

Role of microRNAs in major brain diseases, focusing on neuroinflammation and neuronal apoptosis

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ABSTRACT

MicroRNAs are non-coding small RNA molecules that play a significant role in regulating gene expression. Increasing lines of evidence have highlighted the microRNA dysregulation and neuroinflammation-associated apoptosis in common brain diseases, including Parkinson's disease, Alzheimer's disease, epilepsy, traumatic brain injury, depression, and migraine. In fact, microRNAs regulate multiple physiological and pathological processes, thus implicating them in both health and disease. Though studies have suggested that the alterations or modifications in microRNA-associated regulatory pathways might contribute to the disease pathogenesis, the underlying molecular mechanisms and the targeted genes remain exclusively unknown. We hope that the idea of using microRNAs as therapeutic targets for brain disorders is not far from reality, but important issues must be addressed before moving into clinical practice. The aim of this review is to enlighten the molecular mechanisms and targeted genes of microRNA implicated in the multifaceted brain disorders. Moreover, several microRNAs have been reported to be up-regulated following disease, but their targeted pathways have not been elucidated yet. This review also highlighted microRNAs that are expected to warrant further exploration of their mechanism of action. This comprehensive overview of the prediction of microRNAs' functions might be helpful in providing more efficient insight for the development of microRNA-based therapeutic interventions for neuropsychiatric and neurodegenerative diseases.

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Introduction to miRNA

MicroRNAs (miRNAs) are small (about 22 nucleotides) non-coding RNA molecules that play a significant role in regulating gene expression. The 1st miRNA named lin-4 was discovered in 1993 in the *Caenorhabditis elegans* by Ambros and colleagues, which was a revolution in molecular biology. The miRNAs biogenesis encompasses several steps and defines cellular machinery that facilitate the miRNA transcription as the short stem loops, comprising 70 base pairs (bp) long. RNA polymerase II is responsible for the formation of exons and introns of both the non-coding and protein-coding transcripts from which the miRNAs are produced. Firstly, primary miRNAs (pri-miRNA) are formed (inside the nucleus) as the transcriptional products of the DNA sequences, which are then processed into pre-miRNAs (the precursor). Finally, the mature miRNAs are produced by the endonuclease named Dicer RNase III (1). The pri-miRNA might be relatively longer, and it is characterized by the synthesis of a stem-loop structure. Inside the nucleus, macromolecular machinery (microprocessor) then cuts the precursor (pri-miRNA) by an enzyme known as Drosha. This leads to the formation of pre-miRNA, which is typically b/w 60 and 100 nucleotides in length. The pre-miRNA shifts from the nucleus to the

cytoplasm via the RanGTP-dependent exportin-5 pathway. The pre-miRNA is further cut to the 22-nucleotide length in the cytoplasm by an enzyme named Dicer RNase III to produce mature miRNA (2).

To date, about 3 thousand miRNAs have been reported in the genomes of mammals, and more than 2000 of them belong to the human genome. It is speculated that each miRNA may have the capability of repressing the expression of hundreds of targeted genes. The reported data have revealed that each miRNA can target multiple mRNAs, and several miRNAs can target a single mRNA. They execute their function by binding directly with the 3' untranslated region (UTR) of the targeted mRNA, which ultimately suppresses the protein expression as well as promotes the degradation of that particular mRNA (3). The miRNAs regulate several physiological as well as pathological processes, thus endorse both the health promoting as well as disease promoting effects. A plethora of work has been done to explore the connection of miRNA with brain disorders and traumatic brain injuries. In our review, we have highlighted the recently published data regarding the implications of miRNA in the development of neuropsychiatric and neurodegenerative diseases (NDDs). This can facilitate the researchers to understand the several molecular pathways and numerous

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factors that are being regulated by miRNAs in disease progression or prevention. A comprehensive literature search was conducted using multiple electronic databases, including PubMed, ScienceDirect, and SpringerLink. The search covered peer-reviewed original research articles and review papers published in English. Relevant keywords and their combinations were used, including microRNA, neuroinflammation, Parkinson's disease, epilepsy, oxidative stress, and neurodegeneration. The reference lists of selected studies were also screened to identify additional relevant publications.

Introduction to neuroinflammation

Neuroinflammation is a well-orchestrated and complex process involving glial cells, particularly astrocytes and microglia (4). It is a defensive mechanism that initially aids in inhibiting or removing diverse pathogens. This neuroinflammatory response elicits beneficial effects via the removal of cellular debris, thus promoting neural tissue repair. However, sustained and persistent inflammation is detrimental and inhibits tissue regeneration (5). Neuroinflammation can be initiated by various endogenous and exogenous factors, including infection, toxic metabolites, injury, aging, autoimmune diseases, passive smoke, and air pollution. These factors stimulate the pro-inflammatory chemokines and cytokines that activate microglial cells, elicit primary immune responses in the CNS. Sustained microglial activation allows the recruitment of B or T lymphocytes and macrophages that can cross the compromised blood-brain barrier (BBB), amplifying the chronic inflammation and ultimately neurodegeneration. Excessive and prolonged neuroinflammation acts as a pivotal driver of various neurological disorders, including traumatic brain injury, cerebrovascular disease (CVD), multiple sclerosis (MS), Alzheimer's disease (AD), psychological disorders, epilepsy, and chronic pain. It is a common mechanism connecting the ischemic, traumatic, epileptic, psychiatric, demyelinating, and degenerative pathologies (6).

Physiological role of miRNA

The role of miRNA in biological functions is gradually widening. They are implicated in the physiology and normal development of both plants and animals. In plants, they regulate the floral timing and development, leaf shape and patterning, fertility and vascular development, environmental stress response, and seed biology. In animals and humans, the diversity of miRNAs has been involved in several cellular activities, including apoptosis, cellular proliferation, cell differentiation, renewal of stem cells, metabolism, and embryonic development. They are anticipated to have the capability to regulate almost 60% protein-encoding genes. The miRNAs act by fine-tuning the expression of genes during the development and the maintenance of tissue homeostasis. Under the pathological conditions and/or cellular stress, the cells undergo a condition of alleviated translation and transcription. During these circumstances, the miRNA offers a rapid, potent, and effective source of gene regulation that could allow the cells to recover or become adapted to the abnormal state (7). The experimental evidence indicated that approximately 70% of miRNAs are expressed within the brain and play a crucial role in neural development and functions.

They are primarily enriched in pre- and postsynaptic compartments and implicated in synaptic plasticity during memory formation by coordinating genetic circuitry. In the mature brain, miRNA also modulates the functions and morphology and thereby tightly regulates the neuronal activity. They also modulate the number of behavioral and neuronal phenotypes, such as synapse number, dendrite complexity, synaptic efficiency, and short-term memory, dependent on context. Moreover, miRNAs also control the glial cells differentiation as well as their maintenance in developing and the mature brain (8).

Implications of miRNA in brain diseases

Besides the physiological functions, the miRNAs are also incorporated in the development and progression of numerous pathological conditions, including brain disorders such as AD, Parkinson's disease (PD), psychiatric and behavioral disorders, and many others. MiRNAs have both disease-promoting and disease-modifying roles, and a list of these miRNAs is illustrated in Figure 1.

Alzheimer's disease (AD)

AD is one of the NDDs, and it is characterized by the synaptic functional loss, disorientation, atrophy of certain brain areas, cognitive impairment, and psychiatric symptoms. The neuritic/ amyloid-beta (Aβ) plaques and the neurofibrillary tangles (NFTs) are considered hallmarks in the development and aggravation of AD. The Aβ plaques are generated by the cleavage of amyloid precursor proteins (APP) and β-secretase (beta-site amyloid precursor protein cleaving enzyme, BACE 1), which is mediated by the gamma secretase enzyme (9).

Disease promoting miRNAs	AD	PD	TBI
	34; 200a-3p; 128; 1273g-3p; 139; 25802; 17	132-3p; 155; 17; 485-3p; 15b-5p; 132-5p; 132; 30c-5p; 195-5p	429; 200a-3p; 203; 491-5p; 9-5p; 16-5p; 124-3p; 15a/16-1
	Epilepsy	Depression	Migraine
135a-5p; 135a; 155; 21-5p; 128; 181a-5p; 495; 183; 129-2-3p; 142; 223; 219; 34c; 187-3p; 132; 23a	124; 30; 182; 200a/b-3p; 382-5p; 139-5p; 382; 2002-5p; 15b-5p; 497a-5p	155; 21; let-7g; 382-5p; 34a; 653-3p	
Disease modifying miRNAs	AD	PD	TBI
	29c; 132; 149; 137; 128; 200b/c; 212; 132; 222; 455-3p; 146a; 195; 483-5p; 9-5p; 146a-5p; 129-5p; 181c-5p; 224-5p; 361-3p; 291a-3p; 125b-5p; 204-3p; 22-3p; 195	221-3p; 124; 146a; 124; 144; 218; 124-3p; 335; 106b; 185; 150; 133a; 103a-3p; 218-5p; 126-5p; 218-5p; 30e-5p; 381; 20a-5p; 124; 214-3p; 221	Letc-5p; 124-3p; 873a-5p; 126; 146a; 23a3p; 26a-5p; 302; let-7i; 124; 9-5p; 124-3p; 124; 331; 9a-5p
	Epilepsy	Depression	Migraine
200c-3p; 29a; 136; 139-5p; 194-5p; 155; 322-5p; let-7i; 485; 135b-5p; 129-5p; 211-5p; 488-3p	133b; 211-5p; 204-5p; 26a-3p; 320-3p; 29a-5p; 15a-5p; 16-5p	Has-miR-660-3p; Has-miR-590-5p; 30a;	

AD: Alzheimer's disease PD: Parkinson's disease TBI: Traumatic brain injury SZ: Schizophrenia

Figure 1. MicroRNA in health and disease

Disease-promoting role in AD

The association of aberrant expression of miR-200a-3p with Sirtuin 1 (SIRT1)(anti-apoptotic protein) in the hippocampus was explored by using a mouse model of AD (APP^{swe}/PSDE9). The enhanced level of miR-200a-3p with the reduced SIRT1 level was observed in the hippocampus of the mouse model. Additionally, the PC12 cells were used for *in vitro* investigation to analyze the apoptotic rate when exposed to A β ₂₅₋₃₅. The overexpression of miR-200a-3p could alleviate the SIRT1 expression, which then promotes the neuronal apoptosis by A β ₂₅₋₃₅ (10). Being the most crucial hallmark in the pathogenesis of AD, A β , and tau hyperphosphorylation-related studies have been performed most frequently by researchers. MiR-1273g-3p plays a crucial role in the pathogenesis and progression of AD by increasing A β production through oxidative stress-induced mitochondrial impairments. It was shown that miR-1273g-3p principally integrated with the mitochondrial genes and, thus, down-regulates their expression. In particular, the target gene of miR-1273g-3p is translocase of inner-mitochondrial membrane-13 (TIMM13), which imports as well as inserts the precise proteins into inner-membrane mitochondria (11).

As AD advances, glial cells, such as microglia and astrocytes, become activated and release inflammatory cytokines, which contribute to neurotoxicity and worsen A β and tau protein pathologies, ultimately leading to neurodegeneration. Krüppel-like factor 4 (KLF4) likely acts as a transcription factor influencing the expression of genes involved in the inflammatory response mediated by microglia in AD. Specifically, it may regulate the expression of pro-inflammatory cytokines and other molecules that contribute to neuroinflammation, thereby influencing disease progression (12). By using two mouse models of AD, including age-matched wild-type (WT) mice and 5 \times familial AD (5 \times FAD) mice, as well as AD patients, a study investigated the role of miR-25802 in AD pathogenesis. Through bioinformatics and experimental validation, miR-25802 was found to be up-regulated in AD patients and AD mouse models, correlating with cognitive impairment, A β deposition, and microglial activation towards a pro-inflammatory phenotype. Mechanistically, miR-25802 regulates microglial polarization by targeting KLF4, thereby enhancing NF- κ B-mediated inflammation. Modulating miR-25802 levels altered microglial phenotype and inflammatory responses (13), implicating the miR-25802/KLF4/NF- κ B axis as a potential therapeutic target for AD treatment. In addition, a study explored the therapeutic potential of targeting microglial miR-17 using mannose-coated lipid nanoparticles in C57BL/6 WT and 5 \times FAD AD mouse models. MiR-17, implicated in neuroinflammation and AD pathology, was selectively inhibited using the nanoparticles. The intervention effectively mitigated AD-related pathology and improved behavioral outcomes in the mice. In addition to reducing AD pathology and improving behavior, the targeted inhibition of miR-17 through mannose-coated lipid nanoparticles led to a notable decrease in neuroinflammation markers associated with microglial activation (14). The study underscores the potential of nanoparticle-mediated miRNA modulation as a precise therapeutic approach to address neuroinflammatory mechanisms in AD, suggesting avenues for further clinical exploration and development.

Disease-modifying role in AD

It is notable that a variety of miRNAs are deregulated in AD and are involved in BACE1/APP or neuronal functions. Extensive studies have been done to identify the alterations or mutations in the particular miRNAs that could be considered as the therapeutic targets in the treatment of AD. MiR-132 is implicated in the anti-inflammatory, cognition-promoting, and pro-survival functions in NS. Increasing the expression of miR-132 may have a protective and therapeutic role against AD pathogenesis. The expression of miR-132 could be increased by melatonin treatment and thereby prevent neurotoxicity induced by A β . MiR-132 also improved the cognitive deficits by suppressing FOXA1 in a rat model of AD (15). BACE1 is also the target for miR-149 that inhibits the accumulation of A β and improves the neuronal functions by targeting BACE1 (16). MiR-23b has also been reported to improve cognitive impairment and attenuate A β and tau pathology through activation of the Akt/GSK-3 β pathway (17).

