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REVIEW ARTICLE

MicroRNAs: Key Players in Microglia and Astrocyte Mediated Inflammation in CNS Pathologies

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Abstract: The significance of microglia and astrocytes in neural development, in maintaining synaptic connections and homeostasis in the healthy brain is well established. Microglia are dynamic immune cells of the brain that elicit an immune response during brain damage and also participate in tissue repair and regeneration, while astrocytes contribute to the local inflammatory response by producing proinflammatory cytokines and resolving neuronal damage through production of anti-inflammatory cytokines and neurotrophic factors. Recent efforts have focused on elucidating the epigenetic mechanisms which regulate glial cell behavior in normal and pathologic states. An important class of epigenetic regulators is microRNAs (miRNAs) which are small non-coding RNA molecules that regulate gene expression post-transcriptionally. Certain dysregulated miRNAs contribute to chronic microglial inflammation in the brain, thereby leading to progression of neurological diseases like Alzheimer's disease, traumatic injury, amyotrophic lateral sclerosis and stroke. Further, several miRNAs are differentially expressed in astrocytes after ischemia and spinal cord injury. Despite knowledge about miRNAs in neuroinflammation, little is known about effective delivery routes and pharmacokinetic data for miRNA based therapeutics. This review summarizes the current research on the role of miRNAs in promoting and inhibiting inflammatory response of microglia and astrocytes in a disease-specific manner. In addition, miRNA delivery as a therapeutic strategy to treat neuroinflammation is discussed.

Keywords: Neuroinflammation, microglia, astrocytes, microRNAs, CNS pathologies, neurodegenerative disorders.

INTRODUCTION

Microglia and astrocytes are the predominant glial cells of the central nervous system (CNS) that perform seminal roles in the healthy brain and during CNS pathologies [1-3]. Ramified microglia in the adult brain are dynamic cells that constantly survey the brain parenchyma by extending and retracting their ramifications and are activated during injury and insult [4]. Further, microglia are involved in pruning excessive synapses during brain development [2], and participating in postnatal synaptic remodeling in adulthood [5]. Astrocytes display complex structural and physiological functions, providing metabolic support to neuronal cells and structural stability to the blood brain barrier (BBB). They also respond to neuronal signaling by changes in their internal calcium ion concentrations [6]. Along with neurons, microglia and astrocytes are postulated to form the quad partite synapse, thus actively engaging in information processing [7]. In addition, there exists crosstalk between astrocytes and microglia through secretion of several cytokines and growth factors such as Transforming Growth Factor-beta (TGF-β) [8] and Tumor Necrosis Factor-α (TNF-α) [9], chemokine ligand-receptor interactions [10], complement factor activation [11] and release of neurotransmitters, *i.e.,* adenosine triphosphate (ATP) [12]. Thus, in the healthy brain, astrocytes and microglia actively interact

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with each other and with neurons to maintain brain homeostasis.

During CNS pathologies, microglia and astrocytes elicit an inflammatory response which involves the release of proinflammatory cytokines and chemokines, as well as growth factors that aid in tissue regeneration and repair [13, 14]. Upon stimulation in pathological conditions, microglia are activated; they become hypertrophic, migrate to the site of injury, release a number of proinflammatory cytokines, chemokines, cytotoxic molecules such as nitric oxide (NO) and reactive oxygen species (ROS), and also express major histocompatibility complex (MHC) and costimulatory receptors on their cell surface [15]. Activated microglia are also capable of phagocytosing dead or dying neurons thereby clearing neuronal debris. However, in a number of CNS pathologies, including neurodegenerative diseases and injury, microglia are seen to be chronically activated, exacerbating inflammatory response that contributes to tissue damage and disease progression [16, 17]. In addition, chronic activation of microglia results in an excessive release of proinflammatory cytokines such as TNF-α, Interleukin-1β (IL-1β), Interleukin-6 (IL-6), ROS and NO, thereby worsening neuronal cell death [18].

The hallmark of astrocytic response to CNS injury is astrogliosis which involves rapid proliferation at the site of neuronal injury, and major cellular and morphological changes, that include hypertrophy of cells and increased expression of the intermediate filament Glial Fibrillary Acidic Protein (GFAP) [13]. During chronic inflammation, the proliferating astrocytes surround the site of injury or lesion or the amyloid beta (Aβ) plaques in the case of Alzheimers' Disease (AD) brain, forming an astroglial scar, which isolates the damaged tissue from the healthy tissue and preventing the spread of neuroinflammation to healthy region [19]. On the other hand, chronic astrogliosis appears to be detrimental as it has been found to inhibit neuronal regeneration [20-22]. Taken together, reactive astrocytes and activated microglia are first responders to insult or injury in the CNS and prolonged activation can contribute to substantial neuronal damage by negating the tissue reparative processes during recovery in CNS pathologies. Hence there is an immediate need to understand the mechanisms involved in glia-mediated inflammation towards developing potential therapies to treat neurodegenerative diseases.

The activation of glial cells in neuropathological conditions involves epigenetic mechanisms. The major epigenetic events include modifications of histone proteins, such as methylation and acetylation, DNA methylation, and regulation of small non-coding RNAs that modulate expression of genes. MicroRNAs (miRNAs) have recently emerged as important epigenetic modulators of gene expression and there is much evidence to suggest that miRNAs are involved in inflammatory and immune processes in neuropathogenesis. MiRNAs regulates gene expression by binding to the 3' untranslated region (UTR) of target mRNA sequences, thereby promoting mRNA degradation or preventing protein translation [23]. The seed region of miRNAs, a sequence of 7-8 nucleotides, show affinity for hundreds of mRNA sequences and likewise, the 3'UTR of an mRNA may be targeted by more than one miRNA. Another striking feature of how miRNA exert their functions is that one miRNA may target signaling molecules at different levels of the same signaling cascade [24].

