MicroRNAs: Roles in Regulating Neuroinflammation

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Abstract

MicroRNAs (miRNAs) are small noncoding RNAs that broadly affect cellular and physiological function in all multicellular organisms. Here, the role of miRNAs in neuroinflammation is considered. miRNAs are 21- to 23-oligonucleotide RNAs that regulate translation of specific RNAs by binding to complementary regulatory RNA sequences, thereby causing mRNA degradation or sequestration. More than 5000 miRNAs likely exist in humans, and each miRNA binds an average of 200 RNAs. Specific immunomodulatory miRNAs can regulate a set of RNAs in a coordinated manner, suggesting that effective miRNA-based therapeutic manipulations for neuroinflammatory conditions may be revealed. For instance, miRNAs that preferentially inhibit translation of many cellular anti-inflammatory proteins could drive a pro-inflammatory response. Key pro-inflammatory (*miR-155, miR-27b, miR-326*), anti-inflammatory (*miR-124, miR-146a, miR-21, miR-223*), and mixed immunomodulatory (*let-7* family) miRNAs regulate neuroinflammation in various pathologies, including spinal cord injury, multiple sclerosis, ischemic stroke, and Alzheimer's disease. miRNAs represent a newly revealed layer of physiological complexity, the therapeutic benefits of which remain to be fully explored and exploited. In this review, we discuss the role of miRNAs in neuroinflammatory regulation and discuss how controlling miRNAs could alter cellular machinery to improve neuroinflammatory dynamics.

Keywords

central nervous system, traumatic brain injury, inflammation, immune response, neuropathology

Introduction

In 1993, a new class of small RNA molecules was discovered in *Caenorhabditis elegans* (Lee and others 1993; Wightman and others 1993), though their key regulatory functions remained undefined until 2000 (Pasquinelli and others 2000; Reinhart and others 2000). These small non–protein coding RNAs, called microRNAs (miRNAs), regulate innumerable cellular processes by causing degradation or sequestration of specific RNAs, thereby preventing protein translation (Dong and others 2013). The observation that miRNAs have been conserved throughout evolution highlights their importance; over 5000 miRNAs likely exist in humans (Londin and others 2015), miRNAs target 30% to 80% of protein-coding genes (Friedman and others 2009; Lu and Clark 2012), and each miRNA regulates translation of hundreds of distinct mRNAs (Krek and others 2005). Because microRNAs (and other noncoding RNAs) were only recently discovered, concepts related to our biological systems must be revised to include this additional layer of physiological regulation. Understanding how specific miRNAs regulate key cellular processes could reveal powerful new endogenous combinatorial therapeutic targets. Here, we consider how miRNAs influence neuroinflammatory dynamics.

Although inflammation in the nervous system can be beneficial, it often can worsen pathology (Grace and others 2016; Hooten and others 2015; Kigerl and others 2009; Popovich and others 1999). In models of central nervous system (CNS) trauma, neuroinflammation can exacerbate injury by causing secondary damage (Beck

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and others 2010; David and Kroner 2011; Faulkner and others 2004; Kigerl and others 2016). Inflammation also can modify pathology caused by stress, sickness, or neurodegenerative disease (e.g., multiple sclerosis [MS], Alzheimer's disease [AD], and Parkinson's disease) (Gagne and Power 2010; Hoppmann and others 2015; Pisanu and others 2014). Therapies that harness the beneficial aspects of inflammation, while restricting its ability to cause pathology, could improve neurological function (Peng and others 2009; Stirling and others 2004; Tentillier and others 2016). miRNAs are emerging as novel therapeutic targets for various human diseases, including those that affect the CNS (Christopher and others 2016; Fonken and others 2016b; Gaudet and others 2016b; Huang and others 2016b; Kabaria and others 2015; Kamphuis and others 2015; Severin and others 2016).

In this review, we discuss recent advances in dynamic miRNA regulation of neuroinflammation. First, the contribution of inflammation to various neuropathologies is considered. Next, we provide a brief overview of miRNA production and function. In the following section, specific pro-inflammatory (*miR-155, miR-27b, miR-326*), anti-inflammatory (*miR-124, miR-146a, miR-21, miR-223*), and mixed immunomodulatory (*let-7* family) miRNAs are considered in the context of immunity and neuroinflammation. Finally, we discuss strategies for interrogating the biological role of miRNAs, ideas for research design, and future directions.

