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Deciphering the Function and Regulation of microRNAs in Alzheimer's Disease and Parkinson's Disease

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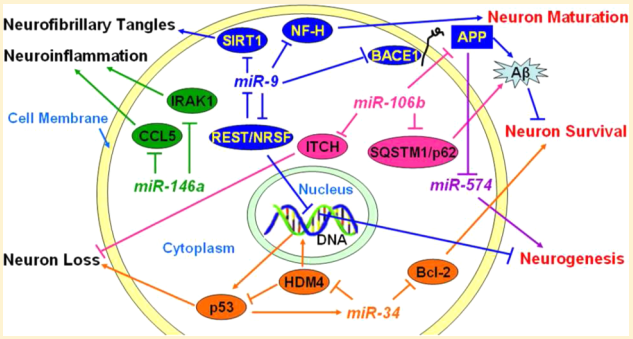
ABSTRACT: MicroRNAs (miRNAs) are single stranded, noncoding RNA molecules that are encoded by eukaryotic nuclear DNA. miRNAs function through imperfect base-pairing with complementary sequences of target mRNA molecules, which is typically via the cleavage of target mRNA with transcriptional repression or translational degradation. An increasing number of studies identified dysregulation of miRNAs in neurodegenerative disease and suggest that alterations in the miRNA regulatory pathway could contribute to the disease pathogenesis. However, molecular mechanisms underlying the pathological implications of dysregulated miRNA expression and regulation of the key genes that are involved in neurodegenerative diseases remain largely unknown. Here, we review the evidence for the functional role of dysregulated miRNAs involved in disease pathogenesis, as well as how miRNAs govern neuronal functions either upstream or downstream of target genes that are disease pathogenic factors. Furthermore, we review the cellular feedback regulation between miRNAs and target genes in neurodegenerative diseases, with a focus on Alzheimer's disease and Parkinson's disease.



KEYWORDS: *MicroRNA, Alzheimer's disease, Parkinson's disease, neurogenesis, neuroinflammation, neuronal survival*

As human society has developed, aging has become a stressful issue in medical care. Neurodegenerative diseases are among the most prevalent diseases in the aging population.[1] Two of the most well-known neurodegenerative diseases in older people, Alzheimer's disease (AD) and Parkinson's disease (PD), have been intensively studied in neuroscience.[2,3] Both AD and PD are characterized by progressive neuronal degeneration in the brain, yet, the degenerated neurons in PD patients are mainly restricted to the substantia nigra,[3] while in AD patients, the neuronal degeneration starts from the hippocampus and then progress to the entire cortex.[2] Clinically, the AD patients show obvious cognitive impairment and dementia,[2] while the symptoms of PD are mainly tremors, rigidity, and bradykinesia.[3] Pathologically, the hallmark of AD is the extracellular accumulation of Aβ peptide and intracellular tangles of hyperphosphorylated tau,[2] while in PD patients, the accumulation of α-synuclein in the lewy bodies is the most prominent cellular change.[4,5] Both of these diseases have been linked to the mutation of certain genes, like amyloid precursor protein (APP) in AD and leucine-rich repeat kinase 2 (LRRK2) in PD.[4−6] However, the mutation of certain genes can only explain the cause of limited familiar AD or PD cases, while the molecular mechanisms of the majority of sporadic AD and PD cases still remain unknown.[1−3]

Recent studies on miRNAs have opened a new door for searching for the biological causes of sporadic AD and PD.[7] miRNAs are small, noncoding RNAs, that are 21−24 nucleotides (nt) long. More than 35000 miRNAs have been identified thus far, and they are widely expressed from plants to primates (miRBase, version 21). The miRNA gene is transcribed by RNA polymerase II or III to generate pri-miRNA, which is cleaved by Drosha/Pasha to yield an approximately 70−100 nt pre-miRNA.[8] The pre-miRNA is exported out of the nucleus by Exportin 5. In the cytoplasm, the pre-miRNA is cleaved again by Dicer to generate a 21−24 nt mature miRNA. The mature miRNA is delivered and forms mismatching-permitted complementary binding with the 3′ untranslated region (3′UTR) of the target mRNA through the RNA-induced silencing complex (RISC).[9] Upon binding with its target mRNA, the miRNA's main function is to induce the degradation or translational inhibition of the target mRNA.[9,10] Based on computational predictions, one miRNA can down-regulate the expression of hundreds of proteins, and this has been experimentally demonstrated as true.[11,12] With pSILAC

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measurements, Selbach and colleagues found that 60−70% of the downregulated proteins contain a seeding sequence, whereas a seeding sequence cannot be found in the upregulated proteins. Strikingly, overexpression or knockdown of certain miRNAs has complementary effects on the proteome, regardless of the seed-containing targets or no-seed-containing effectors.[12] Therefore, the role of miRNA must be considered a crucial aspect in almost every biological process.

