Histol Histopathol (2018) 33: 447-453

http://www.hh.um.es

Histology and Histopathology

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Review

MiRNAs participate in the diagnosis, pathogenesis and therapy of Parkinson's disease

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Summary. MicroRNAs (miRNAs), one kind of post-transcriptional modification, mediate transcriptional silencing of various metabolic enzymes that are involved in various life processes, including Parkinson's disease. At present, the pathogenesis of Parkinson's disease is not clear, although many studies suggest that miRNAs play a very important role in the progress of Parkinsonism. This paper reviews the biological characteristics of miRNAs and summarizes the progress of miRNAs in reference to the diagnosis and pathogenesis of Parkinson's disease. It even considers miRNAs as a potential target for Parkinson's disease therapy.

Key words: Parkinson's disease, MicroRNAs, Diagnosis, Pathogenesis

Introduction

Parkinson's disease (PD), which is the second most prevalent neurodegenerative disorder after Alzheimer's disease and with only symptomatic treatment available, is characterized by selective loss of midbrain dopaminergic (DA) neurons (Mouradian et al., 2012). It is reported that PD occurs in about 1% of all individuals who are more than 65 years of age, and up to 4% of those who are more than 80 years of age (Qiu et al., 2015; Ding et al., 2016; Hass and Barnstable, 2016; Zhou et al., 2016). Its clinical symptoms can manifest as bradykinesia, rigidity, resting tremor and posture instability (Lim et al., 2010). The predominant pathological features that accompany PD are the degeneration of dopaminergic neurons within the substantia nigra pars compacta (Poole et al., 2016; Tatura et al., 2016). Cytoplasmic inclusions that cannot be degraded by proteasomes, accumulation of α-synuclein (α-Syn) that bind to ubiquitin and other proteins in Lewy bodies and Lewy neurites in DA neurons within substantia nigra (SN) appear to be one of the main causes of the disease.

MicroRNAs (miRNAs) have been considered to contribute to many neurodegenerative diseases (Marz et al., 2015; Properzi et al., 2015; Da Silva et al., 2016; Majidinia et al., 2016). The role of non-coding RNAs (ncRNAs) on the pathogenesis and/or progression of PD need to be noted. Many studies that involved those non-coding RNAs have been conducted to explain the mechanisms underlying PD. MiRNAs are mostly small ncRNAs (of 18-25 nucleotide in length) that control the expression of multiple genes at post-transcriptional level, play important roles in some essential biological processes by various mechanisms (Woldemichael et al., 2016). The involvement of miRNAs has been well documented in the development of PD, particularly for gene expression (Lee et al., 2016). The serum miRNAs may represent novel, specific and non-invasive biomarkers for the early detection of PD. Some studies suggest that miRNAs are potential therapeutic targets for Parkinson's disease (Santosh et al., 2009; Harraz et al., 2011; Grunblatt et al., 2012; Shtilbans et al., 2012; Bahnassawy et al., 2013; Dardou et al., 2013). Here, we

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DOI: 10.14670/HH-11-944

sought to provide a brief introduction of the roles of miRNAs in the pathogenesis of PD, as well as to use biomarkers for the early diagnosis and target therapy of PD.

MiRNAs involved in the pathogenesis of Parkinson's disease

It has been reported that only approximately 1.5-2% of the human genome is protein coding region, and that the remainder consists of transcripts without protein-coding capability. The latter is regarded as non-coding RNAs (ncRNAs) that have a critical regulatory activity in normal cellular development, function and pathogenesis of various diseases (Lenz, 2005; Stanislawska and Olszewski, 2005; Slack and Weidhaas, 2006; Felden, 2007; Bhatti et al., 2009). MiRNAs, which function as guide molecules in RNA silencing, constitute a dominating class of small RNAs in most somatic tissues (Trivedi and Ramakrishna, 2009). Mature miRNAs carry out their biological function(s) by pairing with the RISC in complementary sequences in the 3' UTR of target mRNA. This pairing very often represses the expression of target proteins and recruits co-factors to form complexes that are assisted with deacetylation and degradation of related target mRNA, finally suppresses gene expression.

Recently, a large number of miRNAs were found to be expressed in the vertebrate brain (Lee and Ambros, 2001; Lagos-Quintana et al., 2002). Kim and colleagues identified that miR-133b was a critical regulator in the development of midbrain DA neuron (Kim et al., 2007). This suggests that miRNAs have a significant role in the development of vertebrate neuron development (Sempere et al., 2004; Smirnova et al., 2005).

