP3[91].

MiR-29c

MiR-29c has also been found to exhibit anti-inflammatory properties in animal and neuronal models of PD, where its overexpression suppresses pro-inflammatory cytokine release, along with NF-κB and TXNIP/NLRP3 inflammasome activation. In this context, miR-29c may represent a promising target for treating PD by regulating NLRP3 inflammasomes by targeting NFAT5 and decreasing the inflammatory response of MG[92].

MiR-30e

Beforehand, research indicated a significant reduction in miR-30e in the SNpc of the MPTP-induced PD mouse model. The application of miR-30e agomir decreased α-syn protein expression and abated the elevation of COX-2, TNF-α, and iNOS inflammatory cytokines. Additionally, miR-30e aimed at NLRP3, which resulted in the inhibition of NLRP3 mRNA and protein expression, leading to the suppression of NLRP3 inflammasome activation and the preservation of dopamine neurons[93]. (Table 2 and Fig. 2)

Potential clinical applications of miRNAs in conditions of PD

MiRNAs as a promising approach for gene therapy

The exosome transports active miRNAs, making it a promising alternative to virus-based gene therapy. This endogenous carrier has shown the potential to deliver miRNAs, which can be taken up by recipient cells without eliciting an immune response[94]. Additionally, exosomes cross the BBB, making them an ideal carrier for miRNAs compared to conventional RNA interference methods[95]. Furthermore, the animal model has demonstrated the potential of utilising exosomes as a delivery system in the treatment of miRNA[96]. The expression of miRNA varies in several neurodegenerative diseases, and certain miRNAs have been identified as playing a role in the advancement of these diseases. The use of exosomes to regulate these miRNAs is a promising avenue for gene therapy[97,98]. (Fig. 3).

MiRNAs as a novel method of intercellular communication dependent on the function of miRNA

Chemical receptor-mediated events are widely recognised as the primary means of intercellular communication. However, the discovery of exosome transport between cells has expanded our knowledge of this process. MiRNAs, which are a crucial component of this cargo, play a significant role in facilitating intercellular communication[99,100]. MiRNAs play an important role in transferring functional information at the paracrine level, as evidenced by exosomal miRNAs released from cancer cells that can influence the tumour microenvironment containing various cells such as cancer-associated fibrosis and pericytes. Furthermore, research has shown that neurons can transport miRNAs through exosomes to astrocytes, indirectly regulating the protein expression of astrocytes[101,102].

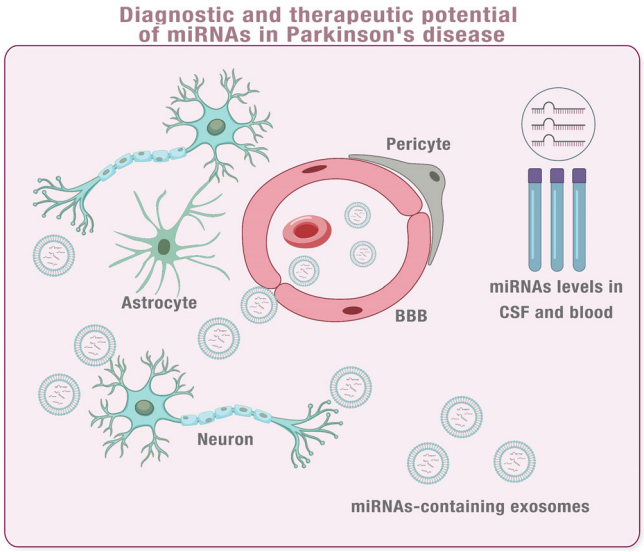

Fig. 3 | Diagnostic and therapeutic potential of miRNAs in PD. Note: this figure is an original figure created by the authors.

The elucidation of this novel exosomal miRNA transfer mechanism between neurons and astrocytes holds profound implications for both the physiology and pathophysiology of the CNS. It has the potential to impact the maintenance and plasticity of neuronal networks[103]. Furthermore, this discovery unveils promising avenues for the development of biomarkers and therapeutics for neurological disorders[52,103].

The current body of research demonstrates that neurons are capable of transporting miRNAs via exosomes to astrocytes, thereby indirectly influencing the protein expression of astrocytes[103,104]. For instance, a study identified the secretion of neuron-specific miR-124-3p by neurons in exosomes, which were subsequently internalised by astrocytes. This internalisation resulted in the downregulation of GFAP, a protein integral to astrocyte activation[104]. Additionally, another study revealed that exosomes derived from astrocytes exhibited differentially expressed miRNAs under pathological conditions such as neuroinflammation and oxidative stress. These miRNAs were implicated in potentially modulating neuronal morphology and synaptic transmission[103].