The voltage-gated Ca²⁺ channels, encoded by the *CACNA1C* gene, also play a crucial role in the pathogenesis of AD. The association of this gene with miR-137 was confirmed in APP/PS1 transgenic mice of AD and SH-SY5Y. The results showed that spatial memory and learning were reduced with the reduction in miR-137 expression, whereas *CACNA1C* gene and A β 1-42 expression were elevated in the cerebral cortex and hippocampus of APP/PS1 AD transgenic mice. Moreover, miR-137 mimics in SH-SY5Y cells significantly repressed *CACNA1C* expression, leading to decreased A β 1-42 levels and instigated tau hyperphosphorylation (18). The peroxisome proliferator-activated receptor gamma (PPAR γ) is involved in the processes of inflammation, morphogenesis, and metabolism, and it is involved in the progression of several NDDs, such as AD. PPAR γ is a target for miR-128, and its level was reported to be down-regulated in AD, with increased expression of miR-128 in the cerebral cortex of mice with AD. This resulted in the formation of amyloid plaques, A β generation, inflammatory responses, and APP processing, whereas the overexpression of miR-128 could counteract these effects (19).

Insulin signaling, due to A β oligomers, is also thought to be compromised in the pathology of AD with cognitive impairment. *In vitro* and *in vivo* studies have shown that MiR-200b and miR-200c can reduce A β secretion and associated memory impairment by stimulating insulin signaling (20). The reduced expression of miR-101a-3p could lead to the APP processing and ultimately aggravate AD. Osthole (bioactive compound in traditional Chinese medicines) can mediate the expression of this miRNA, resulting in protection against AD. In APP/PS1 AD mice, osthole up-regulated the expression of miR-101a-3p, which ameliorated the memory and learning and inhibited the APP processing (21).

MiR-455-3p has recently been identified as one of the circulating biomarkers for early AD, with its increased expression in the brain tissue of patients with AD. It directly targets APP and down-regulates its expression as well as suppresses its toxic effects. MiR-455-3p is also associated with weight gain, indicating a metabolic disturbance. Angiotensin-II converting enzyme-1 (ACE1) is overactive in AD brains and is concomitant with cognitive debility and disease pathophysiology. Overexpression of miR-

455-3p resulted in the reduction in tau, BACE1, and APP expression, as well as modulating the ACE1 activity and improving the cognitive performance in AD mice (22). Recently, high levels of miR-455-3p have been reported in the serum of patients with AD. This elevated expression was also confirmed in AD-associated postmortem brains, B-lymphocytes, fibroblasts, mouse models, and cerebrospinal fluid. This miRNA attenuated the A β -induced neurotoxicity, ameliorated synaptic activity and biogenesis of mitochondria, and sustained the mitochondrial dynamics. This miRNA also improved cognitive performance by targeting APP, tau, and BACE1 (23).

miR-146a is particularly considered a microglia-specific miRNA as being involved in opposing the pathological processes, mainly by neuroinflammation-associated pathways. It can switch the microglial phenotypes, attenuate pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF- α), Interleukin-6 (IL-6), Interleukin-1beta (IL-1 β), and increase the phagocytic functions to protect neuronal cells, as confirmed by both *in vivo* and *in vitro* experiments. MiR-146a also improved the cognitive functions, decreased A β levels, and ameliorated plaque-related neuritic pathology. In addition, miR-146a could also down-regulate the levels of caspase-1, Apoptosis-Associated Speck-Like Protein Containing a CARD (ASC), and NOD-like receptor pyrin domain-containing 3 (NLRP3), thus inhibiting the activation of NLRP3 inflammasome (24). Apoptosis-Associated Speck-Like Protein Containing a CARD (ASC) is an adaptor protein that links NLRP receptors (like NLRP3) to caspase-1, facilitating inflammasome assembly and triggering inflammation and pyroptotic cell death. Another study employed a rat model (APP^{swe}/PS1^{dE9}) in which AD pathology was induced by direct intra-hippocampal administration of the A β 1-42 peptide. Through this model, miR-146a-5p was identified as a promising candidate biomarker detectable in blood samples. Importantly, microRNA-146a-5p was found to exert anti-inflammatory effects specifically within astrocytes, which are pivotal in neuroinflammatory responses implicated in AD progression (25). These findings underscore the potential of miR-146a-5p not only as a diagnostic marker but also as a therapeutic target for mitigating neuroinflammation associated with AD. Enhancing phagocytosis may promote the A β clearance, reduce neuroinflammation, and slow cognitive decline. A study have shown that miRNA-129-5p mediates translational repression of microglial, leading to enhanced phagocytosis (26). These results imply therapeutic opportunities for addressing miR-129-5p in neuroinflammatory conditions, such as AD. Regarding microglia, enhancing microglial A β phagocytosis is beneficial in AD as it reduces amyloid plaque burden and associated neuroinflammation (27), identifying miR-181c-5p as a potential therapeutic target. Using both *in vitro* models, such as SH-SY5Y and BV2 cells, as well as APP/PS1 transgenic mice, the study demonstrated that the down-regulation of miR-181c-5p in AD impairs microglial A β phagocytosis. This diminished capacity to clear A β plaques exacerbates AD pathology (28). Thus, the study suggests that miR-181c-5p enhances the phagocytosis of A β by microglial cells in AD patients, thereby reducing neuroinflammation.

In A β 1-42-stimulated cells and APP/PS1 mice, miR-224-5p was shown to inhibit the expression of NLRP3. Diminazene (DIZE) treatment significantly up-regulated

miR-224-5p in the astrocytes of APP/PS1 mice, with NLRP3 identified as a direct target of this miRNA. The increased expression of miR-224-5p suppressed NLRP3, whereas its down-regulation abrogated this inhibitory effect. Notably, inhibiting miR-224-5p reversed the suppression of the astrocytic NLRP3 inflammasome induced by DIZE. Furthermore, DIZE alleviated cognitive impairment and neuronal and synaptic damage in APP/PS1 mice (29).

The nuclear factor kappa B (NF- κ B) signaling pathway is a key factor involved in the activation of the neuroinflammatory process and the subsequent production of neuroinflammatory mediators, which contributes to the progression of AD. TRAF2 (TNF Receptor Associated Factor 2) plays a pivotal role as a mediator in the NF- κ B signaling pathway, which is crucial for inflammatory responses. In an *in vitro* HMC3 cell model mimicking an AD environment, miR-361-3p targeted TRAF2, whose expression was regulated by miR-361-3p. Triptolide influenced miR-361-3p levels through its interaction with long non-coding RNA (lncRNA) nuclear paraspeckle assembly transcript 1 (NEAT1), subsequently modulating TRAF2 expression. This regulatory cascade led to the suppression of the NF- κ B signaling pathway (30). lncRNA NEAT1 also targets miR-291a-3p, one of the key miRNAs in ameliorating AD, and was found to be down-regulated in both the *in vivo* (mice) and *in vitro* (neural stem cells; NSCs) models of AD. Moreover, Rab22a is implicated in neuroinflammation and A β accumulation, and the NF- κ B pathway affects apoptotic proteins like Bcl-2, highlighting its role in AD pathology, which is crucial for understanding Rab22a's impact. In both *in vivo* and *in vitro* models of AD, Rab22a was identified as a direct target of miR-291a-3p, validated through dual-luciferase assays and modulation experiments using tanshinone IIA (Tan-IIA). Tan-IIA mitigated oxidative stress and neuroinflammation induced by A β 1-42 via activation of AKT/Nrf2 signaling mediated by the NEAT1/miR-291a-3p/Rab22a axis, as evidenced by changes in cellular viability, apoptosis markers, and inflammatory cytokine levels (31). Additional studies further elucidate the role of lncRNAs in AD pathology. For instance, a study on the lncRNA brain-derived neurotrophic factor antisense (BDNF-AS) investigates its role in inducing neuronal cell apoptosis in AD models by targeting miR-125b-5p. The research demonstrates that BDNF-AS negatively regulates miR-125b-5p, a microRNA involved in neuronal survival and function. Down-regulation of miR-125b-5p by BDNF-AS leads to increased neuronal apoptosis, contributing to the progression of AD (32). Using both *in vitro* models, such as primary cerebral cortex neuronal culture and PC12 cell culture, as well as Sprague-Dawley rat models, the study highlighted the potential of targeting the BDNF-AS/miR-125b-5p axis as a therapeutic approach to mitigate neuronal loss in AD.

In addition to the treatments discussed earlier, another promising approach involves Dexmedetomidine (Dex), which is an agonist of the α 2-adrenergic receptor and is commonly utilized in neurosurgical settings owing to its sedative, anesthetic, and neuroprotective properties. Notably, there is observed overexpression of F-box/LRR-repeat protein 7 (FBXL7) in a transgenic mouse model of AD. Researchers found that Dex reduces neuroinflammation in the C57BL/6 mouse model of AD through modulation of the miR-204-3p/FBXL7 signaling pathway via up-regulation

of miR-204-3p and inhibition of FBXL7 (33), making it a potential therapeutic agent targeting neuroinflammation in this context.

Crucial determinants for maintaining the homeostasis of phosphoinositol biphosphate (PIP2) in the brain are apoE proteins, and the dysfunctional apoE4 isoform contributes to the enhanced susceptibility of memory deficits in AD. In the brain, a reduction in PIP2 levels is related to ApoE4, which increases the expression of synaptojanin 1 (*synj1*), a PIP2-degrading enzyme. miR-195 targets *synj1* and its overexpression ameliorated the cognitive function, decreased A β burdens, and hyperphosphorylation of tau in a mouse model of apoE4^{+/+} (34). Employing various functional assays, miR-483-5p has been found to regulate ERK1/2 at both protein and mRNA levels, thereby reducing phosphorylated ERK1/2 levels. Hence, miR-483-5p-mediated ERK1/2 suppression resulted in tau hypo-phosphorylation at epitopes related to tau neurofibrillary pathophysiology in AD (35). It indicates that miR-483-5p up-regulation can repress tau phosphorylation by targeting the ERK signaling pathway, representing a neuroprotective mechanism in AD pathology. *Xenopus* kinesin-like protein-2 (TPX2) has been confirmed to be concomitant with the astrocytoma development, and its up-regulation is associated with the pathology of AD. In AD mice, overexpressed miR-9-5p improved the behavioral alterations and neuronal damage as well as repressed the oxidative stress and plaque deposition in the hippocampus via targeting TPX2 (36).

Circular RNAs (circRNAs) are single-stranded non-coding RNA molecules known for their stable circular

structures and ability to regulate the expression of protein-coding genes by acting as miRNA sponges, thus contributing to the competing endogenous RNA (ceRNA) network. The oncogene zinc finger protein 217 (ZNF217) is often amplified in cancer and represses genes that control cell proliferation, survival, and invasiveness. A study using A β -stimulated SK-N-SH cells demonstrated that inhibiting circ_0049472 and up-regulating miR-22-3p alleviated A β -induced neuronal toxicity, apoptosis, and inflammation by regulating ZNF217 through the activation of the PI3K-AKT signaling pathway (37). Consequently, targeting the circ_0049472/miR-22-3p/ZNF217 axis may represent a promising therapeutic strategy for alleviating AD symptoms. Interestingly, a study on miR-195 liposomes for AD therapy highlighted miR-195's potential in reducing A β levels and alleviating neuroinflammation, thereby mitigating the cognitive deficits associated with AD. Employing liposomal delivery systems to enhance the stability and targeting efficiency of miR-195, the research demonstrated significant therapeutic effects in AD models, including neuronal cell cultures and APP/PS1 mice. The liposome-encapsulated miR-195 efficiently crossed the blood-brain barrier and specifically targeted neuronal cells, resulting in reduced A β production and deposition (38). This approach illustrates the innovative use of liposomes as a promising delivery mechanism for miRNA-based therapies, offering a new avenue for AD treatment by leveraging the regulatory potential of miR-195.

The implications of miRNAs in AD, along with their targets, have been summarized in Table 1.

Parkinson's disease (PD)

PD is one of the common neurodegenerative diseases

Table 1. Implications of miRNA in Alzheimer's disease (AD)

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	miR-200a-3p	SIRT1	↑Neuronal apoptosis	APP ^{swe} /PS Δ E9 mice, PC12 cells (<i>in vitro</i>)	(10)
	miR-1273g-3p	TIMM13	↑A β generation and oxidative stress	AD patients, H4-APP ^{swe} ^{mut} cell line (<i>in vitro</i>)	(11)
	miR-25802	KLF4	Cognitive impairment, A β deposition, and microglial activation	Age-matched WT, 5xFAD, and AD patients	(13)
	miR-17	-	Defective autophagy, ↑A β accumulation, and pro-inflammatory cytokines production	C57BL/6 WT, 5xFAD	(14)
	miR-132	ITPKB, FOXA1	↓A β aggregation improves cognition	AD rats	(15)
	miR-23b	Akt/GSK-3 β pathway	↓A β aggregation improves cognition and neuronal functions	AD patients, SH-SY5Y and HEK293 cell line	(17)
	miR-137	CACNA1C gene	↓tau hyperphosphorylation	APP/PS1 AD transgenic mice, SH-SY5Y cell line	(18)
	miR-128	PPAR γ	↓A β generation and inflammatory responses	3 \times Tg-AD mice, N2a cell line	(19)
	MiR-200b and miR-200c	Insulin signaling	↓A β secretion, improve cognition	C57BL/6J and Tg2576 mice, primary neuronal culture	(20)
	MiR-455-3p	APP, ACE1	↓tau hyperphosphorylation, ↓APP expression, improve cognition,	Null MiR-455 mice	(22)
miR-146a	NLRP3 inflammasome	↓Neuroinflammation	APP/PS1 (B6/JNju-Tg) and C57BL/6J (WT) mice	(24)	
miR-146a-5p	IRAK1, TRAF-6	↓IL-6, IL-1 α , and CXCL1 production	APP ^{swe} /PS1 ^{ΔE9} rats	(25)	

Continued Table 1.