Brain-enriched miRNAs account for less than one-thirtieth of the total identified miRNAs,[13,14] which indicates that the temporal and spatial expression of miRNAs is strictly controlled or regulated. In the nervous system, the roles of miRNA have been the best studied in neuronal development.[15−19] For example, deletion of Dicer, which globally blocks the expression of miRNA, at a stage when ES cells enter the postmitotic state to initiate dopaminergic (DAergic) neuron differentiation can completely eliminate DA neuron differentiation.[20] This phenotype can be rescued by introducing small RNA species, including miRNA, into the ES cells, which means that these small RNA species are crucial for DA neuron generation.[20] In addition to neurodevelopment, accumulating studies have gradually revealed the essential role of miRNA in nervous system morphogenesis, synaptic plasticity, and neurodegeneration.[21,22] For instance, conditional deletion of Dicer in adult brains results in obvious neuronal degeneration in the mouse cortex.[21,22] However, it should also be noted that the functions of individual miRNAs might be quite specialized based on their distinct expression patterns.[13] For example, miR-9, miR-26a, and miR-128 are especially enriched in the hippocampus, and the medulla oblongada has an accumulation of miR-34.[13] In contrast, miR-124a, miR-125b, and miR-128 are more strongly expressed in neurons than in glia, while miR-26a and miR-29 are more enriched in astrocytes than in neurons.[13] All of these findings indicate that miRNA research is becoming increasingly crucial and complicated in neuroscience, including neurodegenerative diseases. Here, we summarize a group of misregulated miRNAs in AD and PD. We will discuss their specific functions in disease pathogenesis and how they regulate target genes that are disease pathogenic factors, which, in turn, provide feedback regulation in neurodegenerative diseases.

■ DYSREGULATED miRNAs IN AD AND PD

Identified by microarray and verified by qPCR methods, several miRNAs, including miR-9, miR-26a, miR-124a, miR-125b, miR-128, and the let-7 family, are highly enriched in the brain. Interestingly, these brain-enriched miRNAs are also the most frequently found to show altered expression in AD or PD.[23−25]

miRNA expression profiling in either the brain or cerebrospinal fluid (CSF) of AD patients has been performed by several groups.[26−34] Using nylon-membrane-bound DNA arrays, Lukiw found that miR-9 and miR-128 were increased in the hippocampus of AD patients.[26] Cogswell and colleagues identified a differential dysregulation pattern in different brain regions of AD patients. Taking the frontal gyrus, for example, 8 miRNAs, including miR-9, -26a, -132, and -146b, were downregulated, and 15 miRNAs, including miR-27, -29, -30, -34, and -125b, were upregulated.[27] However, in CSF, no expression change was detected for miR-9, -26a, -29 or -34, only miR-146b and miR-27a-3p were identified as downregulated,[27,34] and miR-30 family members were upregulated.[27] Meanwhile, many miRNAs that showed dysregulation in CSF did not show expression changes in the brain.[27] Hebert and colleagues detected 13 downregulated and 3 upregulated miRNAs in the cortex of sporadic AD patients. The 13 downregulated miRNAs include the following: miR-181c, -15a, -9, -101, -29b, -19b, -106b, -26b, and others.[29] Using next-generation sequencing to screen the miRNA expression in AD patient blood, Leidinger and colleagues recaptured many miRNAs that were reported to be dysregulated by other researchers, including the miR-30 family, miR-29, miR-106, and miR-107. Furthermore, they identified 12 miRNAs, including the upregulated miR-112, -161, -5010-3p, -26a-5p, -1285-5p, -151a-3p, and let-7d and the downregulated miR-103-3p, -107, -532-5p, -26b-5p, and let-7f-5p, which can distinguish AD patients from other patients suffering from other CNS diseases.[30] Similarly, Muller and colleagues also found that a low level of miR-146a in CSF can be a biomarker of AD.[33] Differential expression profiles are also found in an AD mouse model compared with age-matched controls.[28,31] Seventeen out of 299 miRNAs isolated from the cerebral cortex of APPswe/PSΔE9 mice showed downregulation compared with their age-matched controls, while 20 miRNAs showed upregulation. The downregulated ones include the following: miR-20a, miR-29a, miR-125b, miR-128a, and miR-106b. However, miR-107 and miR-146a did not show expression changes in this transgenic mouse model.[31]

There are relatively fewer reports on the miRNA profiling in PD studies than in AD studies.[35−38] miRNA microarray analyses revealed that only two miRNAs were significantly downregulated in the amygdala from 11 PD patients compared with 6 controls.[36] These two miRNAs include miR-34c-5p and miR-637. Another miRNA, miR-133b, was found downregulated in the midbrain of PD patients compared with the controls.[20] In peripheral blood mononuclear cells (PBMCs), 18 miRNAs were found to be dysregulated in 19 idiopathic PD patients compared with 13 controls. Interestingly, all of these dysregulated miRNAs showed downregulation in PD patients.[37] These miRNAs include the following: miR-335, -374a/b, -199, -126, -151-5p, -29b/c, -147, -28-5p, -30b/c, -301a, and -26a. Asikainen and colleagues also performed miRNA profiling in PD *Caenorhabditis elegans* models. However, no consistent changes were detected between humans and *C. elegans*, in which miR-64/65 and let-7 were downregulated.[38]

