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MiRNAs and neural stem cells
A team to treat parkinson disease?

Thomas Palm,† Lamia'a Bahnassawy† and Jens C. Schwamborn*

Westfälische Wilhelms-Universität Münster; Institute of Cell Biology; Muenster, Germany

†These authors contributed equally to this work.

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Parkinson disease (PD) is a common neurodegenerative disorder with no proven neuroprotective or neurorestorative therapies. During disease progression, degeneration of dopaminergic neurons of the central nervous system occurs. Therefore, therapies that either aim on the inhibition of this degeneration or on the replacement of the degenerated neurons are needed. On the one hand, arrest of degeneration might be achievable through specific inhibition of disease associated genes like α-Synuclein or Leucine rich repeat kinase 2 (LRRK2). On the other hand, based on neural stem cells that bear the ability to generate new dopaminergic neurons, replacement of degenerated cells could be accomplished. Since both approaches can be regulated by micro-RNAs, these molecules have an enormous therapeutic potential. In this review, we will focus on the neurobiological and neurodegenerative implications of miRNAs and highlight their role in stem cell fate decisions. Finally, we will discuss their potential as therapeutic agents and targets for Parkinson disease.

Introduction

The central nervous system (CNS) is characterized by a high cellular diversity organized to form various anatomical regions with different functions.[1,2] During development nearly all brain cells are generated by neural stem cells (NSCs). In the adult mammalian brain NSCs are located within the germinal regions of the subgranular zone of the dentate gyrus and the hippocampus.[3]

Since NSCs have the ability to generate any cell type of the adult brain, they would be the ideal tool for regenerative cell replacement therapies. This cell replacement may be mediated either via transplantation of cells that have been expanded in vitro or via utilization of endogenous adult NSCs. Alternatively, strategies that do not lead to straight regeneration but block neurodegeneration could be extremely beneficial. In principle, considering both approaches—cellular regeneration and inhibition of degeneration—micro-RNAs (miRNAs), which function as regulators of various cellular processes, are very promising tools. MiRNAs are found in multicellular as well as in unicellular organisms suggesting that these molecules and their regulatory function on gene expression are evolutionary conserved elements.[4] They are encoded by miRNA genes and transcribed as "pri-miRNAs." Processing of pri-miRNAs results in a 70-nucleotide hairpin termed "pre-miRNA".[5] Alternatively, pre-miRNAs may be generated by splicing and debranching from introns of protein encoding RNAs.[6,7] Pre-miRNAs are processed by Dicer into 20–25 nucleotide long duplexes. These mature miRNAs bear a 6–8 nucleotide long sequence (called seed sequence) that is fully or partially complementary to the mRNA transcript they target (reviewed in ref. 8). The processing of pre-miRNAs by Dicer is generally related to the recruitment of the Argonaute (AGO) proteins[9] leading to the formation of the RISC (miRNA-induced silencing complexes) and the downregulation of mRNAs presenting the complementary seed sequence.[10]

This review will focus on the implication of miRNAs in the physiological stem cell fate decisions as well as their role in the pathophysiology and potential therapies of the neurodegenerative disorder Parkinson disease (PD).

*Correspondence to: Jens C. Schwamborn; Email: jschwamb@uni-muenster.de
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Micro-RNAs in Brain Development

Through molecular profiling studies it became evident that certain miRNAs play specific roles in defined areas of the brain. In particular, by microarray studies combined with RT-PCR and LNA (locked nucleic acid)-based in situ hybridization techniques the miRNAs miR-206 and miR-497 were demonstrated as being enriched in the cerebellum, whereas miR-132, miR-212, miR-221 and miR-222 showed a strong enrichment in the forebrain.[11,12] Additionally, several studies demonstrated that miRNAs may further play an important role in defined subcellular compartments. For instance, miR-15b, miR-16, miR-204 and miR-221 are significantly enriched in the axons of superior cervical ganglia neurons.[13] On the other hand, it was demonstrated within the E19 rat hippocampus that miR-26a is mainly located in the neural dendrites.[14]

Further evidence for miRNA implication in brain development was underlined by numerous studies where mice with a brain-specific deficiency for the miRNA processing enzyme Dicer display aberrant cortical, hippocampal and retinal development.[15-20] Concomitantly, an embryonic Wnt1-cre mediated conditional knockout of Dicer leads to massive brain malformations,

olfactory bulb degeneration and cerebellum size reductions.[21] Conditional knockout of Dicer within postnatal mouse brains lead to abnormal mixed phenotypes such as hypoactivity, decreased social behavior, ataxia and defects in rear limbs.[22] The brain of these knockout animals showed lowered weight and decreased size of the cortex, the hippocampus and the cerebellum. In good agreement with these data, Kim and coworkers demonstrated that post-natal loss of Dicer within postmitotic midbrain dopaminergic neurons results in their progressive loss and development of PD like symptoms.[23] Taken together, these studies show that particular miRNAs are indispensable for proper brain development and may be involved in the pathophysiology of neurodegenerative processes such as PD (summarized in **Table 1**). Therefore, using miRNAs either to inhibit neurodegeneration or to foster stem cell based regeneration would be a very promising therapeutic approach.