Disease-modifying role	miR-181c-5p	P38 activity	↓TNF-α, IL-6, IL-1β, apoptosis, and Aβ plaques	SH-SY5Y, BV2 cells, and APP/PS1 transgenic mice	(28)
	miR-224-5p	Astrocytic NLRP3	↓TNF-α, IL-6, IL-1β, cognitive impairment, and neuronal and synaptic damage	Aβ1-42-stimulated cells and APP/PS1 mice	(29)
	miR-361-3p	TRAF2	Suppress NF-κB signaling pathway	HMC3 cells	(30)
	miR-291a-3p	Rab22a	↓Neuroinflammatory cytokines, apoptosis, oxidative stress, and Aβ accumulation	Neural stem cells, AD mice model	(31)
	miR-204-3p	FBXL7	↓TNF-α, IL-6, IL-1β	C57BL/6 mice	(33)
	miR-195	synj1	↓Aβ aggregation, ↓tau hyperphosphorylation, improve cognition	AD patients, <i>apoE3^{+/+}</i> or <i>apoE4^{+/+}</i> (KI) mice	(34)
	miR-483-5p	ERK1/2	↓tau hyperphosphorylation	Neuroblastoma SK-N-MC, HEK293 cells, and human dermal fibroblasts (neonatal)	(35)
	miR-9-5p	TPX2	↓Oxidative stress and neuronal damage	APP ^{swe} /PS1 ^{ΔE9} transgenic and C57BL/6 (WT) mice	(36)
	miR-22-3p	ZBF217	↓Neuronal toxicity, apoptosis, and neuroinflammation	Aβ stimulated SK-N-SH cells	(37)

in the elderly, which is caused by dopaminergic neuronal degeneration, particularly in the substantia nigra (SN) pars compacta. It is characterized by severe locomotor deficits, such as gait problems resulting in intermittent walking disturbances during turning and walk initiation. Multiple molecular mechanisms contribute to neuronal cell apoptosis, such as α-synuclein accumulation, oxidative stress, and mitochondrial dysfunction (39). Its etiology

is certainly multifactorial, but a permanent treatment to attenuate disease progression is still lacking. In this scenario, a clear mechanistic understanding would be favorable for proposing therapeutic interventions. The implications of miRNAs in PD are illustrated in Figure 2.

Disease-promoting role in PD

Neuroinflammation plays a significant role in the progression of PD and may prompt the dopaminergic

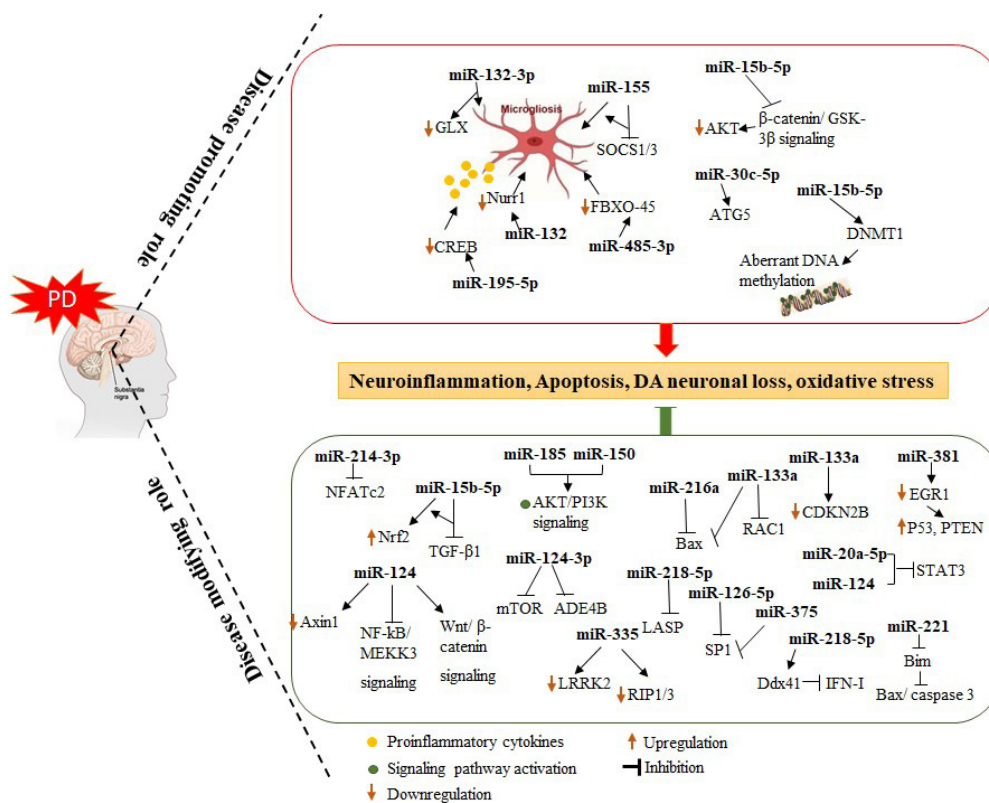


Figure 2. Role of microRNA as disease-promoting and disease-modifying in Parkinson's disease

neuronal degeneration. It leads to the activation of microglial cells that trigger the release of multiple pro-inflammatory factors, including TNF- α , IL-1 β , and IL-6. MiR-132-3p overexpression in PD aggravates the microglial cells activation and ultimately prompts the secretion of cytokines by suppressing GLRX (a glutathione-dependent disulfide oxidation reduction reaction catalyzing protein). Studies in both mouse and cell models have shown that the stimulation of GLRX may overpower the miR-132-3p toxic effects and hence may suppress the dopaminergic neuronal damage and microglial activation in PD (40). A close association of abnormal DNA methylation in the pathogenesis of PD is quite evident. The patterns of DNA methylation are established and maintained by enzymes known as DNA methyltransferases (DNMTs). Down-regulation of DNMT1 in PD is mediated by miR-17 and subsequently results in abnormal DNA methylation (41). miR-485-3p also prompts the neuroinflammation, which is supposed to be executed by targeting FBXO protein-45 (FBXO45), whereas its inhibition halts the pro-inflammatory cytokines release. Its higher expression has also been confirmed in the serum of patients with PD (42).

In patients with PD, the serum expression level of miR-15b-5p and Akt3 has been found to be markedly up-regulated and down-regulated, respectively. Moreover, miR-15b-5p mimic and silenced Akt3 enhanced the caspase-3 activity and apoptosis rate, while miR-15b-5p inhibition and Akt3 overexpression suppressed the apoptotic activity in both animals and cellular models of PD. Additionally, it is noteworthy that miR-15b-5p targets the β -catenin/ GSK-3 β signaling pathway mediated by Akt3 (43). The alterations in the level of miR-132 are widely associated with the worsening of PD. Particularly, overexpression of miR-132-5p increases apoptosis and reduces cell survival, while its inhibition can restrain autophagy by suppressing Beclin-1 and LC3 protein expression levels in PD (44).

Several therapeutic techniques can also regulate miRNA expression to counteract the pathogenesis of PD, including Repetitive Transcranial Magnetic Stimulation (rTMS). In fact, miR-195-5p is associated with the development of PD by directly targeting cyclic AMP-response element-binding protein (CREB), a transcription factor that promotes neuronal survival and neuroprotection and has anti-inflammatory actions. Sun and colleagues explored that rTMS treatment down-regulates the expression of miR-195-5p and up-regulates the subsequent CREB expression, thereby attenuating the neuronal apoptosis and neuroinflammation (45). Autophagy is a very conserved process to maintain homeostasis, which is about the elimination of damaged organelles and the cellular dysfunction of unfolded proteins. Defects in autophagy, particularly in SN, are closely associated with the stimulation of apoptosis in PD, while their restoration could aid in PD treatment. miR-30c-5p directly targets ATG5, a gene related to autophagy, resulting in dopaminergic neuronal loss, aggravating motor functions, increased apoptosis, and oxidative stress (46).

Disease-modifying role in PD

A redox-sensitive transcriptional factor, nuclear factor erythroid 2-related factor2 (Nrf2), facilitates cells to adapt to inflammation and oxidative stress, while TGF- β 1 overexpression is linked with dyskinesia in PD (47). Lately,

it has been reported that miR-221-3p has the capability to suppress TGF- β 1 expression and elevate Nrf2 expression by targeting TGFBR1, making it a novel candidate to prevent and treat PD (48). Up-regulation of miR-124 in a mouse model of PD has the potential to ameliorate motor deficits, attenuate oxidative stress, and improve the dopaminergic neuronal loss. It is one of the most abundant miRNAs in the brain parenchyma compared to other tissues. A direct target of miR-124 is Axin1, which actually suppresses Axin1 and activates the Wnt/ β -catenin signaling pathway, thereby attenuating the progression of PD. Basically, this targeted pathway plays a significant role in the regulation of inflammation and oxidant stress response during neuronal repair and neurogenesis (49).

In PD, the level of microglial activation correlates with the motor impairment and dopaminergic degeneration, suggesting that the resident microglia-induced neuroinflammation contributes to the progressive pathogenesis of PD. Prolonged and excessive activation of type I interferon (IFN-I) response can be the leading cause of microglia-mediated neuroinflammation and ultimately neuronal death. Overexpression of miR-218-5p can alleviate the levels of pro-inflammatory cytokines (IL-6 and IL-1 β) and, thereby, neuroinflammation in microglia by down-regulating the IFN-I pathways in MPTP-induced C57BL/6J mice. Moreover, *Ddx41* was verified as a target gene of miR-218-5p in BV2 cells *in vitro*. Hence, miR-218-5p inhibited microglia IFN-1 responses and inflammation by targeting *Ddx41* (50).

Li and colleagues showed that Nurr1 deficiency results in the down-regulation of miR-30e-5p that exacerbates NLRP3 inflammasome, microglial activation, and pro-inflammatory responses both *in vivo* and *in vitro*. Moreover, reduced expressions of miR-30e-5p and Nurr1 have also been observed in PD patients' plasma samples. On the other hand, overexpression of Nurr1 leads to the up-regulation of miR30e-5p that directly regulates the expression of the NLRP3 gene and thereby alleviates the pro-inflammatory cytokines and neuroinflammation (51). This data suggests the significance of the Nurr1-miR-30e-5p-NLRP3 axis in the regulation of neuronal survival and neuroinflammation in PD.

Another negative regulator of pro-inflammatory pathways is miR-146a. It mediates its effects by regulating NF- κ B, thereby suppressing inflammation and promoting cell survival and immunity (52). A member of mitogen-activated protein 3 kinase (MAP3K) is MEKK3, which is also implicated in the process of inflammation, and it prompts its effect by inducing the activation of NF- κ B. miR-124 inhibits the progression of neuroinflammation by targeting NF- κ B/MEKK3 signaling pathway, thereby regulating the inflammatory process in PD (53). Additionally, down-regulation of miR-144 and miR-218 is also associated with the activation of the NF- κ B pathway, and it was confirmed by a postmortem study of PD brain samples (54). PDE4B is a negative regulator of the inflammatory process, and it is a direct target of miR124-3p. In PD, overexpression of miR-124-3p could inhibit the expression of PDE4B and prevent the phosphorylation of the mTOR signaling pathway, which in turn ameliorates neuronal death and neuroinflammation. In addition, NEAT1 promoted the down-regulation of miR-124-3p in PD experimental models while its knockdown suppressed the PDE4B expression and promoted the miR-

124-3p expression, thereby improving the PD-associated damage (55). Pathogenic mutation in LRRK2, a leucine-rich-repeat kinase-2 gene, is one of the known causes of the monogenic PD (56), and LRRK2 mRNA is the direct target of miR-335. It could significantly reduce the expression of proinflammatory gene triggered by both LRRK2-Wt and α -synuclein. Moreover, miR-335 also has the potential to suppress the other players of inflammatory and necroptotic pathways, named as receptor-interacting protein-1 (RIP1) and RIP3, thereby mitigating the chronic neuroinflammation (57). Mesenchymal stem cells (MSCs) derivative extracellular vesicles (EV) are an effective therapeutic tool that acts as biological nanoparticles associated with beneficial outcomes in PD. Dysfunctional autophagy is involved in the pathogenesis and progression of PD. MiR-106b transported by MSC-derivative EVs ameliorated the autophagy, neuronal survival, Bcl-2 expression, and LC3I/LC3II ratio. It also alleviated the Bax expression and neuronal apoptosis in the mouse model of PD via down-regulating CDKN2B (58). Growing evidence showed that lower levels of IGF-1 are associated with the progression and aggravation of PD (59). miR-185 overexpression could ameliorate the dopaminergic neuron apoptosis in SN by targeting IGF1 and, in turn, activating the AKT/PI3K signaling pathway in PD. It can also improve the behavioral functions and reduce oxidative stress (60). Bcl-2 and Bax are involved in multifaceted cellular activation as anti-apoptotic and apoptotic regulators. If the amount of Bcl-2 is higher than that of Bax, it suppresses apoptosis, while a higher amount of Bax relative to Bcl-2 promotes apoptosis, and Bax is highly expressed in dopaminergic neurons in PD. miR216a attenuates neuronal apoptosis by restraining Bax (61), unraveling a new therapeutic chapter for PD treatment. A study has revealed that overexpression of miR-150 could also suppress the neuroinflammatory response by regulating the AKT3 signaling (62).

