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Review Article

MicroRNA-219 in the central nervous system: a potential theranostic approach

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Abstract

Despite the recent therapeutic advances in neurological disorders, curative therapy remains a serious challenge in many cases. Even though recent years have witnessed the development of gene therapy from among the different therapeutic approaches affecting pathophysiological mechanisms, intriguing aspects exist regarding the effectiveness, safety, and mechanism of action of gene therapies. Micro ribonucleic acid (microRNA-miRNA), as a fundamental gene regulator, regulates messenger ribonucleic acid (mRNA) by directly binding through the 3′-untranslated region (3′-UTR). MicroRNA-219 is a specific brain-enriched miRNA associated with neurodevelopmental disorders that play crucial roles in the differentiation of oligodendrocyte progenitorcells, promotion of oligodendrocyte maturation, remyelination, and cognitive functions to the extent that it can be considered a potential therapeutic option for demyelination in multiple sclerosis and spinal cord injury and reverse chronic inflammation pains. Additionally, miR-219 regulates the circadian clock, influencing the duration of the circadian clock period. This regulation can impact mood stability and is associated with phase fluctuations in bipolar patients. Furthermore, miR-219 also plays a role in modulating tau toxicity, which is relevant to the pathophysiology of Alzheimer's disease and schizophrenia. Finally, it reportedly has protective effects against seizures and Parkinson's disease, as well as neoplasms, by inhibiting proliferation, suppressing invasion, and inducing cell death in tumor cells. Exploring the miR-219 molecular pathways and their therapeutic effects on central nervous system disorders and the mechanisms involved, the present review study aims to illustrate how this information may change the future of gene therapy.

Keywords: Brain malignancies; Gene expression regulation; MicroRNA-219; Nervous system diseases; Neurodegenerative diseases; Neuroprotective.

INTRODUCTION

Central nervous system (CNS) diseases encompass neurodegenerative diseases (ND) and CNS neoplasms. NDs have become significant global challenges, characterized by the progressive loss of neurons leading to cognitive and movement impairments. Despite extensive research and clinical trials, CNS diseases remain incurable and debilitating, particularly with the growing elderly population imposing a strain on national healthcare systems. Consequently, it is essential to reassess potential therapeutic biomarkers associated with conditions such as cancer, aging, and neurodegenerative diseases. MicroRNA (miRNA) comprises gene expression-regulating non-coding biomolecules of great interest for their involvement in NDs and brain cancers.

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The aberrant expressions of several microRNAs contribute widely to the pathogenesis of neurodegeneration and brain malignancies (1,2). miRNAs are endogenous non-coding small RNAs with 19-22 nucleotides that negatively regulate cellular processes through messenger RNAs (mRNAs). miRNAs regulate their post-transcriptional effects as follows: they initially inhibit mRNA translation in ribosomes before they decrease the stability and mRNA degradation by binding to complementary sequences of 3′-UTR to prevent protein synthesis (3). miRNA biogenesis commences with the synthesis of primary transcripts (pri-miRNA) by RNA polymerase II. Pri-miRNA contains double-stranded stem regions and apical loops the characteristic of stem-loop structures. Drosha ribonuclease III (DROSHA) and DiGeorge critical region 8 (DGCR8) are the enzymes that alter the longer hairpin loop RNA sequences to small functional miRNAs. The dicer enzyme cleaves the pre-miRNA to create a double-stranded miRNA loaded onto the Argonaute family of proteins to form the miRNA-induced silencing complexes (miRISC). The RNA-induced silencing complex (RISC)-loaded miRNA identifies the 3′-UTR sequence by the 7-8 base pair.

The miRISC complex regulates gene expression post-transcriptionally by degrading and repressing mRNA sequences using an Argonaute family protein-mediated method. An individual miRNA can target several mRNAs; likewise, a target mRNA may be attached to many different miRNAs to activate more diverse signaling pathways. As miRNAs play essential functions in many vital processes, including proliferation, differentiation, migration, apoptosis, and development, dysregulation of these molecules would lead to numerous diseases (4-6).

Six hypotheses have been put forward to show the relevance of miRNAs to NDs (7,8). The authors of the studies have identified intrinsic and extrinsic factors that contribute to the concentration of a brain-enriched miRNA. The intrinsic parameters include miRNA expression, miRNA intracellular localization, and disease-associated changes in miRNA expression, metabolism, and secretion. These factors are inherent to the miRNA itself and its cellular environment. On the other hand, the extrinsic factors are external influences that affect the concentration of brain-enriched miRNAs. This includes changes in blood supply to a specific brain area, alterations in blood-brain barrier permeability, and the stabilization of miRNAs in the bloodstream. These factors are not directly related to the miRNA's expression or metabolism but impact its availability and distribution within the brain.

miR-219 is encoded by two precursors, miR-219-1 and miR-219-2, on chromosomes 6 and 9 in the human genome and 17 and 2 in the mouse genome, producing identical mature miRNAs. It has been demonstrated that deletion of miR-219-1 does not lead to any significant change in the miR-219 level in the brain. Thus, miR-219-2 may be claimed as the primary precursor to miR-219 expression. The finding is supported by studies showing that miR-219 has a brain-specific expression pattern as a brain-preserved miRNA (9-11).

A previous study has demonstrated the inhibitory miR-219 effects on the proliferation, anchorage-independent growth, and migration of glioma cells and its roles in oligodendrocyte differentiation and myelination induction. Knowledge of the miR-219 target genes could lead to novel treatments to rehabilitate disabled (12,13). MiR-219 plays a role in suppressing some solid tumors, including gastric cancer, breast cancer, colorectal cancer, ovarian cancer, hepatocellular carcinoma, and esophageal squamous cell carcinoma, since miR-219 regulates cell proliferation. Overexpression of miR‑219‑5p may function as a tumor suppressor and serve as a therapeutic strategy (14,15).

Given the theranostic key roles of miR-219, the present article focused on the target genes of miR-219 and their effects on Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), circadian rhythm (CR), Huntington's disease (HD), multiple sclerosis (MS), Parkinson’s disease (PD), schizophrenia (SCZ), and CNS neoplasms (Table 1).

Table 1. mRNAs changing level following the up or downregulation of miR-219 in the CNS. ND, Not determined; NR, not reported.

Diseases	Pathologic expression of MiR-219		Target gene	Pathologic mRNA level change	MiR-219 effect on	The final effect of miR-219 administration	References
Amyotrophic lateral sclerosis	Downregulated		DLX2	↑ (Subventricular zone, hippocampus)	ND	↑ Remyelination	(16,17)
			FOXJ3	↑ (Subventricular zone, hippocampus)	Inhibitory		
			MKNK2	↑ (Subventricular zone, hippocampus)	NR		
			PTEN	↑ (Subventricular zone, hippocampus)	NR		
Medulloblastoma	Downregulated		CD164	↑	Inhibitory	↓ Proliferation, migration, and invasion of medulloblastoma cells	(18-20)
			OTX2	↑	Inhibitory		
Astrocytoma	Downregulated		EGFR1	↑	Inhibitory	Tumor suppressor	(21)
Tumor border	Upregulated		OLIG2	↑	Stimulatory	↓ Tumor recurrence	(22)
			NG2	↑	Stimulatory		
			O4	↑	Stimulatory		
			MBP	↑	Stimulatory		
Tumor	Downregulated		SALL4	↑	Inhibitory	Tumor suppressor	(23,24)
			EGFR	↑	Inhibitory		
			PDGFR	↑	Inhibitory		
			ROBO1	↑	Inhibitory		
Tumor periphery	Upregulated		TNF	↓	Inhibitory	ND	(25)
Alzheimer's disease	Downregulated		MAPT	↑	Inhibitory	↓ Tau phosphorylation	(10,26,27)
			GSK-3β	↑	Inhibitory		
			TTBK1	↑	Inhibitory		
			CAMKIIγ	NR	Inhibitory		
			Tau	↑	Inhibitory		
			CDK5	ND	ND		
Multiple sclerosis	Downregulated	Oligodendrocyte differentiation inhibitor genes	ELOVL7	↑	Inhibitory	↑ Differentiation and remyelination	(28-32)
			PDGFRα	↑	Inhibitory		
			NG2	↑	Inhibitory		
			SOX6	↑	Inhibitory		
			HES5	↑	Inhibitory		
			Nfia	↑	Inhibitory		
			Nfib	↑	Inhibitory		
			LINGO1	↑	Inhibitory		
			ETV5	↑	Inhibitory		
			ZFP238	↑	Inhibitory		
			FOXJ3	↑	Inhibitory		