Inflammation Contributes to Neuropathologies

Neuroinflammation is an adaptive response to tissue injury/infection that can also cause and worsen pathology in neurological disorders (Fig. 1). In the healthy adult CNS, tissue-resident microglia and astrocytes maintain a quiescent yet vigilant state (Nimmerjahn and others 2005). These cells respond to infection or injury by transiently increasing inflammatory actions to isolate and remove the causative agents (Fonken and others 2015; Frank and others 2016; Norden and others 2015). Microglia are the main antigen-presenting cells of the CNS; once activated, they increase expression of major histocompatibility complex class II (MHC II) molecules, which are necessary to present antigens to adaptive immune cells (Frank and others 2007). Activated microglia and astrocytes also release cytokines, chemokines, and other factors that help mount an inflammatory response and subsequently restore CNS homeostasis. Indeed, pro-inflammatory factors in the CNS can be beneficial. For example, the detection and propagation of an immune signal throughout the CNS causes a suite of behavioral and physiological modifications, collectively known as the sickness response, which are critical to host defense (Dantzer and others 2008). Behavioral changes associated with CNS inflammation include reduced food and water intake, increased sleep, decreased exploration and social behavior, hyperalgesia, and global changes in mood and cognition (Dantzer and others 2008). Overall, the sickness response represents a shift in an organism's motivational state and is considered highly adaptive. After successfully removing pathogens or recovering from minor injury, the inflammatory response may resolve. However, neuroinflammation has a "dark side"; pathological neuroinflammation occurs when the inflammatory response is exaggerated or persists long term such as after CNS injury. As an immune-privileged tissue (Engelhardt and others 2017), healthy CNS parenchyma is not typically exposed to peripheral immune cells or robust inflammatory responses and is therefore vulnerable to neuroinflammatory-elicited damage and autoimmune disease.

Uncontrolled neuroinflammation can have pathological effects. For instance, traumatic spinal cord injury (SCI) causes prolonged pro-inflammatory responses that fail to resolve or effectively repair the spinal cord. Instead, prolonged SCI-elicited neuroinflammation is likely neurotoxic and causes secondary damage (Kigerl and others 2009). Below, we discuss evidence that hyperinflammatory CNS responses worsen pathology in several neurological disorders, including neurotrauma, ischemic injury, MS, and AD/aging.

Traumatic Spinal Cord and Brain Injury

Experimental models of traumatic SCI are useful for understanding neuroinflammatory dynamics, because the initial injury occurs at a discrete time and postinjury inflammatory cascades can be assessed systematically. SCI damages the blood-spinal cord barrier and creates a gradient of chemotactic inflammatory factors that promotes the infiltration of peripheral immune cells to the lesion epicenter and perilesional zone (Figley and others 2014; Popovich and others 1996). Thus, SCI causes activation of resident CNS cells (astrocytes, microglia, ependymal cells), but also involves peripheral immune cells that are not typically exposed to CNS antigens. After SCI, the responding peripheral immune cells appear in waves similar to what is observed following peripheral trauma (Donnelly and Popovich 2008). Neutrophils respond to injury by producing chemokines that recruit blood monocytes, which differentiate into lesion-localized macrophages (Gaudet and others 2015; Kigerl and others 2006; Schnell and others 1999). In the periphery, macrophages respond efficiently to environmental cues and participate in the efficient and rapid phagocytic removal of tissue debris, culminating in a switch (within 7–10 days) to a