Ras-related-C3 botulinum toxin-substrate 1 (RAC1) is linked with the reactive oxygen species (ROS) production associated with the apoptotic pathway. miR-133a increases the cellular proliferation while inhibiting the autophagy and apoptosis (increases Bcl-2 and decreases Bax) via inhibiting the expression of RAC1 (63). Parkin is a vital protein that regulates the clearance of damaged mitochondria via mitophagy and sustains cellular homeostasis, and its mutation leads to autosomal-recessive PD (AR-PD). Mechanistically, Parkin mediates mitophagy by recruiting and interacting with activating molecules in Beclin-1-regulated autophagy (Ambra1). Up-regulated miR-103a-3p in PD suppresses the expression of Parkin, while its inhibition promotes neuroprotection in PD that might be involved in the regulation via Parkin/Ambra1 signaling pathway (64). LIM and SH3 protein 1 (LASP1) is involved in the oxidative stress and apoptosis process in dopaminergic neurons with PD. It is a direct target of miR-218-5p, and overexpression of miR-218-5p can counteract the negative effects of LASP1. It inhibits the LASP1 mediated oxidative stress and improved dopaminergic neuronal cells damage in SN of PD brain by repressing the LASP1 expression (65).

Early growth response 1 (EGR1) has been reported to effectively promote dopaminergic neurodegeneration and neuroinflammation in the MPTP-induced mice model of PD. Overexpression of miR-381 has been shown to alleviate oxidative stress and the associated dopaminergic

neuronal apoptosis. Mechanistically, miR-381 binds to EGR1 to counteract its expression, which then elevates the expression of p53 and PTEN (66), providing a novel insight for neuroprotection in PD. Signal transducers and transcriptional activator 3 (STAT3) are one of the factors associated with the pathology of PD (67). Both *in vitro* and *in vivo* models of PD confirmed that STAT3 is the target of miR-20a-5p. Overexpression of miR-20a-5p enhances the viability of BV2 cells as well as reduces the rate of apoptosis. In addition, its overexpression in MPTP-induced PD mice model inhibited STAT3, resulting in the reduction of neuroinflammation-associated markers, microglia activation, and α -synuclein levels (68). Like miR-20a-5p, STAT3 is also a target gene of miR-124 that inhibits the microglial activation and expression of proinflammatory cytokines, including IL-1 β , TNF- α and IL-6 (69). Another transcription factor, nuclear factor of activated T cells, cytoplasmic 2 (NFATc2), is associated with the PD that regulates chemokines and cytokines to build a neurotoxic neuro-inflammatory environment. It has been reported that the overexpression of miR-214-3p in a mouse model of PD suppressed the microglial activation, neuroinflammation, and reduced the dopaminergic neuronal loss by inhibiting the transcription of NFATc2 (70). Furthermore, overexpression of miR-221 has been shown to improve motor behavior and reduce the dopaminergic neuronal loss in SN via promoting their antiapoptotic and antioxidative capacities in 6-OHDA-induced PD mice model. Mechanistically, miR-221 inhibits the Bax/caspase-3 signaling pathways activation via restricting Bim, a proapoptotic member of the Bcl-2 protein family. This alleviates the dopaminergic neuronal apoptosis (71), suggesting a potential target for the treatment of PD.

Higher levels of transcription factor specificity protein 1 (SP1) could trigger neuronal cell death in NDDs. miR-126-5p and miR-375 are the negative regulators of SP1, and both can ameliorate the dopaminergic neuronal loss, attenuate oxidative stress, and neuroinflammatory responses mediated by PD via inhibiting SP1 (72). The implications of miRNAs in PD, along with their targets, have been summarized in Table 2.

Epilepsy

Epilepsy is one of the serious, debilitating, and long-term neurological and neurobehavioral disorders that are characterized by susceptibility to recurring seizure episodes and abnormal, unsynchronized neuronal discharge. It affects over 50 million people globally (73), and about 60% of them have the most common site for epilepsy, the temporal lobe epilepsy (TLE). It is characterized by the unpredictable and spontaneous recurrent seizure episodes (SRS), such as status epilepticus (SE)(74).

3.3.1 Disease-promoting role in epilepsy

Various studies have demonstrated the implications of miRNA and the associated pathways in the development and progression of TLE in humans as well as animal models. They are gradually recognized as the targets for the disruption of epilepsy and also act as biomarkers for the diagnosis of epileptogenesis. It is evident that neuroinflammation plays a critical role in the pathophysiology of TLE, and the CFH-miR-146a-IL-1 β loop circuit is found to be the cause of inflammation, perpetuating inflammation, in the case of TLE. The up-regulation of miR-146a resulted in increased

Table 2. Implications of miRNA in parkinson's disease (PD)

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	MiR-132-3p	GLRX	↑Neuroinflammation and DA neuronal damage	PD patients, BV-2 cells, SH-SY5Y, and (HEK)293T cell line	(40)
	miR-17	DNMT1	Abnormal DNA methylation	PD mice model and C57BL/6 mice (WT), HeLa and SH-SY5Y cell lines	(41)
	miR-485-3p	FBXO45	↑Neuroinflammation	PD patients, BV2 microglial cells	(42)
	miR-15b-5p	β-catenin/ GSK-3β signaling	↑Neuronal apoptosis	PD patients, SH-SY5Y cells	(43)
	miR-132-5p	Beclin-1 and LC3	↑DA neuronal apoptosis, restrain autophagy	MPTP PD mice model, SH-SY5Y cells	(44)
	MiR 195-5p	CREB	↑Neuroinflammation	MPTP-induced PD mice model and primary cortical neurons	(45)
	miR-30c-5p	ATG5	↑DA neuronal apoptosis and oxidative stress	MPTP PD mice model, SH-SY5Y cells	(46)
	miR-221-3p	TGFBR1	Improve PD symptoms	MPTP PD mice model, SH-SY5Y cells	(48)
	miR-124	Axin1, Wnt/ β-catenin signaling	↓DA neuronal apoptosis and oxidative stress, Promote neurogenesis	PD patients and mice	(49)
	MiR-218-5p	Ddx41	↓Neuroinflammation and neuronal damage	MPTP PD mice model and BV2 cells	(50)
Disease-modifying role	MiR-30e-5p	NLRP3	↓Neuroinflammation	PD patients, PD mice model, and primary microglia culture	(51)
	miR-146a	NF-kB	↓Neuroinflammation, improves cell survival	PD patients	(52)
	miR-124	NF-kB/MEKK3 signaling	↓Neuroinflammation	MPTP-HCl PD mice, SH-SY5Y, and BV-2 cells	(53)
	miR-144 and miR-218	NF-kB	↓Neuroinflammation	PD patients, SH-SY5Y cells	(54)
	miR124-3p	PDE4B, mTOR signaling	↓Neuronal apoptosis and neuroinflammation	SH-SY5Y and HEK-293 T cell lines	(55)
	miR-335	LRRK2, RIP1, RIP3	↓Neuroinflammation	MPTP PD mice model, BV-2, and N9 microglial cells	(57)
	MiR-106b	CDKN2B	↓Improve autophagy, Neuronal apoptosis	MPTP PD mice model, primary mouse hippocampus neuronal cells	(58)
	miR-185	IGF1, AKT/PI3K signaling	↓DA neuronal apoptosis and oxidative stress	PD mice	(60)
	miR-150	AKT3 signaling	↓Neuroinflammation	PD patients, BV-2 cell line	(62)
	miR-133a	RAC1	↓DA neuronal apoptosis and oxidative stress	PD patients, SH-SY5Y cell line	(63)
	miR-103a-3p	Parkin/Ambra1 signaling	↓DA neuronal apoptosis	MPTP-HCl PD mice, SH-SY5Y cell line	(64)
	miR-218-5p	LASP1	↓DA neuronal apoptosis	6-OHDA-induced PD rats	(65)
	MiR-381	EGR1	↓Neuronal apoptosis and oxidative stress	MPTP PD mice model	(66)
	MiR-20a-5p	STAT3	↓Neuroinflammation and apoptosis	MPTP PD mice model and BV2 cells	(68)
	MiR-124	STAT3	↓Proinflammatory cytokines and microglial activation	PD patients, SH-SY5Y and BV2 cells	(69)
	MiR-314-3p	NFATc2	↓Microglial activation and neuroinflammation	MPTP PD mice model	(70)
MiR-221	Bim	↓Neuronal apoptosis	PD patients and 6OHDA PD mice model	(71)	
miR-126-5p	SP1	↓Neuroinflammation and oxidative stress	SK-N-SH and SH-SY5Y cells	(72)	

IL-1β expression by down-regulating the complement factor-H (CFH) expression in the hippocampus of rat models of chronic TLE. In turn, the upsurge in IL-1β also elevated miR-146a levels via a positive feedback loop and reduced CFH expression. This mechanism is somehow twisted with the fact that knockdown of CFH did not allow the enhanced miR-146a to up-regulate IL-1β expression level (75).

It is the fact that TLE in children is different from that observed in adults, but miR-135a-5p is found to be up-

regulated in both children and adults. In order to evaluate the role of this miRNA in children with TLE, primary hippocampus neurons were used, mimicking the TLE in children. The results clearly depicted the up-regulated expression of miR-135a-5p with the suppressed expression of Caap1, leading to the TLE-mediated apoptosis in hippocampal cells (76). The expression of miR-135 in the hippocampus is significantly increased with the enhanced TNF-α expression level in both the rats with SE and children with mTLE. Deregulated miR-135a also alters

Mef2a protein expression, thereby affecting plasticity and synaptic function. Fascinatingly, seizure activity at the chronic stage (SRS stage) can be reduced by silencing miR-135a and thereby amending the *Mef2a* protein expression (77). Additionally, the correlation of TNF- α with another miRNA, miR-155, was evaluated in both rats and patients with TLE. The level of both miR-155 and TNF- α was found to be up-regulated in hippocampal tissues of rats with SE at the chronic phase. Moreover, TNF- α expression was also significantly up-regulated in patients with TLE (78), which indicated the implementation of miR-155 and TNF- α in neuroinflammatory responses during TLE pathogenesis. Another study in patients with TLE explored that miR-155 leads to the development and progression of epilepsy via Akt/PI3K/mTOR signaling pathways (79). Moreover, the overexpression of miR-155 also regulates the increased matrix metalloproteinase 3 (MMP3), which promotes epileptogenesis, induced by the stimulation of IL-1 β in astrocytes. These increased expressions were also marked in the TLE rat model as well as patients with TLE hippocampal sclerosis (TLE-HS)(80).

MiR-21-5p is linked with apoptosis-induced cell death and cellular proliferation by regulating the cell cycle via directing phosphatase and tensin homolog (PTEN). PTEN inhibits the mTOR pathway in protection from the diseased condition. In the KA-induced rat model of SE, the expression level of MiR-21-5p and mTOR was reported as up-regulated, while PTEN was down-regulated. Additionally, the knockdown of this miRNA resulted in down-regulation of mTOR and up-regulation of PTEN. It also contributed to the memory and cognitive improvement and alleviation of neuronal damage (81). miR-199a is also associated with apoptosis-induced damage in several disease conditions. SIRT1 acts as a significant endogenous apoptosis suppressor in NDDs and also supports axonal regeneration and promotes neurite outgrowth. In the pilocarpine-induced SE rat model, miR-128 was found to be up-regulated with the reduced expression of SIRT1, which led to apoptosis and neuronal loss (81). This concept was also supported by the *in vitro* epilepsy model, where overexpressed miR-128 suppressed the SIRT1 expression and elevated the activity of caspase 3/9, also with enhanced expression of disease-promoting factors (tumor protein p53, Cytochrome c, and Bcl-2-linked X), and stimulated neuronal apoptosis (82). Another report also supported the role of SIRT1 in neuroprotection against apoptosis-induced neuronal damage in a lithium-pilocarpine immature rat model. The expression of miR-181a-5p enhances seizure susceptibility, so its inhibition suppresses seizures through the regulation of SIRT1. Additionally, its inhibition also prevented the hippocampal insult, activation of microglia and astrocytes, neuroinflammation, mitochondrial dysfunction, neuronal apoptosis, and oxidative stress (83).

The Nrf2 has the ability to bind with antioxidant response element (ARE), and the activation of this (Nrf2-ARE) signaling pathway can protect the brain from damage, followed by the epileptic seizure. It was found that elevated levels of miR-495 reduced the NRF2 expression level (84), indicating the role of the Nrf2-ARE pathway in protection from epilepsy. The Janus Kinase (JAK) and signal transducer and activator of transcription (STAT) signal pathway also play a critical role in the development of epilepsy. The overexpressed miR-183 also activated the JAK/STAT

pathway, which suppressed the Foxp1 in hippocampal neurons, resulting in apoptosis and hippocampal neuronal injury, which aggravated the epilepsy in rats (85). Its expression is negatively regulated by miR-146a following SE, mediating the synaptic plasticity in neurons of the hippocampus via activating the STAT3 pathway, while its suppression could lessen the synaptic connections and shorten the neurite length (86). Moreover, miR146a is also associated with seizure frequency.