MiRNAs serve an important role in regulating gene expression in the healthy brain. Surveying or "resting" microglia express receptors that respond to neurotransmitters like Glutamate and ATP and show lowered expression of antigen presentation molecules as compared to activated microglia found during pathology [25]. This surveying state of microglia in the healthy brain is attributed to a miRNA, miR-124 which targets CCAAT enhancer-binding proteins (C/EBP-α) and PU.1 that regulates expression of genes involved in microglial activation [26]. Further to its role in mediating the functions of ramified microglia, miR-124 controls fate specification of neural stem cells into astrocytes and neurons by regulating levels of a histone methyltransferase, *Ezh2* [27], emphasizing its role in glial development and functions. In addition to diverse roles of miRNAs in the brain, spatial difference in miRNA expression in human astrocytes, specifically, a higher expression of pro-inflammatory miRNAs was observed in white matter astrocytes as compared to grey matter [28], which is crucial to understanding astrogliosis associated with pathologies such as stroke, traumatic injury and tumors. Astrocyte-specific deletion of *Dicer-1*, the endoribonuclease required for the processing of mature miRNA transcripts, resulted in neurological decline and premature death of the mutant mice. This was ascribed to an immature/reactive-like state of astrocytes with impaired functions leading to death of cerebellar Purkinje neurons [29]. Further studies show that astrocyte specific deletion of *Dicer* resulted in decreased number of spinal cord white matter astrocytes, without affecting the progenitor pool of cells, underlining the importance of miRNA biogenesis in development and maturation of astrocytes [30].

Given that miRNAs fine tune gene expression during various cellular processes in a healthy brain, miRNAs involvement in causing dysregulated gene expression has been observed in various CNS pathologies. This review discusses in detail the dysregulated miRNAs in microglia and astrocytes (Fig. **1**) in different CNS pathologies and how they contribute to disease maintenance and progression. The roles of specific miRNAs in mediating astrocyte and microglia inflammatory signaling cascades are summarized. Finally, the prospect of miRNAs as therapeutic agents and possible means for miRNA delivery to the brain is evaluated.

MiRNAs IN CNS PATHOLOGY

Viral and Prion Infection

During insult and injury in the brain, several signaling pathways are activated in microglia and astrocytes, contributing to a state of inflammatory response. For instance, Human Immunodeficiency Virus (HIV) infection is accompanied by infected macrophages carrying viral particles into the CNS through the blood brain barrier (BBB), where viral regulatory proteins like HIV-Tat are released into the brain parenchyma [31, 32]. During the HIV infection, activated microglia participate in production of ROS through membrane-associated NADPH oxidases (NOX) which leads to neuroinflammation. HIV-Tat treatment in microglial cells increased the intracellular ROS generation by modulating the expression levels of miR-17, *NOX-2* and *NOX-4*, leading to neuroinflammation [33]. Furthermore, miR-32 is seen to be upregulated in microglial cells in response to HIV-Tat proteins with a concomitant decrease in cellular TNF Receptor Associated Factor-3 (TRAF-3) levels, a key signaling mediator involved in suppression of immune functions mediated by the Interferon Regulatory Factors (IRF) IRF3 and IRF7 [34]. Significantly, HIV-Tat proteins have been shown to inhibit a subset of miRNAs including miR-181 and let-7i that regulate the Wnt-β catenin signaling pathway in astrocytes [35], signifying an RNA interference mechanism by which HIV-Tat proteins induce neuroinflammation [36]. Additionally, during a prion infection, miR-146a is upregulated in activated microglia and involved in regulating microglial morphology and phagocytic response by suppressing Nuclear Factor-kB (NFkB) and Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway [37, 38]. The Japanese Encephalitis Virus (JEV) infection in humans induces neuroinflammation, resulting in long-term neurologic and psychiatric complications as well as motor dysfunction [39]. MiR-15b and miR-19b-3p positively regulate glial cell-mediated neuroinflammation in the JEV by suppressing Ring Finger Protein-125 (RNF-125) and RNF-11, respectively, thereby enhancing production of inflammatory cytokines [40, 41]. In

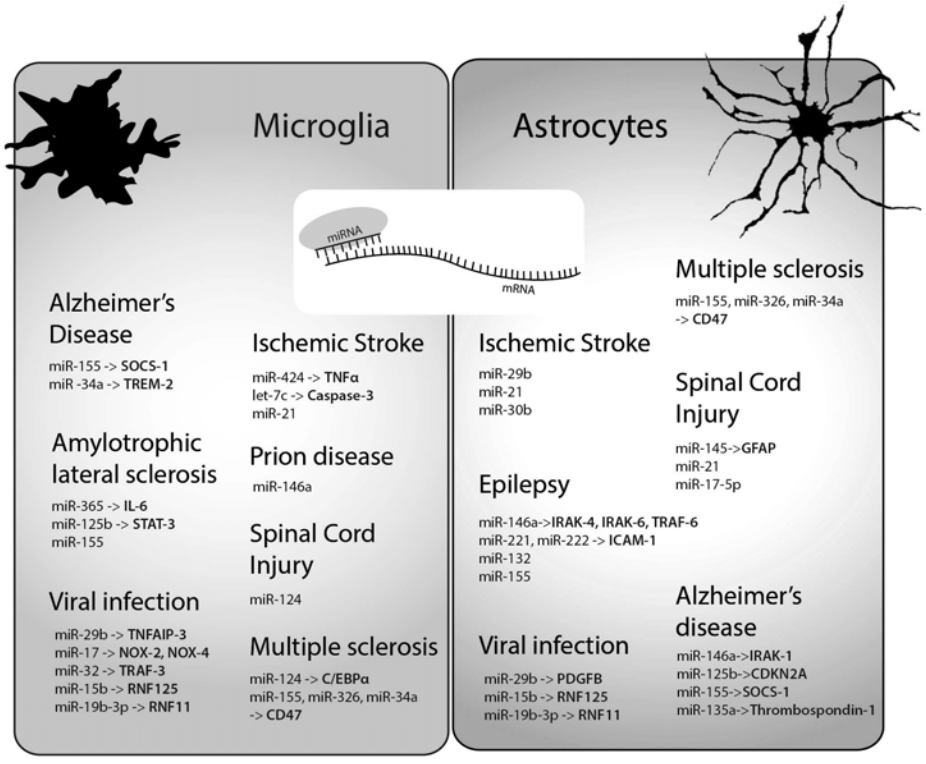

Fig. (1). MiRNAs involved in microglia- and astrocyte-mediated neuroinflammation in various CNS pathologies.

JEV infection, the proinflammatory miRNA-29b is seen to promote microglial activation by targeting tumor necrosis factor alpha-induced protein 3 (TNFAIP-3), a negative regulator of NFkB signaling pathway [42]. Thus, these studies [43] have identified potential candidate miRNAs that can be inhibited to mitigate JEV induced- neuroinflammation, thereby attenuating the infection-induced neurological sequelae.

