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REVIEW

MicroRNAs: Possible Role in Pathogenesis of Parkinson's Disease

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Abstract—Parkinson's disease is one of the most common human neurodegenerative disorders caused by the loss of dopaminergic neurons from the *substantia nigra pars compacta* of human brain. However, causes and mechanisms of the progression of the disease are not yet fully clarified. To date, investigation of the role of miRNAs in norm and pathology is one of the most intriguing and actively developing areas in molecular biology. MiRNAs regulate expression of a variety of genes and can be implicated in pathogenesis of various diseases. Possible role of miRNAs in pathogenesis of Parkinson's disease is discussed in this review.

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Parkinson's disease (PD) is a severe neurological disorder, which is one of the most common human neurodegenerative disorders (NDDs). PD invariably progresses with time, because of the death of dopaminergic (DA) neurons in substantia nigra pars compacta of human brain. A number of genes involved in PD pathogenesis is known to date, however, mechanisms of PD progression are not sufficiently clarified.

Recently discovered class of RNA, miRNAs, is actively studied in context of their role in functions of both individual cell and whole organism. miRNAs are short single-stranded RNAs 21-24 nucleotide in length. The first miRNA, *lin-4*, was found in *Caenorhabditis elegans* in 1993 [1], and by 2001 several tens of miRNAs were found in humans and insects, all possessing similar mechanism of activity. This has enabled establishment of a novel RNA type, miRNAs [2]. More than 1600 plant and 6900 animal miRNAs are known to date [3].

miRNAs are supposed to regulate expression of about 30% of human genes [4, 5]. One of main mechanisms of miRNA activity is supposed to be blocking the translation initiation [6-8]. Individual miRNAs can regulate translation of hundreds of different mRNAs [9-13].

The role of miRNAs in biological processes is actively studied. In particular, involvement of miRNAs in neuronal differentiation is confirmed by functional changes in expression of miRNAs during brain development [14-16]. The role of miRNAs in physiology of the nervous system is also supported by data on the involvement of miRNAs in nervous cell differentiation, both *in vitro* and *in vivo* [17-19]. Besides, it was shown in a series of works that miRNAs could be implicated in pathogenesis of various diseases [20-22]. The role of miRNAs in NDD, especially PD, is of particular interest [20, 23, 24]. This review summarizes the contemporary data on implication of miRNAs in function of DA-neurons and their possible effect on development of pathological processes in PD.

ROLE OF miRNA BIOGENESIS PROTEINS IN PD

Several reports have suggested that disturbance of miRNA biogenesis can significantly affect functions of the nervous system and the whole organism as well [19, 25].

The role of miRNAs and proteins of their biogenesis in pathogenesis of PD was first reported in 2007 by Kim et al. [19]. According to their data, tissue-specific removal of the *Dicer* gene *in vivo* from DA-neurons of mouse brain *substantia nigra* leads to death of these cells. Behavioral studies of the animals with knocked out *Dicer*

Abbreviations: DA-neuron, dopaminergic neuron; NDD, neurodegenerative disease; PD, Parkinson's disease; SNP, single nucleotide polymorphism; UTR, untranslated region.

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by the open field method revealed decrease in their mobility resembling the PD phenotype. It was also found that deletion of *Dicer* is partially compensated by transfection with small RNAs isolated from fetal midbrain of healthy mice [19].

Experiments *in vitro* also demonstrated that removal of *Dicer* results in disturbance of DA-neuron differentiation from mouse embryo stem cells due to blocking of miRNA biogenesis. Nevertheless, the maturation rate of DA-neurons differentiating from these cells can be partially restored by transfection with low molecular weight RNA fraction isolated from the wild-type mouse embryo midbrain cells [19].

Interestingly, neurodegeneration is also observed in mice with deletion of *Dicer* in the cerebellum. The absence of the Dicer protein leads to the death of Purkinje cells, which results in ataxia. A model of Purkinje cell degeneration in the absence of miRNAs demonstrates obvious similarities with processes occurring in slowly progressing NDDs such as Alzheimer's and Parkinson's diseases [26].

In another work, *Dicer* was removed from mouse striatum neurons carrying receptors for dopamine [27]. These animals demonstrated some physiological abnormalities, such as decrease in size of brain and neurons, ataxia, atrophy, and premature death [27], but the number of DA-neurons was unchanged [28, 29].