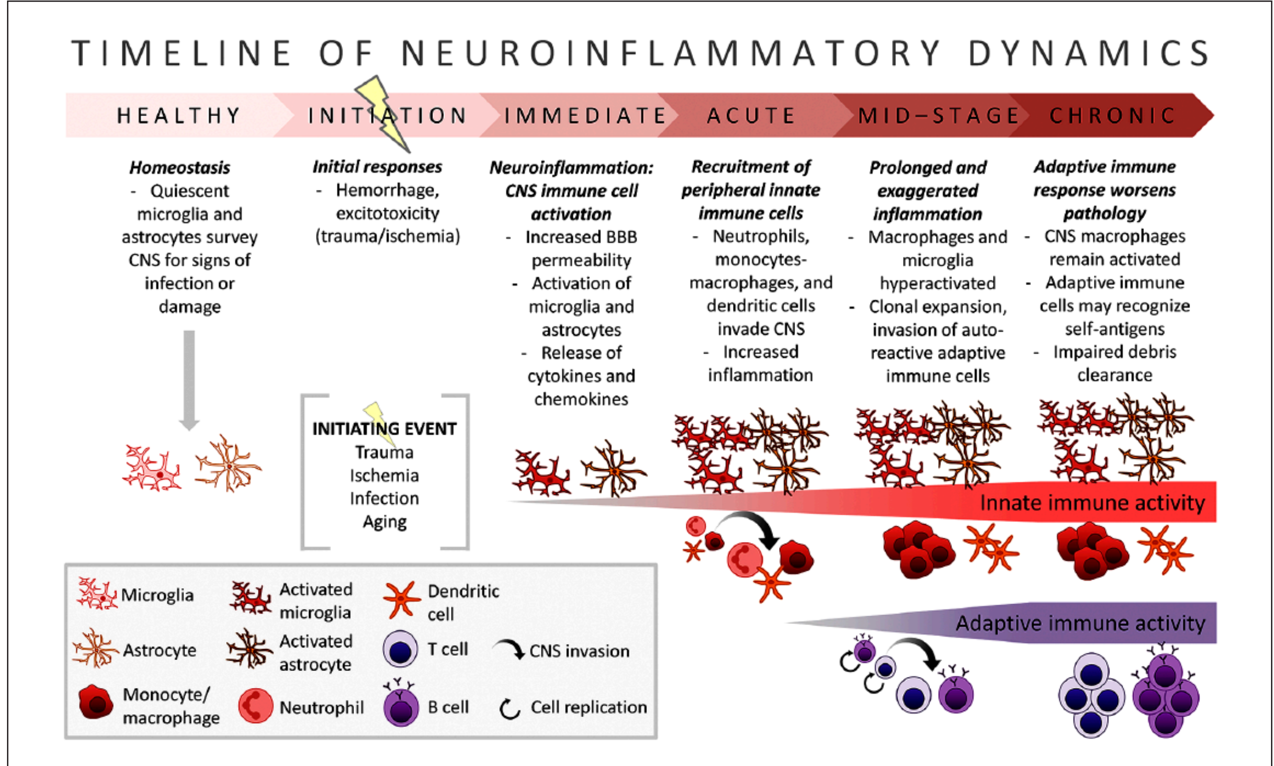

Figure 1. Inflammatory dynamics follow a stereotyped pattern in neuroinflammatory disorders. Upper portion describes neuroinflammatory events, whereas lower portion depicts immune cell responses over time. In healthy tissue, quiescent microglia and astrocytes sample the local CNS microenvironment for signs of infection or damage. Neuroinflammation can be initiated by trauma (brain or spinal cord injury), ischemia, infection, aging, or unknown causes. Microglia and astrocytes detect the immune stimulus and respond by becoming activated, proliferating, and releasing cytokines/chemokines. These cytokines/chemokines cause peripheral immune cells (which usually have limited CNS access) to translocate into CNS parenchyma. Initially, neutrophils and macrophages (and likely dendritic cells)—cells of the innate immune system—enter the CNS compartment. Macrophages in particular persist in the CNS for long periods and maintain a potentially cytotoxic pro-inflammatory phenotype. Since the blood-brain barrier (BBB) becomes more permeable and new antigens become exposed with CNS damage (e.g., inner portions of myelin), CNS antigens may be newly presented to naïve cells of the adaptive immune system (acute-mid-stage neuroinflammation). Many of these antigens may not have been presented outside the CNS before, so CNS antigen-specific adaptive immune cells may exist and undergo clonal expansion during neuroinflammation. At mid-stage to chronic neuroinflammation, these potentially autoreactive T cells and B cells translocate into the CNS parenchyma. A strong adaptive response to nonresolving neuroinflammation could exacerbate pathology. The course of neuroinflammatory dynamics is similar in traumatic, ischemic, autoimmune, and neurodegenerative disorders.

reparative and/or resolving anti-inflammatory cell type (Gaudet and others 2011). In contrast, in the CNS, macrophages maintain and even exaggerate their pro-inflammatory phenotype into chronic stages (Kigerl and others 2009; Kroner and others 2014), which may amplify signaling and activation of adaptive immune cells (T cells and B cells, which typically have no CNS access) to further drive pro-inflammatory cascades (Fleming and others 2006; Kigerl and others 2006; Rieckmann and others 2017; Sroga and others 2003). Thus, feed-forward inflammatory cascades caused in part by inefficient phagocytosis of debris, the accumulation of damage-associated molecular patterns (DAMPs), and ineffective immune cell clearance (e.g., phagocytosis of apoptotic cells) likely contribute to chronic, nonresolving neuroinflammation after SCI.

Dampening or shifting the post-SCI inflammatory response could improve neuroprotection and neurological function. Ablating peripheral macrophages reduced SCI pathology (Popovich and others 1999), and macrophages in the spinal cord cause axon dieback (Busch and others 2009; Evans and others 2014) and neurotoxicity (Kigerl and others 2009). Pathologic B cell and T cell responses also alter post-SCI outcomes (Ankeny and others 2009; Jones and others 2002). Astrocytes form a scar that limits the spread of immune cell infiltrates beyond the site of primary trauma (Faulkner and others 2004), but also restricts axon plasticity and regeneration (Alilain and

others 2011; Bartus and others 2014; McKeon and others 1991). Thus, modifying post-SCI neuroinflammatory responses to improve neuroprotection, remyelination, and axon plasticity could benefit neurologic recovery.