Alzheimers' Disease

AD is a well characterized neurodegenerative disease that is associated with memory loss and behavioral changes. Classified within the spectrum of dementia, the main pathological feature of AD is the presence of extracellular Aβ plaques and intracellular Tau protein aggregates in neurons [44]. AD is accompanied by loss of synapses and death of neurons, with a chronic inflammatory response of microglia and astrocytes [45]. Numerous studies have evaluated the miRNA profiles of brain tissue [46, 47], blood monocytes and macrophages [48] and body fluids such as cerebrospinal fluid (CSF) and blood [49, 50], underlining a crucial role of dysregulated miRNAs in the progression of the AD [51-53]. Certain miRNAs that regulate immune responses such as miR-146a, miR-155, miR-125a and miR-9 show altered expression, suggesting that disruptions in miRNA expression result in chronic activation of glial cell during AD pathogenesis [54]. Upon exposure to Aβ peptides, glial cell-mediated immune responses in the brain occur through inflammatory signaling cascades such as NFkB and JAK-STAT signaling by activation of the Toll-Like Receptors-4 and -6 (TLRs) [55, 56]. Studies involving Aβ-treated microglia and astrocytes indicate that a prolonged expression of proinflammatory cytokines is supported by increased levels of miR-155 in microglia and astrocytes, through targeting Suppressor of Cytokine Signaling-1 (SOCS-1), a negative regulator of inflammatory gene response [57].

One of the striking features of AD pathology is the aggregation of Aβ plaques in the brain parenchyma as a result of defective phagocytosis by microglia [58]. The proinflammatory miRNA-34a, which is an NF-kB-regulated transcript is found to be significantly increased in activated microglia and its increased levels downregulate its target *Trem-2*, an innate immune receptor involved in phagocytosis, subsequently leading to impaired phagocytosis and Aβ accumulation as observed in AD [59]. Impaired phagocytosis and an exaggerated inflammatory response by microglia in AD is also attributed to decreased levels of presenilin, a catalytic component of the γ-secretase complex that is responsible for Aβ peptide processing [60]. Studies indicate that microglia from presenilin knock-out mice show decreased expression level of miR-146a and increased expression levels of interleukin-1 receptor-associated kinase-1 (IRAK-1) and increased NFκB transcriptional activity. This provides evidence that presenilin epigenetically regulates proinflammatory function of microglia in AD brains through modulation of miR-146a [61].

Astrogliosis as a result of exposure to Aβ plaques during AD progression includes proliferation and hypertrophy of astrocytes, expression of chemokines and cytokines, increased glial GFAP expression and cytoskeletal rearrangement [62]. Increased GFAP and decreased cyclin-dependent kinase (CDK2N) are found to be correlated with high levels of miR-125b in AD brains. Moreover, inhibiting miR-125b decreased astroglial proliferation, supporting the possibility of targeting miR-125b as a therapeutic strategy [63]. In human astrocytes exposed to Aβ, increased levels of miR-146a was reported, coupled with decreased levels of *IRAK-1* levels and increased *IRAK-2* levels, both genes being important mediators of the inflammatory TLR signaling [64, 65]. This confirms that AD progression is characterized by distinct events of neuroinflammation involving dysregulated expression of miRNAs in glial cells. Targeting such events might be identified as a potential therapeutic strategy to treat AD progression.

Epilepsy

Epilepsy is a neurological condition characterized by recurrent spontaneous seizures that occur due to hyperexcitability and hypersynchrony of neurons in the brain [66]. Recent studies implicate glia in the pathophysiology of epilepsy and suggest a direct relationship between dysfunctional glia and epileptogenesis [67]. Epilepsy is associated with chronic accumulation, activation and proliferation of astrocytes and microglia promoting hyperexcitability of neurons. In recent years, epigenetic mechanisms that contribute to epileptogenesis have been widely reported. Several studies have assessed the miRNA profiles of animal models of epilepsy and a set of miRNAs such as miR-146a, miR-146b, miR-142 and miR-27a have been implicated in epileptogenesis [68-70]. In rat models of status epilepticus (SE), miR-146a is upregulated in reactive astrocytes which are in close proximity with dying neurons. It is postulated that miR-146a is involved in expression of proinflammatory cytokines by astrocytes during epileptogenesis by targeting members of the NFkB path-

way [71, 72]. Furthermore, the brain enriched miR-124 was found to exhibit pro- and anti-epileptogenic roles in SE, wherein it was found to regulate both neuronal signaling and microglial activation, thereby emphasizing the cell-type specific roles of miRNAs during disease development and progression [73-75]. Recently, a genome wide miRNA profile of human mesial temporal lobe epilepsy (mTLE) identified a number of deregulated miRNA such as miR-92b, miR-637, or miR-665 to be significantly mislocalized in the nucleus of astrocytes of mTLE brain samples compared with cytoplasmic expression in control samples, raising speculation that mislocalization of miRNAs are responsible for impaired regulation of molecular mechanisms in glial cells [76]. MiR-221 and miR-222 are found to be downregulated in astrocytes in mTLE samples corresponding to an increased expression of their target protein, intercellular adhesion molecule-1 (ICAM-1), which is involved in various aspects of inflammation [77]. The differential expression of miRNAs in mTLE tissue samples underscores the complex role of miRNAs in disease progression.

Spinal Cord Injury

Spinal cord injury (SCI) is caused by mechanical disruption of spinal cord tissue by external blunt force, causing neuronal damage and death, an event exacerbated by microglia- and astrocyte-mediated inflammatory response [78, 79]. A number of miRNAs have been implicated in influencing glial cell behavior post traumatic injury. Astrogliosis at the site of SCI involves the increased proliferation and hypertrophy of astrocytes, resulting in the formation of a glial scar that has both beneficial and detrimental effects [80]. The hypertrophic astrocytes show upregulation of GFAP expression and reduced levels of miR-145 which is predicted to target *Gfap* [81]. Furthermore, miR-21 is found to be upregulated in astrocytes during astrogliosis post SCI. Inhibition of miR-21 is found to enhance axonal regeneration by attenuating hypertrophy and glial scar progression, thereby identifying miR-21 as a therapeutic target for mitigating astrogliosis during brain injury [82].

Recent studies show that the miRNA function is vital to injury-induced proliferation of astrocytes. It is reported that conditional deletion of *Dicer-1* gene, which is essential for mature miRNA generation, impairs activation and proliferation of astrocytes during injury. Moreover, overexpression of miR-17-5p in *Dicer-1*-null astrocytes rescues the *Dicer-1* deletion-induced inhibition of astrocytic proliferation during SCI [83]. This study underlined the importance of the miRNA processing machinery in regulating key cellular processes such as astroglial proliferation during neuroinflammation.