It should be noted that there are many discrepancies in the data reported from different groups.[26,27,29] This discrepancy might result from insufficient sample sizes, different detection methods, or different genetic backgrounds, or the fact that tissues from different brain regions were used. These are all limitations due to using patient post-mortem samples as the material resource.[26,27,29] Another concern about using human tissue as an experimental material is that the tissues are usually achieved at a very late stage of the disease, thus the altered expression of miRNA in late-stage AD patients can be either a primary cause or secondary consequence of the neurodegeneration. However, some important consistencies and correlations are still found for different lines of evidence. This is especially true when a similar expression change of one particular miRNA can be found in both human patients and mouse models[27,29,31] because the genetic background and breeding environment of the transgenic mouse are more pure and the profiling of miRNA expression can be explored at various stages, even before other pathology phenomena occur. Significant dysregulation of miRNAs in neurodegenerative brains both in humans and in animal models strongly indicates

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Table 1. Dysregulated miRNAs in AD and PD Pathogenesis

miRNA	disease	expression change in NDD	possible mRNA target	biological processes involved
miR-9	AD	decrease in cortex of sporadic AD patients[29] decrease in AD mouse model[31] decrease in response to Aβ treatment in primary neurons[49] increase in cortex and hippocampus of AD patients[26,45]	PSEN1; REST; BAF53a; Tlx; NF-H; SIRT1	cell proliferation; neurogenesis
miR-128	AD	increase in cortex of AD patients[26] decrease in AD mouse model[31]	SIRT1	cell proliferation; neurogenesis
miR-125b	AD	decrease in AD mouse model[31] decrease in response to Aβ treatment in primary neurons[49]	p53	neurogenesis; apoptosis
miR-133b	PD	decrease in the human PD substantia nigra[20]	Pitx3	DA neuron differentiation
miR-34c	AD	increase in AD patients[80] increase in AD mouse model[80,31]	SIRT1; Bcl-2; Cdk4; cyclin D1	apoptosis; cell cycle
	PD	decrease in PD patients[36]		
miR-181	AD	decrease in the human AD cortex[85,44,29,27] decrease in response to Aβ treatment in primary neurons[49]	ATM	apoptosis
miR-107	AD	decrease in cortex of AD patients[46,71] decrease in AD mouse model[31]	BACE1; cofilin; progranuli;CDK6	apoptosis; cell cycle
	PD	decrease in midbrain of PD patients[20]		
miR-29a/b-1	AD	decrease in cortex of sporadic AD patients[29] decrease in AD mouse model[31]	BACE1; NAV3; Bim; Bmf; Hrk; Puma	apoptosis
miR-146a	AD	increase in AD patients[26,45] decrease in AD patients[27] increase in AD mouse model[92] decrease in response to Aβ treatment[49]	CCL5; IRAK1	immune response
miR-205	PD	decrease in PD patients[100]	LRRK2	neurite outgrowth
miR-106b	AD	decrease in cortex of sporadic AD patients[29,67] decrease in AD mouse model[31,67]	APP	cell cycle

the involvement of miRNAs in the pathology of neurodegenerative diseases.[7]

DYSREGULATED miRNAs IN AD AND PD PATHOGENESIS

miRNAs Regulate Neurogenesis. In addition to being important for brain plasticity in early development, neurogenesis also plays a role in neurodegenerative diseases.[39−41] This is indicated by the observation that the brain regions showing adult neurogenesis are also the regions that are impaired in the early stages of neurodegenerative diseases.[42] Additionally, adult neurogenesis impairment is frequently observed in an AD mouse model.[41] However, most of the evidence can only show a correlation between adult neurogenesis and neurodegenerative diseases, and the causative role of neurogenesis in neurodegenerative disease has not been established yet.

In terms of function, miR-9, miR-124a, miR-125b, and miR-128 are all known to be involved in neurogenesis.[43] Several independent studies have found an altered expression of miR-9 in AD brains. However, both upregulation and downregulation were reported.[26,27,29,44−48] For example, Lukiw and colleagues reported an upregulation of miR-9 in the temporal cortex and hippocampus of AD patients compared with age-matched controls.[26,45] However, Hebert and colleagues found a decrease in the miR-9 in the cortex of sporadic AD patients.[29] In an animal model of AD, miR-9 shows a significant decrease in the hippocampus of 6-month-old but not 3-month-old APPswe/PSΔE9 mice.[31] Because Aβ plaques form in 6-month-old APPswe/PSΔE9 mice, this decreased expression of miR-9 might indicate that miR-9 decreases in response to Aβ accumulation. This hypothesis is consistent with what Schonrock and colleagues found in a cell culture model. They detected miRNA expression changes in response to Aβ treatment in primary neurons.[49] Interestingly, most of the miRNAs that show significant expression changes compared with untreated cells show downregulation in response to Aβ treatment. The proportion of the upregulated miRNAs is much smaller. miR-9 is one of the miRNAs that are rapidly downregulated in response to Aβ treatment in primary neurons.[49] Nevertheless, until today, no studies have indicated a dysregulation of miR-9 in PD patients. This might be because miR-9 is hippocampus-enriched but less expressed in the substantia nigra. In other brain regions that were enriched for miRNA, miR125b and miR-128 were also found to be dysregulated in AD patients. Lukiw had reported an upregulation of miR-128 in the brain of AD patients.[26] However, as identified by microarrays, miR-128 showed downregulation in APPSwe/PS1ΔE9 mice compared with age-matched controls.[31] miR-125b is also downregulated in APPSwe/PS1ΔE9 mice, and miR-125b also shows significant downregulation in response to Aβ treatment in primary neurons.[31,49]