Micro-RNAs in Parkinson Disease

Parkinson disease (PD) is the second most prevalent neurodegenerative disorder with an incidence of about 1% after the age of 65 y,[24] increasing to 5.1% by the age of 85.[25] The pathology of PD is characterized by selective loss of dopaminergic neurons mainly in the substantia nigra, which is usually accompanied by accumulation of protein inclusions called Lewy bodies. Loss of these neurons causes the typical PD associated clinical manifestations such as bradykinesia, resting tremor and rigidity.[24] Although PD was first described by James Parkinson in 1817,[26] the etiology of PD is still incompletely understood. However, genetic studies led to the identification of mutations in several genes that segregate with the rare familial forms of the disease.[27] For at least two of these genes, α-Synuclein and Leucine rich repeat kinase 2 (LRRK2), interesting associations to miRNAs are described (summarized in **Table 1**).

α-Synuclein—miR-7/miR-153/miR-433. α-Synuclein is a 140 amino acid protein that is widely expressed in the adult brain with highest levels in the neocortex, hippocampus and substantia nigra.[28] There, it is mainly expressed in presynaptic terminals[29] where it is speculated to associate with the plasma membrane[30] and to be involved in the regulation of vesicle cycling and neuronal plasticity.[31] Mutations within the α-Synuclein gene are associated with autosomal dominant familial PD. The three main mutations are the A30P, E46K and A53T substitutions.[32] The overexpression of the human wild-type form (in addition to the endogenous α-Synuclein) and the expression of these α-Synuclein mutant forms are both characterized by a higher tendency to form insoluble aggregates and thereby constitute the main structure of Lewy Bodies.[33-37] Deposition of these aggregates results in increased susceptibility of the affected neurons to oxidative stress. However, the underlying mechanism of this phenomenon is yet unclear.[33,38-43] Furthermore, Bennett and coworkers demonstrated that mutant α-Synuclein is less efficiently degraded by the proteasomal system than the wildtype form.[44,45] Concomitantly, the PD associated mutation A53T alters the ubiquitin proteasome system.[42,43]

By utilizing several target prediction software tools, Junn and coworkers searched for miRNAs that would target α-Synuclein expression.[46] MiR-7 was identified as promising candidate especially because it is highly expressed in human, mouse and zebrafish brains.[11,47,48] This was further confirmed by the identification of potential miR-7 and miR-153 binding sites in the 3' UTR region of α-Synuclein.[49] Accordingly, overexpression of miR-7 and/or miR-153 resulted in a concentration dependant decrease of α-Synuclein expression at the mRNA and protein levels.[46,49] MiR-7 and miR-153 directly interact with the 3' UTR of α-Synuclein and genomic mutations within the seed sequence abolish their post-transcriptional inhibitory effect. Moreover, the effect of both miRNAs is synergistic; while miR-7 causes a sustained translational inhibition, miR-153 exerts a transient repression.[49] However, these studies either used the neural cell line SH-SY5Y or cultured cortical neurons but not dopaminergic neurons. Therefore, in order to elucidate more clearly the effects of miR-7 and miR-153 on PD, the exact role of both miRNAs in dopaminergic neurons needs to be established.

In accordance with the observed effects of miR-7, its distribution in the mouse brain is significantly higher in the substantia nigra, striatum and olfactory bulb when compared with brain regions not involved in the pathogenesis of PD. In those regions, its expression level is more than 40-fold higher in neurons than in astrocytes. Similarly, miR-153 is mainly expressed in the midbrain region.[49] Together, these data indicate that miR-7 and miR-153 are preferentially expressed in cells where they can exert their inhibitory action on α-Synuclein.[28,46] This was further confirmed by the observation that throughout brain development miR-7 and miR-153 have distribution patterns similar to α-Synuclein mRNA and protein.[49]

As previously mentioned, both the expression of mutant α-Synuclein or overexpression of wildtype α-Synuclein result in Lewy Body formation, increased susceptibility to oxidative stress and proteasome impairment.[41-43,46] Through their inhibitory action on α-Synuclein, miR-7 and miR-153 could modulate α-Synuclein levels and hence protect cells against the α-Synuclein induced deleterious events. Although inhibition of α-Synuclein induced damages would not lead to regeneration, treatment with miR-7/miR-153 could have a protective function on the dopaminergic neurons of PD patients, at least by slowing down disease progression. Consequently, miR-7 and miR-153 are very promising therapeutic agents. An alternative way to counteract the deleterious effects of α-Synuclein could be via short interfering (si) RNAs directed against the α-Synuclein mRNA. Yet, off-target effects of the siRNAs should be taken into consideration. Furthermore, using miRNAs would probably modulate several additional targets that might be as well involved in the α-Synuclein induced pathology as well.