Given the crucial function of astrocytes in the CNS, it is not unexpected that they have been linked to the development and advancement of neurodegenerative illnesses. The aforementioned findings indicate that neurons might influence astrocyte protein expression by emitting miRNA-containing exosomes, which could be involved in the pathogenesis of neurodegenerative conditions. This could pave the way for further research on the correlation between exosomal miRNA and neurodegenerative diseases.

MiRNAs as biomarkers for PD

Early detection of neurodegenerative diseases is crucial, but also difficult due to pathological changes occurring years prior to symptom onset. As exosomes are natural carriers of miRNAs and cross the BBB, miRNA expression is known to be altered in various neurodegenerative diseases. It is, therefore, reasonable to suggest that exosomal miRNAs in peripheral blood may vary across different diseases. To explore this possibility, exosomal miRNAs were analysed in blood samples from patients with Parkinson's and Alzheimer's diseases[105,106]. Earlier research has examined the exosomal miRNA profiles found in the CSF of individuals with Parkinson's and Alzheimer's disease. These studies revealed notable changes in the miRNAs when compared with those found in healthy individuals. In the future, as miRNA profiles continue to be analysed and data from various expressions are integrated over time, exosomal miRNAs have the potential to become a valuable biomarker for identifying neurodegenerative diseases[107,108].

Molecular markers are substances that are produced by cells and can be continuously detected in body fluids, tissues, or cells. Exosomal miRNAs are an example of molecular markers found in body fluids, which remain stable and intact due to their protection from degradation by ribonuclease (RNase). In addition, these miRNAs can be safely stored for up to 48 hours at 4 °C in vitro, making them an excellent option for research and clinical applications. The role of micro-RNA as molecular markers is essential for understanding the diagnosis and treatment of various diseases[109]. The favourable properties of exosomal miRNAs aid in the quality of samples tested, highlighting their potential clinical use as biomarkers for specific diseases. Numerous research works have explored the use of miRNAs as biomarkers for neurodegenerative ailments[109–112].

Gui et al. found that during the initial stages of PD, there were 27 exosomal miRNAs originating from the CSF of patients with anomalous expressions. Among them, miR-153, miR-409-3p, miR-10a-5p, and Let-7g-3p were markedly raised, whereas miR-1 and miR-19b-3p were significantly lowered. This suggests that these miRNAs could be promising biomarkers for early detection of PD. These results further emphasise the critical role of micro-RNA in identifying and treating PD[107]. Moreover, it is believed that decreased levels of miR-19b and elevated levels of miR-24 and miR195 in serum exosomes could be indicative of PD in patients. Furthermore, a different investigation has proposed that miR-331-5p and miR-505 in plasma exosomes could be useful biomarkers. However, these findings are not uniform, similar to research on Alzheimer's disease[105,113].

Several miRNAs showed increased expression in plasma, including miR-155–5p, which normalised after treatment and could potentially serve as a marker for disease progression monitoring[114]. Moreover, four miRNAs (let-7 g-3p, miR-10a-5p, miR-153, and miR-409–3p) consistently showed higher levels in exosomes from CSF[115]. Conversely, miRNAs such as miR-146a-5p[114], miR-1, miR-19b-3p[115], and miR-133b[14] were downregulated, with miR-34b and miR-34c showing reduced expression in early PD stages[116]. Modulating these miRNAs is proposed as a strategy for PD treatment. Additionally, miR-7 depletion was noted in PD-affected regions[117]. The current literature only provides weak, but promising evidence about circulating miRNAs supporting their potential as biomarkers, including specific miRNA profiles identified in PD patients and the importance of larger cohort studies for validation. (Table 3).

Challenges in miRNA research in the field of PD

Multiple candidate miRNAs have been identified that might influence the progression of PD either through their effects within the CNS or in peripheral tissues. miRNAs can modulate numerous signalling pathways because each miRNA has the potential to target and bind to an average of 100–200 genes, acting as powerful regulators of gene expression[118]. Consequently, understanding the mechanisms behind the dysregulation of miRNAs in various diseases is crucial, as these miRNAs and their targets offer significant therapeutic potential for developing treatments.