			PRKCI	NR	Inhibitory		
			PARD3	NR	Inhibitory		
		Anti-inflammatory	ENPP6	↓	Inhibitory	↓ Inflammation	
			FGFR2	↑	Inhibitory		
		Suppressing neurogenic products	NeuroD1	NR	Inhibitory	↓Neurogenesis and proliferation	
			Isl1	NR	Inhibitory		
			OTX1	NR	Inhibitory		
		Myelination regulatory genes	FADS2	↑	Inhibitory		
			UBASH3B	NR	Inhibitory		
			MYRF	↓	Stimulatory		(33)
			ZEB2/SIP1	↓	Stimulatory		
			SOX10	↓	Stimulatory	↑ Remyelination	
			CNP	↓	Stimulatory		
		Myelin-associated genes	MAG	↓	Stimulatory		(34)
			MOBP	↓	Stimulatory		
			PLP	↓	Stimulatory		
		Oligodendroglial lineage marker	NESTIN	↑	Inhibitory	↑ Oligodendrocyte differentiation and remyelination	(35)
			OLIG2	↑	Inhibitory		
		Astrocyte related gene	GFAP	NR	Inhibitory	↓ Astrocyte activation	(34)
Schizophrenia	Upregulated		CAMKIIγ	↑	Inhibitory	Behavioral aberrations and alteration of behavioral manifestations	(36-38)
			GRIA2	NR	NR		
			DAZAP1	NR	Stimulatory		
			PKNOX1	↑	NR		
			EPHA4	NR	NR		
			ESR1	↓	NR		
			PDGFR	NR	NR		
Circadian rhythm	Oscillatory		SCOP	Inversely	Inhibitory	Regulatory	(39,40)
			BMAL 1	Oscillatory	Inhibitory		
			BMAL1	Oscillatory	Stimulatory		
			CLOCK	Oscillatory	NR		
			Per mRNA	Oscillatory	Stimulatory		
Arsenic-induced Memory impairment	Upregulated		CAMKII	↓	Inhibitory	Arsenic-induced neurotoxicity learning and memory impairments and synaptic damage	(41,42)
Parkinson's disease	Downregulated		GSR	↑	Inhibitory	Antioxidant	(43,44)
Krabbe disease	Downregulated		Cleaved	↑	Inhibitory	↑ Oligodendrocyte differentiation and myelination	(45)
			PLP1	↓	Stimulatory		
			MBP	↓	Stimulatory		
Spinal cord injury	Upregulated		MCT-1	↓	Stimulatory	Regulation of inflammation and oxidative stress and ↑ recovery	(31,44,46,47)
			LRH-1	↓	Inhibitory		
			NEUROD2	↑	Inhibitory		

ALS

ALS is a lethal neurodegenerative disease of unknown cause. It is characterized by the selective degeneration of upper and lower motor neurons, affecting regions such as the motor cortex, brain stem nuclei, and spinal cord. Genetics plays a crucial role in around ten percent of the patient population, with different mutations occurring in various sets of genes. In the pathogenesis of ALS, altered expressions of specific neural miRNAs have been observed. These miRNAs are related to cell cycle regulation and glial function. Additionally, their targets in selected brain regions of ALS models suggest the significant involvement of miRNAs in the development of ALS. Despite advancements in understanding the mechanisms underlying ALS, effective treatment for the disease needs yet to be developed (48).

Neurodegeneration and astrogliosis are highly engaged in the pathophysiology of ALS. The spinal cord ventral horn and brainstem motor nuclei are the main sites of neurodegeneration, while most symptoms are related to hypoglossal, trigeminal, ambiguous, and facial nuclei damage. Meanwhile, the subventricular zone (SVZ), subgranular zone (SGZ), and the motor cortex are involved in proliferation and astrogliosis. It has been reported in several studies that miR-219 has a significant impact on both stimulating differentiation and repressing the proliferation of neurons. These features provide a practical ALS therapeutic approach (49).

The activities of neural stem progenitor cells (NSPCs) in the late stages of ALS were studied in a G93A-superoxide dismutase 1 (SOD1) transgenic mouse model to find elevated NSPCs proliferation and differentiation in the SVZ and SGZ (*i.e.* the main neurogenesis sites) in response to neurodegeneration of motor neurons when compared with the control mice. Reportedly, this led to unsuccessful regeneration and neurogenesis in the damaged sites (50-52).

Mouse brains in the late stages of the disease were studied in the ALS model to investigate possible alterations in oligodendrocyte-related miR-219 expression; the expression profile (expression profile/ expression pattern/expression level analysis) analysis showed a significant down-regulation of miR-219 expression in SVZ and the hippocampus, which might have been due to an imbalance between precursors of neurons and oligodendrocytes during NSPCs differentiation. The altered expression was observed in the primary motor cortex and brainstem nuclei. The target genes of miR-219 were found to be forkhead box protein J3 (FOXJ3), mitogen-activated protein kinase (MAPK) interacting serine/threonine kinase 2 (MKNK2), phosphatase and tensin homolog (PTEN), and specific E3 ubiquitin-protein ligase 1 (SMURF1); except for SMURF1 that showed no significant changes in the ALS model; all the rest were found upregulated in the SVZ and hippocampus, in contrast to the miR-219 expression that was downregulated (53).

Astrogliosis may also play a role in ALS formation as a physical barrier that inhibits axonal regeneration and neurodegeneration. Astrogliosis may be characterized by a complex of changes in astrocytes and altered expressions of proteases, cytokines, and growth factors, all of which lead to cell hypertrophy and glial scar formation (54).

The astrocyte-related miR-215b overexpression in ALS neurodegeneration sites leads to astrogliosis and motor neuron degeneration characteristic of ALS. As previously reported, miR-219 is capable of inhibiting astrocyte activation *in vivo* by targeting SRY-box containing gene 6 (SOX6), hes family bHLH transcription factor 5 (HES5), zinc finger protein 238 (ZFP238), and FOXJ3 downstream genes. miR-219 inhibits SOX6, HES5, ZFP238, and FOXJ3 gene expressions to inhibit oligodendrocyte progenitor cell proliferation and enhance oligodendrocyte differentiation. The study has shown that these properties exhibit the potential therapeutic effects of miR-219 on neuron injuries like ALS, MS, and spinal cord damage (16,34,50,55).

It has been established that NSPCs can generate distal-less homeobox 2 (DLX2) expressing neuroblasts (which are migratory and proliferative neuronal precursors) in SVZ. DLX2 is related to neurogenesis and significantly more DLX2-positive neuroblasts

have been observed in ALS SVZ than in the corresponding control samples. On the other hand, TagetScan database investigations have revealed that DLX2 is a potential target for miR-219. Moreover, miR-219 overexpression in SVZ and hippocampus might reportedly result in inappropriate neurogenesis followed by DLX2 suppression; thus, miR-219 could serve as an effective therapeutic approach for ALS by affecting not only FOXJ3, MKNK2, and PTEN, but also DLX2 as a probable target which is not confirmed yet (16,17,51).