Ischemic Stroke

Stroke is a cerebrovascular infarction caused by loss of oxygenated blood to the brain tissue [84]. Stroke can be of two types: ischemic (due to lack of blood supply) and hemorrhagic (due to vascular bleeding) [85]. Ischemic stroke leads to rapid neuronal cell damage and death, resulting in an inflammatory response by microglia and astrocytes that proliferate and invade the penumbra zone. Massive influx of activated microglia and hypertrophic astrocytes (reactive astrogliosis) is evident in the infarct zone after ischemic stroke.

Restoration of oxygenated blood supply to the ischemic tissue ironically causes additional neuronal damage by initiating an inflammatory response [86]. Inflammation that occurs post-ischemic stroke is both deleterious and beneficial, a feature that reflects the multifaceted response of glial cells in CNS pathology. In this context, some studies have shed light on miRNA changes in activated microglia and astrocytes upon reperfusion following an ischemic injury. Certain brain-specific and inflammation-specific miRNAs such as miR-146a and miR-21 are found to be differentially expressed in microglia after oxygen-glucose deprivation (OGD) conditioning [87]. Additionally, several miRNAs including miR-21, miR-29b and miR-30b are upregulated in astrocytes exposed to normoxic conditioning (reperfusion) after an *in vitro* model of stroke. It has been speculated that miR-29b plays a role in inducing apoptosis in neurons and astrocytes and this could be a new avenue for investigating cellular apoptosis machinery in ischemia [88]. Further, it has been shown that miR-21 promotes neurotoxicity by activating the TLR7 signaling pathway in neuropathogenesis [89]. In both astrocytes and microglia, miR-21 is significantly upregulated in *in vitro* studies of stroke possibly playing a role in neuroinflammation. This suggests that certain miRNAs have overlapping functions in both microglia and astrocytes during neuroinflammation in CNS pathology.

Some members of the let-7 miRNA family play critical roles in modulating microglial and astrocyte activation. The expression levels of let-7c-5p, a miRNA involved in promoting alternative activation of microglia, and miR-424 which inhibits microglial activation by arresting microglial proliferation and decreasing the secretion of proinflammatory cytokine,

TNF-α, are found to be downregulated in plasma samples of patients and mice after ischemic stroke [90-92]. After reperfusion in Middle Cerebral Artery Occlusion (MCAO) mouse models, overexpression of let-7c-5p suppressed neuroinflammation by decreasing expression of proinflammatory markers and apoptotic marker such as cleaved Caspase-3. Inhibition of let-7f after ischemic stroke conferred neuroprotection *in vivo via* increase in insulin like growth factor-1 (IGF-1) in microglial cells [93]. Moreover, differential expression levels of let-7f and its target, *IL-6* cytokine was discovered in the sera of ischemic stroke patients with and without hemorrhagic complications, implicating the role of let-7f in inflammation during massive cerebral infarction [94]. These studies highlight the varied roles of let-7 family in inflammation and stress the importance of understanding the roles of different miRNAs within a family in order to develop effective therapeutic strategies to counteract stroke pathology.

Multiple Sclerosis

Multiple sclerosis (MS) is a neurodegenerative disease involving demyelination of neurons, resulting in the formation of plaques that consist of astrocytes, microglia, peripheral macrophages and T-cells [95]. An inflammatory response mounted by microglia and astrocytes in response to demyelination is paradoxically both neuroprotective [96, 97] and neurotoxic [98]. One of the salient miRNAs involved in microglial activation during MS is miR-124. Intravenous administration of miR-124 decreased the disease progression by deactivating peripheral macrophages and restoring the "resting" state of microglia [26]. The crucial role of miR-124 in regulating microglial activation in several disease pathologies, thus, makes it an attractive target for neurotherapeutics. Furthermore, the pro-inflammatory response of astrocytes was diminished by miR-873 inhibition in experimental autoimmune encephalomyelitis (EAE) which is the commonly used mouse model for the MS [99]. The suppression of EAE progression upon miR-873 inhibition is promising and further studies may focus on the effect of miR-873 on microglial activation in the progression of MS. A comprehensive miRNA profiling of MS lesions has identified dysregulated miRNAs in astrocytes and immune cells and specifically, expression of several miRNAs such as miR-155, miR-326 and miR-34a were shown to regulate *CD47* [100], a crucial membrane receptor involved in the process of phagocytosis in MS [101]. The pro-inflammatory role of miR-155 was validated in EAE, wherein inhibition of miR-155 resulted in decreased T-helper cells [102] and reduced expression of pro-inflammatory cytokines in microglia and macrophages [103]. Other differentially expressed miRNAs in MS lesions include immune miRNAs-146a, -146b, -21and -142 and future studies could focus on understanding their roles in glial cell activation in MS and evaluate their potential in mitigating MS disease conditions.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a motor neuron degenerative disorder that results in progressive paralysis and death due to respiratory failure [104]. ALS pathology in the brain is characterized by reactive astrocytosis which is implicated in inefficient clearance of the excitotoxic neurotransmitter glutamate and impaired secretion of neurotrophic factors, along with microgliosis which contributes to neuroinflammation [105]. Recently, dysregulated miRNAs in microglia have been shown to modulate genes involved in neuroinflammation, contributing to neuroinflammatory diseases such as ALS. About 20% of familial ALS cases are shown to be caused by superoxide dismutase 1 (SOD1) mutations [106]. In mutated *SOD1* overexpressed transgenic mice which develop symptoms like ALS pathology, a number of immune related miRNAs such as miR-21, miR-155, let 7a/b and miR-146b are seen to be upregulated in microglia [107]. In addition, miR-365 and miR-125b directly target the IL-6/STAT3 pathway in ALS associated microglia, which was reported to enhance the proinflammatory state of microglia [107]. Interestingly, inhibition of miR-155 in ALS mice reduced the proinflammatory signaling response in microglia [108], and improved disease condition and survival of ALS mice significantly [109], thereby showing promise as a potential therapeutic target. These studies provide additional evidence to the role of these miRNAs in modulating microglial activation in different brain disorders.

Role of miRNAs in Regulating Inflammatory Gene Response in Glia

The first miRNAs to be linked to microglial activation was miR-155, which is induced upon lipopolysaccharide (LPS) challenge and is found to target *Socs-1*, a negative regulator of the inflammatory response, thus regulating microglial inflammatory response by increasing the secretion of proinflammatory cytokines and NO [110]. In Interferon-γ (IFNγ) challenged astrocytes, overexpression of IRF-3 transgene is found to downregulate miR-155, leading to a phenotypic switch from a proinflammatory state to an anti-inflammatory state [111]. More recently, miR-9 was seen to play a similar role in promoting proinflammatory response of

activated microglial cells by targeting the monocyte chemotactic protein-induced protein 1 (MCPIP1), an RNase that brings about degradation of *Il-1β* and *Il-6* mRNAs [112]. In addition, miR-200b has been identified as a novel inflammatory mediator in microglia by interfering with the cJun/MAP Kinase pathway, a signaling cascade that is crucial to the proinflammatory activation state of microglia [113]. These results form the basis of new therapeutic strategies for the treatment of microglia-mediated neuroinflammation using a panel of miRNA regulators.