Also, the role of other enzymes of miRNA biogenesis in development and functions of the nervous system was studied in a series of works, but clear data on their implication in the pathogenesis of PD was not obtained [30].

ROLE OF miRNAs IN REGULATION OF GENES INVOLVED IN PATHOGENESIS OF PD

Many miRNAs are known that can be implicated, directly or indirectly, in development of PD. In the human genome 17 loci are mapped that are associated with PD. For eight of them, the genes are identified, particularly *SNCA*, *PARK2*, *PINK1*, *PARK7*, and *LRRK2*, whose mutations lead to monogenic PD forms. Expression of these genes can be regulated by different miRNAs and influence development of the pathological process [23, 30-32].

miRNAs and *SNCA*. The first identified gene that is associated with familial PD is the alpha-synuclein gene (*SNCA*) encoding the protein SNCA; it is one of the key genes implicated in the development of PD [33]. The specific role of this protein is still unknown. Some data suggest that it is a molecular chaperone that regulates protein–protein and protein–lipid interactions and can play an important role in the metabolism of synaptic vesicles and storage and compartmentation of neurotransmitters, particularly dopamine [34].

In a recent work a previously unknown mechanism was found by which the level of *SNCA* transcript is regulated in the nervous system; its elevated expression is a characteristic feature of PD [23]. In particular, it was shown that the miRNAs miR-7 and miR-153, which are abundantly expressed in brain, preferentially bind to the *SNCA* mRNA 3′-untranslated region (3′-UTR) and significantly decrease the level of SNCA synthesis; also, miR-7 inhibits *SNCA*-dependent cell death [31]. Quantitative analysis of gene transcripts and SNCA protein showed coexpression of miR-7, miR-153, and *SNCA* both in the developing and the mature nervous tissue. Thus, it was shown that, first, miR-7 and miR-153 exert synergic effect; second, just *SNCA* mRNA 3′-UTR is necessary for regulation of the expression of this gene; third, miRNAs do not interact with the coding region of *SNCA* to regulate its expression; fourth, miRNAs act at a pre-translational level [23]. Since none of these miRNAs is completely complementary to *SNCA* mRNA, regulation of this mRNA level is likely due to miR-7- and miR-153-induced elevation of mRNA de-adenylation and uncapping [35, 36]. High expression levels of miR-7, miR-153, *SNCA* mRNA, and SNCA proteins are found in nervous tissue, particularly, in midbrain, hippocampus, and cortex. Moreover, the levels of miR-7, miR-153, and *SNCA* mRNA are significantly higher in neurons compared to astrocytes. In other organs, such as lung and heart, the level of these RNA transcripts was considerably lower. Interestingly, miR-7, miR-153, and *SNCA* mRNA are actively synthesized in midbrain. miR-7 was found in *substantia nigra*, and this fact suggests its possible implication in maintenance of normal function of DA-neurons. Furthermore, both the level mRNA expression and the amount of SNCA protein demonstrate that in the course of development the protein is translated at constant *SNCA* mRNA level regulated by miRNAs. These results indicate that mir-7 and mir-153 are co-expressed with SNCA in neurons to regulate its level through a transcription feed-forward loop [23]. It is worth noting that miR-7 decreases sensitivity of neuroblastoma cells to the oxidative stress induced by a mutant SNCA, which confirms the stress-protective effect of this miRNA in nervous cells [31, 37]. Thus, these data support an important role of miR-7 and miR-153 in regulation of SNCA level in the nervous system.

Other miRNAs can also influence the *SNCA* expression. In particular, a correlation was found between elevated expression of *SNCA* and elevated translation of FGF20 in cell cultures and brain tissues of patients with PD. *FGF20* is preferentially expressed in *substantia nigra*, and it stimulates maturation of DA-neurons [32]. In 2001, association analysis demonstrated the link between the risk of development of PD and single-nucleotide polymorphisms (SNPs) in the region of chromosome 8 containing the fibroblast growth factor 20 gene (*FGF20*) [38]. Later, in this gene an association was found between

the SNP rs12720208 and risk of PD. This SNP is localized in the *FGF20* 3′-UTR, and it was shown *in vitro* that this region contains the recognition site for miR-433, the miRNA that is actively expressed in brain [32].