PTEN-induced kinase (PINK) is a protective kinase, regulated by healthy microglia, which protects the cells from mitochondrial dysfunction induced by stress. Its deficiency leads to oxidative stress, mitochondrial fragmentation, and suppression of mitophagy. PINK is a direct target of miR-142, which results in a reduction of PINK expression, while its inhibition in epileptic rats resulted in alleviation of oxidative stress and hippocampal damage, as well as stimulation of mitochondrial autophagy (87). MiR-223 is closely associated with the aggravation of epilepsy-linked abnormalities by targeting ATG16L1 and thus inhibiting microglial autophagy (88). The miR-181b and miR-219 also regulate the expression of excitatory neurotransmitter receptor AMPA-GluR2 and NMDA-R1, respectively, in the amygdala and hippocampus of patients with mTLE, contributing to the pathogenesis of epilepsy. Surprisingly, the association between miR-219 and NMDA-NR1 expression was different in the hippocampus and amygdala of mTLE patients. The expression of NMDA-NR1 was reported to have increased in the amygdala and decreased in the hippocampus, while miR-129 was alleviated in the amygdala and overexpressed in the hippocampus (89). The increased level of NMDA-NR1 may contribute to the generation of seizures and neuronal hyperexcitability, giving a new direction to researchers in the field of epilepsy. MiR-34c exerted negative impacts on cognition (memory and learning functions) via dysregulation of N-methyl-D-aspartate (NMDA) receptors in pentylenetetrazol (PTZ) induced TLE rats (90).

The brain-derived neurotrophic factor (BDNF) and tropomyosin-related kinase type B (TrkB) also aggravate the pathogenesis of epilepsy. It has been reported that miR-132 up-regulation resulted in the down-regulation of BDNF expression level, promoting the epileptogenesis in hippocampus neuron culture of SE (91). The shreds of evidence have indicated that oxidative stress is prompted by the seizure insult, leading to epileptogenesis. Recently, Zhu and co-workers have shown that miR-23a contributes to the generation of oxidative stress damage as well as neuronal injuries with spatial memory deficits in the hippocampus of TLE by targeting ADAM10. They observed that the up-regulation of miR-23a by its agomir aggravated the neuronal injuries, impairment of spatial memory, and oxidative stress in the hippocampus, while the miR-23a antagomirs alleviated these adverse effects (92).

Disease-modifying role in epilepsy

As mentioned above, the increased level of matrix MMP3 could promote the epileptogenesis induced by the stimulation of IL-1 β in astrocytes. A protein, reversion-inducing cysteine-rich protein with kazal motifs (RECK), suppresses the MMPs' activity, and it acts as neuroprotective against epilepsy. It was shown that miR-200c-3p decreased the RECK expression in hippocampal tissues of rats with

epilepsy. Conversely, alleviation of miR-200c-3p elevated the expression of RECK, which reduced the apoptosis in the hippocampus. It also decreased the expression of IL-1 β , IL-6, and TNF- α , as well as inactivated the Akt signaling pathway (93). In the epilepsy-associated neuroinflammatory process, high mobility group box-1 (HMGB-1) accompanies the process of neurodegeneration and reactive gliosis. Overexpressed HMGB-1 can lead to the activation of monocytes and macrophages that contribute to the neuronal damage, aggravating the progression of SE (94). The miR-29a inhibits the TLE-induced release of inflammatory cytokines (TNF- α and IL-6) and neuronal apoptosis through targeting HMGB1 (95). Being enriched in miRNAs, exosomes are considered a significant communication tool b/w the cells and have been proven as a potential therapeutic technique for the treatment of neurological diseases. Systemic injection of exo-miR129-5p in the SE mice model suppressed the neuroinflammatory factors (TNF- α , IL-6, and IL-1 β) and neuronal damage in the CA3 region of the hippocampus. It did so by inhibiting the proinflammatory encoding HMGB1 and the downstream TLR4 gene signaling axis, hence protecting the neurons against degeneration mediated by SE (96). These data provide evidence that exosomes loaded with miR129-5p may be a potential therapeutic strategy to relieve the pathological damage in an epileptic brain.

Ferroptosis is an iron-dependent mechanism of cellular death characterized by lipid peroxide accumulation. P2RX7, a nonselective ligand-gated homotrimeric cation channel, mostly enhances neuronal activity during epileptic episodes. It is particularly activated in pathological conditions, such as neuroinflammation (97). It has been shown that the up-regulation of P2RX7 in epilepsy is associated with the reduction of miR-211-5p expression levels, resulting in hypersynchronization as well as both convulsive and non-convulsive seizures. Li and coworkers have demonstrated that the genetic silencing of P2RX7 or the induction of miR-211-5p expression attenuated the oxidative stress and ferroptosis *in vivo* (98). These results indicate that the miR-211-5p/P2RX7 axis is a unique target for regulating ferroptosis and epilepsy.

Forkhead box D3 (FOXO3), a transcription factor, is confirmed to be involved in the progression of epilepsy by inducing neuron damage via suppressing the expression of sodium voltage-gated channel alpha subunit 2 (SCN2A) (99). Using an epilepsy cell model, researchers confirmed that miR-488-3p inhibits neuronal apoptosis and neuroinflammation by down-regulating FOXO3 and up-regulating SCN2A (100).

The β -catenin/Wnt pathway can affect several cellular processes, including differentiation, proliferation, cell motility, and apoptosis. Its abnormality can result in the development and progression of multiple diseases. The activation of β -catenin/Wnt signaling can be inhibited by up-regulation of miR-136, resulting in reduced neuroinflammatory cytokine levels (TNF- α , IL-6, and IL-1 β), inhibition of apoptosis, and thus reducing the duration and frequency of seizures (101).

Insulin-like growth factor 1 receptor (IGF1R) is found in the cytomembranes of microglia, astrocytes, and neurons. In pentylentetrazole and pilocarpine rat models of epilepsy, IGF1R inhibition has been reported to improve the epileptiform activities, suggesting it is a target for epilepsy therapy (102). Overexpression of miR-194-5-p alleviated

the TLE development and the hippocampal cell apoptosis induced by TLE. As IGF1R is the direct target of miR-194-5p, this protective effect was speculated to be executed via targeting IGF1R, but further research is still needed in this field (103). Reduced or dysregulated expression of miR-15a-5 in children with TLE has been confirmed by researchers, but reports on its mechanism of action and molecular targets remain lacking. However, its overexpression can inhibit the hippocampus cellular apoptosis and promote the cell viability (104).

Sex-determining region Y box 7 (SOX-7) has been recognized to prevent apoptosis in hippocampal neuronal cells of epilepsy (105). CircRNA Ubiquilin-1 (circUBQLN-1) serves as a sponge of miR-155. Interestingly, circUBQLN1 has the capability to suppress the process of epileptogenesis by stimulating the expression of SOX-7 by serving as a miR-155 sponge (106). This miR-155/circUBQLN-1/SOX-7 signaling network contributes to the widespread understanding of the unique mechanisms involved in epilepsy. Hence, opening a new avenue to find a novel treatment for epileptogenesis. Acquired functional modifications or genetic mutations lead to a GABAergic neurotransmission dysfunction. A strong relationship b/w inflammatory networks and reduced inhibitory neurotransmitter activity, Gamma Aminobutyric acid (GABA) activity, has already been reported in the process of epileptogenesis. Notably, the GABA levels are being regulated by an enzyme known as glutamate decarboxylase-1 (GAD-1). Altogether, these enzymes and signaling circuits play a crucial role in the occurrence of epileptogenesis. The overexpression of miR-322-5p plays a significant role in counteracting the inflammation-associated circuits by targeting NF- κ B and toll-like receptor 4 (TLR4), thereby increasing the expression of GABA (107). It also participates in improving the neuronal apoptosis process induced by epileptic insult (108).

The miR-let-7i elicits its effects by mediating the TLR4 signaling network, providing insight into SE pathogenesis. In particular, this miRNA could significantly attenuate the SE degree and prolong the SE latent period, which could be reversed by its antagomir. It might also reduce the action potential frequency and cellular apoptosis following SE (109). A downstream regulator of histone deacetylase-5 (HDAC-5) is a proinflammatory factor, which is known as Hypoxia-inducible-factor-1 α (HIF1 α), where the downstream target of HIF1 α is the PFKFB3 enzyme that may promote neuronal damage in epilepsy. Overexpression of miR-485 can alleviate neuronal apoptosis and neuroinflammatory cytokine production via inhibition of HIF1 α , HDAC5, and PFKFB3 in epilepsy (110). It has been reported that the overexpression of miR-135b-5p has attenuated the seizure-induced cellular apoptosis and improved the cell viability by targeting SIRT1 (111). The implications of miRNAs in epilepsy, along with their targets, have been summarized in Table 3. Graphical representation of disease-promoting and disease-modifying miRNAs is shown in Figure 3.

Traumatic brain injury

Traumatic brain injury (TBI) is defined as the modifications in brain functionality, or other pathological alterations, following external force, such as accidents, etc. Globally, it is a cause of serious injuries leading to neurological disability and even death. Every year, around 69 million individuals suffer from TBI, and approximately

Table 3. Implications of miRNA in epilepsy

	MicroRNA	Target	Outcomes	Study model	Reference	
Disease-promoting role	miR-146a	CFH, NF-κB	↑Neuroinflammation	KA-IH rat model, U251 cells, TLE patients	(75)	
		STAT3 pathway	↑Abnormal synaptic connections	PTZ mouse model, Primary hippocampus neuronal cells	(86)	
	miR-135a-5p	Caap1	↑Neuronal apoptosis	Children with TLE	(76)	
	miR-135a	<i>Mef2a</i>	↑Abnormal plasticity and synaptic functions	KA-IAK mouse model	(77)	
	miR-155	Akt/PI3K/mTOR signaling	↑Neuroinflammation	HT22 mouse hippocampal cells	(79)	
		MMP3	↑Epileptogenesis	TLE patients, primary astrocyte culture	(80)	
	MiR-21-5p	PTEN	↑Cognitive impairment and neuronal damage	KA-IH rat model	(81)	
	miR-128	SIRT1	↑Neuronal apoptosis	Pilocarpine-induced TLE rat model	(81)	
	miR-181a-5p	SIRT1	↑Neuronal apoptosis and seizure susceptibility	Lithium-pilocarpine rat model	(83)	
	miR-495	Nrf2-ARE signaling	↑Neuronal damage and oxidative stress	Lithium-pilocarpine rat model, hippocampal neuronal cell culture	(84)	
	miR-183	JAK/STAT signaling	↑Neuronal apoptosis	Lithium-pilocarpine rat model, hippocampal neuronal cell culture	(85)	
	miR142	PINK	↑Oxidative stress and hippocampal damage, restrain mitophagy	Lithium-pilocarpine rat model	(87)	
	MiR-223	ATG16L1	Restrain microglial autophagy	TLE patients, KA-ICV mice model	(88)	
	miR-219	NMDA-NR1	↑Neuronal hyper-excitability	TLE patients	(89)	
	MiR-34c	NMDA receptor	Cognitive impairment	PTZ rat model	(90)	
	miR-132	BDNF	↑Epileptogenesis	Children with TLE	(91)	
	miR-23a	ADAM10	↑Oxidative stress and neuronal damage, cognitive decline	Primary hippocampal neuronal cell culture	(92)	
	Disease-modifying role	miR-200c-3p	RECK	↓Neuronal apoptosis and neuroinflammation	Lithium-pilocarpine rat model	(93)
		miR-29a	HMGB1	↓Neuronal apoptosis and neuroinflammation	TLE patients, primary hippocampal neuronal cell culture	(95)
		MiR-129-5p	HMGB1	↓Neuronal apoptosis and neuroinflammation	KA-IP mice model	(96)
MiR-211-5p		P2RX7	↓Neuronal apoptosis and oxidative stress	Epileptic patients, KA-IH mice models	(98)	
MiR-488-3p		FOXD3	↓Neuronal apoptosis and neuroinflammation	SH-SY5Y cells, Pilocarpine rat model	(100)	
miR-136		β-catenin/Wnt	↓Neuronal apoptosis, neuroinflammation, and seizure frequency and duration	Lithium-pilocarpine rat model	(101)	
miR-194-5p		IGF1R	↓Neuronal apoptosis	Children with TLE	(103)	
miR-155		circUBQLN-1/SOX-7 signaling network	↓Neuronal apoptosis and epileptogenesis	TLE patients, human hippocampus neuronal cell line	(106)	
miR-322-5p		NF-κB, TLR4	↓Neuroinflammation and neuronal apoptosis	Lithium-pilocarpine rat model	(108)	
miR-485		HIF1α, HDAC5, and PFKFB3 signaling	↓Neuronal apoptosis and neuroinflammation,	Huh7 and HepG ₂ human HCC cell line	(110)	
miR-135b-5p		SIRT1	↓Neuronal apoptosis, ↑Cell viability	Children with TLE	(111)	

80–90% of such cases account for mild TBI (mTBI)(112). Instead of progress in the pathophysiological understandings of TBI, people are still suffering from lifelong neurological deficits with mild to severe TBI.