Certain miRNAs play a role in resolving a state of neuroinflammation. Recently, miR-146a overexpression in microglial cells was shown to increase *Il-10* expression which is essential in resolving a proinflammatory state of activation [37]. In IL-1β treated astrocytes, miR-146a overexpression was found to downregulate inflammatory factors like IL-6 and COX-2 by directly targeting *IRAK-1* and *TRAF-6* genes, which are key regulatory components of the NFkB pathway. These studies indicate the induction of miR-146a as a negative-feedback regulator during glial cell activation [114].

Another widely studied miRNA in the context of inflammation in microglia and astrocytes is the miR-181 family of miRNAs [115, 116]. In astrocytes treated with LPS, miR-181 was found to be downregulated, leading to an increased production of proinflammatory cytokines such as IL-6, IL-1β and TNF-α. Similar to the role of miR-146a in activated microglia, overexpression of miR-181 led to an increase in IL-10, thereby, helping to resolve a proinflammatory state of activation [117]. In microglia, miR-181c appears to be neuroprotective as it has been shown to control the microglia-mediated neuroinflammation and apoptosis by targeting the proinflammatory cytokine, *Tnf-α* [118].

A number of diseases are associated with immune cells existing in varied state of alternative or classical activation. The functional distinctions of classical and alternative activation states have been established depending on the stimulus used *in vitro* for activation and have emerged as an important tool for studying glial cell activation in CNS disease progression. M1 (classical activation) phenotype is induced by proinflammatory factors like LPS and IFNγ [119-121] and is observed in chronic pathological conditions such as ischemic stroke and traumatic injury [122-124]. The tissue reparative functions of glial cells are carried out by M2 polarized cells, which are induced *in vitro* by multiple stimuli such as IL-13 and IL-4 [125, 126] and have been shown to enhance remyelination of neurons by promoting oligodendrocyte differentiation [96]. MiRNA profiling studies have determined certain miRNAs that are crucial for the M1-M2 phenotypic switch. In astrocytes challenged with LPS/IFNγ, miR-351 and miR-125b were identified to target the TNF-α signaling pathway by direct binding to the 3' UTR of *Tnf-α* during astrocyte activation [121]. In addition, miR-125b targets members of the STAT signaling pathway in ALS associated microglia and is known to regulate astrogliosis during AD progression, underlining its importance in regulating immune functions. In an attempt to map the miRNA profile of polarized microglia, murine microglia were exposed to LPS (classically activated) and IL-4 (alternatively activated). Low levels of miR-124 and miR-689 were associated with the classical activation of microglia while induction of miR-145 and miR-214 was associated with the alternative activated phenotype of microglia, shedding light on miRNA profiles in microglia during disease conditions displaying instances of microglial polarization [127].

In chronic neuropathic pain, an imbalance in the M1/M2 ratio of spinal microglia during hyperalgesia was found to be correlated to decreased levels of miR-124. Intrathecal injection of miR-124 mitigated persistent hyperalgesia by increasing expression of anti-inflammatory TGFβ in spinal microglia, suggesting that miR-124 is crucial in the M1-M2 polarization phenomenon [128]. In contrast to the M1/M2 functional states, macrophages within glioblastomas have been identified as unpolarized M0 phenotype, showing a distinctive molecular signature that supports glioma progression [129]. A number of miRNAs including miR-146, miR-125a-5p, miR-142 and miR-155 were found to be differentially expressed in glioblastoma infiltrating immune cells, thereby providing potential candidates for designing therapeutics for glioma therapy. These studies [129, 130] signal a shift in our understanding the role of immune cells within gliomas, as glioma infiltrating microglia were previously thought of as alternative activated cells [131-133]. The functional polarization states thereby serve as *in vitro* experimental paradigms to study neuroinflammation during CNS pathologies. These studies have identified several dysregulated miRNAs (Table **1**, Fig. **2**) underlying common inflammatory signaling pathways in activated microglia and astrocytes in different CNS pathologies.

MiRNAs as Diagnostic and Prognostic Markers

Currently, diagnosis of neuropathologies and monitoring their progression is hindered by the absence of

Table 1. Important miRNAs and their targets that are involved in regulating astrocyte and microglia mediated neuroinflammation during CNS pathology.

CNS Pathology	Cell Type	MicroRNA implicated	Targets (mRNA)	Role in inflammation	References
HIV infection	Microglia	miR-32 ↑	*TRAF-3*	Promotes proinflammatory response	[34]
	Microglia	miR-17 ↑	*NOX-2, NOX-4*	Results in increased intracellular ROS generation	[33]
	Astrocytes	miR-29b	*Pdgf-b*	Release of miRNA through exosomes subsequently taken up by neurons	[32]
Prion infection	Microglia	miR-146a↑	-	Suppresses NFkB and JAK-STAT signaling pathways	[37, 38]
JEV infection	Microglia	miR-29b ↑	*Tnfaip-3*	Promotes proinflammatory response	[42]
	Astrocytes and microglia	miR-15b and miR-19b-3p↑	*Rnf-125* and *Rnf-11*	Positively regulates of inflammatory signaling	[40, 41]
Alzheimer's Disease	Microglia and astrocytes	miR-155 ↑	*Socs-1*	Promotes production of proinflammatory cytokines	[57]
	Microglia	miR-34a ↑	*Trem-2*	Impairs phagocytosis of Aβ peptides	[59]
	Microglia from Presenilin KO mice	miR-146a ↓	*Irak-1*	Exaggerated NFkB response	[61]
	Astrocytes	miR-146a ↑	*IRAK-1*	Promotes proinflammatory response	[64]
	Astrocytes	miR-125b ↑	*Cdkn2a*	Promotes astrogliosis	[63]
	Astrocytes	miR-135a ↑	*Thrombospondin-1*	Suppresses angiogenic response	[54]
Epilepsy	Astrocytes	miR-146a ↑	*Irak-4, Irak-6, Traf-6*	Negatively regulates inflammatory response	[64, 71]
	Astrocytes	miR-221 miR-222 ↓	*ICAM-1*	-	[77]
Spinal Cord Injury	Astrocytes	miR-145↓	*Gfap*	Promotes proliferation and hypertrophy of astrocytes	[81]
	Astrocytes	miR-21 ↑	-	Suppresses beneficial response of astrocytes	[82]
	Astrocytes	miR-17-5p↑	-	Regulates astroglial proliferation	[83]
	Microglia	miR-124	-	Reduces microglial activation	[128]
Ischemic stroke	Astrocytes	miR-29b ↑	-	Possible role in regulation of apoptosis	[88]
	Astrocytes and microglia	miR-21↑	-	Possible role in inflammation induced apoptosis	[87]
	Microglia	let-7c in plasma samples ↓	*Casp-3*	Suppresses expression of pro-inflammatory molecules	[91]
	Microglia	miR-424 in plasma samples ↓	*Tnf-α*	Inhibits microglial activation	[92]
	Microglia	let-7f	*Igf-1*	Promotes expression of anti-inflammatory factor IGF-1	[93]
Multiple Sclerosis	Microglia	miR-124 ↓	*Cebp-α*	Suppresses microglial activation	[26]