In PD, the key protein, which has been named α-synuclein, accumulates and aggregates in fibrillar form in the DA neurons. This results in the pathological hallmark lesions that are known as lewy bodies and Lewy neurites (Spillantini et al., 1997; Spillantini and Goedert, 2000). The human α-synuclein mRNA has a 3' untranslated region (3'-UTR) that is more than twice as long as its coding sequence (Sotiriou et al., 2009). Further, several putative target sequences for a number of miRNA species are present in the 3'-UTR. Several species of miRNAs have been demonstrated to down-regulate α-synuclein expression through their 3'-UTR, such as miR-7, miR-153 and miR-34b (Junn et al., 2009; Doxakis, 2010; Kabaria et al., 2015). Furthermore, an inhibitor of miR-7 could increase α-synuclein protein expression, which is associated with impairing of proteasome and cell death (Junn and Mouradian, 2002; Jiang, 2007). MiR-153 is another miRNA species that has been predicted to bind to the α-synuclein 3'-UTR and represses α-synuclein expression at both the mRNA and protein levels (Doxakis, 2010). As expected, there is significant synergy between miR-7 and miR-153 in α-synuclein repression (Doxakis, 2010).

In addition to studies of the direct functional interaction between particular miRNAs and their target mRNA encoding for PD associated proteins, these small RNAs can have indirect effects on the molecular underpinnings of PD. A recent study showed that several miRNAs, including miR-130, miR-98, miR-124, miR-204 and miR-142, could be putative post-transcriptional regulators of genes that are involved in the autophagy-lysosomal pathway (Jegga, 2011). These miRNAs are considered to play a critical role in the clearance of proteins, including α-synuclein, and organelles in PD and other neurodegenerative disorders (Cuervo, 2010).

MiRNAs for the diagnosis of Parkinson's disease

Currently, the diagnosis of PD is based mainly on neuroimaging and clinical manifestations using the UK PDS Brain Bank Criteria, Unified Parkinson's Disease Rating Scale and the modified HoehneYahr stage (Qiu et al., 2015; Da Silva et al., 2016). These examinations are very subjective and lack sensitivity. They can be applied only when the patient has certain motor features. PD clinical manifestations will appear when about 50%-70% of the dopaminergic neurons have been lost, causing patients to lose an opportunity for early treatment (Batistela et al., 2017). The observation of Lewy bodies in the midbrain by histopathological analysis can confirm a diagnosis of Parkinson's disease. However, obtaining the brain tissue sample from a living person is impracticable.

Some cell types, including neurons, are known to secret small membranous vesicles that are known as exosomes. Apart from their protein content, these vesicles have been shown recently to contain many kinds of mRNA and miRNA species (Yilmaz et al., 2016). MiRNAs can exist in a stable state in biological fluids, such as blood, urine and cerebrospinal fluid (CSF), because they are encapsulated in exosomes or found in complexes with Argonaute proteins and lipo-proteins, which cause them to be resistant to RNase that are present in the surrounding environment. Physical and pathological conditions may affect the secretion of micro-vehicles and change internal miRNAs' content copies. Because miRNAs in the blood can be directly detected by the RT-PCR method, they may serve as a sensitive indicator of various diseases.

It has been reported that PD patients and patients with other neurodegenerative diseases have significantly different tissue miRNA profiles (Alieva et al. 2015; Qiu et al., 2015). MiR-133b was first reported to be involved in PD in 2007, and the mechanism by which miR-133b contributes to the pathogenesis of PD has remained undiscovered (Kim et al., 2007; Zhao et al., 2014). One study found a significant decrease in the expression levels of serum miR-133b in PD patients in comparison to those of control subjects. Another experiment revealed that there was a significantly lower lever of expression of the serum biomarkers, including miR-29c, miR-146a, miR-214 and miR-221 in PD patients compared to healthy control populations (Santosh et al.,