Disease-promoting role in TBI

Among the multifaceted pathological alterations in TBI, neuroinflammation plays a significant role as a secondary injury process, exerting either beneficial or detrimental effects in the process of CNS damage following TBI. Dual

specificity phosphatase-1 (DUSP1), a MAPK phosphatase-1 (MKP-1), can modulate the MAPK signaling pathway, thus regulating cellular proliferation and cell death. miR-429 targets the DUSP1 signaling pathway in activated microglia and stimulates increased expression of pro-inflammatory factors following TBI. Hence, its inhibition can impede the NF-κB and MAPK-p38 pathways regulated by DUSP1, thereby inhibiting the microglia activation (113). Persistent and robust neuroinflammatory responses after TBI are also associated with elevated expression of miR-155 in

well as cognitive function, such as learning and memory (123). These pathways are being targeted by miR-124-3p, resulting in disease aggravation and cognitive decline after TBI. Disruption or down-regulation of miR-124-3p has intensified the activation of Ras and PI3K/Akt signaling pathways, and thus improved the neuronal survival and cognitive performance in a mouse model of TBI (124).

Research on ischemic stroke indicated that both pharmacological inhibition and genetic silencing of miR-15a/16-1 in murine models led to a notable reduction in brain infarction and neuronal apoptosis. These interventions were associated with enhanced short-term sensorimotor function following ischemic stroke (125). Then, a study investigates the role of miR-15a/16-1 in experimental TBI models. The research used various experimental models to demonstrate that inhibiting miR-15a/16-1 reduced neuroinflammation, neuronal apoptosis, and enhanced neurogenesis. The recovery was also linked with the improved motor and cognitive functions in TBI models (126).

Disease-modifying role in TBI

Nevertheless, excessive and sustained neuroinflammation can aggravate the neuronal apoptosis post-TBI. It is principally propagated by microglia in the injured brain, and the altered ratio of M2/M1 has been reported to be involved in the exacerbation of brain damage after TBI. It has been reported that the overexpression of let-7c-5p can attenuate the TBI-mediated brain edema as well as neurological dysfunction. It inhibits the neuroinflammation and alleviates microglial activation, both by elevating M2 polarization and reducing or halting M1 polarization. Moreover, it also inhibits the expression of caspase-3 by targeting PKC-d, as it mediates the effects of caspase-3 (127). Likewise, miR-124-3p also promotes the M2 polarization in microglial cells, and exosomal miR-124-3p inhibits the neuronal inflammation by suppressing the mammalian target of rapamycin (mTOR) signaling activity mainly via inhibiting the PDE4B gene expression (128). It is noteworthy to mention that exosomes (Exos) are a type of bioactive nanomaterial with the potential to regulate cellular functions. They achieve this by releasing active cargo, including miRNAs, which can bind to target mRNAs to control their expression and degradation, with minimal impact from internal and external environmental factors. In addition to promoting M2 polarization in microglial cells and inhibiting neuronal inflammation, miR-124-3p also exhibits neuroprotective effects against Endoplasmic reticulum (ER) stress. ER stress contributes to neuronal damage following repetitive mild TBI that can trigger apoptotic pathways, inflammation, and oxidative stress (129). Wang and colleagues explored that microglia-derived exosomes enriched with miR-124-3p effectively reduce apoptosis and ER stress.

The miR-124-30 alleviates the IRE1 α expression, which was confirmed by the specific binding of miR-124-3p to an ER stress-related protein, inositol-requiring enzyme 1 α (IRE1 α), thereby mitigating ER stress in injured neurons. microglia-derived exosomes containing miR-124-3p were intranasally delivered in a mouse model of repetitive mild TBI, which significantly reduced apoptosis and ER stress in hippocampal neurons (130). Hence, this suggests that the miR-124-3p transferred via microglia-derived exosomes may offer neuroprotection by reducing ER stress, indicating

a promising therapeutic approach for repetitive mild TBI.

It is also speculated that activated microglia may suppress synapse recovery and neurite outgrowth after TBI, partially by down-regulating exosomal miR-5121. Both *in vitro* and *in vivo* studies have confirmed that miR-5121 overexpression in microglia-derived exosomes can somewhat reverse the suppression of synapse recovery and neurite outgrowth following TBI (131). Hence, microglial exosomes manipulated by miRNAs can be a novel therapeutic strategy for TBI and other neurological diseases as well. One of the significant components of astrocyte-derived exosomes is miR-873a-5p, which allows microglia-astrocyte interaction. These miR-873a-5p-enriched astrocyte-derived exosomes promote M2 microglial polarization through inhibition of NF- κ B p65 and ERK phosphorylation, thereby improving cerebral injury and ameliorating neurological function following TBI (132). MiR-124 is also implicated in microglia M2 polarization. Using the C57BL/6 TBI mouse model and BV2 microglia culture, the research demonstrates that miR-124 inhibits TNF receptor-associated factor 6 (TRAF6) expression, thereby attenuating activation of neuroinflammatory pathways, including the toll-like receptor (TLR4) pathway, and promoting M2 microglial polarization. Apart from its function of inhibiting TRAF6-induced neuroinflammation, miR-124 has also been related to the enhancement of neuronal survival and promotion of neuroprotection after traumatic brain injury. It increased the expression of anti-inflammatory factors (IL-4, IL-10, and TGF- β) and decreased the expression of pro-inflammatory chemokines (IL-1 β , TNF- α , and IL-6)(133). The research highlights the therapeutic potential of miR-124 regulation as a potentially effective approach to alleviate the deleterious consequences of neuroinflammation in traumatic brain injury.

Interestingly, MiR-126 also executes its neuroprotective effects against sepsis-induced injury by inhibiting the activity of the NF- κ B signaling pathway, thereby impeding the neuroinflammatory responses and oxidative stress post-TBI (134). miR-146a mimics also ameliorate the severity of TBI by inhibiting the NF- κ B signaling pathway, followed by a relative reduction of phosphorylated I κ B α and JNK. It rescued the NVU dysfunction and improved the memory and learning ability as well as alleviated the level of IL-1 β , TNF- α , and IL-6 both in serum and brains of TBI mice model (135). It has been well demonstrated that the activation of the mTOR/AKT signaling pathway mediates the neuroprotective effects after TBI by suppressing neuronal apoptosis. Whereas PTEN acts as a negative regulator of this signaling pathway, and its inhibition could also improve the TBI-associated neuronal damage. Li and colleagues have reported that miR-23a up-regulation can inhibit neuronal apoptosis and neuroinflammatory responses by preventing activation of the PTEN/mTOR/AKT signaling pathway (136).

Significantly, miR-331 shows substantial down-regulation in brain tissue within 12 hours of TBI (137). Research demonstrated that intranasal delivery of miR-331 mimics can suppress the reactive gliosis, reduce neuroinflammation, and enhance cognitive function in a mouse model of hippocampal stab injury (HSI). Mechanistically, IL-1 β is directly targeted by miR-331 following HIS (138).

In TBI patients with fractures, it has been speculated that sustainers of TBI have faster healing times as compared

to individuals with isolated fractures. It has been shown that miRNA-26a-5p overexpression has improved fracture healing by down-regulating PI3K/AKT and PTEN signaling (139). So, it could be a novel therapeutic strategy to improve fracture healing. It has been thought that elevated connexin43 phosphorylation by ERK1/2 is linked with the early cerebral ischemia-induced brain damage (140). In the shear stress-induced cell model of TBI, augmented miR-302 expression repressed the connexin43 phosphorylation and ERK1/2. It has also significantly ameliorated the cognitive impairment and improved TBI-associated brain damage in rats by suppressing edema (141).

Stimulator of interferon genes (STING) plays a significant role in neuroinflammatory response after brain injury (142). A downstream target of let-7i is STING after traumatic brain injury, making it a novel candidate for neuroinflammation-related injury. Let-7i agomir significantly reduced the neuroinflammatory response, glial scars, and neuronal apoptosis and improved the cognitive deficits following brain injury via targeting STING (143). Death-associated protein kinase-1 (DAPK-1) stimulates neuronal apoptosis during ischemic stroke and other NDDs via phosphorylation of NR2B (p-NR2B). It is a subunit of the NMDA receptor that regulates calcium influx, which is important for the maintenance of neuronal plasticity and normal cellular function (144). Evidence has shown that inhibition of NR2B phosphorylation can reverse the neurological impairments induced by TBI (145). Overexpression of miR-124 could inhibit the expression of DAPK-1 and thereby reduce the phosphorylation of NR2B, improve motor and behavioral functions, and attenuate apoptosis associated with TBI (146).

With important consequences for the development of ischemic injury, ELAVL1 regulates ischemia/reperfusion injury, cancer, and cellular iron death. According to earlier

studies, autophagy regulation via ELAVL1 activation by FOXC1 increases iron death in myocardial ischemia/reperfusion injury. TBI is also associated with vascular endothelial growth factor (VEGF), with higher levels of VEGF and MMP-9 following a TBI leading to the disruption of the blood-brain barrier and subsequent neurological impairment. By inhibiting ELAVL1 and down-regulating VEGF expression, MiR-9a-5p reduces brain tissue injury in TBI rats by targeting the ELAVL1/VEGF signaling system (147), indicating that these molecules may have therapeutic promise in the treatment of brain tissue injury. Because of its proven neuroprotective, anti-inflammatory, and antioxidant qualities, ursolic acid (UA) is a viable treatment option for a number of neurological conditions. Numerous studies have shown that UA is neuroprotective against brain damage. It dramatically lowers oxidative stress, neuroinflammation, neuronal death, and cerebral edema. It has been demonstrated that UA enhances TBI outcomes in mice by up-regulating the PDCD4/PI3K/AKT signaling pathway, which is mediated by miR-141. Furthermore, in neurons injured by TBI, miR-141-3p specifically targets PDCD4, a regulator of the PI3K/AKT pathway. These results lend credence to UA's possible therapeutic use in the management of traumatic brain injury (148).

The implications of miRNAs in TBI, along with their targets, have been summarized in Table 4. Graphical representation of disease-promoting and disease-modifying miRNAs is shown in Figure 4.

Depression

Depression is a prevalent psychiatric disorder characterized by loss of self-confidence and anhedonia, driven by public health issues. Almost 17% of the global population is affected by depression and other stress-associated mood disorders, which are associated with an

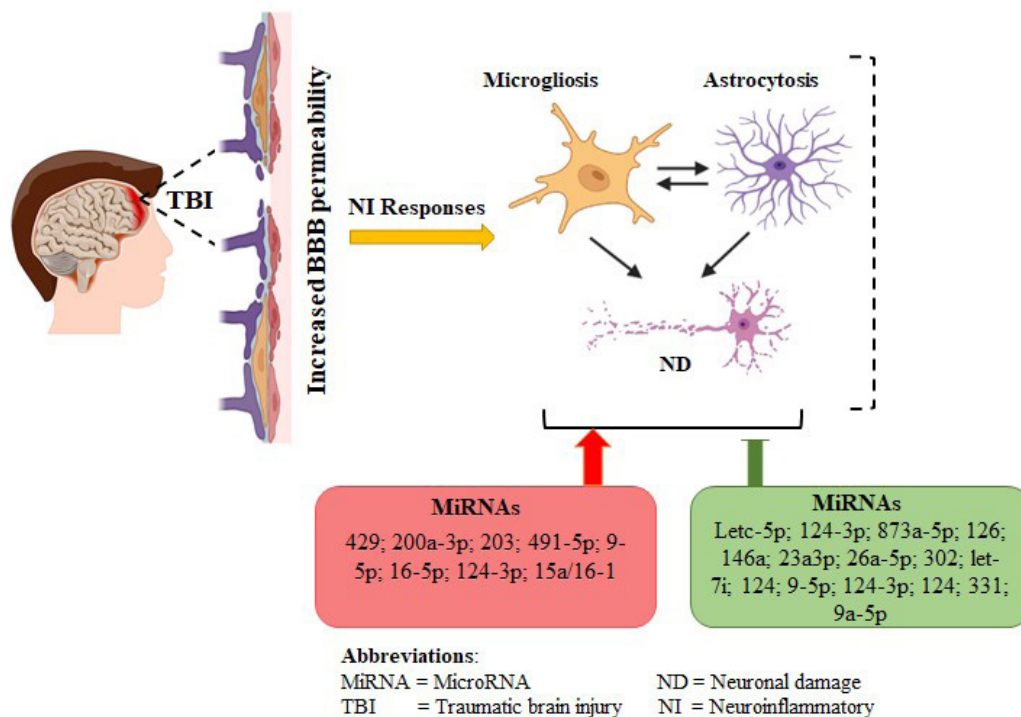


Figure 4. Role of microRNA as disease-promoting and disease-modifying in traumatic brain injury

Table 4. Implications of miRNA in traumatic brain injury (TBI)

