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MicroRNAs in Parkinson's Disease

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Abstract

MicroRNAs are small non-protein coding RNAs that regulate gene expression through post-transcriptional repression. Recent studies demonstrated the importance of microRNAs in the nervous system development, function and disease. Parkinson's disease is the second most prevalent neurodegenerative disease with only symptomatic treatment available. Recent success in using small RNAs as therapeutic targets hold a substantial promise for the Parkinson's disease field. Here we review recent work linking the microRNA pathway to Parkinson's disease.

Keywords

microRNA; small noncoding RNA; RNA induced silencing; Parkinson's disease; neurodegenerative diseases

1.0 Introduction

1.1 Parkinson's disease

Parkinson's disease (PD) is a progressive age-dependent neurodegenerative disorder that affects an estimated 1% of the population over 50. It is characterized clinically by resting tremor, bradykinesia, cogwheel rigidity, and postural instability (Savitt et al. 2006). In 1893 Blocq and Marinesco reported their findings from the autopsy of a 38 years old patient with unilateral Parkinsonism. They described a 2–5 cm lesion in the contra-lateral half of the

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Author contributions:

M.M.H prepared a draft of the article. T.M.D and V.L.D revised the article. All authors have approved the final article.

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mid-brain that destroyed the right substantia nigra (SN) and nearby parts of the ventral tegmentum (Blocq 1893). Thereafter, cumulative evidence confirmed that loss of dopaminergic neurons in the SN pars compacta, which results in loss of dopamine in the striatal projections of these neurons, underlies the motor syndrome of PD. Pathologically, PD is characterized by intraneuronal inclusions called lewy bodies containing abnormal aggregates of the presynaptic protein α -synuclein as their main component. While PD is mainly a sporadic disease, several genes have been linked to the rare monogenic forms of the disease such as α -synuclein, leucine-rich repeat kinase 2 (LRRK2), parkin, PTEN-induced kinase 1 (PINK1) and DJ-1. Recent evidence indicates that dysfunction of these pathways play a direct role in the etiology of the sporadic form of the disease as well. For a more detailed discussion of the molecular pathogenesis of PD, the reader is referred to more in depth reviews (Dawson and Dawson 2003; Gasser 2009).

Since the description of PD by James Parkinson in 1817 (Parkinson 1817), the only therapeutic breakthrough was made in the 1960s by the use of Levodopa to replace endogenous dopamine deficiency (Cotzias 1968). Despite the major strides made in our understanding of the pathophysiology of the disease, our ability to intervene remains stagnant at symptomatic management. Recent characterization of druggable molecules such as microRNAs carries therapeutic potential for complex disease processes such as PD. In this article, we review the current evidence in the literature linking the miRNA pathway to PD pathophysiology.

1.2 MicroRNA biogenesis

The discovery of microRNAs (miRNAs) 10 years ago uncovered a complex layer of post-transcriptional regulation of gene expression (Lagos-Quintana et al. 2001; Lau et al. 2001; Lee and Ambros 2001). MicroRNAs are small non-coding regulatory molecules that are important in multiple physiologic and disease processes such as stem cell biology and neurodegeneration. Due to their small size and relative ease of delivery, miRNAs are promising therapeutic tools/targets in major diseases such as cancer, cardiovascular diseases and neurodegenerative disorders.

MiRNAs are transcribed by RNA polymerase II into a primary transcript (pri-miRNA) forming a self-folded hairpin structure, which is recognized and processed by the Drosha/DGCR8 enzyme complex into a ~70 base pair (bp) long precursor miRNA (pre-miRNA). Pre-miRNAs are actively transported from the nucleus to the cytoplasm where they are further processed by dicer into a ~23 bp double stranded miRNA/miRNA*. One strand (sometimes each strand) is incorporated into the RNA-induced silencing complex (RISC), which contains an argonaute (Ago) family member protein as a core component. Mature miRNAs guide RISC to recognize their target mRNAs through partial complementarity to target sequences localized mostly in the 3'UTR, which lead to mRNA degradation or translation repression (Bartel 2009).

1.3 Role of translation regulation in PD

Recent evidence suggests that translation regulation is an important process in the pathophysiology of PD. For example, post-transcriptional regulation of protein expression levels was linked to DJ-1 in sporadic PD (Blackinton et al. 2009). Another study demonstrated that overexpression of the translation inhibitor *Thor* (Drosophila homolog of mammalian eukaryotic initiation factor 4E-binding protein; 4E-BP) inhibits the abnormal phenotypes as well as limits dopaminergic neurons loss in *parkin* and *PINK1* Drosophila models of PD (Tain et al. 2009). In addition, genetic and biochemical evidence suggest that LRRK2 modulates the maintenance of DA neurons by regulating protein synthesis through phosphorylation of 4E-BP. This phosphorylation seems important in mediating the

pathogenicity of mutant *Drosophila* LRRK (Imai et al. 2008). These studies emphasize the emerging role of post-transcriptional regulation of protein expression in PD. In this review we focus on the miRNA mediated translation regulation relevant to PD pathophysiology.