In one of first works on the search for human blood miRNAs implicated in the development of PD, six miRNAs were found whose levels differed from control. The levels of miR-1, miR-22*, and miR-29a were lower in untreated patients compared with healthy persons, while the levels of miR-16-2*, miR-26a-2*, and miR-30a were higher in treated patients compared with untreated ones. It is worth noting that all these miRNAs can be indirectly associated with the functioning of SNCA. It is known that miR-1 and miR-30a are involved in regulation of dopamine transport. Targets of miR-1 are the gene *TPPP/p25* encoding tubulin polymerization-promoting protein found in plaques in PD brain and the gene *CLTC* encoding clathrin heavy chain 1 [39]. Elevated expression of TPPP/p25 can serve as a marker of pathological processes associated with SNCA aggregation [40]. In turn, clathrin can be implicated in microglial endocytosis of aggregated SNCA and be associated with activation of microglia [41]. The target of miR-30a is the dopamine transporter gene *DAT* (*SLC6A3*) encoding a protein that – in complex with other proteins – provides reuptake of free dopamine in the synapse. SNCA modulates the activity of DAT, thus regulating the synaptic concentration of dopamine [42]. Thus, miR-1 and miR-30a can be implicated in the pathogenesis of PD. Besides, miR-30a can bind to *FGF20*, which also has a binding site for miR-16-2* [39]. The targets of miR-22* can be the gene *TP53BP2* encoding a tumor suppressor – protein p53 binding protein 2 – and the gene *GRIA1* encoding the glutamate receptor 1 precursor, which is also a target of miR-26a-2* and miR-30a [43]. The target of miR-29a is the septin gene *SEPT4*. The concentration of septin 4 is elevated in PD postmortem tissue of *substantia nigra*. In parallel with increase in septin 4 level, the level of SNCA is also increased in PD patients [44].

miRNAs and *LRRK2*. The *LRRK2* gene encoding kinase 2 with leucine-enriched repeats (the protein is also known as dardarin) was identified in 2004 in families with late-onset autosomal dominant PD [45, 46]. Numerous missense mutations have been revealed in the *LRRK2* gene to date, and these can substantially contribute to the etiology of both familial and sporadic PD [47]. Dardarin is supposed to possess GTPase activity, which is typical of ROCO family protein members. LRRK2 can participate in apoptosis, regulation of neuronal survival, control of the synaptic vesicle cycle, axon growth and branching, as well as in functioning of Golgi apparatus, lysosomes, and mitochondria [48-50].

Analysis of transgenic Drosophila carrying a mutant *lrrk* gene (I1915T) or expressing human *LRRK2* gene with G2019S mutation has demonstrated that defective LRRK2 does not possess GTPase activity. The *LRRK2* gene therewith ceased regulating the translation of transcription factors E2F1 and DP [30], which are involved in cell cycle control and cell survival [51]. miRNAs of the let-7 and miR-184* families were found to inhibit activity of these factors as well. Deletion of the *let-7* gene, blockage of let-7 and miR-184*, and blockage of binding sites for let-7 and miR-184* in 3′-UTRs of their target mRNAs led to increase in E2F1 and DP synthesis and development of toxic effect resembling that observed in *LRRK2* transgenic flies. This, in turn, resulted in decrease in motor activity and number of DA neurons. On the other hand, the elevation of let-7 and miR-184* levels alleviates the unfavorable effect of mutant LRRK2 [30].

***PARK2*, *PARK7* and miRNAs.** In accordance with numerous studies, the genes *PARK2* and *PARK7* are also involved in the pathogenesis of PD. In 1997 the *PARK2* gene was mapped to the chromosomal region 6q25.2-q27 [52]. This gene encodes the parkin protein [53], whose dominant function is E3 ubiquitin ligase. Ubiquitinylation of damaged proteins catalyzed by parkin is followed by their subsequent proteasomal degradation. At present, more than 100 families with autosomal recessive juvenile Parkinsonism are described, in which various mutations in the *PARK2* gene are the cause of the development of PD [54].

PARK7 gene encodes DJ-1 protein. The protein has antioxidant properties that remove peroxides via their autooxidation. Besides, DJ-1 can be involved in regulation of apoptosis; it can also act as a redox chaperone inhibiting the aggregation of SNCA [55]. Some data suggests that DJ-1 can bind to parkin during oxidative stress and protect mitochondria from damage, thus indicating the common neuroprotective role of these two proteins [56].