On the molecular level, it could be demonstrated that the expression levels of α-Synuclein increase upon binding of FGF20 to the corresponding FGF-receptors.[50-53] FGF20 is expressed in midbrain dopaminergic neurons of rat brains[50] as well as in the substantia nigra of humans.[54] Interestingly, FGF20 maps to a PD linkage area located on chromosome 8.[55] Concomitantly,

van der Walt and coworkers could show a correlation between Single Nucleotide Polymorphisms (SNPs) in the FGF20 gene and susceptibility to PD. Two of these SNPs (rs1721100 and ss20399075) are located within the 3' UTR region of the FGF20 gene and could therefore play a role in differential binding abilities of regulatory miRNAs.[55]

Wang and coworkers examined samples from about 700 white Caucasian families with both PD affected and unaffected individuals excluding all Parkin-mutation carriers from this study. In addition to the previously detected SNPs, this study identified four new 3' UTR SNPs which are located within the genomic region of FGF20 and associated with increased risk for developing PD. One of these SNPs (rs12720208) lies within a possible binding site for miR-433 of the FGF20 gene. This SNP results in the exchange of one Cytosine moiety (C allele) to a Thymine moiety (T allele). The differential binding of miR-433 either to the C or to the T allele of this SNP results in inhibition or activation of FGF20 translation, respectively.[53] Examining expression levels of FGF20 in three human brains carrying either the C or the T allele demonstrated that the T allele homozygous brains had significantly higher levels of the FGF20 protein.[53] Altogether, mutations in the 3' UTR region of the FGF20 mRNA result in a failure in miR-433 binding. Consequently, the expression levels of FGF20 are increased and therefore the susceptibility to develop PD is higher.[53,55] However, it is important to note that other studies failed to replicate this association. For instance, samples from Greek, Finnish and Spanish populations could not relate the described SNPs to an increased risk for developing PD.[56,57] Additionally, even no nucleotide variations in the miR-433 sequence itself were identified among the Spanish patient samples.[57] So it seems that effects and consequences of different SNPs and the resulting interaction with miR-433 may differ between groups of different ethnic origins or genetic backgrounds.

LRRK2—let-7/miR-184*. Leucine rich repeat kinase 2 (LRRK2) is the most commonly reported gene to be involved in PD.[36] The LRRK2 protein consists of several domains, including leucine rich repeats, mitogen activated kinase and a Roc GTPase domains. LRRK2 is highly expressed in the brain, with hippocampus and striatum showing the highest expression levels.[58,59] The role of LRRK2 under physiological conditions is yet not clear but mutations in the functional domains of this protein have been strongly associated with PD. The main mutations, I1122V, R1441C, R1441G, Y1699C, G2019S and I2020T are linked to both autosomal dominant and sporadic forms of PD. The G2019S mutation is the most commonly reported one and lies within the kinase domain, leading to enhancement of the kinase activity.[60] This mutation results in inhibition of peroxidase phosphorylation leading to mitochondrial dysfunction and oxidative damage.[61]

A comprehensive study conducted by Gehrke and coworkers utilized the Drosophila model to elucidate whether LRRK2 can influence miRNAs or vice versa. Indeed, LRRK2 was able to decrease the activity of the miRNA Let-7. LRRK2 proteins carrying the human G2019S [hLRRK2 (G2019S)] or the drosophila equivalent I1915T LRRK2 [dLRRK (I1915T)] mutation showed even a higher inhibition of Let-7 activity. In correlation with this observation, inhibition of dLRRK by RNAi enhanced Let-7 activity. The inability of an inactive kinase to inhibit Let-7 strongly suggested that the repressor activity of LRRK2 is mediated through its kinase function.[62] In addition to Let-7, miR-184* was also shown to be inhibited by pathogenic LRRK2. The investigated target genes of these miRNAs are DP1 and E2F1 respectively. Consequently, LRRK2 transgenic flies showed an upregulation of E2F1 and DP1 protein levels, which contributed to the neuronal degeneration phenotype in the dLRRK (I1915T) mutant flies. This provides possible insight on the use of Let-7 and miR-184* to counteract the function of mutant LRRK2 in PD patients.

Transgenic hLRRK2 (G2019S) or dLRRK (I1915T) flies have unchanged Let-7 expression levels. Therefore, LRRK2 is influencing miRNA activity not by changing the expression level but by utilizing a different way of regulation. Strikingly, in the previously described flies, the expression level of the gene Brat was affected. This is of prime importance because Brat, and its mammalian homolog TRIM32, have been described as activators of certain miRNAs, including Let-7.[63,64] Furthermore, TRIM32 is an important regulator of stem cell differentiation.[64,65] As will be discussed below, stem cells and their differentiation into dopaminergic neurons propose great potential for therapeutic cell replacement strategies. Therefore it is necessary to establish a solid link between miRNAs involved in PD pathology and other factors that influence neural stem cell differentiation, as it is the case with TRIM32 and Let-7. Thereby an interesting link between PD pathology and potential stem cell based regenerative approaches becomes evident (described below).