Brain neoplasms

It is widely accepted that miRNAs are among the fundamental regulators of human cancers (56). Their aberrant expressions can contribute to oncogenic or tumor suppressor properties that affect tumoral events such as unlimited proliferation, apoptosis inhibition, migration, and invasion. Since the multiple genetic and epigenetic alterations bring about high cellular heterogeneity levels, brain cancers are highly progressive and resistant to available treatments. A previous study has demonstrated that miR-219 is one of the six crucial miRNAs engaged in glioblastoma multiforme (GBM) (57). Many studies have also reported the suppressive roles of miR-219 in CNS malignancies through its effects on target genes (23).

The significance of miR-219 in CNS cancers was investigated in four different neoplasms. Among these, astrocytoma is the most common type of glioma, which is a primary cancer originating within the CNS. Astrocytoma can be categorized into four stages based on its location and morphological characteristics: pilocytic (grade I), diffuse (grade II), anaplastic (grade III), and glioblastoma (GBM, grade IV). Each stage has different median survival rates and treatment approaches, particularly for the malignant grade III and IV forms. Therefore, accurately distinguishing between these two grades is crucial. A study identified 23 miRNA expression signatures specifically associated with the malignant grades of astrocytoma. Among them, miR-219 was found to play a significant role in differentiating between the grades. Previous research has shown that decreased expression of miR-219 is closely linked to the growth and recurrence of brain tumors. To further investigate the effects of miR-219 on glioma cells, the precursor of miR-219 was introduced into these cells. The results demonstrated that overexpression of miR-219 led to slight repression of cell proliferation, reduced formation of colonies in soft agar, and induced apoptosis. These findings indicate the impact of miR-219 on glioma cells and its potential therapeutic implications (58).

The mutation or up-regulation of growth factors or their receptors (platelet-derived growth factor (PDGF) A and B, epidermal growth factor (EGF), transforming growth factor-a (TGF-a), and insulin-like growth factor-1 (IGF-1)) are attributed to gliomas. The potential roles of PDGF and EGF genes and their receptors as the targets of miR-219 have been specified in glioblastoma development on glial progenitor cells. The miR-219 declines proliferation, migration, and anchorage-independent growth by inhibiting PI3K, MAPK, and RTK pathways. The inhibitory effects of miR-219 can rescue the mutated or wild-type epidermal growth factor receptor (EGFR) without a 3'-UTR site. However, the mechanisms of the other growth factors and their interactions with miR-219 remain unknown (12).

Jiang *et al*. demonstrated the relationship between miR-219 and the roundabout homolog 1 (ROBO1), upregulated in both mRNA and protein levels. ROBO1 down-regulation induced by miR-219 inhibits proliferation, invasion, and cell apoptosis (24). Sal-like protein 4 (SALL4) has been demonstrated as another direct target of miR-219 which is negatively regulated, however, the inhibitory effects of miR-219 upregulation on tumor progression have been observed to diminish due to SALL4 overexpression. Moreover, in addition to induced drug resistance, SALL4 has been claimed to have a functional role in tumor cell growth, metastasis, and angiogenesis (23). In addition to the downstream targets of miR-219, an upstream regulator has been identified for miR-219. HOX transcript antisense ribonucleic acid (HOTAIR) is a long non-coding ribonucleic acid (lncRNAs) transcriptionally and post-transcriptionally regulating coding transcriptome. Recent studies

have demonstrated its significant upregulation in malignancies. While the repression of HOTAIR by siRNA has been shown to bring about miR-219 overexpression, no significant change has been reported in the mRNA expression level of HOTAIR after miR-219 knockdown (59).

As mentioned, miR-219 inhibits cell proliferation, invasion, and migration and induces the death of immortalized primary cells in medulloblastoma, meningioma, and gliomas. miR-219 downregulation is reportedly associated with advanced clinical stages and higher recurrence rates in meningioma. More specifically, miR-219 overexpression exerts these effects by targeting orthodenticle homeobox 2 (OTX2) and cluster of differentiation 164 (CD164). Exactly OTX2 overexpression in the cerebellum, pons, and medulla has been shown to serve as an oncogene in medulloblastoma (18). CD164 is a transmembrane sialomucin and cell adhesion molecule that contributes to glioma pathogenesis and controls the proliferation, attachment, and migration of hematopoietic progenitor cells found in the whole brain (19). As a result, miR-219 may serve as a potential therapeutic agent for glioma and medulloblastoma by targeting CD164.

Expressions of miR-219 and other miRNAs associated with oligodendrocyte differentiation show a significant upregulation of approximately eight-fold at the tumor border compared to their levels within the brain tumor mass. This finding suggests these miRNAs may regulate oligodendrocyte differentiation in the tumor vicinity. This synchronization in the region between the tumor mass and the peripheral tissues is five-fold higher in the periphery like the co-existence of tumor and normal cells. These show the border accumulation of oligodendrocyte lineage cells, including oligodendrocyte progenitor cells (OPC), which leads to chemo-radio resistance of the GBM cells microenvironment (20). Moreover, miR-219 overexpression at the tumor border plays anti-apoptotic roles in macrophages through decreasing tumor necrosis factor expression as a proinflammatory cytokine in microglia, suggesting an effective treatment for gliomas (25,60) (Fig. 1).

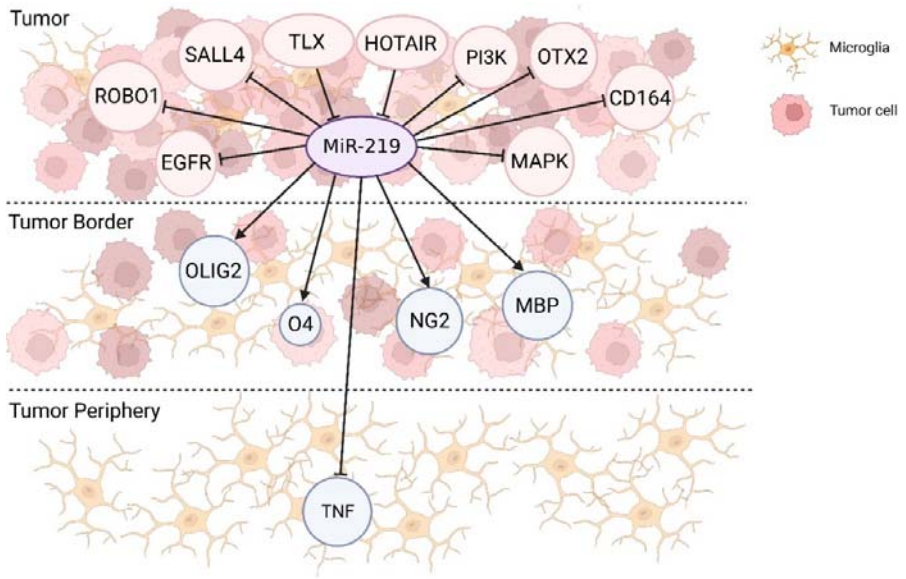

Fig. 1. miR-219 and target gene network in brain cancers. miR-219 can be affected by specific genes such as TLX and HOTAIR, and this miRNA can reciprocally regulate the other target genes in the brain tumor, tumor border, and tumor periphery, which are involved in the pathophysiology of brain cancer.