2009). According to another study, five miRNAs (miR-195, miR-15b, miR-221, miR-181a and miR-185) were shown to have a significant difference in effects for PD patients and in healthy cohorts. Among the MiR-195 family members, including miR-195 and miR-15b, only miR-195 was able to influence the apoptosis of neural progenitor cells and modulate the proliferation of neural stem cells. This was due to its capability to directly suppress ADP-ribosylation factor-like protein 2 (ARL2) and Methyl-CpGbinding protein 1 (MBD1). The increase of miR-195 predicts more apoptosis and is associated with PD (Dong et al., 2016). MiR-221 decreased expression of Foxo3a and Apaf-1 which protects against neural stem cell unlock apoptosis and plays a critical role in neuronal differentiation. MiR-221 and miR-195 can be used as the biomarker to test apoptosis by estimating the degree of loss of the DA (Asci et al., 2013; Zongaro et al., 2013; Ma et al., 2016). Applying miR-181a, which is enriched in the brain, can reduce astrocyte dysfunction. The common targets of above 5 miRNAs include BCL2, CDC42, VEGFA and CDKN1B, which are closely related to neuronal apoptosis, regeneration, development and growth in the SN of the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse model. The loss of miR-124 contributes in part to the calpain/cdk5 pathway protein expression and increases with interaction to calpain 1 mRNA in the dopaminergic neurons. Also, it was found that overexpression of miR-124 can improve cell viability whereas using methy-pheny-pyridinium (MPP+) diminishes the expression of calpain/cdk5 pathway protein. In other experiments, scientists found that plasma circulating miR-1826/miR-450b-3p, miR-626 and miR-505 will achieve the highest predicted power of 91% sensitivity, 100% specificity, 100% positive predicted value and 88% negative predicted value by k-TSP1 analysis for PD, all of which may be candidates for the diagnosis of PD (Khoo et al., 2012).

MiRNAs are very sensitive to drug therapy. Thus, using the changes in levels to measure the therapy effecting, miRNAs and their target genes in patients with Parkinson's disease can serve as an excellent biomarker in clinical application. Recently, Schwienbacher et al. reported that miR-30a-5p upregulated in the plasma of L-dopa treated PD patients and silico analyses suggested that miR-30a-5p might have a regulatory role in mitochondrial dynamics and autophagy (Schwienbacher et al., 2017). Another study found that the levels of miR-7, miR-9-3p, miR-9-5p, miR-129 and miR-132 were increased by more than three times in treated patients with Parkinson's disease compared with those of the controls. These indicate a good start for the evaluations of the therapeutic effect and prognosis after drug or other therapy (Soreq and Wolf, 2011; Hebert et al., 2013). Above observations highlight the role of miRNAs in the origin and development of PD, and demonstrate the feasibility of using plasma-based circulating miRNAs as biomarkers for PD (Fig.1).

Low serum ceruloplasmin levels are always accompanied by Parkinson's disease, although the cause has yet to be clarified. Some studies have shown that the expression of MiR-133b was correlated with the ceruloplasmin level in patients with PD. More and more miRNAs have been investigated and related to the development of PD. These miRNAs are expected to become useful biomarkers for the clinical diagnosis of PD (Kim et al., 2007; de Mena et al., 2010; Schlaudraff et al., 2014; Kong et al., 2015).

It is very likely that the future diagnosis of PD will rely on the combination of clinical, laboratory, imaging and molecular genetic data. Using miRNA biomarkers for the detection of PD will play a more and more important role in the diagnosis of PD.

MiRNAs contribute to the progression of PD and provide the candidate targets for its therapy

PD is the second most common age-related neurodegenerative disorder. Its main clinical features are movement disorders. It is believed that about six million people worldwide suffer from PD. More and more research has suggested that miRNAs have the ability to regulate the expression of known PD-associated genes and gene products, including leucine-rich repeat kinase and α-synuclein. Although the detailed mechanisms of miRNAs in the development of PD still need to be explained (Nagatsu and Sawada, 2007; Haixia et al., 2012 ; Palm et al., 2012; Jebbink et al., 2015; Wang et al., 2015; Zhou et al., 2016), an increasingly close relationship between miRNA and PD has been revealed. The related miRNAs are summarized below (Table 1).

MiR-7

The progressive loss of dopaminergic neurons in substantia nigra compacta (SNc), accumulation of α-synuclein in Lewy bodies and neurites and excessive neuroinflammation all have important roles in the pathogenesis of PD. NLRP3 is considered to be the main inflammasome activation inducer, which leads to DA

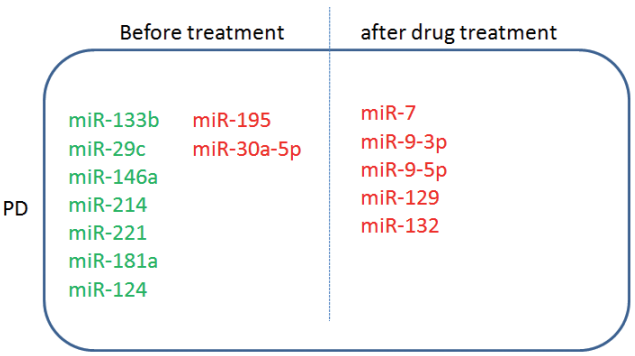

Fig. 1. miRNA expression in PD. Upregulation (red) and downregulation (green) miRNAs in plasma of PD before and after drug treatment.