(Table 1) contd….

CNS Pathology	Cell Type	MicroRNA implicated	Targets (mRNA)	Role in inflammation	References
	Microglia and astrocytes	miR-155, miR-326 and miR-34a ↑	*CD47*	Regulates glial cell mediated phagocytosis	[100]
	Microglia	miR-155 ↑	-	Promotes production of proinflammatory cytokines	[103]
Amyotrophic Lateral Sclerosis	Microglia	miR-125b and miR-365 ↑	*Stat-3* and *Il-6* respectively	Promotes microglial activation	[107]
	Microglia	miR-155 ↑	-	Promotes proinflammatory response	[108]

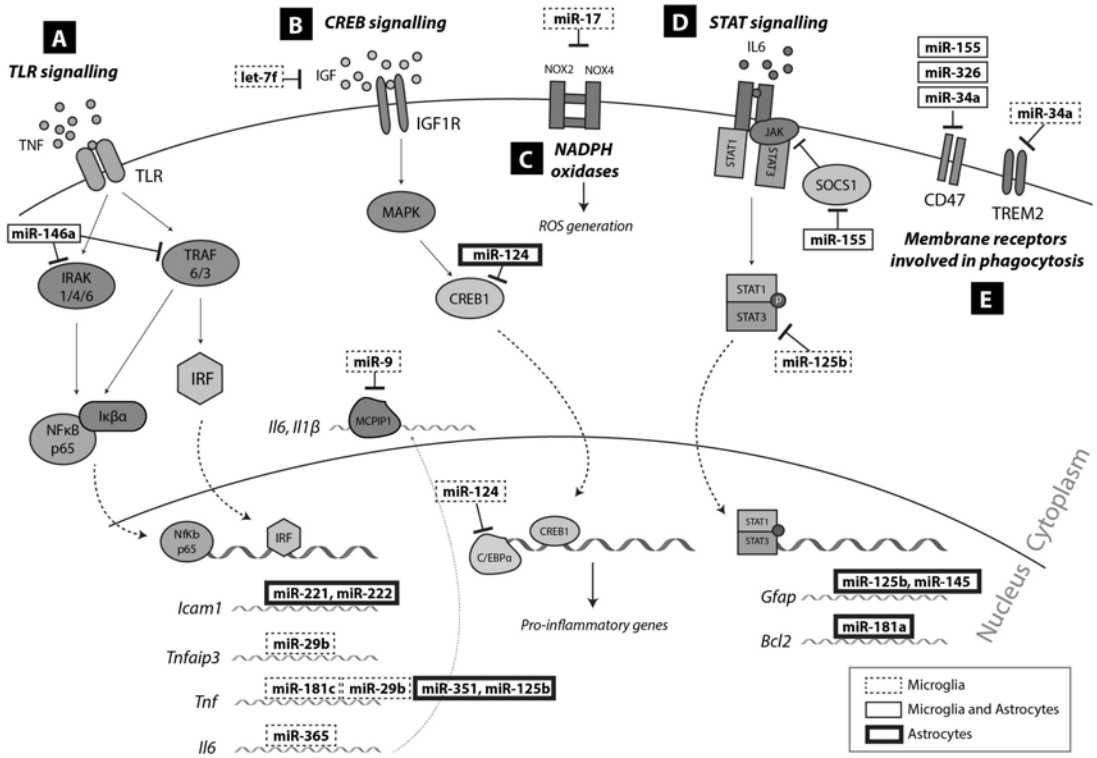

Fig. (2). The schematic diagram represents the key immune related miRNAs that target important genes in inflammatory signaling pathways. The cell type of the miRNA-mRNA pairing is designated by dashed box (microglia), thick box (astrocytes) and thin box outlines (both astrocytes and microglia). **[A]** The TLR receptors are activated by pro-inflammatory cytokines such as TNF-α and are mediated downstream by the IRAK and TRAF proteins, which are targeted by miR-146a. Transcription factors such as NFκB-p65 and IRF proteins are involved in the transcription of several pro-inflammatory signals that are regulated by miRNAs as represented in the figure. **[B]** The CREB1 and C/EPB-α transcription factors are regulated at the mRNA level by miR-124, which is vital for maintaining microglial homeostasis in the healthy brain. **[C]** ROS generation during neuroinflammation is mediated by transmembrane NADPH oxidases NOX-2 and NOX-4. **[D]** JAK-STAT signaling pathway is negatively regulated by SOCS-1, the mRNA of which is targeted by miR-155. Phosphorylated STAT proteins dimerize and translocated to the nucleus, wherein they transcribe genes such as *Gfap* and *Bcl-2*, which are targeted by miR-125b, miR-145 and miR-181a. **[E]** mRNA levels of membrane receptors *CD47* and *Trem-2*, essential components of phagocytic activity of glial cells are regulated by miRNAs like miR-34a and miR-155.