AD and primary age-related tauopathy

AD is the most prevalent reason for dementia in the elderly population. Molecular hallmarks of AD and its pathology associated with miRNA dysregulation consist of neurodegeneration, extracellular accumulation of protein β-amyloid (Aβ), and tau expansion, the multifunctional brain protein in neurofibrillary tangles. Primary age-related tauopathy is a pathological condition like AD but develops neurofibrillary tangles independent of Aβ. The downregulation of miR-219, a highly conserved brain miRNA, has been detected in AD postmortem brains. The present study aims to shed light on the potential therapeutic effects of miRNA expression by targeting the pathways associated with neurofibrillary degeneration. Previous studies have revealed that the expression of miR-219 is downregulated in both *Drosophila* models of AD and the brains of AD patients. Furthermore, it has been demonstrated that depletion of miR-219 leads to increased tau toxicity, a hallmark of AD. miR-219 exerts its positive inhibitory effects on AD through various mechanisms, including post-transcriptional mRNA destabilization, translational regulation, and post-translational modifications, ultimately preventing neurodegeneration. These findings suggest that miR-219 holds significant therapeutic potential as a candidate for the treatment of AD (10,61).

miR-219 binds uniquely and directly to the predicted and highly conserved recognition element of the tau 3'-UTR mRNA and represses its synthesis at the post-transcriptional level. Moreover, tau-tubulin kinase 1, calcium/calmodulin-dependent protein kinase two gamma subunit (CAMKIIγ), and glycogen synthase kinase three beta are the three predicted direct targets of miR-219 that would upregulate in AD patients. These three enzymes bring about aberrant hyperphosphorylation of tau, its accumulation, and accelerated neurodegeneration. miR-219 inhibits tau phosphorylation through direct binding to protein kinases 3'-UTR sites. Following miR-219 overexpression, the levels of phosphorylated tau would decline. No alterations have been reported in mRNA levels for any of these kinases in the human brain tissue, which supports post-transcriptional regulation of the three kinases by miR-219. It is also maintained that the restriction of miR-219 expression is noteworthy in cases with sparse-moderate pathology, lending support to the claimed potential effect of miR-219 on the onset of the disease (26,62).

Cyclin-dependent kinase 5 (CDK5) as a proline-directed Ser/Thr kinase functions crucially in the different cellular events during normal brain development and neurodegeneration. For instance, it plays crucial roles in neurotransmission, neuronal development, neuronal trafficking, and synaptic plasticity. In the brain, overexpression of p35 as a neuronal-specific activator leads to the specific activation of CDK5 in postmitotic neurons. However, its definite regulatory activity is related to mitotic neurons and needs to bind to either p35 or p39, neuron-specific regulatory subunits. Excessive neuronal stress and toxic factors may stimulate CDK5 hyperactivation leading to abnormal cytoskeletal protein hyperphosphorylation such as tau. Intriguingly, investigations of the TargetScan database have revealed that CDK5 regulatory subunit 1 (p35) and subunit 2 (p39) as targets of miR-219 might be exploited in a potential therapeutic approach for treating AD patients (27,63).

miR-219 destabilizes tau mRNA by interacting with the tau mRNA which is wildly conserved. Finally, miR-219 regulates nerve growth factor-induced tau protein synthesis by directly silencing the microtubule-associated protein tau in a well-established neurite outgrowth model. According to these findings, miR-219 silences tau expression through direct interaction with the predicted highly conserved recognition element in tau's 3'-UTR (10).

The coincidence of Dicer deficiency with a neuronal accumulation of proteins is typically associated with neurodegenerative disorders. For instance, endogenous tau hyperphosphorylation, a microtubule-associated protein and the component of neurofibrillary tangles that is a significant characteristic of AD and other dementias was observed in mice with Dicer deletion throughout the forebrain (64).

Coninx *et al.* recently showed that an epigenetic clock correlated AD with an accelerated epigenetic age in humans. Differences in chronological and epigenetic ages, defined as the acceleration of aging, may reflect biological aging and aging-related diseases. The first signs of AD pathology appeared in the epigenetically older AD mice, albeit with slower acceleration rates over time. Epigenetic mechanisms, including DNA methylation and histone modifications, could influence miRNA expression. However, a recent study has indicated that some 5'-cytosine-phosphate-guanine-3' (CpGs) reveal opposite age-associated DNA methylation patterns that positively correlate with neurodegenerative diseases such as AD. It has been shown that age-dependent CpG sites accumulate extensively in genomic regions encoding for developmental, aging-related, neuronal changes, and in the vicinity of specific genes, such as 7 CpGs in mir-219. For miR-219. Methylation levels were found to elevate with age in AD mice but to decrease with age in others (65). Indeed, 7 CpGs were discovered in mir-219 that showed an overall decrease in methylation with age in C57BL/6J mice but an increase in AD ones. mir-219 expression is known to decrease in the brains of AD patients which has been linked to neurodegeneration and disease progression. These CpGs were detected in clusters near specific genes, including 7 CpGs in mir-219, 6 CpGs in netrin-G2 (Ntng2), 5 CpGs in deleted in lymphocytic leukemia 2 (Dlue 2), and 2 CpGs in cytochrome c oxidase assembly factor 6 (Coa6). For mir-219, Ntng2 and Dlue 2 methylation levels increased with age in AD mice but decreased in C57BL/6J control mice (65).

MS

MS is a demyelinating and chronic neuroimmune disease of CNS in young adults worldwide. The primary pathological hallmarks of MS are demyelinated plaques in the CNS. Myelin is a multilamellar differentiation of the plasma membrane of oligodendrocytes that surrounds axons to facilitate electrical conduction. Oligodendrocytes are responsible for myelination in CNS. There are large numbers of OPCs in MS lesions; however, OPCs cannot differentiate into mature myelin-forming cells. Thus, remyelination fails and the resulting disabilities will not rehabilitate. Lack of remyelination is the dominant mechanism underlying MS neurodegeneration that results in patients' symptoms (66).

Previous studies have demonstrated the miR-219 potential as a differentiating biomarker of MS patients' cerebrospinal fluid.

It has been found that the mean relative expression of miR-219 in healthy individuals is significantly higher than that in secondary progressive MS (SPMS) and primary progressive MS (PPMS) cerebrospinal fluid samples. The detectable expression level of miR-219 was upregulated by 10 to 100-fold during the differentiation of OPCs to oligodendrocytes. It should be noted that miR-219 plays a crucial role in advancing oligodendrocyte and myelin development (67).

miR-219 stimulates the OPCs' transition from proliferation and self-renewal to differentiation before they exit the cell cycle. Apical protein retention following miR-219 downregulation causes the cells to remain in the cell cycle and prevents OPC differentiation to oligodendrocytes. Various protein complexes, including partitioning-defective (PAR) proteins, partitioning-defective 3 homolog (PARD3), and protein kinase C iota (PRKCI; also known as atypical protein kinase C (aPKC)) that are associated with the apical membrane as well as the PARD3 and PRKCI 3'-UTR sequences, are negatively affected by miR-219 to take the cells in this way (28).

Another mechanism whereby miR-219 induces differentiation is the direct suppression of anti-differentiation targets in OLs, including platelet-derived growth factor receptor alpha (PDGFRα), HES5, SOX6, FOXJ3, ZFP238, leucine-rich repeat immunoglobin-like domain-containing protein 1 (LINGO1), and ETS variant transcription factor 5 (ETV5) to improve oligodendrocyte differentiation (32). miR-219 also greatly enhanced monocarboxylate transporter 1 (MCT1) expression through suppression of oligodendrocyte differentiation inhibitors like SOX6 and HES5. Moreover, treatment with the MCT1 inhibitor, α-cyano-4-hydroxycinnamate (4-CIN), scaled down the oligodendrocytes

number and the 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP) and myelin basic protein (MBP) protein levels (31).

miR-219 has been observed to promote the downregulation of certain critical factors to maintain oligodendrocyte precursors in an undifferentiated state. Three transcription factors have been reportedly identified: LINGO1b, nuclear factor 1 A-type (NFIA), and ETV5a, which are highly conserved in humans, zebrafish, and mice. miR-219 binds to 3′-UTR and brings about mRNA degradation post-transcriptionally. Following miR-219 knockdown, overexpression of the target mRNA genes and increased protein levels were observed (29). Inhibitory pathways, including bone morphogenetic protein (BMP), neurogenic locus notch homolog protein (NOTCH), wingless-related integration site (Wnt), and LINGO1 signaling, can form other miR-219 targets that carry out oligodendrocyte maturation capable of myelinating axons. miR-219 antagomir administration was found to induce significant decreases in the expressions of mature oligodendrocytes (MOGs) marker genes, including myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), proteolipid protein (PLP), and myelin basic protein (MBP). However, an opposite effect was observed in the case of OPC marker genes (SOX10 and PDGFRα).