Overexpression of miR-9* and miR-124 inhibits the proliferation of neural progenitor cells (NPCs) and promotes neuronal morphogenesis by repressing the expression of BAF53a (ACTL6A), which inhibits neurogenesis by regulating chromatin remodeling.[50] Meantime, Krichevsky and colleagues found that overexpression of miR-9 and miR-124 promotes NPCs to differentiate into Tuj1 positive cells, while the number of GFAP positive cells decreased dramatically.[43] These researchers also claimed that this pro-neurogenesis effect of these miRNAs is mediated by the phosphorylation of STAT3.[43] However, considering the divergent effect of miRNAs on the proteome, it is highly likely that miR-9 and miR124b promote neurogenesis by regulating various protein targets.[12] Thus far,

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confirmed miR-9 targets include the following: REST/NRSF (neuronal restricted silencing factor/RE-1 silencing transcription factor),[51] Tlx,[52] neurofilament H (NF-H),[21] sirtuin (SIRT1)[53] and BACE1.[29] REST is a transcription repressor that represses the expression of neuronal genes.[54] It is found to be induced by aging in the human cortex and hippocampus and decreased in AD brains compared with age-matched controls.[55] Tlx is involved in neuronal stem cell self-renewal.[56] NF-H is a neurofilament protein that is important for axon maturation. SIRT1 is a class III histone deacetylase. It is decreased in AD brains.[53,57,58] SIRT1 is implicated in Tau pathology, regulating metabolic process, and epigenetic gene regulation.[59] SIRT1 is also associated with cellular senescence, and overexpression of SIRT1 can enhance longevity.[60] BACE1 is an even more important target of miR-9 in AD pathology than the others. BACE1 is a β secretase which cleaves APP and is a rate-limiting enzyme in Aβ generation.[61] Taken together, overexpression of miR-9 might promote neurogenesis via multiple pathways by depressing the expression of various proteins.

In sporadic PD patients, miR-133b is significantly downregulated.[20] MiR-133b is a midbrain-enriched miRNA. Overexpression of miR133b moderately promotes the differentiation of DA neurons in the initial stage, while inhibiting terminal differentiation, as indicated by the reduced expression of DAT and TH.[20] Dopamine release is also reduced in miR-133b overexpressing cells. Conversely, inhibition of miR133b in ES cells potentiates DA neuron terminal differentiation and enhances dopamine release.[20] Pituitary homeobox 3 transcription factor (Pitx3) is one of miR-133b's targets.[20] Pitx3 is important not only for DA neuron differentiation but also for the long-term survival of these neurons.[62] Thus, it seems that the decreased expression of miR-133b in PD patients might participate in pathogenesis by affecting the DA neuron differentiation.

To summarize, the altered expression of miR-9, -125b, -128, and -133b might potentiate disease onset by impairing neurogenesis (Table 1). Otherwise, it might also be possible that miRNAs, which are involved in neurogenesis, are also important for neuronal survival. However, because this is a brain-enriched group of miRNAs, the significant change in the expression of these miRNAs in degenerated brains might just be a consequence of the increased degeneration of neurons.

miRNAs Regulate Neuronal Survival. Cell death is the fundamental pathology of neurodegenerative diseases.[63,64] Genes and environmental factors that are identified as responsible for neurodegeneration commonly converge to cell death pathways.[64] Several miRNAs that are frequently involved in AD and PD also play important roles in cell death/apoptosis pathways.[25] Here, we describe some representative ones, including the following: miR-29, miR-107, miR-34, and miR-181 (Table 1).

miR-29 is strongly expressed in astrocytes and, to a lesser extent, in mature primary neurons.[65,66] It has a dramatic increase with aging.[67−69] miR-29 was decreased in sporadic AD patients' brains.[29] Consistently, the decrease of miR-29 was also observed in the cerebral cortex of APPSwe/PS1ΔE9 mice.[31] Although altered expression of miR-29 is frequently found in PD patient blood, no reports emphasize altered expression of miR-29 in PD patient brains.[37,70] The emerging role of miR-29 is to protect cells from apoptosis by targeting and repressing a family of pro-apoptotic proteins, including Bim, Bmf, Hrk, and Puma.[65] Overexpression of miR-29 protects cells from various stimuli induced cell death. These stimuli include growth factor deprivation, ER stress, and DNA damage.[65] In addition to pro-apoptosis proteins, BACE1 is another confirmed target of miR-29, and the decrease in miR-29 in AD patients is correlated with the increase of BACE1 in these patients.[29] Therefore, decreased expression of miR-29 in AD patients might accelerate Aβ generation by derepressing BACE1. In summary, miR-29 executes a protective role in neuronal survival via both the apoptosis and APP pathways.