2.0 the microRNA pathway and PD

2.1 Differential miRNA expression in Parkinson's disease

Asa Abeliovich and his colleagues carried out miRNA profiling using qPCR in RNA samples from PD patients and normal controls. Among a panel of 224 precursor miRNAs, 8 were enriched in midbrain; pre-let7a-1, pre-miR7-2, -99a, -130, -133b, -136, -224, and -143. Notably, pre-miR-133b was downregulated in PD samples more than 6 times. Several other pre-miRNA were expressed in high levels in the midbrain and downregulated significantly in PD samples such as pre-miR-218-2, -15b, -101-1, -107, -335, -345. Conversely, pre-miR-132 demonstrated low expression level in midbrain compared to cerebral cortex and cerebellum yet it was upregulated about 70-fold in PD patients' midbrain samples (Kim et al. 2007). While the observed downregulation of miRNAs might be due to the loss of midbrain dopaminergic neurons, it also raises the possibility that these miRNAs might be involved in PD pathogenesis.

2.2 miRNA pathway and dopaminergic neuron development

Current therapy for PD is only symptomatic while the progressive disability takes place. The promise for changing the course of the disease is in regenerative medicine. Stem cell or reprogrammed cell disease modeling and therapy carry a lot of potential for PD management in the near and distant future. Understanding the factors involved in midbrain dopamine neurons development is essential for successful cell replacement therapy in PD (Goya et al. 2007). Many studies demonstrated that miRNAs are required for the survival and differentiation of neuronal committed progenitors and immature neurons but not for earlier stages of neuronal progenitors (Choi et al. 2008; Conaco et al. 2006; De Pietri Tonelli et al. 2008; Makeyev et al. 2007). From a stem cell therapy standpoint, postmitotic immature neuron stage is safer for grafting since earlier stages of neuronal progenitors carry greater risk of developing tumors. These findings emphasize the importance of the miRNA pathway role in stem cell transplantation therapy for PD.

Both in vitro and in vivo evidence demonstrate that the miRNA pathway is required specifically for midbrain dopaminergic neuronal differentiation. Dicer deficiency in murine ES-derived immature dopamine neurons enhanced cell death and inhibited differentiation resulting in loss of differentiated (TH positive) dopamine neurons. Moreover, small RNA species from murine embryonic midbrain rescued midbrain dopaminergic neurons differentiation in dicer deficient cells (Kim et al. 2007). In mice, Wnt1-cre-mediated conditional Dicer knockout led to malformation of the midbrain, cerebellum and mandible. Dicer deletion almost eliminated TH positive neurons in midbrain and led to impaired differentiation of midbrain dopaminergic neurons demonstrated by partial expression of mature midbrain dopaminergic neuronal markers (Huang et al. 2010).

Deletion of dicer in postmitotic dopamine neurons (*DAT^{CRE/+};Dicer^{flox/flox}*), resulted in progressive loss of midbrain dopaminergic neurons between postnatal 2–6 weeks of age (Kim et al. 2007). On the other hand, Dicer deletion in postmitotic striatal dopaminergic neurons (*DR-1^{CRE/+};Dicer^{flox/flox}*) was not associated with significant neuronal cell loss. These conditional knockout mice had astrogliosis, movement behavioral deficits, and reduced brain size probably due to smaller neurons (Cuellar et al. 2008). These different outcomes raise interesting questions demanding further investigations to explore the mechanism(s) by which the striatal dopamine receptive neurons escaped cell death in the absence of miRNAs.

miR-133b is enriched in the human and mouse midbrain but reduced in PD patient midbrain samples as well as in mouse dopamine neuron deficient models. In midbrain dopaminergic neurons, miR-133b suppresses pituitary homeobox 3 transcription factor (Pitx3) expression. Pitx3 deficiency results in selective loss of nigrostriatal DA. Pitx3 activates miR-133b expression in midbrain dopaminergic neurons. Overexpression of miR133b reduces and conversely inhibition of miR-133b enhances DA neurogenesis and function of DA neurons. Thus miR-133b and Pitx3 create a negative feedback loop in which Pitx3 enhances the expression of miR-133b that, in turn represses pitx3 translation. This negative feedback loop regulates midbrain dopaminergic neurons terminal differentiation and activity (Kim et al. 2007). In a search for polymorphism in miR-133b and Pitx3 in 1,027 PD patients versus 860 healthy controls, no association was found between genetic variants and PD risk (de Mena et al. 2010b). Regulation of midbrain dopaminergic neurons differentiation and function by miR-133b makes it a candidate therapeutic target in PD cell replacement transplantation therapy.

2.3 miRNA and PD linked genes

α -Synuclein plays important role in PD pathogenesis. While point mutants are linked to PD, elevated levels of synuclein lead to PD development as well (Singleton et al. 2003). Two microRNAs were recently described to regulate endogenous synuclein levels; miR-7 (Junn et al. 2009) and miR-153 (Doxakis 2010). MiR-7 regulated endogenous α -synuclein protein level. Inhibition of α -synuclein expression by miR-7 protected against oxidative stress mediated cell death. Despite the adequate verification of synuclein targeting by these miRNAs, the physiological significance and relevance to the mechanism of PD pathology is still unclear. However, both miRNAs provide candidate therapeutic targets for modulating synuclein levels in PD.