non-invasive diagnostic procedures. The discovery of exosome-mediated miRNA exchange between mammalian cells represents an intricate system of gene network regulation yet to be used for therapeutic advantage. The presence of miRNA exosomes in extracellular body fluids such as blood and CSF gives rise to the possibility of developing miRNA based biomarkers to track disease progression [134]. With the advent of

high throughput screening and next generation sequencing, extensive research has been focused on identifying robust miRNA candidates in brain tissue and body fluids that can be developed as biomarkers for diagnostic and prognostic value in CNS pathologies like AD [135-138], ischemic stroke [139-141], Huntington's disease [142, 143], neuropsychiatric ailments [144, 145], MS [146, 147], ALS [148, 149] and Parkinsons' Disease [150]. In CNS pathologies associated with significant neuroinflammation, certain immune-related miRNAs have been observed in blood serum, plasma and CSF of patients and animal models of disease. The let-7 family of miRNAs has been shown to mediate crucial aspects of glial cell activation in different pathologies including stroke, and brain injury and its expression levels have been documented in circulating body fluids such as plasma, CSF and blood. Given the therapeutic efficiency of let-7 in animal models of stroke [93, 94, 151], further studies are required to understand its role in microglial and astrocyte activation during traumatic brain injury [152]. Furthermore, the miR-124 has emerged as a critical brain-enriched miRNA that plays important roles in neuronal physiology during stroke, traumatic injury and AD and regulates inflammatory signaling pathways in activated microglia and astrocytes. In addition, this miRNA has been observed in patient serum and plasma in brain injury, MS and stroke and thus, may serve as a potential biomarker to evaluate disease progression. MiR-146a is upregulated in activated glial cells [153, 154] and differential levels of miR-146a have been documented in the plasma and CSF of AD patients [155, 156]. Recent studies have established that miRNA profiles accurately differentiate tumors of different origins and predict neoplastic changes within tumors, thereby serving as diagnostic and predictive markers for cancer [157, 158]. The miRNA expression profile of CSF samples from glioblastoma multiforme patients revealed the increased expression levels of miR-10b, miR-200b and miR-21 as compared to control subjects, highlighting a miRNA signature that can be used to distinguish between different brain tumors [159]. However, such results must be treated with caution as there are number of challenges associated with miRNA based biomarker discovery. For example, miR-523-3p found in the CSF of stroke patients is completely absent in the blood of patients and in control subjects [140]. It is likely that altered miRNA expression in the CSF during CNS disease progression may not represent the glial and neuronal miRNA expression levels always. It has also been suggested that efforts to identify miRNAs as biomarkers may be confounded by variables such as blood contamination in the CSF which could influence the expression of miRNAs [160]. Furthermore, there is increasing evidence that miRNA profiles vary between different racial populations, complicating the process of biomarker development. There is a pressing need for studies with larger cohorts that span multi-racial populations to identify miRNA biomarker for CNS pathology.

Developing miRNA Based Therapeutics to Treat Neuroinflammation

The possibility of treating neurological disorders with miRNA based strategies is an exciting avenue. Modulation of miRNA levels *in vitro* has been achieved by miRNA antagonists which inhibit endogenous miRNAs, and miRNA mimics which reintroduce or overexpress specific miRNA [161]. Currently, miRNA inhibition is possible by chemically modified oligonucleotide sequences that pair with the mature miRNA and prevent binding to the target gene. MiRNA "sponges" or "erasers" have been developed to scavenge the miRNAs continuously in cell cultures. MiRNA sponges, containing multiple complementary binding sites to a miRNA of interest are transfected into cells, and behave as competitive inhibitors of the endogenous miRNA within the cell [162]. On the other hand, miRNA mimics or overexpression vectors are used to rescue expression levels of repressed endogenous miRNA within the cell. Effective viral based vectors have been developed for a robust and continued expression of miRNAs and the use of tissue specific promoters allow for greater specificity of the miRNA mimic vector [163, 164]. Such transgenic methods have become potential tools to examine the miRNA functions in various cell types and may also be developed as therapeutic agents in the future. A similar miRNA replacement therapy involving the use of mimics of tumor suppressor miRNAs have already been demonstrated in treatment of lung and liver cancer lending promise to the therapeutic efficacy of this technology [165-167].

In order to effectively use miRNAs as therapeutics, several chemical modifications (Fig. **3**) have been developed to enhance stability and half-life of the miRNA *in vivo*. As a potential drug, salient features such as biodistribution and pharmacokinetic properties are improved by chemical modifications to miRNA molecule. Chemical modifications may also improve potency of the miRNA-mRNA binding by increased loading of the miRNA into the miRNA-induced silencing complex. The most commonly used modification is Locked-Nucleic-Acid (LNA) modi-

Nucleic-Acid (LNA) modification wherein a 2' 4' Methylene bridge is added across the ribose group that provides greater durability against nucleases [168]. Other modifications that alter the ribose group include the 2'-O-Methyl (2' OMe) modification that shows lesser resistance to serum nucleases [169]. Both LNA and 2'-O-Methyl modified anti-miR-21 showed effective inhibition of miR-21 in glioblastoma cells leading to induction of apoptotic signaling [170]. The phosphorothioate or phosphodiester linkage increases stability against serum exonucleases while the 2'-Fluoro and the 2'-O-methyoxyethyl are other modifications that offer enhanced stability for *in vivo* [171, 172].

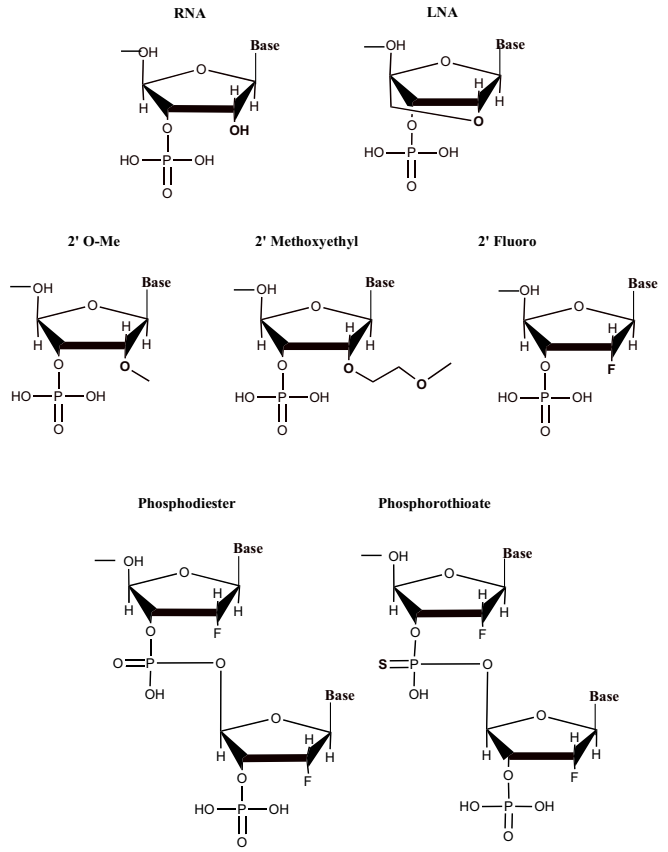

Fig. (3). Modifications to the nucleic acid backbone to enhance stability include the Locked Nucleic Acid (LNA) structure and presence of a Methyl group (2'-OMe), Methyoxyethyl (2' Methyoxyethyl) and fluoro (2' Fluoro) modification at the 2' position of the ribose moiety. Sulphur substitution of the oxygen atom in the phosphate linkage gives rise to the Phosphorothioate modification.