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	miR-429	DUSP1	↑Neuroinflammation	TBI patients, TBI mice model	(113)
	miR-200a-3p	Keap1/HO-1/ROS/Nrf2 pathway	Promote sepsis	TBI mouse model, HBMEC cell line	(115)
	miR-203	Bcl-2, caspase-3	↑Neuronal apoptosis, cognitive decline	TBI mouse model	(118)
	miR-491-5p	HIF-1α/VEGF	↓Neovascularization, ↑oxidative stress	TBI mouse model, BMEC cell line	(120)
	miR-16-5p	cyclin-D1 and Bcl-2	↑Apoptosis, halts the cell cycle	Fracture and TBI patients and a mouse model, MC3T3-E1 cells	(122)
	miR-124-3p	Ras and PI3K/Akt	↑Neuronal apoptosis, cognitive decline	TBI rat model	(124)
	miR-15a-161	-	↑Neuronal apoptosis, neuroinflammation, and ↓neurogenesis	miR-15a/16-1-KO and WT mice, C57BL/6J mice	(126)
Disease-modifying role	let-7c-5p	PKC-d	↓Neuroinflammation	TBI mouse model, primary mouse microglia	(127)
	Exosomal miR-124-3p	PDE4B	↓Neuroinflammation	TBI mouse model, microglial BV-2 cells, primary cortical neuronal cells	(128)
	MiR-124-3p	IRE1α	↓ER stress and apoptosis	rmTBI mouse model and HT22 neuronal cells	(130)
	miR-873a-5p	NF-κB and ERK phosphorylation	Improve neuronal functions and cerebral injury, ↓neuroinflammation	TBI patients, TBI mouse model, primary astrocytes, and microglial cells	(132)
	MiR-124	TRAF6	↓IL-1β, IL-6, and TNF-α ↑IL-4, IL-10, and TGF-β	C57BL/6 TBI mice model and BV2 microglia culture	(133)
	MiR-126	NF-κB	↓Neuroinflammation and oxidative stress	Sepsis rat model	(134)
	miR-146a	NF-κB	↓Neuroinflammation, ↑NVU recovery,	TBI mice model	(135)
	miR-23a-3p	PTEN/mTOR/AKT	↓Neuroinflammation and neuronal apoptosis	TBI mice model	(136)
	MiR-331	IL-1β gene	↓Neuroinflammation, reactive gliosis, improve cognitive functions	C57BL/6J TBI mice model, Astrocyte and microglia culture	(138)
	miR-302	connexin43, ERK1/2	Improve cognition	TBI rat model, SH-SY5Y cells	(141)
	let-7i	STING	↓Neuroinflammation and neuronal apoptosis	TBI mice model	(143)
	miR-124	DAPK1	Improve motor and behavioral functions, neuronal apoptosis	TBI patients, TBI mice model	(146)
	MiR-9a-5p	ELAVL1	Improve brain tissue injury	TBI rat model	(147)
	miR-141-3p	PDCD4	↓Neuroinflammation, oxidative stress, and neuronal apoptosis	TBI mice model	(148)

elevated suicide rate. The pathophysiology of depression includes aberrant processing of information in brain circuits and disruption of cellular networks that regulate cognition and mood. This can lead to altered structural and synaptic plasticity, which can be critical in the development and progression of major depressive disorder (MDD)(149).

Disease-promoting role in depression

Dysregulated expression of miRNA has been observed in both the human brain tissues (post-mortem) and animal models suffering from depression. MiR-124 is abundantly found in the brain and has the potential to regulate adult neurogenesis, synaptic plasticity, and neuronal differentiation. The expression of miR-124 can be dysregulated by the elevated corticosterone (CORT) and cortisol levels. Stress exposure leads to increased corticosterone (CORT) levels in rodents, which in turn up-regulate miR-124 expression in the prefrontal cortex. In humans, elevated cortisol levels have been similarly associated with higher miR-124 expression in the serum of patients with MDD (150). Moreover, the higher level of CORT also altered the brain-derived neurotropic factor (BDNF). Alternatively, miR-124 inhibition ameliorated the changes in BDNF induced by CORT and produced the

antidepressant-like actions via activation of the BDNF/TrkB signaling pathway (151). From these reports, one can postulate that miR-124 is strongly associated with depression pathophysiology, and it could be a great target for antidepressant treatments and drug development as well.

Chronic stress exposure can also negatively impact synaptic plasticity by stimulating alterations in the trophic factors production, neurogenesis in adult hippocampus, and neuronal morphology, leading to impairment in memory and learning processes. MiR-30 family’s miRNAs mediate the depression like phenotypes by modifying the hippocampal neuroplasticity and neurogenesis via modulating the transcription and epigenetic regulators like *Runx1* and *Mll3*, as well as cell signaling mediators such as *Nrp1*, *Gpr125*, *Ppp3r1*, and *Socs3* (152).

Up-regulation of miR-200a and 200b-3p (miR-200a/b-3p) is associated with the chronic unpredictable mild stress (CUMS) that promotes anxiolytic behavior and apoptosis via targeting nuclear receptor sub-family-3 group C-member-1 (NR3C1). It executes its effects by down-regulating the expression of NR3C1, elevating the expression of Bax and cleaved caspase-3, and alleviating Bcl-2 (anti-apoptotic protein), thereby promoting neuronal death and stress-related behaviors (153). miR-382-5p also modulates the

expression of NR3C1 following stress and depression. In the rat model of depression, it reduced the expression of p-TrkB and NR3C1, downstream targets of BDNF, in hippocampal tissues, highlighting its role in depression. It was also confirmed by using lentivirus miR-382-5p and lentivirus si-miR-382-5p. BDNF, p-TrkB, and NR3C1 were up-regulated by si-miR-382-5p, while opposite effects were observed by using si-miR-382-5p (154). As it is known that a single protein can be targeted by several miRNAs, here is another target of NR3C1, named miR-139-5p. In an animal model of depression, its inhibition significantly elevated the sucrose-preference index, alleviated neuronal damage, increased NR3C1, BDNF, p-TrkB/TrkB, p-CREB/CREB, and p-ERK/ERK. On the other hand, up-regulated miR-139-5p expression reduced its novel target NR3C1 (155). The miR-182 and miR-382 directly target the BDNF and reduce its expression in post-stroke depression (PSD), indicating the involvement of miR-382 and miR-182/BDNF signaling pathways in PSD (156). Another BDNF-targeting miRNA is MiR-202-3p, which is associated with the aggravated depression-like behavior and reduced BDNF levels in the hippocampus (157).

The miR-345-5p induces the inflammation-associated damage in neuronal cells of the hippocampus via activation of microglia. The SOCS-1 can potentially inhibit the TLR and cytokines signaling pathway, thus terminating the signal cascade in time (158). The miR-345-5p directly targets the SOCS-1, resulting in a reduction in Bcl-2 and SOCS-1 expression and an increase in Bax level, hence aggravating the neuronal apoptosis in the hippocampus (159). Epigenetic regulator miR-15b inhibits the proliferation of neuronal progenitor cells (NPCs) and is reported to be up-regulated in the medial prefrontal cortex, suggesting a role in major depression. The miR-15b-5p could critically attenuate the excitatory synaptic transmission, VAMP-1/STXB3A (synaptic proteins) expression, and activities in the nucleus accumbens following CUMS (160).

A study showed that the knockdown of miR-497a-5p could alleviate the depression-like behaviors in rats as well as repress the microglial activation, thereby inhibiting neuroinflammation (161). Elevation of HECT domain E3 ubiquitin protein ligase 1 (HECTD1) could restore the neuronal functions and improve the BBB injury. Moreover, it could also regulate the activation of astrocytes (162). Another study claimed that the up-regulated HECTD1 expression might inhibit the activation of microglial cells, thereby alleviating the symptoms of depression (163). Consistent with these studies, Chen and Cao (2023) confirmed that miR-497a-5p targets the HECTD1 to promote neuroinflammation and neuronal apoptosis in depression, while its inhibition can restrain these effects in BV2 cells and hippocampal neuron cells (HT22). Interestingly, Circular RNA (circRNA) circ-Bnc2 can inhibit neuronal apoptosis and neuroinflammation by positively regulating HECTD1 expression via miR-497a-5p sponging (164), suggesting a potential therapeutic target for depression treatment.

Disease-modifying role in depression

Some studies have indicated the health-promoting role of miR-132 (brain-enriched miRNA) during adult neurogenesis, such as differentiation and proliferation of neural stem cells, synaptic plasticity, and dendritic

morphogenesis regulation (165, 166). It is also predicted to be involved in the regulation of multiple neuronal membranes and biological pathways, and dysregulation of miR-132 may contribute to the pathogenesis of MDD (167). Dysregulation of MiR-132 in MDD is also linked with lower volume of grey matter and fractional amplitude of low frequency fluctuations (fALFF) in amygdala and hippocampal nuclei, thus resulting in cognitive impairment associated with the relevant brain region (168). Connective tissue-growth factor (CTGF) plays a significant part in both the pathological and physiological activities. Implications of CTGF in the pathogenesis and progression of depression have already been confirmed. miR-133b is poorly expressed in the hippocampus, whereas CTGF is highly expressed following depression. Conversely, up-regulation of miR-133b and inhibition of CTGF in rats could control neuronal apoptosis in the hippocampus, suppress the inflammatory response, and enhance BDNF expression in hippocampal tissues, highlighting the protective efficacy of miR-133b against neuronal injury and subsequent depression (169). It is noteworthy that overexpressed miR-133b could repress the CTGF expression, providing protection against hippocampal neuronal apoptosis and inflammatory reactions in depression.

CUMS results in the activation of ASK1/Dyrk1A/JNK signaling pathway leading to neuronal apoptosis and stress-like behaviors, particularly in the cornu Ammonis (CA1) of the hippocampus. miR-211-5p promotes anti-depressant effects by targeting ASK1/Dyrk1A/JNK signaling pathway, resulting in restrained neuronal apoptosis in CA1 (170). Therefore, the Dyrk1A/miR-211-5p pathway could critically be involved in the depression pathogenesis and may serve as a novel therapeutic candidate to treat depression.

Lately, it has been found that the miR-204-5p expression within the dentate gyrus (DG) of the hippocampus is considerably down-regulated after chronic unpredictable stress (CUS), in association with the deterioration of neurons induced by oxidative stress in the rat model of CUS. In contrast, miR-204-5p overexpression in DG alleviated the neuroinflammation and oxidative stress via directly targeting a G-protein signaling-12 regulator (RGS-12), concomitant with improvement in depression like behaviors. In particular, RGS-12 is a downstream targeted gene of miR-204-5p that stimulates the inflammation and oxidative stress in DG by regulating the NF- κ B/Nrf2 signaling pathway (171). The miR-26a-3p could alleviate neuronal damage coupled with CUMS induced depression by suppressing, via suppression of the PI3K/Akt/PTEN signaling pathway. The protective efficacy of this miRNA was also confirmed by knocking down miR26a-3p in a rat model of CUM induced depression. The suppression of miR-26a-3p in the DG induced depression-linked phenotypes, accompanied by PI3K/Akt/PTEN pathway activation and neuronal anomalies, including autophagy repression, synaptic plasticity impairments, and elevated neuronal apoptosis (172).

Microglial activation is associated with the development and progression of numerous neurological diseases, leading to inflammation aggravation and neuronal apoptosis. Notably, the correlation between neuroinflammation and psychiatric disorders has been reported, and the expression levels of inflammatory markers act as crucial indicators of the occurrence and development of depression (173). In a

CUMS mouse depression model, miR-29a-5p was shown to be down-regulated, which consequently promoted the microglia M1 polarization via up-regulating the TMEM33 expression. This increased inflammatory chemokines, resulting in neuronal apoptosis. On the contrary, the miR-29a-5p up-regulation in the prefrontal cortex (PFC) repressed the expression of TMEM33, facilitated the M2-polarization of microglia, and improved the depressive-like behaviors (174). The data suggest that the miR-29a-5p/TMEM33 axis may serve as a potential therapeutic target for depression treatment. However, this study has some limitations because patient samples were not included.

Another catalyst for the activation of microglia is enhancer of zeste homolog 2 (EZH2), which is a regulator of methylation in the neuroinflammatory process in the development of depression. In the mouse forebrain, it retarded the neuronal activities and induced depression-like behavior (175). Chemokine C-X-C ligand 10 (CXCL10) expression has also been reported to be up-regulated in patients with depression, which is a functional target of miR-15a (176, 177). It has been reported that elevation of miR-15a-5p or down-regulation of EZH2 attenuated the hippocampal proinflammatory cytokines, improved depressive behaviors, and inhibited the hippocampal neuronal apoptosis by inhibiting the expression of CXCL10 (178). Neural stem cells (NSCs) derived extracellular vesicles (EVs) are highly rich in proteins and miRNAs involved in anti-apoptosis, neuroprotection, anti-oxidant, anti-inflammatory, BBB repair, and neurogenic activities, as well as proteins and miRNAs that promote synaptic plasticity and synaptogenesis. The MYB, a family of proteins, is associated with the pro-apoptotic activity. Min *et al.* (2014) showed that NSC-EVs carry miR-16-5p, which reduces neuronal apoptosis and injury by targeting MYB, both *in vivo* and *in vitro* (179).

Bone marrow (BM) mesenchymal stem cells (BM-SCs) derivative exosomes have been widely used as disease

therapeutics. In depressed rats, BM-SCs derivative exosomes increased the expression of miR-26a in hippocampal tissues, resulting in restrained apoptosis and improved neuronal damage. Moreover, BM-SCs associated up-regulation of miR-26a elevated the superoxide dismutase (SOD), whereas reduced the level of lactate dehydrogenase (LDH), IL-1 β , tumor necrosis factor α (TNF- α), and malondialdehyde (MDA) in serum and hippocampal tissues (180). However, further studies need to be done for better clarification of the precise mechanism of the BM-SCs-derivative exosomes in depression. Corticotropin-releasing hormone-receptor-1 (CRHR-1) and nuclear enriched-abundant transcript-1 (NEAT-1) have been associated with the progression of depression and depression-like behaviors. NEAT-1, in particular, binds with miR-320-3p to upsurge the expression of CRHR-1, thus promoting apoptosis and neuronal injury in the hippocampus of depressed rats. Fascinatingly, up-regulating miR-320-3p and silencing NEAT-1 improve behavioral phenotypes, suppress apoptosis, and attenuate neuronal anomalies in the hippocampus (181). This study enlightens the binding relation b/w miR-320-3p and NEAT-1 and the targeting relation b/w CRHR1 and miR-320-3p. The implications of miRNAs in depression, along with their targets, have been summarized in Table 5.