Bingwei Lu and colleagues demonstrated that let-7 and miR-184* mediate LRRK2 pathogenicity in drosophila DA neurons and identified the transcription factors E2F1 and DP as their direct targets. Pathogenic LRRK2 inhibited let-7 and miR-184* function and consequently E2F1 and DP were upregulated. Such effects were dependent on LRRK2 kinase activity. Moreover, inhibition of let-7 or miR-184* in wild-type flies resulted in a pathogenic phenotype similar to that associated with pathogenic LRRK2. While E2F1 and DP have well characterized roles in cell cycle regulation, the authors speculated that in neurons their upregulation might result in abortive cell division and cell death. In addition, the RISC core protein argonaute co-immunoprecipitated with pathogenic LRRK2, which negatively regulated argonaute level in aged but not young flies and promoted its association with the phosphorylated 4E-BP (Gehrke et al. 2010). This raises mechanistic questions for the role 4E-BP plays in LRRK2 mediated regulation of the miRNA machinery. These findings demonstrate that the role of LRRK2 in the pathogenesis of PD is mediated through the miRNA pathway, thus, paving the way for new therapeutic strategies for PD.

2.4 Genetic polymorphisms of miRNA related sequences and risk for PD

Fibroblast growth factor-20 (FGF20), a neurotrophic factor preferentially expressed in SN pars compacta enhances the survival of DA neurons (Ohmachi et al. 2000). Jeffery Vance and colleagues demonstrated that FGF20 polymorphism in one intronic single nucleotide polymorphism (SNP), rs1989754, and two 3'UTR SNPs, rs1721100 and ss20399075, influence the risk of PD in a USA family study (van der Walt et al. 2004). Interestingly, in a Japanese population study, the 3'UTR rs1721100 was found to be associated with risk for PD as well (Satake et al. 2007). However, a study conducted in Finnish and Greek PD patients did not detect association between the above-mentioned SNPs and PD (Clarimon et al. 2005). It is worth noting however that the latter study had a much smaller sample size.

Whether these variations in the FGF20 3'UTR disrupt an miRNA binding site and regulates FGF20 expression levels remains unclear.

More recently another FGF20 3'UTR SNP, rs12720208 was identified that is associated with risk for PD. The authors used 3'UTR luciferase assay to demonstrate that rs12720208 disrupts a miR-433 target site in FGF20 3'UTR. Moreover, increased levels of FGF20 led to upregulation of α -synuclein. Human brain samples homozygous for the variant allele demonstrated upregulation of both FGF2 and α -synuclein. The authors propose that elevated FGF20 might predispose to PD through long-term upregulation of α -synuclein and further speculated that FGF20 might enhance neurogenesis early in life but chronic elevation leads to degeneration during later life stages (Wang et al. 2008). Along the same lines, the association of rs12720208 with larger hippocampal volume using magnetic resonance imaging (MRI) in young adults but steeper decrease in hippocampal volume with aging, reduced verbal episodic memory and increased levels of FGF20 mRNA suggests that FGF20 plays important role in regulating these processes (Lemaitre et al. 2010). Conversely, a USA study and another Spanish population study found no association between rs12720208 and risk for PD in a relatively large datasets (de Mena et al. 2010a; Wider et al. 2009). Thus, FGF20 probably plays an important role in subpopulations of PD.

3.0 Concluding remarks

Emerging evidence strongly indicate a major role for translational regulation in PD pathophysiology. The miRNA pathway is one of the major translation regulation pathways. Multiple miRNAs have been linked to PD (Table 1) opening new avenues for therapeutic targets. While translational applications of research findings in the field are still to be developed, lessons learned from miRNA use as biomarkers and therapeutic targets in cancer research pave the way for PD applications development.

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Research Highlights

- Differential miRNA expression in Parkinson's disease.
- The microRNA pathway regulates dopaminergic neuron development and function.
- Synuclein regulation by miRNAs.
- LRRK2 regulates the microRNA pathway.
- Genetic polymorphism of miRNA related sequences confers risk for PD.

Table 1

MicroRNAs potentially involved in PD pathophysiology.

miRNA	target	function	reference
miR-133b	Pitx3 ^a	regulates DA neurons differentiation and activity	(Kim et al. 2007)
miR-7	α -synuclein	regulates oxidative stress mediated cell death	(Junn et al. 2009) (Doxakis 2010)
miR-153	α -synuclein	unexplored	(Doxakis 2010)
let-7 & miR184*	E2F1 & DP ^b	regulate DA ^c neurons survival and activity	(Gehrke et al. 2010)
miR-433	FGF20 ^d	unexplored	(Wang et al. 2008)

^a Pitx3 (pituitary homeobox 3),

^b E2F1 & DP (transcription factors),

^c DA (dopaminergic),

^d FGF20 (fibroblast growth factor 20).