Other micro-RNAs. Screening for differentially regulated miRNAs using microarray technology in the α-Synuclein (A30P) transgenic mouse model for PD revealed significantly lower levels of the miRNAs miR-10a, miR-10b, miR-212, miR-132 and miR-495. Additionally, using 2-D DIGE, expression levels of two potential miR-132 target genes, namely sorting nexin-12 and an ubiquitin-conjugating enzyme E2, were elevated in the mutant mice. The functional consequences of this observation still remain open for investigation.[66]

Expression pattern analysis of miRNAs in the amygdala of idiopathic PD patients showed more than 40% reduction of miR-34c in 9 out of 11 patients.[67] Also the expression of DJ1 and Parkin, two additional proteins associated with PD, was significantly decreased upon miR-34b/c depletion in these patients. This indicates that miR-34b/c may indirectly regulate the levels of both proteins. Interestingly, differentiation of SH-SY5Y cells into dopamine like neurons correlate with increased miR-34b and 34c expression, suggesting that they might also play a role in the development and physiology of these neurons.[67]

In order to identify PD relevant miRNA-gene interactions as well as novel genes or pathways implicated in PD development Santosh and coworkers performed a computational study to create an interaction map between miRNAs and PD associated genes. Twenty-nine genes involved in PD pathogenesis were selected from Parkinson disease pathways described in the Kyoto Encyclopedia of Genes and Genomes (KEGG) as well as in literature resources. Then the miRanda software was utilized

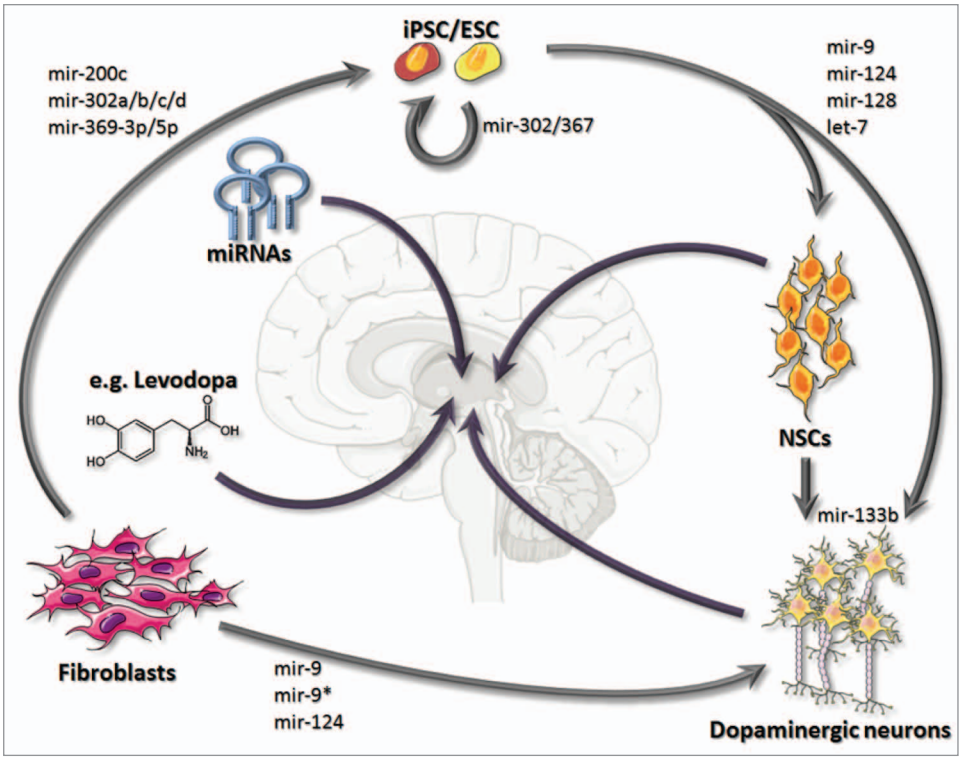

Figure 1. Potential molecular and cellular therapies for Parkinson disease. Under physiological conditions micro-RNAs (miRNAs) are involved in brain development by directing embryonic stem cell (ESC) differentiation into neural stem cells (NSCs) and finally into neurons. During these differentiation steps, particular miRNAs are involved in the control of cell fate commitments. Recently, exogenous expression of miRNAs enabled both the reprogramming of fibroblasts into induced pluripotent stem cells (iPSCs) as well as the direct conversion of fibroblasts into neurons. In vitro control of these molecular (de) differentiation and conversion mechanisms renders an autologous cellular therapy conceivable. This could be achieved by transplanting either NSCs or specific neurons into the lesioned area. Additional miRNA-based therapeutic strategies could be based on the use of exogenous miRNAs that would repress the deleterious disease causing genes or by activating/repressing the miRNAs of interest upon administration of particular chemical compounds.

to predict miRNA target sites on these genes (employing 866 human miRNAs downloaded from the miRBASE). For this map, the ten miRNAs with highest number of PD associated target genes were selected according to the highest threshold match scores. Strikingly, miR-612, one of the selected miRNAs, highlighted interactions with 19 different PD associated genes.[68] Such models and further developments on similar maps could be the basis for the identification of specific PD-associated miRNAs and the determination of therapeutic agents and targets.