Downregulation of miR-107 in the temporal cortex is frequently observed in AD patients.[29,46,47] Interestingly, Kim and his colleagues reported that the downregulation of miR-107 is also found in the midbrain of PD patients.[20] Similar to miR-29, miR-107 targets BACE1,[46] and the decrease of miR-107 parallels the increase of BACE1 in AD patients,[46,71] which might be the cause for elevated Aβ generation. Moreover, miR-107 also targets progranulin, which is a secreted growth factor as well as a major genetic cause of frontal temporal dementia.[72,73] However, progranulin is protective, and loss of function can lead to dementia, which functionally cannot align with a decrease in miR-107 in AD and PD patients. Interestingly, miR-107 is also involved in cell cycle regulation through targeting CDK6, which is important for entering the G1 phase.[74,75] Because cell cycle re-entry commonly leads to cell death in postmeiotic neurons, the decreased miR-107 may lead to an increased expression of CDK6 and then the promotion of cell cycle re-entry, which finally causes cell death.

Similar to miR-29, miR-34 is significantly increased in aging.[76−80] This is noteworthy because age is the most prominent risk factor for AD and PD. miR-34 is reported to increase in AD patients[80] as well as in the cortex of 3-month-old APPswe/PSΔE9 mice compared with controls.[31,80] Unlike for miR-9, the significant change in miR-34 expression in the AD mouse model is observed before the accumulation of Aβ because Aβ deposition can only be found in 6-month-old APPswe/PSΔE9 transgenic mice.[31] This evidence indicates that a consistent and early increase of miR-34 in the AD brain might be a possible cause of neuronal degeneration. This increased expression of miR-34 in AD is intriguing because miR-34 is commonly decreased in various cancers.[81−83] Targets of miR-34 include SIRT1,[53,81,83] Bcl-2,[31] Cdk4, and cyclin D2.[84] Bcl-2, which is an antiapoptotic protein, showed an increase in the response to miR-34 inhibition and might protect cells from apoptosis. Cdk4 and cyclin D2 are cell cycle regulators that are involved in cell cycle re-entry, which will trigger cell death in mature neurons.[84] Taken together, increased expression of miR-34 might induce neuronal apoptosis in AD by decreasing the expression of Bcl-2 or regulating cell cycle re-entry. However, a decreased expression of miR-34 is found in various brain regions of PD patients compared with age-matched controls.[31] The decreased expression of miR-34 in PD patients is an early stage event, indicating that it is not a secondary response to disease development or drug treatment. The authors found that reduction of miR-34 in differentiated SHSY5Y cells can lead to disruption of the mitochondrial membrane and increased oxidative stress. They claimed that the reduction in miR-34 compromises the function of mitochondria and leads to decreased cell viability.[31] Bioinformatic studies indicated that Parkin is a target of miR-34; however, this relationship cannot be proven by Western blot analysis.

miR-181c is downregulated in the cortex of AD patients.[27,29,44,85] Interestingly, 1 h after treatment with Aβ, miR-181c is significantly downregulated in primary neurons,[49] suggesting that the altered expression of miR-181c in the AD

brain might be a secondary effect in response to Aβ deposition. miR-181c is supposed to protect cells from DNA damage by regulating the expression of ataxia telangiectasia mutated (ATM).[47] ATM is a DNA damage inducible kinase that can initiate the apoptosis response by activating its downstream targets, including p53, CHK2, and H2AX.[86]

miRNAs Regulate Neuroinflammation. Neuroinflammation is a prominent phenomenon in neurodegenerative diseases.[87] It is speculated to cause a significant portion of neuronal cell death in AD and PD. miR-146a might be involved in the immune response by targeting chemokine ligand 5 (CCL5)[88] and IRAK1.[89] The functions of CCL5 and IRAK1 include attracting immune cells to the reactive site and activating the NF-κB signaling pathway.[90] Therefore, miR-146a is supposed to be an inhibitor of immune responses and might be protective in neurodegenerative diseases.[91] miR-146a is reported to be both upregulated[26,45] and downregulated[27] in the brains of AD patients, and it is also increased dramatically in AD mouse model compared with control.[92]miR-146a also shows moderate downregulation in response to Aβ stimuli in primary neurons.[49] Thus, miR-146a might not be either a cause or a result of the neurodegenerative disease; it could instead be a protective response that the brain uses for defense. Another interesting miRNA that is involved in the immune response in neurodegenerative disease is let-7. miRNA let-7b is increased in the CSF of AD patients comparing with control.[32] The increased level of let-7b in CSF might contribute to neurodegeneration by binding to RNA-sensing Toll-like receptor (TLR) 7, which is an innate immune receptor.[32]