A recent study demonstrated that low levels of miR-34b and miR-34c in DA-neurons differentiated from SH-SY5Y neuroblastoma cells were accompanied by a decrease in parkin and DJ-1 concentrations that led to disturbance of mitochondria function and decrease in viability of the cell. Besides, substantial decrease in miR-34b/c levels was found in the brain of PD patients compared with healthy control. Note that brain samples from PD patients with decreased miR-34b/c levels also contained significantly decreased concentrations of parkin and DJ-1 proteins. Genes for these miRNAs are located on chromosome 11 and are transcribed as a single miRNA precursor. The levels of miR-34b and miR-34c are decreased by 40-65% in *corpus amygdaloideum*, *substantia nigra*, and frontal cortex of PD patients, but it is still unknown whether this decrease results from the death of DA-neurons or from specific processes in the residual DA-neurons [57]. Nevertheless, there is no experimental evidence for miR34b/c targeting to genes encoding parkin and DJ-1.

miRNA and other candidate genes in the pathogenesis of PD. The work of Kim et al. (2007) was the first study focused on the expression profiles of 224 miRNA precursors in the brain of PD patients [19]. A high level of miR-133b expression was found in the midbrain control samples, but no miR-133b was found in samples from the PD patients [19]. Besides, the *in vivo* blockage of miR-133b in DA-neuronal culture obtained from embryonic stem cells or midbrain enhanced expression of DA-neuronal markers by elevating transcription levels of tyrosine hydroxylase and dopamine transporters in DA-neurons. The effect of miR-133b as an inhibitor of the last stage of DA-neuron maturation was additionally revealed: elevated level of miR-133b resulted in decrease, and lowered level in increase in number of DA-neurons in cell cultures [19].

Some recent data suggest miR-133b targeting to *PITX3*, which is considered as a PD candidate gene and a marker of DA-neurons. PITX3 is a transcription factor that is necessary for differentiation and viability of DA-neurons in midbrain *substantia nigra*. Besides, two polymorphisms associated with sporadic PD were revealed in the *PITX3* gene [58]. A murine model of PD demonstrated that miR-133b and Pitx3 regulate expression of each other via a negative feedback mechanism [19]: Pitx3 favors the transcription of miR-133b, which, in turn, suppresses Pitx3 activity [59]. Nevertheless, an important question remains unsolved concerning the possible contribution of the loss of this miRNA to the development of PD. Although a miR-133b knockout mouse model is not yet developed [24], most probably PD is resulting from the loss of Pitx3-dependent gene expression rather than the lack of miR-133b. However, these results need further verification.

Alteration in levels of 12 miRNAs was revealed when analyzing 115 miRNAs in *C. elegans* with overexpression of human *SNCA* carrying the A53T mutation. The model organisms with the mutant gene encoding vesicular catecholamine transporter (*cat-1*) demonstrated altered levels of five miRNAs, and the organisms with mutant parkin ortholog *pdr-1* (functional deletion) demonstrated alteration in levels of three miRNAs. Of all the studied miRNAs, only levels of miR-64 and miR-65 were lower in nematodes with SNCA overexpression and in *cat-1* transgenic organisms. The level of miRNA let-7 was lower in organisms with elevated SNCA synthesis or in *pdr-1* mutants. Possible targets for miR-64 and miR-65 are *mdl-1* and *ptc-1*, whose expression increases in *SNCA* transgenic nematodes as well as in nematodes with blocked synthesis of miR-64 and miR-65. The *mdl-1* gene encodes a transcriptional factor (dHLH) similar to MAD transcriptional regulators in vertebrates. The *ptc-1* gene encodes an ortholog of human PTCH protein containing a sterol-sensitive domain. These miRNAs might also be involved in the pathogenesis of PD in humans [60].

Thus, during recent years numerous studies have been devoted to the role of various miRNAs in PD pathogenesis. The data suggest that miRNAs can be involved in pathogenesis of this disorder and participate in disturbance of processes associated with regulation of expression of genes implicated in its development. The most important results of these studies are summarized in the table.

Numerous miRNAs have been found in plants, animals, and humans. Biogenesis and mechanisms of functioning of these miRNAs are under comprehensive study. miRNAs are involved in regulation of very different metabolic pathways. A number of miRNAs is known to be regulators for processes associated with development and functions of the nervous system. Besides, modulation of gene expression managed by miRNAs may be crucial for pathogenesis of various neurodegenerative disorders. The study of microRNA in NDD is a novel but actively developing research field proposing an alternative approach to elucidation of molecular mechanisms underlying these diseases; moreover, it opens previously unknown pathways of their development [59].