neuronal degeneration and plays a critical role in accumulation of α-synuclein. Transfection of miR-7 significantly reduced NLRP3 protein levels, then subsequently inhibited inflammasome activation and protected DA neurons against degeneration in PD model mice (Junn et al., 2009; Doxakis, 2010; Zhang et al., 2012; Choi et al., 2014; Zhou et al., 2016). This suggests that miR-7 might be a therapeutic target for PD.

MiR-155

MiR-155 also has an essential role in the inflammatory response and neurodegeneration caused by α-synuclein in the brain. MiR-155 can upregulate the pro-inflammatory responses and promote α-synuclein-induced neurodegeneration. In one experiment, a notable repressed inflammatory response to α-synuclein fibrils, with attenuation of major histocompatibility complex class II (MHCII) and pro-inflammatory inducible nitric oxide synthase expression were observed in the primary microglia derived from miR-155(-/-) mice. By treating these microglia with a synthetic mimic of miR-155, the inflammatory response to α-synuclein fibrils is reversed. The data suggested that miR-155 can serve as a potential therapeutic target for downregulating the inflammatory response to α-synuclein in PD (Thome et al., 2016).

MiR-22

Overexpression of miR-22 significantly promoted the survival and proliferation of 6-OHDA-induced PC12 cells through upregulating the activity of caspase-3, and miR-22 inhibitor was able to reverse these effects. MiR-22 can also prolong the survival time of DA neurons by adjusting cell cycles. It appears that miR-22 could be a candidate target for the therapy of PD (Margis et al., 2011; Vallelunga et al., 2014; Ding et al., 2016; Yang et al., 2016). A luciferase reporter assay implied that transient receptor potential melastatin 7 (TRPM7) is a direct target gene of miR-22.

MiR-124

MicroRNA-124 (miR-124) is normally well-expressed in the DA neurons and its expression level decreases after treating with MPTP. Either MPTP-treated mice or MPP (+) -intoxicated SH-SY5Y cells appear as autophagosomes (AP) accumulation and lysosomal depletion. We employed miR-124 agonist or miR-124 mimics to upregulate miR-124 expression in MPTP-treated mice and MPP (+) -intoxicated SH-SY5Y cells, respectively. The loss of DA neurons was significantly reduced. Bim was proved to be a target gene of miR-124. This suggests that upregulation of miR-124 could exert anti-apoptosis and impaired autophagy process in the MPTP model of PD and, then, reduce the loss of DA neurons. Overexpression of miR-124 subsequently decreased the expression of the calpain 1/p25/cdk5 proteins and improved cell survival. MiR-124 attempts to control the expression of calpain/cdk5 pathway proteins in the dopaminergic neurons to reduce the loss of DA (Soreq and Wolf, 2011; Kanagaraj et al., 2014; Wang et al., 2016a,b).

MiR-34

MiR-34 can be divided into three distinct types. (A) Nrf2 is the target of miR-34a in both dopaminergic SH-SY5Y cells and PD mice. Overexpression of miR-34a could inhibit the neuroprotection and decrease cell survival through Nrf2. (B) MiR-34b and miR-34c have the effect of repressing the expression of α-synuclein and promoting the aggregation of α-synuclein in SH-SY5Y cells. When miR-34b/34c were decreased in several affected brain regions in PD, polymorphisms in the 3'-UTR of α-synuclein showed that α-synuclein expression was up-regulated (Mouradian et al., 2012; Vallelunga et al., 2014; Ba et al., 2015). In addition,

Table1. miRNAs and targeted therapy of PD.