miRNA–TARGET INTERACTIONS POTENTIALLY INFLUENCE NEURODEGENERATION

miRNAs Regulate Disease Genes. Many studies indicate that miRNAs directly target the genes that can cause familiar AD or PD, like APP, PSEN1, BACE1, Lrrk2, α-synuclin, Parkin, and so on.[7] However, few of them are dysregulated in degenerated brains. miR-106b, which directly targets APP,[67] shows downregulation in both the human AD brain[29,67] and APPSwe/PS1ΔE9 mice.[31] Although it is unclear whether the downregulation of miR-106b is triggered by Aβ accumulation, the decreased expression of miR-106b can possibly enhance the expression of APP, which may accelerate Aβ accumulation (Figure 1a). However, we need to bear in mind that miR-106b might contribute to AD pathology in other ways. One possibility is that miR-106b might regulate cell cycle re-entry by targeting retinoblastoma protein 1[93,94] and p21.[95] Both retinoblastoma protein 1 and p21 are involved in cell cycle regulation. Additionally, miR-106 also targets ITCH, which is an E3 ubiquitin ligase that is involved in the p73 apoptotic signaling pathway[96] and Wnt signaling pathway.[97] Furthermore, miR-106b can also be involved in autophagy regulation, which is closely related to Aβ accumulation[98] by targeting to SQSTM1/p62.[99] Therefore, miR-106b might participate in AD pathology by regulating APP expression, cell cycle re-entry, apoptosis, or even neuronal differentiation.

In sporadic PD patients, Lrrk2 is considered an important pathogenic factor; Lrrk2 is significantly increased in patients compared with controls.[5] Interestingly, miR-205, which targets the Lrrk2 3′UTR and can regulate Lrrk2 expression (Figure 1a), was significantly downregulated in the frontal cortex and striatum of sporadic PD patients compared with controls.[100] In contrast, miR-181, -19, and -410, which also contain the Lrrk2 3′UTR binding site, lacked a significant expression change in sporadic PD patients. Overexpression of miR-205 in Lrrk2 R1441G mutant primary neurons rescued the shortened neuritis phenotype.[100] Interestingly, overexpression of miR-29, which works in the apoptosis pathway, cannot rescue the phenotype,[100] which means that miR-205 works through Lrrk2 in regulating neuronal survival, and the downregulated miR-205 contributes, at least in part, to the PD pathology induced by elevated Lrrk2 activity.[100]

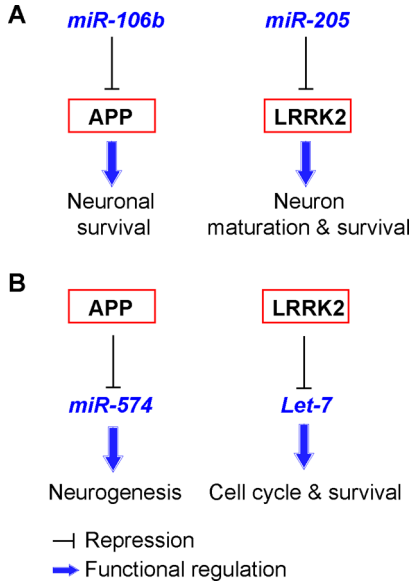

Figure 1. miRNA interacts with disease pathogenic factors in neurodegeneration: (a) miR-106b and miR-205 as upstream regulators of APP and Lrrk2, respectively, in mediating neuronal survival and maturation; (b) miR-574 and Let-7 as downstream mediators of APP and Lrrk2, respectively, in contributing to neurogenesis and neuronal survival.

miRNAs Downstream of Disease Genes. The miRNA pathway has been indicated to have a critical effect on the disease-causing gene. The regulation of miR-574 by APP is an example of how neurodegenerative disease causing genes can regulate biological processes through miRNA.[101] Upon phosphorylation, APP can be cleaved into several fragments, including Aβ and the APP intracellular C-terminal domains (AICDs).[102] The AICD can translocate into the nucleus and act as a transcription factor.[102] Additionally, AICD can regulate neurogenesis.[103] However, the downstream targets of AICD that are key mediators in this process are still unknown. Based on the increasing importance of miRNAs in neurogenesis, Zhang and colleagues searched for downstream miRNA targets of APP by detecting the differential expression of a cohort of miRNA between APP KO mice and WT controls using microarray and qPCR.[101] miR-574 is significant upregulated in E14.5 APP knockout (KO) mice compared with the age-matched control mice. The upregulation of miR-574 was also observed in the APP KO NPCs, and consistently, miR-574 was downregulated in APP-overexpressing NPCs (Figure 1b). The authors vigorously investigated the functional correlations between APP and miR-574 in both the APP KO mouse model *in vivo* and NPC cells *in vitro*. miR-574 overexpression in NPCs increased neurogenesis by approximately 30% and decreased cell proliferation by 40%. Conversely, miR-574 knockdown decreased neurogenesis in NPC cells by approximately 30% and increased cell proliferation by 22%, which was exhibited with a BrdU pulse chase experiment. miR-574 has the

same effect on cell proliferation and neurogenesis *in vivo*. Furthermore, miR-574 knockdown inhibits the increased neurogenesis that is induced by APP KO. miR-574 might promote neurogenesis by directly regulating the expression of Sox12, which is a confirmed target of miR-574. Altogether, these findings indicated that miR-574 is a downstream effector of APP in mediating neuronal differentiation.[101]