Neural Stem Cells and their Potential as Therapeutic Agents

NSCs have the documented potential to generate neurons that are lost in the course of neurodegenerative diseases.[69,70] Additionally, with the advent of the induced pluripotent stem cell (iPSC) technology, it seems conceivable that autologous cells could be used in regenerative medicine in order to replace degenerated cells.[71] An imaginable strategy would be to make use of patient specific fibroblasts, which can be reprogrammed into iPSCs and further differentiated into NSCs and neurons.[71] Those NSCs or neurons could be transplanted into the marred substantia nigra or striatum of the patient's brain (**Fig. 1**). As an alternative strategy it is conceivable to employ endogenously present adult NSCs.[72] This approach seems to be particularly feasible because numerous studies demonstrated that brain insults induce proliferation of NSCs[73,74] and that newly generated cells migrate toward the lesion.[75] Both transplantation of in vitro expanded stem cells or utilization of endogenously present NSCs depend on their efficient differentiation into the specific neuronal subtype that degenerates during disease progression. In the case of PD these neurons are the dopaminergic neurons. Although protocols for the in vitro generation of dopaminergic neurons either from embryonic stem cells (ESCs) or from iPSCs improved significantly during the last years,[76-79] they are still relatively inefficient. Nevertheless, NSCs or neurons (derived from ESCs, iPSCs, NSCs or fibroblasts) have the promising potential to mediate regenerative cellular replacement to treat PD. Indeed, recently it was shown that dopaminergic neurons derived from human ESCs (hESCs) can successfully integrate into primate brains.[77] Strikingly, these transplanted dopaminergic neurons were able to ameliorate motor functions that were lost upon experimentally induced PD.

Importantly, stem cell derivation, maintenance and neuronal differentiation of NSCs are tightly regulated by miRNAs. For instance, terminally differentiated human fibroblasts can be efficiently reprogrammed into iPSCs just by using a defined cocktail of certain miRNAs.[80,81] Furthermore, Yoo and coworkers succeeded in using miRNAs to directly generate neurons from human fibroblasts.[82] Therefore, miRNAs are extremely promising therapeutic agents or targets to manipulate these cells in the desired way (**Fig. 1**).

Micro-RNAs in Stem Cell Behavior

As previously mentioned, miRNAs play important roles in maintenance and differentiation of pluripotent cells. Mouse ESCs (mESCs) that lack the miRNA processing factors Dicer or Dgcr8 are unable to run their differentiation program.[82-84]

In hESCs the maintenance of pluripotency is regulated by the miRNA cluster miR-302/367. Members of this miRNA cluster

Table 1. Summary of described miRNAs

Process	miRNA	Reference
Brain development	miR-9; miR-15b; miR-16; miR-26a; miR-124; miR-132; miR-204; miR-206; miR-212; miR-221; miR-222; miR-497	11–14, 91, 92, 98, 100–104
PD	miR-10a; miR-10b; miR-34b; miR-34c; miR-132; miR-212; miR-495; miR-612	66–68
PD: α-Synuclein	miR-7; miR-153	46, 47, 49
PD: FGF20	miR-433	53, 55
PD: LRRK2	Let-7; miR-184*	62
Maintenance of pluripotency	miR-302/367 cluster	85–87
iPSC/neuron-reprogramming	miR-9; miR-9*; miR-124; miR-200c; miR-302a; miR-302b; miR-302c; miR-302d; miR-369–3p; miR-369–5p	80, 81, 97
Neurogenesis	miR-21; miR-124; miR-223	105, 107
Neuronal differentiation	Let-7; miR-9; miR-124; miR-128	91–95, 97–104, 112, 119–123
Dopaminergic neuron specification	miR-9; miR-124; miR-133b; miR-218	21, 23
DM: Stroke	miR-124	125, 126
DM: Brain traumata	miR-16; miR-92a; miR-210; miR-765	127, 128
DM: Schizophrenia	miR-34a; miR-449a; miR-564; miR-432; miR-548d; miR-572; miR-652	129
DM: PD and treatment	miR-1; miR-16–2*; miR-22*; miR-26a2*; miR-29a; miR-30a	130

PD, Parkinson disease; DM, diagnostic marker.

are strongly expressed in hESCs and their expression level rapidly declines upon initiation of differentiation.[85,86] Furthermore, a regulatory circuit of the factors Oct4-Nr2f2-miR-302 in hESCs controls the balance between pluripotency and neuronal differentiation.[87] Under maintenance conditions Oct4 and its downstream target miR-302 suppress the expression of Nr2f2 at the transcriptional and post-transcriptional level. However, upon induction of differentiation, Nr2f2 inhibits expression of the pluripotency factor Oct4 and induces neuronal commitment by increasing the expression of pro-neuronal factors such as Pax6, Six3, Zic1, N-cad and Lhx2.[88] This example demonstrates that, via regulation of numerous protein coding genes, miRNAs play an important role in the maintenance of the pluripotent stem cell state.