Migraine

Migraine is one of the extremely persistent neurological conditions, and its one-year prevalence in Western Europe and the United States is 6% in males and 15 to 18% in females (11% average). According to the World Health Organization (WHO), it is listed as the 6th leading cause of death because of its heavy social and economic burdens (182). It is awfully disabling for the suffering individuals because of high-intensity pain and the characteristics of linked symptoms during attacks, such as vomiting, nausea, photophobia, and phonophobia. The quality of life is more disturbed in the case of migraine with aura, happening in

Table 5. Implications of miRNA in depression

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	miR-200a/b-3p	NR3C1	↑Anxiety and neuronal apoptosis	Rat depression model	(153)
	miR-382-5p	NR3C1	↑Anxiety and neuronal apoptosis	Rat depression model	(154)
	miR-139-5p	NR3C1	↑Neuronal apoptosis	Mice depression model, HT22 cells	(155)
	miR-182 and miR-382	BDNF	Aggravate depression-like behavior	Post-stroke depression rat model	(156)
	MiR-202-3p	BDNF	Aggravate depression-like behavior	SK-N-MC and SH-SY5Y cells	(157)
	miR-345-5p	SOCS-1	↑Neuroinflammation	BV-2 microglial cells	(159)
	miR-497a-5p	HECTD1	↑Neuroinflammation and neuronal apoptosis	BV2 and HT22 cells	(164)
	miR-133b	CTGF	↓Neuroinflammation and neuronal apoptosis	Rat depression model	(169)
Disease-modifying role	miR-211-5p	ASK1/Dyrk1A/JNK	↓Neuronal apoptosis	Rat depression model	(170)
	miR-204-5p	RGS-12	↓Neuroinflammation and oxidative stress	Rat depression model	(171)
	miR-26a-3p	PI3K/Akt/ PTEN	↓Neuronal damage	Rat depression model	(172)
	MiR-29a-5p	TMEM33	↓Neuroinflammation and neuronal apoptosis	CUM mice model	(174)
	MiR-15a-5p	CXCL10	↓Neuroinflammation and neuronal apoptosis	CUM mice model	(178)
	miR-16-5p	MYB	↓Apoptosis and neuronal injury	CORT mice model. PC12 cells	(179)
	miR-320-3p	CRHR1	↓Neuronal damage	Rat depression model	(181)

approximately 1/3rd of individuals, where pain is generally accompanied or preceded by a transient focal neurological symptom, recurrently involving paresthesia, language, or visual disturbance. At present, there is still a dearth of existing clinical markers for migraine, and their diagnosis is strictly dependent on the clinical symptoms, which brings substantial difficulties for clinical diagnosis (182). Indeed, patients with migraine are 2-fold more prone to ischemic stroke risk, and this risk can also be elevated by the enhancement in attack frequency, with young people and women being typically affected. Despite progress in recent years, the complete pathophysiology remains unclear, which directly reflects the limited availability of therapies and the frequent unsatisfactory medical reduction or control of symptoms (183). So, the enhanced interest has consequently been developed in researchers to hunt for the new biomarkers that could not only be helpful in early diagnosis of disease but also provide the sufferers with different therapeutic options. On the basis of this, altered miRNA expression levels in migraine patients have also been hypothesized, although insufficient preliminary work has so far been done in this respect.

Disease-promoting role in migraine

Endothelial dysfunction (ED) has been acknowledged in both patients with syncope and migraine patients. The ED is characterized by endothelial cell dysregulation, including abnormal proliferation, migration, and morphogenic capabilities. Patients with migraine have been documented with impaired function and reduced numbers of endothelial progenitor cells, as well as vascular dysfunction. Remarkably, the miRNAs have the capability to regulate the functions of vascular endothelium, and a study was also carried out to investigate the association of altered circulating levels of endothelial-specific miRNAs (miR-155, miR-21, Let-7g, and miR-126) with endothelial function in migraine sufferers. Surprisingly, the researchers found the elevated expression of miR-126, Let-7g, and miR-155. Moreover, the levels of miR-126 and miR-155 were connected with the syncope frequency in past years of migraine patients (184) miR-126, miR-21, and Let-7g. Microglia-pathic pain is thought to be stimulated by aberrant neuronal discharge by reactive microglial cells. They release pro-inflammatory factors to promote central sensitization, thereby inducing pain in chronic migraine (185, 186). MiR-155 acts as a pro-inflammatory factor during activation of microglia via down-regulating SIRT1 expression (regulates inflammation), resulting in hyperalgesia and central sensitization (187).

By considering the clinical characteristics and patient groups, a pilot study was carried out in order to identify the differential expression of circulating miRNA(s) in patients with migraine without aura (MWA) during pain-free periods. The outcomes of the study clearly demonstrated the differential expression of 4 miRNAs (miR-27b, miR-181a, miR-22, let-7b). The expression level of miR-181a, miR-22, and let-7b was down-regulated, whereas the level of miR-27b was found to be up-regulated in a significant manner. Moreover, miRNAs are not only the biomarkers for migraine in adults, but also in children with MWA. In order to confirm this, the expression level of hsa-miR-375 and hsa-miR-34a-5p was evaluated in both the saliva and serum of young subjects (4-17 years) with MWA having four attacks/month. Higher levels of both miRNAs were

found in serum as well as saliva, whereas the treatment with acetaminophen significantly alleviated their level (188). So, they can be useful biomarkers of migraine disease and also of the efficacy of drugs in patients suffering from MWA. So far, no data have been reported on the molecular targets of these miRNAs.

Neurogenic inflammation has been considered to be involved in the migraine pathogenesis, and lately, it has been reported that migraine with aura is linked with neuroinflammation and neuro-immune activation (189). An endogenous pro-inflammatory inhibitor of IL-1 β signaling is IL-10 receptor- α , which is negatively modulated by miR-382-5p, thus interfering with anti-inflammatory signaling (190). MiR-34a suppresses SIRT1 by elevating NF- κ B subunit p65, ultimately increasing the transcription of IL-1 β , TNF- α , and IL-6. GABA is predominantly an inhibitory neurotransmitter, which is also speculated to be the target of miR-34a (191).

Lack of insulin-like growth factor 1 (IGF1) causes a decrease in myelinated oligodendrocytes and axons, while its overexpression promotes the neural progenitors' proliferation and decreases apoptosis. It is well known that transient receptor potential cation channel subfamily V member 1 (TRPV1) is a key protein in NO₂-induced migraine, aggravating the NO₂-stimulated neurotoxicity in migraine (192). Mechanistically, NO₂ modulates the AKT/TRPV1 signaling pathway by decreasing levels of AKT phosphorylation and increasing the expression of TRPV1 protein. Moreover, NO₂ overexpresses miR-653-3p, which targets IGF1, thereby down-regulating its expression and contributing to the activation of inflammatory cells to release IL-1 β and TNF α (193). This data highlights the complexities of the etiology of migraine, underscoring the need for more research into preventive and control strategies.

Disease-modifying role in migraine

The ketogenic diet (KD) is well-recognized for the treatment of neurological diseases, including migraine, by reducing neuroinflammation. In a 6-week study, it was shown that biphasic KD could also influence circulating miRNAs associated with energy metabolism, with improvements in migraine conditions. It was found that the level of has-miR-660-3p and has-miR-590-5p was strongly influenced by KD, and it was concluded that KD could counteract the neuroinflammation in order to improve migraine pain (194). Collectively, these data highlight that the investigation of miRNA patterns in migraine could absolutely enhance the understanding of migraine pathogenesis and could open up the channels for better diagnosis, origin determination, associated comorbid conditions, dietary factors, and therapeutic treatments monitoring in migraine.

Indeed, one of the key factors involved in the pathogenesis of migraine is CALCA. Various clinical studies have revealed that the CALCA concentration in plasma was raised during both the non-episodes as well as episodes, signifying the existence of constant CALCA abnormality in patients with migraine. The expression of CALCA has also been found to be linked to the level of miR-30a. Its level was significantly decreased in migraine-suffering individuals, whereas its overexpression reduced the level of CALCA (195). Its overexpression can also inhibit the Akt/PI3K/mTOR pathway, resulting in pain relief and attenuated central sensitization (196, 197). The relationship b/w

cardiovascular risk (atherosclerotic lesions) and migraine is complicated and probably encompasses multiple aspects, but one of the promising pathophysiological connections lies in the ED.

To date, there remains a scarcity of data on the mechanism of action of certain miRNAs in migraine. Research should also focus on molecular targets of migraine-associated miRNAs to find novel strategies for the treatment of migraine. The implications of miRNAs in migraine, along with their targets, have been summarized in Table 6.

Conclusion

miRNAs are small (about 22 nucleotides) non-coding RNA molecules that play a significant role in regulating gene expression. To date, about 3 thousand miRNAs have been reported in the genomes of mammals, and more than 2000 of them belong to the human genome. Interestingly, a single miRNA may have the capability of repressing the expression of hundreds of targeted genes. They elicit their function by binding directly with the 3' untranslated region (UTR) of the targeted mRNA, which ultimately suppresses the protein expression as well as promotes the degradation of that particular mRNA. The miRNAs regulate several physiological as well as pathological processes, thus implicated in both health and disease. The diversity of miRNAs is involved in multifaceted cellular activities, which include apoptosis, cellular proliferation, cell differentiation, renewal of stem cells, metabolism, embryonic development, etc. In addition, they might have the capability to regulate almost 60% protein encoding genes. Under the pathological conditions and/or cellular stress, the cells underwent a condition of alleviated translation and transcription. During these circumstances, the miRNA offers a rapid, potent, and effective source of gene regulation that could allow the cells to recover or become adapted to the abnormal state.

This review highlights the several physiological and pathological pathways being regulated by a plethora of miRNAs in the most common brain disorders globally. This comprehensive overview of the prediction of miRNAs functions might be helpful in providing more efficient insight for the modulation of brain disorders related factors. Though various molecular pathways have been involved in brain diseases, neuroinflammation and apoptotic pathways are most often being studied in miRNA-based research lately. Following brain insults, neuroinflammation plays a significant role as a secondary injury process, exerting either

beneficial or detrimental effects. It is a common mechanism connecting the ischemic, traumatic, epileptic, psychiatric, demyelinating, and degenerative pathologies. In addition to neuroinflammation, microglia and astrocyte activation, mitochondrial dysfunction, neuronal apoptosis, and oxidative stress are the main pathological hallmarks in brain disorders, resulting in cognitive impairment and neuronal loss. For instance, Overexpression of miR-21-3p has been reported be associated with BBB damage aggravation after TBI by promoting inflammation and cellular apoptosis. MiR-132-3p overexpression in PD aggravates the activation of microglial cells and ultimately prompts the secretion of cytokines. The miR-30c-5p directly targets a gene related to autophagy, resulting in dopaminergic neuronal loss, aggravating motor functions, increased apoptosis, oxidative stress, and so on.

It should be noteworthy that extensive work is required to investigate both the therapeutic role and pathological mechanisms for migraine. There is also a scarcity of data regarding molecular targeted pathways of several reported miRNAs that are found up-regulated following disease development. For example, up-regulation of a few miRNAs, including miR-183-5p, miR-382-3p, miR-493-3p, miR-202-3p, and miR-3573-5p, has been reported following depression. Marked reduction of miR-29 and hsa-mir144-3p has been associated with cognitive impairment and coagulation process, respectively, in PD patients, but the associated molecular mechanisms need to be unraveled.

In a nutshell, mounting evidence has provided compelling support for the involvement of multiple miRNAs in health and disease. Hence, the current findings offer a foundation to develop novel miRNA-targeted strategies for the prevention and treatment of NDDs and neuropsychiatric disorders, including AD, PD, epilepsy, depression, migraine, and TBI. Although this review did not cover schizophrenia in detail, it is important to note that miRNAs also play a significant role in this disorder, representing a promising avenue for future investigation.

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Table 6. Six implications of miRNA in migraine

	MicroRNA	Target	Outcomes	Study model	Reference
	miR-155, miR-21, Let-7g, miR-126	-	↑Syncope frequency	Mice migraine model	(184)
Disease-promoting role	MiR-155	SIRT1	↑Neuroinflammation, hyperalgesia	Migraine patients	(187)
	MiR-34a	SIRT1, GABA	↑Neuroinflammation	Migraine patients	(191)
	MiR-653-3p	IGF1	↑Neuroinflammation and neuronal damage	NO ₂ -induced migraine rat model, bilateral trigeminal ganglion culture	(193)
Disease-modifying role	has-miR-660-3p and has-miR-590-5p	-	↓Neuroinflammation	Migraine patients	(194)
	miR-30a	CALCA	Promote pain relief	Migraine patients	(195)

preparation of this review article.

Authors' Contributions

N A designed, prepared, and approved the publication version. G H and Q A revised the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration

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