miRNA	Target	Function	Reference
miR-7	NLRP3	miR-7 inhibited inflammasome activation and protected DA neurons by reducing NLRP3 protein expression in PD model mice	Zhou et al., 2016
miR-155	MHCII, pro-iNOS	MiR-155 can upregulate the pro-inflammatory responses and promote α-synuclein-induced neurodegeneration	Thome et al., 2016
miR-22	TRPM7	Overexpression of miR-22 significantly promoted the survival and proliferation of 6-OHDA-induced PC12 cells through upregulating the activity of caspase-3	Ding et al., 2016; Yang et al., 2016
miR-124	calpain 1/p25/cdk5	upregulation of miR-124 could exert anti-apoptosis and impaired autophagy process in the MPTP model of PD and, then, reduce the loss of DA neurons	Soreq and Wolf, 2011; Kanagaraj et al., 2014; Wang et al., 2016a,b
miR-34	Nrf2, α-synuclein	Overexpression of miR-34a could inhibit the neuroprotection and decrease cell survival through Nrf2. MiR-34b and miR-34c have the effect of repressing the expression of α-synuclein and promoting the aggregation of α-synuclein in SH-SY5Y cells	Mouradian et al., 2012; Vallelunga et al., 2014; Ba et al., 2015
miR-126	IGF-1/PI3K/AKT	miR-126 could downregulate IGF-1/PI3K/AKT signaling and increase the neurotoxic effect of 6-OHDA	Kim et al., 2016
miR-494	DJ-1	MiR-494 could decreased the abundance of DJ-1 which rendered cells more resistant to oxidative stress	Xiong et al., 2014

miR-34b inhibitor could increase the expression of endogenous A2AR, which is another important marker of loss of dopaminergic denervation (Minones-Moyano et al., 2011; Villar-Menendez et al., 2014; Kabaria et al., 2015). All of these studies indicate that the downregulation of miR-34b/c is an early event in PD patients. Along with the progression of PD, miR-34b was reduced in the SN of PD patients. MiR-34 can be seen as the best candidate therapy target.

MiR-126

MiR-126 is associated with insulin/IGF-1/PI3K signaling. Overexpression of miR-126 could downregulate IGF-1/PI3K/AKT signaling and increase the neurotoxic effect of 6-OHDA. MiR-126 may be a candidate of PD therapy (Kim et al., 2016).

MiR-494

DJ-1 is thought to be an oxidative sensor that protects cells from oxidative insult. Abnormal DJ-1 expression might contribute to PD pathogenesis. MiR-494 could bind to the 3'UTR of DJ-1, and inhibit the protein expression of DJ1. *In vitro* experiments showed that overexpression of miR-494 significantly decreased the abundance of DJ-1 which rendered cells more resistant to oxidative stress. In an MPTP mouse model, overexpression of miR-494 down-regulated DJ-1 expression and exacerbated MPTP-induced neurodegeneration, as illustrated by the loss of dopaminergic neurons (Xiong et al., 2014).

Other miRNAs

MicroRNAs (-144, -199b, -221, -488, -544) were also found to be upregulated in the progression of PD. It has been suggested that they target and reduce the expression of their target genes (Tatura et al., 2016). These target genes include: (1) the DNA damage regulated autophagy modulator 1 (DRAM1) that is regulated by miR-144, (2) Ellis Van Creveld (EVC) protein that is regulated by miR-221, (3) Zinc Finger Protein 440 (ZNF440) that is regulated by miR-199b, (4) Mitochondrial Methionyl-tRNAFormyltransferase (MTFMT) that is regulated by miR-488 and (5) Xin Actin Binding Repeat Containing (XIRP2) that is possibly regulated by miR-544a.

Another study showed that dme-miR-133-3p, dme-miR-137-3p, dme-miR-13b-3p, dme-miR-932-5p and dme-miR-1008-5p were upregulated in PD profiles. Three of them, miR-13b, miR-133 and miR-137, are brain enriched. MiR-137 was reported to regulate most of the certain targets in the signaling pathway of PD pathogenesis, including dopamine receptor (DopR, D2R), gamma-aminobutyric acid (GABA) receptor (GABA-B-R1, GABA-B-R3) and N-methyl-D-aspartate (NMDA) receptor (Nmdar2). Expression of miR-137 and its targets was negatively correlated in α- synuclein aggregation. This is an important character of PD progression (Kong et al., 2015). In addition, an experiment has revealed a novel regulatory mechanism in which miR-16-1 could down regulate the expression of Hsp70, which negatively regulates α- synuclein aggregation and might contribute to PD development (Zhang and Cheng, 2014).

Conclusion

Parkinson's disease is a progressive neurological disease, and the pathogenesis has not been elucidated. MiRNAs play an important regulatory role in the process of cell growth, differentiation and function. More and more Parkinson-related miRNAs have been found. These findings help us to understand, diagnose and treat disease. In the near future, we will be able to cure Parkinson disease.

Acknowledgements: This work was supported by the Beijing municipal science and technology commission (Grant No. Z151100004015219), the National Nature Science Foundation of China (Grants No. 81172384 and No.30873029).

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Accepted November 14, 2017