Micro-RNAs in stem cell differentiation. ESCs have the ability to give rise to NSCs, while NSCs can generate neurons. During this commitment the cell type specific transcriptome has to transit toward the transcriptome of a more differentiated cell type. Various studies analyzed these transitions with regards to miRNAs[48,88-90] (**Fig. 1 and Table 1**). In the following section we will focus on four miRNAs that are particularly well characterized in this context.

Micro-RNA-9. MiR-9 is an important control element in the brain development of various species.[91] In mice, miR-9 controls the development of the telencephalon by repressing numerous transcription factors such as Nr2e1, REST, Gsh2, Meis2, BAF53a and Islet1.[92] Furthermore, by regulating Foxg1 expression levels miR-9 is important for the differentiation of Cajal-Retzius cells.[93] In good agreement with its function during brain development miR-9 levels increase dramatically during neuronal differentiation of ESCs.[94] Additionally, electroporation of miR-9 in NSCs of the embryonic mouse brain leads to abnormal neuronal differentiation.[95]

During neuronal differentiation NSCs that are characterized by the neural-progenitor-specific BAF complex have to switch toward the neuron-specific BAF complex.[96] MiR-9, miR-9* and miR-124 (see below) target BAF53a, an element of the neural-progenitor-specific BAF complex, which is, after mitotic exit, replaced by BAF53b an element of the neuron-specific BAF complex.[97] Interestingly, expression of these three miRNAs was sufficient to reprogram human fibroblasts directly into neurons[97] (**Fig. 1**). Collectively, these in vitro and in vivo studies demonstrate the importance of miR-9 during neuronal differentiation.

Micro-RNA-124. The miR-124 is the most enriched miRNA in the mouse brain and is associated with multiple neuron-specific molecular functions.[98] Strikingly, transfection of non-neuronal HeLa cells only with miR-124 induces the switch toward a transcriptome that is highly similar to a typical neuronal expression profile including high expression levels of neuronal genes and simultaneous repression of transcription of non-neuronal genes.[99]

During brain development and with advancing neuronal differentiation the expression levels of miR-124 are constantly increasing.[100] During adult neurogenesis NSCs (so called type B-cells) have low levels of miR-124. While the cell progresses toward a more fate-committed neuronal cell type, i.e., by transiting through the stages of transient amplifying cells (so called type C-cells) and neuroblasts (so called type A-cells) the levels of miR-124 continue to increase.[101] To further evaluate the role of miR-124 during neurogenesis, Cheng and coworkers performed a knock-down experiment using modified miR-124 oligonucleotides. Such downregulation of miR-124 led to an increased number of type C and A cells.[102] At the molecular level miR-124 induces neuronal differentiation by negatively regulating the Notch pathway which is of importance for NSC maintenance.[103] Additionally, miR-124 is also targeting the transcription factor

Sox9 and thereby facilitates cell cycle exit.[102] Finally, by targeting Cdc4, and thus influencing the sub-cellular localization of Rac1, miR-124 further stimulates neurite outgrowth.[104] Together, these data strongly suggest that miR-124 is a major control element in the regulation of adult neurogenesis within the subventricular zone.

This is further supported by the observations that after focal cerebral ischemia miR-124 is downregulated and allows expression of the Notch ligand Jagged-1 as well as the Notch receptor. Hence, proliferation of NSCs is supported.[105] Also in spinal cord contusions an implication of miRNAs in molecular repair mechanisms has been described. Microarray studies revealed that up to 32 miRNAs, including miR-124, were downregulated, whereas SNORD2 (small nucleolar RNA, C/D box 2; predicted as being important for ribosome-associated translation initiation[106]), miR-223 and miR-21 showed increased expression levels.[107] Interestingly, the repression of miR-21 was shown to cause apoptosis in NSCs.[108-110] Thus the upregulation of miR-21 together with activated neurogenesis probably allows an increased number of newborn cells to survive and to induce regeneration.[107]

Micro-RNA-128. Besides miR-9 and miR-124 also miR-128 has been identified as a brain-specific miRNA.[111] It is highly expressed in neurons while this transcript is nearly absent in glial cells.[112,113]

MiR-128 potentiates its impact on gene regulation by targeting the nonsense-mediated RNA decay machinery.[112] Nonsense-mediated RNA decay is a regulatory mechanism that targets transcripts with premature termination codons and thus protects the cell from deleterious effects that may result from truncated proteins.[114] The impact of nonsense-mediated RNA decay on proper brain development is underlined by the fact that mutations of *UPF3B*, a core gene of this mechanism are causative of various neurological disorders such as intellectual disability,[115] schizophrenia and autism[116] as well as mental retardation.[117] Recently, miR-128 function was associated with nonsense-mediated RNA decay malfunction by targeting two of its key factors, namely UPF1, an RNA helicase, and MLN51, a core protein of the EJC (exon-junction complex).[112] The ability of miR-128 to repress nonsense-mediated RNA decay in a brain specific manner may correlate to its brain specific expression pattern.[111] Therefore, it is highly suggestive that this "nonsense-mediated RNA decay miR-128 circuit" acts specifically within the nervous system and leads to upregulation of transcripts that are involved in processes like neural differentiation, maturation and function.[112]