To evaluate the miR-219 effect on oligodendrocytes, the marker gene expression levels (MAG, MOG, PLP, and MBP for MOGs, and SOX10 and PDGFRα for OPCs) for mature oligodendrocytes were detected. The marker genes of MOGs were positively upregulated while OPCs marker genes were remarkably downregulated (68).

The medial entorhinal cortex (MEC) is characterized by its laminar structure and is involved in processes that are related to navigation and spatial memory formation. Each layer of the MEC consists of distinct cell types possessing unique physiological characteristics. Alterations in the functioning of these cells have been found to contribute to the development and progression of certain neurological disorders. In a study, parts of MEC were investigated to verify the role of miR-219 in the CNS and to determine other possible gene targets. Examination of the miRNA profile of cell types revealed that the significantly downregulated miRNA in layer II comprised miR-219-5p to regulate myelination. Furthermore, investigation of miR-219 revealed the cell-specific localization of its expression and, thereby, its role in MEC lamination. miR-219 expression was also observed in ependymal cells, oligodendrocytes, and glia in the tissue, confirming the miR-219 roles in oligodendrocyte differentiation, neuron development, and myelin regulation. Elongated very long-chain fatty acid protein 7 (ELOVL7) is a gene involved in final maturation and myelin maintenance, whose expression pattern is positively correlated with miR-219-5p (30).

The other gene targets identified to regulate myelination are fatty acid desaturase 2 (FADS2), PDGFRa, and ubiquitin-associated and SH3 domain-containing B (UBASH3B). PDGFRa also has a role in OPC differentiation to oligodendrocytes. FADS2 is involved in myelination while UBASH3B inhibits the endocytosis of EGFR and may play a role in oligodendrocyte development indirectly through the EGFR signaling pathway (33). A series of behavioral tests have provided further support for these findings. For instance, the distance traveled was observed on one test to decrease significantly after the microinjection of antagomir but to increase after the agomir-219 microinjection (29).

It is worth noting that miR-219 alone plays the necessary and sufficient roles not only in the proliferation and early differentiation of OPCs but in the metabolic regulation of lipid formation and myelin assembly as well, all of which enable it to counteract at least partially the severe oligodendrocyte defects due to Dicer loss (68). Several genes have been identified as regulators of oligodendrocyte proliferation and differentiation. Previous research has highlighted the important role of miRNAs in promoting the differentiation of OPCs. Specifically, miR-219 is essential and effective in halting proliferation and inducing differentiation, ultimately leading to remyelination in areas of brain damage. miR-219 targets different known and unknown genes to enhance the differentiation of

oligodendrocytes from OPCs. It also suppresses the production of unwanted neurogenic factors that could potentially divert OPCs towards inappropriate pathways. Furthermore, miR-219 helps maintain myelin homeostasis, ensuring the proper functioning of oligodendrocytes in the CNS.

One way to increase remyelination is to grow OPCs by inhibiting the proliferation of such other neuron lineages as astrocytes from neural stem cells (NSCs) and conducting them to OPCs by suppressing the neurogenesis-promoting transcription factors such as neuronal differentiation 1 (NEUROD1), ISL LIM homeobox 1 (ISL1), and OTX2 genes. While NSCs are conducted in the differentiation pathway to produce myelinating oligodendrocytes following OPC transition, miR-219 inhibits the expression of PDGFRα, SOX6, FOXJ3, FGFR2, HES5, and ZFP238 to induce mature oligodendrocytes formation from OPCs. Furthermore, oligodendrocytes enriched with ELOVL7 synthesize very-long chain-fatty acids (VLCFAs) through condensation of fatty acyl-CoA and malonyl-CoA, whereby their accumulation in cells leads to membrane instability, oxidative damage, inflammation, neuronal degeneration, and demyelination. miR-219 is specifically capable of inhibiting ELOVL7 as its target to diminish ELOVL7 degenerative effects in MS patients through inducing mature oligodendrocyte conversion to myelinating oligodendrocytes (30,69).

miR-219 increases the expression of neuroprotective proteins that contribute to protection against cognitive impairment. These proteins include MCT1 which participates in neuronal repair similar to the orphan nuclear receptor tailless homolog (TLX), cAMP response element-binding (CREB), methyl-CpG binding protein 2 (MECP2), and C-FOS that play roles in memory (70).

miR-219 injection to mice was reportedly observed to enhance two OPC markers; PDGFRα and neural/glial antigen 2 (NG2) expressions significantly inhibited the anti-differentiated agent and not only promoted the transition of neural precursor cells into OPCs but augmented oligodendrocytes differentiation and maturation as well (34).

It has been observed that in the spinal cord of CNP-Cre: Sox2fl/fl mutants mice in which SOX2 was specifically deleted to inhibit the oligodendrocytes differentiation, ectonucleotide pyrophosphatase/ phosphodiesterase protein 6 (ENPP6) mRNA expression as a premyelinating oligodendrocyte-enriched gene was downregulated. In addition, its downregulation was correlated to the suppression of oligodendrocyte differentiation. On the other hand, Targetscan software showed the ENPP6 gene as a probable target for miR-219. Thus, further studies are required to confirm the therapeutic effects of miR-219/ENPP6 in MS (30,71,72).

Neuroepithelial stem cell protein (NESTIN) is the type VI intermediate filament protein expressed primarily in nerve cells. It is responsible for developing glial and neural progenitor cells from neuroepithelial stem cells. Studies have shown the NESTIN overexpression in the astrocytes during CNS injuries, such as MS. These NESTIN-expressing cells were correlated to more inflammation and macrophages in the proximity of MS lesions. Moreover, following the increased miR-219 expression, a significantly lower expression of NESTIN was observed (35,73).

Oligodendrocyte transcription factor 2 (OLIG2) is a marker specific to oligodendrocyte stages. When evaluating the effects of miR-219 on promoting oligodendrocyte development, it was found that the expression of OLIG2 was reduced after ectopic upregulation of miR-219 (73,74). Thus these two are other new insights into MS treatment through the miR-219 regulatory network.

Following treatment with miR-219, overexpression of the middle and late oligodendrocyte markers (*i.e.* CNP, MBP, and MAG) was reportedly observed while the astrocyte activator (glial fibrillary acidic protein-GFAP) exhibited a significant downregulation. Reactive astrocytes lead to the formation of glial scars which are inhibitory factors for axonal regeneration. This finding, however, is reversed by miR-219 which suppresses GFAP expression, as it is typically upregulated during astrocyte reactivation (34).

Ermakov *et al.* identified 23 MS fingerprint IgG antibodies that hydrolyze four site-specific neuroregulatory miRNAs, including miR-219-2-3p and miR-219-5p (75). DNA methylation can suppress miRNA transcription, like coding genes, whereby CpG islands are methylated in miRNA promoter regions. Based on the combined and visualized data from MRE-seq, MeDIP-seq, ATAC-seq, and histone methylation CHIP-seq (H3K4me1, H3K4me3, and H3K27ac), Ling *et al.* hypothesized that triclosan (TCS) suppresses miR-219 expression in the hyper-methylated transcription regulatory region of the miR-219 coding gene. Thus, they synthesized three probes for WISH trials for pre-miR-219-1, pre-miR-219-2, and pre-miR-219-3 to find that the expression level of pre-miR-219-2 at 48-hour postfertilization was higher than those of pre-miR-219-1 and pre-miR-219-3, indicating that the most mature miR-219 originated from pre-miR-219-2 encoded by miR-219-2 in the zebrafish genome. In further investigation of the epigenetic changes on miR-219-2's promoter region, they selected five CpG islands within 4500 bp regions, out of which they selected five CpG islands with high GC percentages. MRE-seq methylation sites were generally found constant with those predicted by CpG. Significantly, high chromatin accessibility sites correlated with MRE-seq and CpG predictions. Moreover, H3K4me3 and H3K27ac peaks were observed nearby in the TSS of miR-219-2. Compared to the higher H3K4me3 and H3K27ac peaks, the H3K4me1 ones were much lower, indicating that miR-219-2 was significantly expressed. After TCS exposure, methylation-specific PCR was performed to confirm the methylation sites for the five recognized CpG islands. According to this analysis, the methylation site number elevated with exposure to increasing TCS concentrations. The authors concluded that TCS promoted miR-219 downregulation *via* DNA hypermethylation (29) (Fig. 2). A recent study showed possible relationships of miR-219 with apolipoprotein E and alpha crystalline B (76).