Since the pathogenesis of NDDs involves various cellular processes, there is a reason to suppose that miRNA-dependent regulation is altered in damaged tissues. It has been shown that some miRNAs can fulfill functions associated with neuroprotection from degradation and death, and alteration of miRNA expression can lead to development of pathological processes. It has been reported in several works that about 15 miRNAs could be somehow involved in the development of PD via their influence on both causative genes of monogenic PD and other candidate genes. It is worth noting, however, that a significant fault of these studies is that the role of some of these miRNAs in pathogenesis of PD is insufficiently determined, and their effect on the development of PD is only demonstrated in model systems. In connection with this, elucidation of distinct functions of these miRNAs is the goal of further studies.

Nonetheless, alteration of miRNA expression profiles in cerebrospinal fluid and peripheral blood in some NDDs can be used as molecular biomarkers for diagnosis and prognosis of the diseases. Besides, already at this stage active attempts are being made to develop therapy based on small RNAs (including both miRNAs and siRNAs). Because some miRNAs may have a neuroprotective effect, they can be used for prevention or, at least, retardation of progression of neuronal loss in the brains of PD patients [20]. The described advances open up broad prospects for finding new therapeutic drugs compensating the missing miRNAs or blocking their expression.

Thus, identification and study of miRNAs regulating gene expression will enable better understanding of the molecular mechanisms forming an organism, particularly

miRNAs in development of PD

miRNA	Target genes	Organs and tissues	Object of study	Function
miR-133b	Pitx3	DA-neurons of midbrain	ESC (1) *Mus musculus*, mice with aphakia, lacked Pitx3, mice with 6-hydroxydopamine-induced parkinsonism, HB (2)	regulation of maturation and functioning of midbrain DA-neurons [19]
miR-433	*FGF20*	blood of PD patients, DA-neurons of midbrain [32]	HB, fibroblast cell lines, SH-SY5Y (3) [32], PD patients, healthy volunteers	suppression of *FGF20* expression [32]
miR-7	*SNCA*	*substantia nigra*, striatum [31], midbrain, hippocampus [23]	HEK293T (4), SH-SY5Y, NS20Y murine neuroblastoma, mouse brain, MPTP-model on SH-SY5Y [31], HEK293 (5), cortical neurons of mouse and rat, mouse brain tissue [23]	regulation of *SNCA* expression in nervous system [23, 31], protection from oxidative stress and proteasomal degradation induced by SNCA [31]
miR-153	*SNCA*	midbrain, hippocampus [23]	HEK293, cortical neurons of mouse and rat, mouse brain tissue [23]	regulation of *SNCA* expression in nervous system. miR-153 is a synergist of miR-7; it initiates *SNCA* mRNA degradation [23]
miR-1	*TPPP/p25, CLTC*	blood lymphocytes	human blood lymphocytes [39]	not proven by experiments
miR-22*	*TP53BP2, GRIA1*	–"–	–"–	–"–
miR-29a	*SEPT4*	–"–	–"–	–"–
miR-16-2*	*FGF20*	–"–	–"–	–"–
miR-26a-2*	*GRIA1*	–"–	–"–	–"–
miR-30a	*SLC6A3*, *GRIA1*	–"–	–"–	–"–
miR-34b	not found	DA-neurons	SH-SY5Y, HB [57]	probably regulates expression of PARK2 and PARK7 [57]
miR-34c	–"–	–"–	–"–	–"–
miR-let-7	pdr-1 [60], E2F1 [30]	neurons	*C. elegans* [60], HEK293T, *D. melanogaster* [30]	influence on expression of parkin ortholog pdr-1 [60]; influence on pathogenicity of mutant LRRK2 via E2F1 and DP [30]
miR-64	*mdl-1*, *ptc-1*	no data	*C. elegans* [60]	not proven by experiments
miR-65	*mdl-1*, *ptc-1*	–"–	–"–	–"–
miR-184*	DP	neurons	HEK293T, *D. melanogaster* [30]	influence on pathogenicity of mutant LRRK2 via E2F1 and DP [30]

Note: ESC, embryonic stem cells; HB, postmortem human brain tissue; SH-SY5Y, human neuroblastoma cell culture; HEK293T, human embryonic kidney cells transfected with T-antigen of SV-40 virus; HEK293, human embryonic kidney cells.

the nervous system, and pathogenesis of various NDDs, as well as the development of diagnostics and treatment of severe human disorders including PD.

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