Let-7. The development of *Caenorhabditis elegans* is coordinated by a hierarchical and time dependent organization of specific genes.[118] Some elements of this gene cascade are tightly controlled by the two regulatory miRNAs, namely lin-4 and Let-7.[119,120] In their study, Reinhart and coworkers[120] showed that aberrant expression of these miRNAs has a direct impact on the expression levels of the protein coding genes lin-28, lin-14, lin-41, lin-42, daf-12 and hbl-1 which in turn are important regulators that ensure the transition from early to later developmental stages.[120-122]

In undifferentiated cells lin-28 binds the pre-Let-7 transcripts, inhibits the processing by Dicer and thereby stabilizes the immature form of Let-7 miRNA. However, upon induction of differentiation, Let-7 and lin-4 expression levels increase which results in downregulation of their target gene lin-28 and thus in the transition toward differentiated neurons.[123]

The fact that expression of Let-7 increases during neuronal differentiation is in good concordance with the findings that Let-7a is activated through TRIM32, an inducer of neuronal differentiation.[64,65] Furthermore, recent observations highlighted that Let-7b, another member of the Let-7 miRNA family, targets the stem cell regulator TLX and the cell cycle regulator cyclin D1.[124] It was further demonstrated that Let-7b overexpression leads to simultaneous repression of stem cell maintenance and activation of neural differentiation. On the other hand, repression of Let-7b strongly inhibited neuronal differentiation. Together, these data show that members of the Let-7 miRNA family are, in collaboration with cell fate determinants such as TRIM32, of prime importance for the induction of neuronal differentiation.

Micro-RNAs in dopaminergic fate specification. Therapeutic approaches aiming on the replacement of neurons lost during PD depend on the generation of dopaminergic neurons from neural stem cells (**Fig. 1**). Also in this specific differentiation process miRNAs play important roles.

In mice, the Wnt1-cre-mediated conditional knockout of Dicer resulted in numerous developmental brain defects.[21] More specifically, this knockout led to a lack of miR-124, miR-9 and miR-218 expression and a strong impairment of midbrain dopaminergic neuron development. Moreover, miRNA expression profiles generated from PD patients show significantly lower levels of miR-133b when compared with profiles established from unaffected individuals.[23] In two mouse models for PD, i.e., the Pitx3 deficient "Aphakia mice" and the 6-OHDA injected PD model, expression of miR-133b is dramatically reduced. In fact, within dopaminergic neurons Pitx3 specifically induces transcription of miR-133b which in turn downregulates Pitx3 expression at the post-transcriptional level.[23] Thereby a regulatory feedback loop is established. These data suggest that maturation and maintenance of dopaminergic neurons is controlled by miR-133b.

Together, the here discussed studies demonstrate that, beyond others, miR-9, miR-124, miR-128, miR-133b and Let-7 are of prime importance for governing NSC maintenance and neuronal differentiation. By these means they could be used as basis for setting-up a cell replacement strategy designed to cure neurodegenerative diseases such as PD (**Fig. 1**).

Micro-RNAs as Diagnostic Markers

Besides their use as therapeutic agents miRNAs could find a useful application as diagnostic markers. Indeed, their tissue specificity and dynamic expression in response to external stimuli makes them promising biomarkers to monitor particular events (summarized in **Table 1**). Additionally, their stability within the blood plasma renders them even more applicable as common diagnostic markers in routine clinical tests. Nowadays with the emergence of very sensitive analytical techniques even very low levels of particular transcripts can be detected. Accordingly, numerous studies performed on rats analyzed miRNA expression

levels after different kinds of toxic treatments or within stroke models.[125] Interestingly, the brain specific miR-124 was undetectable in the plasma of healthy rats; however, shortly after induced stroke miR-124 levels strongly increased in the plasma.[126] In this study, the authors could not identify a significant correlation between the size of the induced infarcts and miR-124 expression levels in the plasma. Additionally, the reason why miR-124 concentration increases in the plasma while it is repressed in the affected brain area[105] remains to be elucidated. Nonetheless, this observation might be of significant medical importance since reliable and accessible blood markers for early diagnosis of brain infarcts are missing.