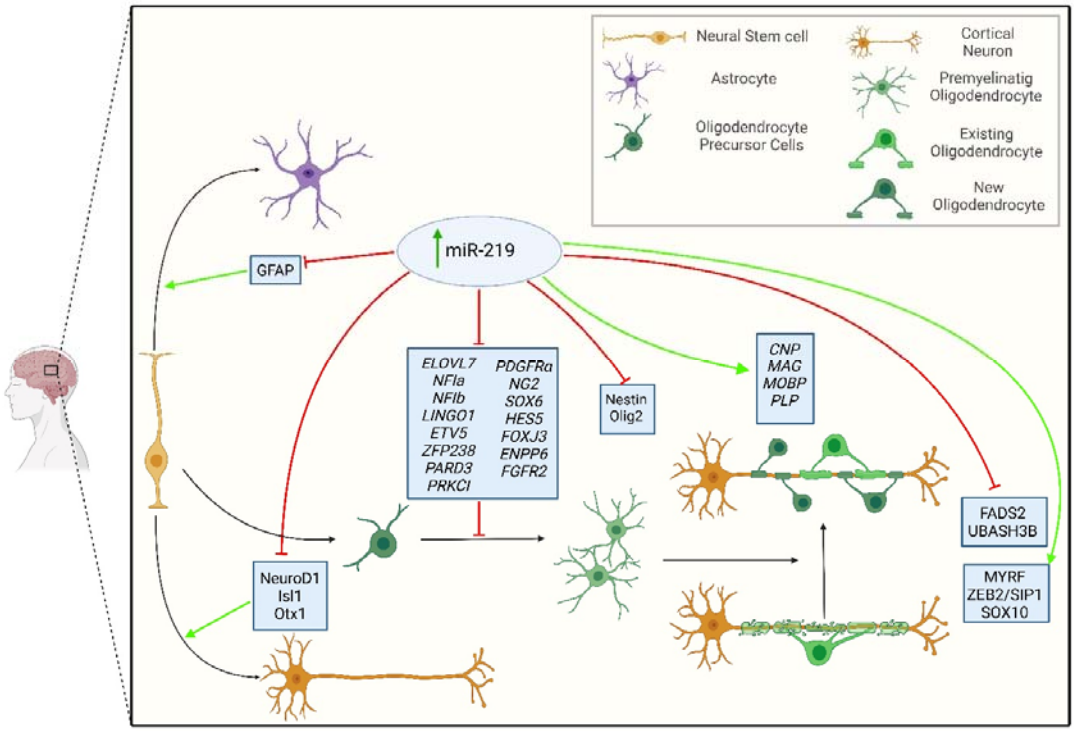

Fig. 2. The role of increased miR-219 mediated cell lineage progression and transition in multiple sclerosis. miR-219 regulates different target genes which leads to the final consequence of neurogenesis, inflammation, proliferation, and astrocyte activation suppression. Moreover, it stimulates oligodendrocyte differentiation and remyelination.

Krabbe disease

Krabbe disease (KD), also known as globoid cell leukodystrophy, is a congenital demyelinating disease characterized by early cerebral demyelination, apoptosis of oligodendrocytes, and ultimately, death. In KD, there is an accumulation of a cytotoxic lyso-derivative of galactosylceramide called psychosine (galactosylsphingosine). Previous studies have indicated that the downregulation of miR-219 expression plays a role in KD pathology. Conversely, the overexpression of miR-219 has been found to reverse the toxicity caused by psychosine accumulation and developmental defects and to prevent apoptotic cell death. Cleaved caspase-3, an enzyme involved in apoptosis, serves as a marker for apoptotic cells. Psychosine mediates apoptotic cell death by activating caspase-3, which increases in KD. miR-219 stimulates the suppression of cleaved caspase-3, thereby rescuing oligodendrocytes from apoptotic death. The mentioned study highlights the crucial role of miR-219 in the pathologies of oligodendrocytes in KD and other demyelinating diseases. It demonstrates that miR-219 has the potential to counteract the harmful effects of psychosine accumulation and promote the survival of oligodendrocytes (45).

spinal cord injury

Spinal cord injury (SCI) is a traumatic injury to the motor system that often leads to a significant loss of sensory and motor functions. It can result in either partial or complete deficiency in these functions. SCI occurs in two phases: the primary neural injury, which is caused by immediate mechanical changes, and the secondary tissue damage, which is induced by vascular and biochemical changes. The secondary damage can lead to the death of oligodendrocytes and demyelination of axons, which are more prone to degeneration. Several factors can exacerbate the condition, including reduced blood flow to the spinal cord, excessive inflammatory response, and neuronal apoptosis. Demyelination, occurring as a result of oligodendrocyte death in SCI, can further worsen the neurological deficits. Moreover, surviving oligodendrocytes in the injured area are postmitotic and incapable of self-renewal for remyelination and regeneration. Consequently, the generation of new myelinating oligodendrocytes relies solely on OPCs which are abundantly expressed in the CNS throughout its lifespan. miR-219 plays a significant role in modulating SCI symptoms by influencing cell differentiation, remyelination, proliferation, and inhibition of apoptosis. Its regulatory functions contribute to mitigating the effects of SCI and promoting the recovery of neurological function. MCT-1 is dominantly expressed by oligodendrocytes in the CNS. MCT-1 is an essential protein that transfers lactate from oligodendrocytes to axons to provide enough energy for CNS when glucose is insufficient *in vivo*. MCT-1 is also involved in the differentiation of OPCs induced by miR-219 and is related to the regulation of OPC proliferation and differentiation after SCI. MCT-1 expression was observed to downregulate during SCI, which would be reversed by miR-219 upregulation. Conversely, miR-219 silencing exacerbated the MCT-1 deduction after SCI. Further research should be carried out to consider whether the miR-219-associated increase in MCT-1 is related to its role in OPC proliferation and differentiation (47).

Neuroplasticity and apoptosis are involved in the functional defects observed in SCI patients. Moreover, the liver receptor homolog-1 (LRH-1) contributes to biological progress; it not only regulates cell proliferation, apoptosis, and cell cycle as a coactivator of the Wnt/β-catenin signaling pathway but modulates the Wnt/β-catenin and p53 signaling pathways as well. LRH-1 can interact with transcription factor 4 and β-catenin to promote the expression of c-Myc and cyclin D1/E1. This motivated an analysis of β-catenin, cyclin D1, and c-Myc. It was reported that miR-219-5p inhibitors rescued the SCI-induced inhibitory effects of the LRH-1/Wnt/β-catenin pathway and LRH-1 silencing would eliminate the effects of miR-219-5p inhibitor on SCI (44).

The secondary phase of SCI is accompanied by alterations in cellular metabolism and gene expression, including excitatory amino acid release, calcium influx, free radical damage, inflammation, and apoptosis. The secondary injury immediately starts several minutes after

the primary one to lasts for several weeks or even months. The inflammatory response is closely related to secondary SCI and some other neurodegenerative diseases such as MS. Moreover, differentially expressed genes also play essential roles in the pathophysiology of acute SCI.