Considering Lrrk2 as another example, by using co-immunoprecipitation (co-IP), Gehrke and colleagues found a direct interaction between hLrrk2 and hAgo2 in both HEK293 cells and fly brain extracts.[104] Ago2 is a key component of RISC that is responsible for miRNA biogenesis. The gain-of-function mutant of Lrrk2 significantly decreases the expression of dAgo1 in aged flies and leads to dysfunction of the miRNA signaling pathway. The author found that miR-184/let-7 regulates the expression of E2F1/DP and plays a weighted role in the LRRK2 pathogenesis (Figure 1b).[104]

Feedback Regulation between miRNAs and Target Genes in Neurodegeneration. The discovery of the involvement of miRNAs in neurodegenerative diseases makes our understanding of the molecular mechanism of neurodegenerative diseases more complete.[7,71,81] This is especially true considering that accumulating evidence has revealed feedback regulations between miRNA and proteins.[105] This interaction complexity reminds us to interpret our findings in a more systematic way. By using serial analysis of chromatin occupancy (SACO) and chromatin immunoprecipitation (ChIP) methods, Conaco and colleagues identified a group of miRNAs whose transcription can be regulated by REST.[106] As mentioned above, REST is a key regulator in neuronal differentiation, neuronal aging, and neurodegenerative diseases.[54,55] This group of miRNAs includes miR-9, miR-124a, and miR-132. Verified by qPCR, REST represses the transcription of this group of miRNAs.[106] It is noteworthy that REST is also a target of miR-9 and that both miR-9 and miR-124a may regulate hundreds of genes to promote neuronal differentiation.[51] Additionally, miR-9 and Tlx also form a regulatory feedback loop, which regulates neurogenesis.[51] This protein−miRNA feedback regulation loop works in a magnifying manner or fine-tune modification manner in neurogenesis, serving as an example of how miRNA and proteins might function synergistically in cellular behaviors (Figure 2).

miR-133b and Pitx3 also form a feedback loop in regulating DA neuron differentiation. Bioinformatics searches predicted that Pitx3 is one of miR133b's targets (Figure 2). This was confirmed by a luciferase assay. However, overexpression of Pitx3 in differentiating ES cells causes an increase in the expression of miR133b. The regulation of Pitx3 on miR133b seems direct because the binding between Pitx3 and the promoter of miR133b was also confirmed by a luciferase assay.[20,107] Therefore, this positive-then-negative feedback between Pitx3 and miR-133b is different from the double-negative feedback between REST and miR-9 in the sense that the downstream product of Pitx3 stops its role without amplifying it.[20,107]

Various apoptosis-associated miRNAs, which also show dysregulation in AD, PD, or both, are direct transcriptional targets of p53.[108−110] As a DNA-binding protein, p53 can activate the expression of a cohort of genes that function in anticancer, pro-apoptosis, and sustaining genome stability processes.[111] Seven miRNAs, including miR-23a, miR-26a, miR-34a, miR-30c, miR-103, miR-107, and miR-182, exhibit

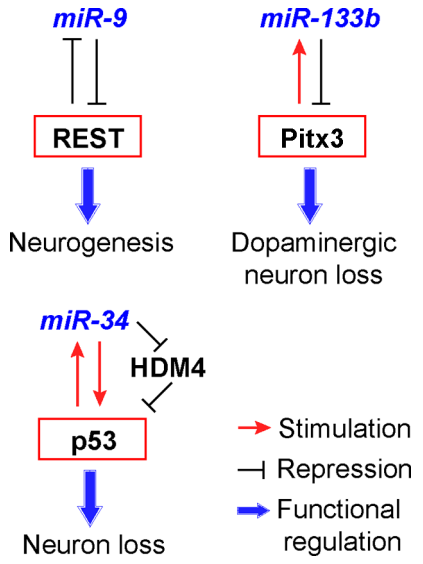

Figure 2. The feedback regulation between miRNA and targets in neurodegeneration. Feedback regulation between miR-9 and REST, miR-133b and Pitx3, and miR-34 and p53 are shown. miR-9 represses the expression of REST, which in turn represses the expression of miR-9, forming a double-negative feedback loop in the neurogenesis process. MiR-133b represses the expression of Pitx3, which in turn stimulates the expression of miR-133b, forming a negative−positive feedback loop in dopaminergic neuron differentiation and cell death processes. p53 stimulates the expression of miR-34, which in turn stimulates p53 expression by repressing the expression of HDM4, forming a double-positive feedback loop to regulate neuronal cell loss.

changes that are greater than 3-fold in response to DNA-damaging stimuli and greater than 2-fold changes in p53 knockout cells compared with p53 wild-type cells.[108] The authors further confirmed the direct binding of p53 on the promoter of miR-34a, which showed the biggest changes in response to p53 deletion, according to a luciferase assay.[108] Moreover, both p53 and miR-34 are closely related to the aging process.[111] Conversely, p53 is not a target of miR-34a, but its presence is important for elevating miR-34a to induce apoptosis.[109] This puzzle is solved when the researchers found that miR-34a can indirectly regulate the expression of p53 by repressing the expression of HDM4, which can inhibit the expression of p53 by its RING domain.[109] Thus, the double-positive feedback between p53 and miR-34a forms a locked checkpoint to execute the pro-apoptosis or antitumor program (Figure 2). In addition to miR-34, p53 also directly upregulates the expression of miR-107.[110] Using a luciferase assay and ChIP methods, Yamakuchi and colleagues identified a p53 binding site in the 5′UTR of the miR-107's parent gene, pantothenate kinase enzyme 1 (PANK1). The genotoxic stress induces increased expression of miR-107 in a p53 dependent manner, which is very similar to miR-34a.[110]