For the last 10 years, miRNAs have been established as important regulators in various human diseases and miRNA based therapeutics have entered preclinical and clinical trials [173]. Considerable developments have been made in determining the roles of miRNAs in regulating inflammatory signaling cascades in astrocytes and microglia. However, miRNA based therapy for neuropathology has not been well established despite significant advancements in understanding the miRNA roles in neuroinflammation. A number of hurdles are associated with administering miRNA therapeutics to the brain. Intracerebral infusions of miRNA therapeutics are highly invasive procedures wherein the risks outweigh the benefits. The presence of a vascular barrier such as the BBB complicates the process of delivery as it restricts the entry of therapeutic molecules. Several studies currently focus on developing synthetic agents for miRNA delivery to the brain. Polymer based routes of delivery to the brain depend on ionic interactions between the cationic polymer and the anionic backbone of the RNA strand which aid in the endocytosis of the complex into the cell [174]. In this context, cationic polymer polyethylenimines (PEI) are well characterized delivery vehicles that are endocytosed within the cell and release DNA or RNAi molecules to regulate gene expression [175]. Recently, miR-124a was successfully administered to the brain using modified PEI nanocarriers [176].

Dendrimers are a type of synthetic polymers with a well-defined architecture [177]. Poly (amidoamine) (PAMAM) dendrimers used to administer miR-21 and 5-fluorouracil to glioblastoma cells, dramatically induced apoptosis and inhibited migration of glioma cells, indicating dendrimer based miRNA delivery as a viable delivery system [178]. In rodent models, intracerebroventricular infusion of antagomirs and mimics were carried out to modulate miRNA levels in astrocytes and microglia [93, 179]. In a mouse orthotopic xenograft model of neuroblastoma, silver nanoparticles conjugated to GD2 (cell surface antigen disialoganglioside) antibody targeted the pro-apoptotic miR-34a in the tumor, bringing about reduced tumor growth and increased apoptosis [180]. It is acknowledged that absence of cell specific delivery vehicles would mean that the miRNAs are taken up by more than one cell type and may lead to off target effects. Moreover, most of these *in vivo* studies fail to address critical questions regarding bioavailability of the miRNA and pharmacokinetic data regarding half-life of the miRNA complexes within the body. To study therapeutic efficiency of a miRNA in the brain, a number of studies utilize intracerebroventricular injections of miRNA mimics or inhibitors. However, such routes of delivery are highly invasive and given the delicate nature of the brain tissue, other routes like intranasal and intravenous injections must be explored for miRNA delivery to the brain.

Table 2. Summary of miRNAs used as therapeutic targets through different routes of delivery in animal models of CNS pathologies.

MiRNAs deregulated	Disease	*In vivo* model	Route of delivery	Target (mRNA)	Expression in body fluids
miR-155	stroke	distal MCAO	Intravenous injection [182]	*Rheb*	-
	MS	EAE	Tail vein injection- nanoparticle delivery system [102]		Sera
	ALS	$SOD1^{G93A}$ Transgenic mice	Intraventricular osmotic pumps- inhibitors with phosphorothioate backbone and alternating 2′-MOE and 2′fluoro sugar modifications [109]	*Ship1*	-
let-7f	stroke	MCAO	Intracerebroventricular injection- LNA modified antagomirs [93]	*Igf-1*	serum and CSF [151]
let-7c	stroke	MCAO	Intracerebroventricular injection [91]	*Caspase-3*	Blood
miR-124	stroke	MCAO	Intracerebroventricular injection		Plasma [183, 184]
	Chronic pain	Spared nerve injury	Intrathecal administration [128]		-
	Multiple sclerosis	Experimental autoencephalomyelitis	Intracranial and intravenous Administration using liposome complexes of the mimics and inhibitors [26]	*Cebp-α*	Sera [185]
	Epilepsy	Pilocarpine induced status epilepticus	Intrahippocampal injections using cholesterol conjugated 2′-OMe phosphoramidites [75]	*Creb-1*	-
	Traumatic injury	Spinal cord injury by transection of the C3 spinal cord segment and intraperitoneal injections	Chitosan/miR-124 polyplex particles [186]		Plasma [187]
miR-210	stroke	Rice–Vannucci hypoxia-ischemia model	intracerebroventricular injection, intranasal [188]	Glucocorticoid receptor	-
miR-203	Epilepsy	Mouse chronic epilepsy	Intranasal [189]	Glycine receptor-β (*Glrb*)	[76, 190]

CONCLUSIONS AND FUTURE DIRECTIONS

The role of miRNAs in regulating astrocyte and microglia mediated neuroinflammation during neuropathologies has been summarized in this review. It has been well established that miRNAs regulate expression of genes involved in various signaling pathways in glial cells contributing to neuroinflammation. Disrupting these signaling cascades can be achieved by overexpression or inhibition of miRNAs (Table **2**), thereby directing glial cells to a neuroprotective phenotype engaged in repair and restoration of CNS. In recent years, several studies focused on the interaction of miRNAs with their target transcriptome to understand the molecular mechanism of disease progression.

There is ample evidence that miRNAs have an intricate role during neurodevelopment, healthy brain function and in neuropathologies. In particular, several mRNAs have been shown to regulate key inflammatory pathways in both microglia and astrocytes, thereby proving to be ideal targets for miRNA centered therapeutics and biomarker discovery for neuroinflammatory diseases. Profiling miRNAs in body fluids such as blood and CSF will establish a biomarker catalogue that may help diagnosis and prognosis of CNS disorders. Although miRNA therapy holds great promise, ensuring cell specific delivery of miRNAs in the brain *in vivo* remains challenging. Unlike gene therapy, which appears to be a better therapeutic option as it

allows targeted expression of transgene in a specific cell type, miRNA-centered therapy is complex as one signaling pathway is targeted by many miRNAs. The advantage is that the miRNA–based therapy is reversible as both inhibitors and mimics can be characterized, some even being in clinical trials for the treatment of cancer [181]. Developing therapies involving miRNA cocktails and combinatory miRNA-gene therapy will have immense potential and would open new avenues to personalized medicine for the treatment of neurological diseases. It is of clinical importance for future studies to address this gap in knowledge in order to use miRNAs as therapeutic strategies.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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