A miRNA-microarray study performed on human brain traumata patients in comparison with healthy volunteers indicated that the plasma levels of particular miRNAs are statistically different.[127] In particular, it was shown that miR-16, miR-92a and miR-765 are reliable markers of severe traumatic brain injuries with perfect specificity and sensitivity. However, within mild traumatic brain injury patients the expression level of miR-765 were unchanged whereas levels of miR-92a and miR-16 were significantly increased. Studies analyzing the miRNA plasma levels of stroke patients demonstrated a statistically significant increase of miR-210 levels.[128] Moreover, the plasma isolated miRNAs miR-34a, miR-449a, miR-564, miR-432, miR-548d, miR-572 and miR-652 showed strong upregulation in schizophrenia patients.[129]

A recent study confirmed that miRNAs may also be usable as diagnostic markers for PD. It was shown that patients not receiving any symptomatic therapy displayed decreased expression of miRNAs miR-1, miR-22* and miR-29a when compared with healthy control individuals.[130] In the course of this study another cohort of PD patients received the Dopamine agonist Levodopa. When treated and non-treated patients were compared, the increased expression of miR-16-2*, miR-26a2* and miR-30a upon Levodopa uptake became evident. These results would suggest that treatment with Levodopa not only improves the motor-functions of patients, but also the miRNA expression profile is changed. Based on these interesting results a better understanding of the miRNA directed pathophysiology of PD as well as of the molecular downstream effects of Levodopa treatment are probably within reach.

Together these data show that plasma levels of specific miRNAs may reflect pathological conditions. Specificity of these miRNAs as diagnostic makers still has to be confirmed in differential analysis of various disease types and not only in comparison to the expression profiles of healthy individuals. Nevertheless, the discovery that plasma levels of certain miRNAs can serve as biomarkers for pathological conditions is very recent. Taking into consideration the availability and stability of miRNAs as well as the reliability of these early results, such approaches seem to be extremely attractive as future diagnostic techniques.

Perspectives—Therapeutic Approaches and Applications

MiRNA based therapeutic treatments for PD may follow two different strategies. The first one could be to use the miRNA associated target-gene-specificity in order to downregulate the expression of the aberrant gene within the cell of interest. The second approach would be to use miRNAs to direct NSCs differentiation in the desired direction (e.g., in the case of PD toward dopaminergic neurons) (**Fig. 1**). For both approaches miRNA overexpression (gain-of-function) as well as repression (loss-of-function) are conceivable.

Gain of function of specific miRNAs may be achieved by using "miRNA-mimics."[131] These molecules resemble pre-miRNAs and lead to the downregulation of the desired gene. One challenge is to ensure that the miRNA-mimics are delivered to the right cell. Another challenge of this approach is to avoid off-target effects by downregulating unintended target genes. Additionally, when considering treatment of neurological diseases, the blood-brain-barrier has to be overcome. An interesting tool able to manage numerous of these obstacles are exosomes.[132] Upon injection, these vesicles may cross the blood-brain barrier and deliver the cargo to the brain cell of interest.[133] Furthermore, gain of function therapies may be confronted with the problem of finding the right level of expression of the miRNA in order to avoid overloading the miRNA bio-processing machinery.

Loss of function of the miRNA of interest may be achieved by different approaches. One approach consists of synthetic sponge mRNAs containing a complementary sequence to the seed sequence of the miRNA of interest. Expression of these sponge mRNAs leads to sequestration of the miRNA.[134] Another approach directing the downregulation of endogenous miRNAs is the use of antagomirs. These chemically engineered oligonucleotides have a specific, efficient and long-lasting effect on the expression levels of the targeted miRNA.[135] However, because they couple to cholesterol they are unable to cross the blood brain barrier. Nevertheless, direct injection into the brain region of interest was able to attain the desired effect.[136] Both approaches, i.e., sponge mRNA and antagomirs, might be limited by the fact that different miRNAs are characterized by the same seed sequence and thus non-pathological miRNAs may be sequestered as well. LNA (locked-nucleic acids)-antimiRs are an additional way to inhibit the function of miRNAs. LNAs are conformational RNA analogs with the ability to exert high and specific binding to complementary miRNAs. In a recent study, Elmén and coworkers applied a LNA-antimiR antagonizing the liver-expressed miR-122 to African green monkeys. This resulted in the formation of stable heteroduplexes between the LNA-antimiR and miR-122 in the cytoplasm of primate hepatocytes causing the depletion of mature miR-122 and yielding a dose-dependent lowering of plasma cholesterol levels. Importantly, no evidence for LNA-associated toxicities or histopathological effects were observed.[137] The use of various chemical compounds may block expression of particular miRNAs as well. For example, a low-dose administration of Paclitaxel has been shown to downregulate expression of miR-192 and thereby attenuate renal fibrosis in a rat model of remnant kidney disease.[138]

In conclusion, the discussed studies demonstrate the increasing knowledge of miRNA's role in disease origin and progression as well as in stem cell fate specification. This understanding opens numerous perspectives on how these molecules could

either be the target or the instrument of yet missing curative treatments. The development of miRNAs-based methods that are specific for neural stem cells of the adult mammalian brain and that allow their differentiation into specific neuronal subtypes would be a major breakthrough with high therapeutic relevance for Parkinson disease as well as for other neurodegenerative disorders.

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