Although miRNA research is crucial, there is a significant gap in the literature regarding miRNA activity in PD. Additionally, the findings from various miRNA studies have been inconsistent. Several potential limitations exist in the published research. One major challenge in identifying clinically significant miRNAs in diseases is the small sample sizes of clinical studies, which may lack the statistical power to detect meaningful differences in effect size. Additionally, the methods employed to characterise the miRNA profile in each study vary in sensitivity, influencing the resulting data. The absence of a standardised protocol for miRNA isolation and detection has resulted in the identification of distinct and non-replicable sets of potentially dysregulated miRNAs. Variations in study designs, experimental conditions, tissue sources, PD models, and sample characteristics—including sample size, clinical features, and pharmacological treatments—can lead to inconsistent results among studies. Consequently, clinical papers on the same disease might present vastly different miRNA expression profiles, complicating the process of identifying or validating biologically significant miRNAs[119,120].

Table 3 | summary of four different studies that investigated the potential of using exosomal miRNAs as biomarkers for diagnosis

Study	PD group(n)	Control(n)	Exosome source	RNA extraction	RNA identification	miRNAs expression	Exosomal miRNAs	Accuracy of diagnosis(AUC)
Gui et al. [115]	47	27	CSF	Qiagen miRNeasy Serum/Plasma Kit	TaqMan Real-Time PCR	Upregulated	ex- miR-10a-5p	0.900
							ex-miR-153	0.780
							ex-miR-409-3p	0.970
						Downregulated	ex-miR-1	0.920
							ex-miR-19b-3p	0.705
Cao et al. [105]	109	40	Serum	miRNeasy Mini Kit	RT-PCR followed by qPCR	Upregulated	miR-24	0.908
							miR-195	0.697
						Downregulated	miR-19b	0.753
Yao et al. [147]	52	48	Plasma	Exosomal RNA and Protein Extraction kit	RT-qPCR	Upregulated	ex-miR-331-5p	0.849
						Downregulated	ex-miR-505	0.898
Barbagallo et al. [148]	30	30	Serum	miRNeasy Mini-Kit (Qiagen)	TaqMan RT-PCR	Upregulated	ex-let-7d,	0.753
							ex-miR-22	0.845
							ex- miR-23a	0.869
							ex-miR-24	0.779
							ex- miR-142-3p	0.783
							and ex-miR-222	0.816

miR/miRNA microRNA, *PD* Parkinson's disease, *AUC* area under the curve, *CSF* cerebrospinal fluid, *RT-qPCR* quantitative reverse transcription polymerase chain reaction.

Challenges in miRNA-based therapeutic therapies

Using miRNAs as therapeutic agents presents a considerable challenge due to the difficulty in delivering them across the BBB into the CNS. This barrier restricts the entry of active substances, thus hindering the effectiveness of miRNA transfection. To overcome this obstacle, two approaches have been devised: restoring diminished miRNA levels using miRNA mimics (agonists) and inhibiting miRNA activity with anti-miRs (antagonists) to counteract excessive miRNA function[121–127].

The potential of miRNA-based therapies is significant, due to their potency, effectiveness, ability to silence genes for optimal durations, simplicity, safety, and easier manufacturing. However, there are challenges to overcome. Extracellularly, barriers like low RNA availability, enzymatic breakdown in the bloodstream, quick removal by the kidneys, uptake by immune cells, and toxicity due to immune responses pose obstacles. Intracellularly, like imprecise targeting, inefficient cellular uptake, and ineffective endosomal processing hinder their effectiveness. Addressing these hurdles is crucial for enhancing miRNA therapy's effectiveness by improving its pharmacokinetic and pharmacodynamic properties[124,125].

The uptake of miRNA-based therapeutic agents by unintended tissues can result in potential off-target effects. Additionally, the distribution of various therapeutics in the CNS is influenced by the presence of numerous specific transporters and receptors[123,128]. Another limitation is the susceptibility of bare nucleic acids to degradation by enzymes before reaching their intended destinations. Hence, a biologically responsive delivery system can shield the nucleic acids from degradation in serum and facilitate their penetration into targeted cells[128].

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Nour Shaheen: conceptualisation, methodology, writing- original draft preparation, and writing- reviewing and editing. Ahmed Shaheen: writing- reviewing and editing. Mahmoud Osama, Abdulqadir J. Nashwan: writing- reviewing and editing. Vishal Bharmauria and Oliver Flouty: writing- reviewing and editing. All authors approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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