The neurogenic differentiation factor, neurogenic differentiation factor 2 (NEUROD2), belongs to the bHLH family. Functionally, NEUROD2 plays an important role in the differentiation and maturation of central and peripheral neurons during the late stages of spinal cord development. When SCI occurs, ischemia, hypoxia, and spinal cord hemorrhage stimulate the release of oxygen-free radicals. Oxidative stress, excessive release of excitatory amino acids, and inflammatory responses exacerbate the effects of SCI. Moreover, SCI stimulates the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the body. miRNAs play a crucial role in regulating calcium signals, oxidative stress, and astrocyte activation following SCI. They are also associated with cell apoptosis a significant consequence of SCI. As the injury time increased in mice with SCI, gradual upregulation of NEUROD2, a specific gene, has been observed in previous studies.. This upregulation suggests that NEUROD2 is involved in the process of SCI. While, miR-219-5p was significantly downregulated in SCI mice. TargetScan investigations detected NEUROD2 as the target gene of miR-219-5p. Further, *in-vitro* experiments demonstrated that miR-219-5p regulated NEUROD2. Although the inflammation-related genes might gradually return to average levels in the late stages of SCI, significantly downregulated inflammatory factors and oxidative stress have been reportedly observed after miR-219-5p mimic administration to SCI mice. It is more important to note that motor function recovery in mice with SCI was remarkably enhanced following the overexpression of miR-219-5p (77). It might be concluded that miR-219 may be recommended as a potential therapeutic approach for SCI treatment due to its effects on MCT-1, LRH-1, and NEUROD2.

Schizophrenia

Schizophrenia is a common psychiatric disorder associated with N-methyl-D-aspartate (NMDA) glutamate receptor dysfunction. NMDA receptors are responsible for synaptic plasticity and fast neurotransmission in the brain, the disruption of whose signal pathway might lead to schizophrenia. This might be explained along the following lines. miR-219-1 is a vital regulator in the n-methy1-d-aspartate glutamate receptors-mediated glutamate signal pathway; schizophrenia accrues when this signal pathway is disrupted. CAMKIIγ is a constituent of the signal pathway and a targeted gene for miR-219-1. Inhibition of miR-219-1 in the murine brain causes significant modulations in the behavioral responses as the result of disrupting NMDA receptor signal transmission *in vivo* (78).

Rs107822 is an allele T/C alternated polymorphism located in pre-miR-219-1. Single nucleotide polymorphisms (SNP) are the probable candidates that engage in disorders such as schizophrenia. They could be found in miRNA or 3′-UTR of its target gene and may cause disruption in the transcription process or the interaction between hsa-miR-219-1 and mRNA 3′-UTR of its targeted gene, which brings about the rs107822 within pri-miR-219-1 would affect its expression or structure. It should be reminded that both receptor activity and second message signaling hypofunction are the primary pathologies of schizophrenia (78).

Furthermore, it has been widely demonstrated that miR-219 is downregulated in the prefrontal cortex of schizophrenic patients. This downregulation is believed to be a compensatory mechanism aimed at restoring the function of NMDA receptors. Evaluation of miR-219 in the whole brain tissue and synaptosomes revealed that miR-219-3p and miR-219-5p were upregulated in the whole tissue, but downregulated in the cortical synaptosomes of schizophrenic patients (79,80). NMDA receptors suppress miR-219 and its disinhibition effect on CAMKIIγ. In return, miR-219 negatively regulates NMDA receptors, whereby its upregulation attenuates the NMDA receptor's activity. However, Kocerha *et al.* reported the downregulation of

miR-219 following the acute application of NMDA antagonists to rodent brains (66).

Additionally, brain-derived neurotrophic factor (BDNF) contributes significantly to schizophrenia pathology (36,81). The inciting impression of miR-219 has been reported on CAMKIIγ and the enhanced CAMKIIγ-dependent BDNF expression (82). However, the mechanism underlying its effect on schizophrenia remains unclear. Finally, miR-219 serum has also been used as a biomarker to determine schizophrenia status besides family history and disease diagnosis (83).

Schizophrenia and bipolar disorder are related to prenatal stress because miR-219 modulates excitatory synaptic plasticity through NMDA glutamate receptors. It is reported that miR-219 and its accepted gene target DAZ-associated protein 1 (DAZAP1) were upregulated by prenatal stress in newborns, representing their role in schizophrenia and bipolar affective disorders causes (37).

The TLX regulates NSC self-regeneration and cell cycle progression in embryonic NSC, boosting memory and learning which accomplishes its effects as a transcriptional regulator. miR-219 is one of the TLX downstream targets that has been shown to downregulation of TLX while miR-219 upregulation in schizophrenia patients has been proven to reduce proliferation. TLX interacts with the p68/DROSHA/DGCR8 complex and inhibits miR-219 processing and binding to miR-219 primary form. As NSC proliferation and neurogenesis are involved in schizophrenia pathogenesis, miR-219 repression or TLX stimulation were both found to serve as potential therapeutic approaches for treating schizophrenia patients (84).

The methylation status of three gene targets has been correlated with hippocampal status. Another gene targeted by miR-219 is estrogen receptor 1, which is encoded by the estrogen receptor 1 gene. Estrogen binds to this receptor and regulates human emotions and cognitive abilities, which are known to be affected in schizophrenia. Additionally, miR-219 is predicted to target the ephrin type-A receptor 4 (EPHA4) gene, a member of the ephrin receptor subfamily of protein-tyrosine kinases, which is predominantly expressed in the hippocampus. Lastly, another gene targeted by miR-219 and found to be overexpressed in schizophrenia is PKNOX1 (PBX/knotted 1 homeobox 1) (38).

PDGFRα) is responsible for NSCs proliferation and self-renewal, which is regulated by T cell leukemia homeobox (TLX) through miR-219, so TLX's effect on miR-219 biogenesis is suppressive. A previous study demonstrated upregulated miR-219 and downregulated TLX in schizophrenic brains (84,85).

A recent study reported the possible role of glutamate ionotropic receptor AMPA type subunit 2 (GRIA2) in some psychiatric phenotypes, including a rare form of schizophrenia called "childhood-onset schizophrenia". GRIA2 encodes an AMPA-sensitive glutamate receptor (GLUA2) subunit that functions as a ligand-gated ion channel in the CNS. Additionally, TargetScan analysis has shown GRIA2 to be a potential target for miR-219 (86,87).

CR

Almost all organisms possess a circadian clock, an internal mechanism that helps them adapt to the 24-hour environmental cycle. In mammals, the subjective duration of day and night is synchronized with the external day cycle through oscillators located in the hypothalamic suprachiasmatic nucleus (SCN) (88).

miR-219 is a circadian length-controlling gene with several regulatory targets that mediate the miR-219 effect on clock timing. One regulator is the SCN circadian oscillatory protein (SCOP), which shows a robust rhythmic expression in SCN peaking at night and involves intracellular signaling (89). Being a member of the leucine-rich repeat (LRR)-containing protein family, SCOP is a potential target for miR-219 which regulates the length of the circadian day. miR-219 expression peaks at subjective day and its knockdown lengthens the circadian period while the SCOP level inclines in the subjective night; the significantly lower level of SCOP protein follows miR-219 expression. The SCOP protein has a negative regulatory effect and is able to suppress the MAPK pathway. Finally, SCOP interacts with k-ras through its LRR in SCN (90,91).

On the other hand, exploiting its capacity for suppressing cellular excitability, miR-219 might negatively affect the clock by debilitating the depolarizing reaction of glutamate, NMDA, and internal calcium ion responsiveness. Furthermore, miR-219 overexpression attenuates the level of CAMKIIγ protein involved in cell plasticity. Although miR-219 is a calcium/cAMP response element binding (CREB) protein target gene, the pre-miR-219 transcription is not influenced by light pulses during the circadian phases. However, the overexpression of the transcriptional activator's circadian locomotor output cycles kaput (CLOCK) (Npas2 in neuronal tissue) and brain and muscle ARNT-like protein 1 (BMAL 1) bring about a significant escalation in the pre-miR-219 transcription level (39,92). miR-219 not only has an inhibitory effect on BMAL1 mRNA but is also a BMAL1 target.