■ COMMONLY DYSREGULATED miRNAs IN NEURODEGENERATIVE DISEASES

Apart from AD and PD, dysregulated miRNAs are also found in other neurodegenerative diseases such as Huntington's disease[54,112−114] and amyotrophic lateral sclerosis (ALS),[21,115,116] Interestingly, recent studies also showed that some of the miRNAs are commonly dysregulated in the neurological disease. The overlapping involvement of miRNAs

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across neurodegenerative diseases suggests the common underlying mechanisms for brain disorder.

For example, inflammation is a common event of acute injuries of the central nervous system (CNS) and neurodegenerative disorder. Glial cells play an important role in neuroinflammation. The miR-181 family is found to be highly expressed in astrocytes compared with neurons. Gain-of-function of miR-181 in cultured astrocytes leads to an increase in cell death in response to lipopolysaccharide (LPS), an inflammation inducer.[117] In wild-type (WT) and transgenic mice that lack the inflammatory receptor cytokine TNF-a, miR-181 expression is altered under LPS treatment. Furthermore, knockdown of miR-181 enhances LPS-induced expression of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, IL-8, whereas overexpression of miR-181 led to a significant increase in the expression of cytokine IL-10, an anti-inflammatory marker,[117] suggesting that miR-181 negatively regulates the cytokinesisin response to neuroinflammation. Interestingly, downregulated miR-181a was found in AD CSF, compared with that of healthy individuals.[27] miR-181a has a role in lymphocyte lineage determination,[118,119] and affects T cell sensitivity,[119] which linked between the alterations of miRNA to neuroinflammatory pathway in AD CSF.

In the sporadic AD (sAD) patients, there are decreased Aβ clearances in the CNS.[120] The lysosomal system plays a neuroprotective role by decreasing protein accumulation disorders.[121] miR-128 is found to be upregulated in AD mononuclear cells, and it reduced the level of lysosomal cathepsin B, D, and S and further inhibited $A\beta^{1-42}$ degrading ability in blood mononuclear cells derived from sAD.[122] Moreover, inhibition of miR-128 from AD monocytes enhances the amount of lysosomal factors and the $A\beta^{1-42}$ degrading ability. The molecular mechanisms underlying the miR-128 mediate lysosomal expression that affect the imbalance between the Aβ production and clearance are involved in the pathogenesis of AD. Apart from the AD patient study, miR-128a was found dysregulated in transgenic Huntington's disease monkeys. miR-128a was downregulated in the HD monkey model by the time of birth.[112] In the miRNA microarray profiling, there are 11 miRNAs dysregulated in the cortex of HD. Among them, miR-128a was further analysized and results showed that miR-128a was downregulated in the HD monkey and patients. In addition, miR-128a was shown to target Huntingtin interaction protein 1 (HIP1), which is involved in regulating the expression of activated caspase-3 and glial fibrillary acidic protein (GFAP) in HD monkey frontal cortex.[112] The studies suggest that miR-128a may play a critical role in HD and could be a viable candidate as a therapeutic or biomarker of the disease.

CONCLUSION AND FUTURE DIRECTIONS

miRNAs appeared to serve as a powerful therapeutic tool for gene regulation due to their size, abundance, tissue specificity, and relative stability in plasma.[123] They hold promise as biomarkers that have therapeutic potential in AD and PD.[30,123] However, a single miRNA might regulate the expression of a few proteins or a large network of proteins. Additionally, the cellular feedback loops and mechanisms of feedback regulation of miRNA expression are not clear. Therefore, a precise understanding of the molecular mechanism underlying the function and regulation of a miRNA with neuronal signaling events has facilitated progress toward how miRNAs govern function either upstream or downstream of key disease pathogenic factors. It potentially regulates several pathways that are involved in disease progression and coordinates the network of events, leading to severe neurodegeneration.

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L.Q. E.K.T. and L.Z. designed the review and wrote the paper; W.Z. contributed to the figures and table.

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ABBREVIATIONS

AD, Alzheimer's disease; PD, Parkinson's disease; APP, amyloid precursor protein; LRRK2, leucine-rich repeat kinase 2; miRNAs, microRNAs; DAergic, dopaminergic; RISC, RNA-induced silencing complex; CSF, cerebrospinal fluid; PBMCs, peripheral blood mononuclear cells; NPCs, neural progenitor cells; NRSF/REST, neuronal restricted silencing factor/RE-1 silencing transcription factor; ATM, ataxia telangiectasia mutated; AICDs, APP intracellular C-terminal domains; ChIP, chromatin immunoprecipitation; ALS, amyotrophic lateral sclerosis; LPS, lipopolysaccharide; CNS, central nervous system; sAD, sporadic AD; HIP1, Huntingtin interaction protein 1; GFAP, glial fibrillary acidic protein

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