Additionally, miR-219 plays a pivotal role as a positive regulator of CLOCK and BMAL1-dependent Per1 transcription, regulating the mammalian CR system. . Meanwhile, it activates the Per1 mRNA transcription and translation. It is also affected by the BMAL1/CLOCK complex, whereby the combination of these two has a more weighty effect on increasing Per1 mRNA transcription (40,93,94).

Memory

miRNAs play a crucial role in regulating calcium signals, oxidative stress, and astrocyte activation following a SCI. They are also associated with cell apoptosis, which is a significant consequence of SCI. In previous studies, it was observed that NEUROD2, a specific gene, was gradually upregulated in mice with SCI as the injury time increased. This upregulation suggests that NEUROD2 is involved in the process of SCI. SCOP protein, already described concerning the CR, positively regulates long-term memory but negatively regulates extracellular regulated kinase 1/2 (ERK1/2), which is essential for long-term memory. The stimulation of Cre-mediated transcription and dendritic translation is mediated through ERK1/2 activation. As a result, SCOP overexpression blocks long-term memory completely but does not affect short-term memory, including fear conditioning. However, both types of learning (short-term memory and long-term memory) decline SCOP expression (90,91). Moreover, miR-219 is an integral constituent of the NMDAR signaling cascade that was downregulated during the long-term potentiation induction and maintenance. A study revealed miR-219 overexpression in the arsenic-induced learning impairment and memory and its effect on memory by negatively regulating CAMKII translation. In the CNS, CAMKII is reported to affect gene expression, memory processing, learning, and neuroplasticity. Thus, its inhibition would affect the long-term potentiation attenuation, the long-lasting form of synaptic plasticity and memory. Additionally, CAMKII activates the early expression of some immediate genes (c-Fos and c-Jun) and transcription factors (CREB). miR-219 binding might abet the CAMKII deduction and block the translation. The transcription factors change the nuclear gene expression leading to different protein synthesis. CAMKII changes may result in the NMDA receptor expression that was changed following the miR-219 disturbance (41,42,95). On the other hand, TLX is a neuroprotective protein that can inhibit miR-219 processing as a downstream target and the miR-219 target itself. This is while miR-219 might act as a protective agent against cognitive impairment through increasing TLX levels (70,84,96) (Fig. 3).

PD

Loss of dopamine-producing neurons in the substantia nigra pars compacta causes dopamine neurotransmitter insufficiency in the striatum, which mainly gives rise to PD motor symptoms, glutamatergic transmission, and inflammatory response alterations. Moreover, the most common medicine capable of alleviating PD symptoms is a dopamine precursor called levodopa. Inflammatory response, organismal injury, and abnormalities are the changes in miRNA expression related to the mechanisms activated by oxidative stress signaling in PD. The postmortem PD patients' striatum tissues have been examined in several studies to evaluate miRNA expression to find miR-219-2-3p downregulation in their putamen tissues. The downregulated hsa-miR-219 mediates neurobehavioral dysfunction by interacting with the NMDA receptor. Furthermore, it has been shown that miR-219 has a role to play in cell antioxidant processes.

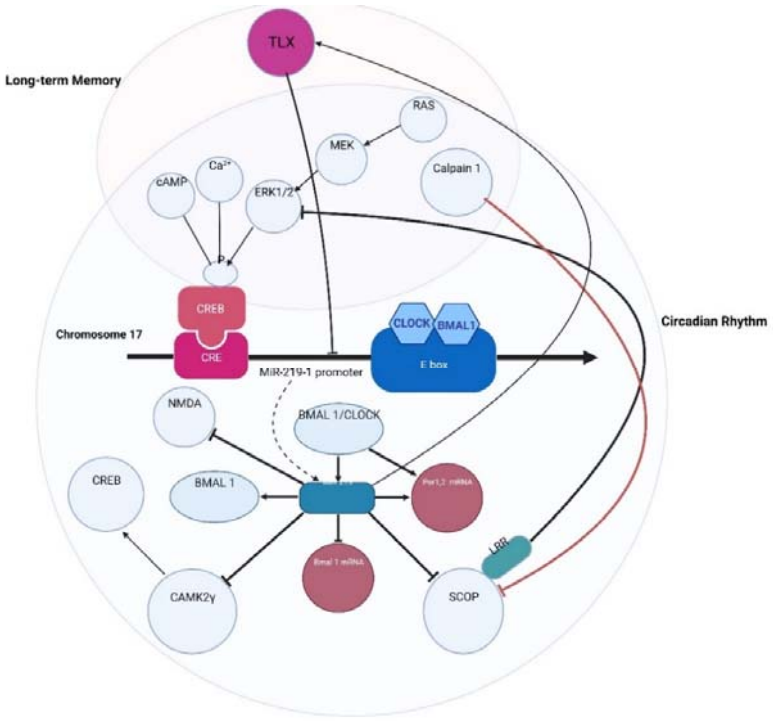

Fig. 3. Circadian rhythm and long-term memory correlation mediated by the miR-219 regulatory network. The direct targets and indirect effectors of miR-219 with their multiple functions are represented. The upstream miR-219 regulators have been shown as well.

Upregulation of the glutathione reductase (GSR) gene in PD has been reported (97). GSR, which is involved in reducing oxidized glutathione disulfide to sulfhydryl form glutathione, was predicted as the hsa-miR-219-3p target. GSR is an essential enzyme in the body's endogenous antioxidant systems and plays a crucial role in maintaining cellular redox homeostasis. In an experiment conducted on tissues from PD patients, dopaminergic agonists were administered. The results of the study revealed that the upregulation of the GSR gene was consistent with previous reports, which suggested that L-dopa induces intercellular mechanisms of antioxidation. This upregulation of GSR and the antioxidative effects of L-dopa are believed to have a neuroprotective role in preserving dopaminergic neurons in patients with PD. The predicted potential interactions of GSR with hsa-miR-219-3p indicate the oxidative stress-signaling network members of this miRNA might be involved in mediating the antioxidant effect of L-dopa in PD by suppressing pro-inflammatory factors while simultaneously upregulating antioxidant factors (43,98).

CONCLUSION

Several neurological disorders can be affected by miRNAs, including MS, AD, PD, hypertension, schizophrenia, epilepsy, cerebral ischemia, and brain tumors. Recent studies revealed that miR-219, as a potential therapeutic agent, can be effectively employed for neurological disorders treatment by targeting various genes. It is through the manipulation of miR-219 expression and its downstream targets that disease symptoms could be alleviated. In this review study, a possible relationship is established between miR-219, on the one hand, and DLX2 and CDK5, on the other, whose verification calls for further investigation.

Based on the above considerations, miR-219 might be an ideal therapeutic target/agent for neurological disorders. Additionally, the results obtained from exogenous administration of miR-219 or its antagomir in previous studies confirm the promising function of miR-219 as a therapeutic agent. Therefore, it is essential to gain more knowledge about the miR-219 interplay and its regulatory mechanisms in a

pathological context. The current study is hoped to highlight points of importance toward a better understanding of the signaling pathways/feedback loops involved in modulating the expression and action of miR-219, identifying miR-219 off-targets, and miR-219 molecular pathology. The knowledge thus gained might be exploited for future investigation about pathological regulators, diagnostic biomarkers, and therapeutic strategy developments in clinics. There is strong proof that miR-219 dysregulation is associated with neurodegenerative diseases. The development of miRNA-based therapeutics as a new potential has emerged as one of the most promising approaches for the treatment of incurable neurological disorders. More investigations are certainly demanded to clarify their exact clinical effects, design pharmacological formulations and delivery systems that can penetrate the BBB to target brain parts, and devise standard methods to reduce off-target effects.

Conflict of interest statement

The authors declared no conflict of interest in this study.

Authors' contributions

N. Shamaeizadeh wrote the manuscript after a precise literature review and M. Mirian critically read and revised the manuscript. All authors read and approved the finalized article.

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