Although reducing the inflammatory response to traumatic SCI could boost neuroprotection, there are also beneficial aspects of the pro-inflammatory response. Microglia activated by the pro-inflammatory cytokine interferon-γ (IFN-γ) promote adult neural progenitor cells to differentiate into neurons (Butovsky and others 2006). In the injured peripheral nerve, $CD11b^+$ myeloid cells are required for myelin clearance, growth factor induction, angiogenesis, and effective axon regeneration (Barrette and others 2008), suggesting that optimizing CNS microglial/macrophage responses could improve spinal cord repair (e.g., McPhail and others 2004). In the spinal cord, axons from transplanted fluorescent neurons extend toward foci of activated macrophages, but these axons are destroyed on closely approaching or touching activated macrophages (Gensel and others 2009). In demyelinating models, activating microglia can improve remyelination and oligodendrocyte progenitor cell proliferation (Döring and others 2015; Olah and others 2012; Plemel and others 2014). Therefore, there are aspects of the pro-inflammatory response that, if modulated specifically and cautiously, could help improve tissue repair.

Traumatic brain injury (TBI)–elicited neuroinflammation is similar to that caused by SCI (Corps and others 2015; Gyoneva and Ransohoff 2015; Johnson and others 2013). After TBI, microglia develop a mixed pro- and anti-inflammatory phenotype that polarizes toward pro-inflammatory activation over time (Kumar and others 2016). Limiting microglial hyperactivation by deleting NOX2, an enzyme that produces cytotoxic superoxide, reduced post-TBI neuropathology (Dohi and others 2010). After TBI in humans, microglial/macrophage activation and neuropathology often persist for years postinjury (Johnson and others 2013). Although individuals with TBI often achieve apparent complete cognitive and functional recovery, these patients are more susceptible to neuropsychiatric disorders (e.g., depression, cognitive impairment, and neurodegenerative disease) (Witcher and others 2015). As with other neuroinflammatory conditions, TBI-elicited inflammation has both detrimental and beneficial aspects (Russo and McGavern 2016); thus, one must optimize the timing, duration, and intensity of any immunomodulatory treatment.

Ischemic Brain Injury

The brain consumes 20% of whole-body oxygen intake (Raichle and Gusnard 2002); thus, loss of cerebral blood flow (via vessel blockade or hypoperfusion) causes devastating neuropathology. Ischemic stroke, which is the most prevalent stroke subtype, is caused by obstruction of a brain-supplying artery that prevents oxygen delivery (Gesuete and others 2014; Roger and others 2012). The only current treatments for ischemic stroke are fibrinolytic therapy (Shobha and others 2011), which degrades the blood clot to restore blood flow, and clot removal by surgery. Ideally, these procedures are initiated within 3 hours of stroke onset. Unfortunately, there is nearly complete cell death in the ischemic core (Morrison and Filosa 2013), and reperfusion after a period of ischemia can drive pathological neuroinflammation.

Cerebral ischemia-elicited neuroinflammation has a similar course and function to that observed after SCI and TBI (Yilmaz and Granger 2010). Ischemia activates brain-resident cells, including microglia, astrocytes, and endothelia. Increased production of endothelial cell adhesion molecules and inflammatory cytokines/chemokines, combined with increased blood-brain barrier permeability, enable ischemia-induced peripheral immune cell infiltration and activation. Within the first 4 hours after ischemia-reperfusion, neutrophils are the major immune cell infiltrate (Yilmaz and others 2006). Other cell types (monocytes/macrophages and T cells) become more prevalent at/after 24 hours after ischemia.

Dampening the responses of several immune cell types has often proven protective in cerebral ischemia-reperfusion models. After middle cerebral artery occlusion (MCAO), rats treated with an anti-neutrophil antibody (i.p., 24 hours prior and immediately after) showed reduced infarct size (Matsuo and others 1994). Oxygen-glucose deprivation causes microglia/macrophages to develop an initially more balanced inflammatory response that eventually biases toward a pro-inflammatory phenotype, which could exacerbate injury (Hu and others 2012). For instance, HMGB1, which is a chromatin binding protein that is normally expressed intracellularly, is released by stressed or necrotic cells into the extracellular space. Extracellular HMGB1 acts as a DAMP that can bind to immune receptors on microglia/macrophages to drive inflammation. Blocking HMGB1 and other DAMPs can reduce post-MCAO microglial/macrophage activation and infarct size (Kim and others 2006; Shichita and others 2017). T cells can also exacerbate ischemic injury: MCAO mice lacking $CD4^+$ or $CD8^+$ T cells exhibit reduced inflammation and ameliorated neuropathology (Yilmaz and others 2006). Neuroinflammatory activation also occurs in humans after ischemic stroke (Denes and others 2010), and identifying effective neuroprotective therapies is a top priority (Chamorro and others 2016). Although there are some protective roles of neuroinflammation prior to (preconditioning) and after ischemia (Karelina and others 2009; Yilmaz and Granger 2010), it is most clear that neuroinflammation exacerbates pathology after cerebral ischemia.

Multiple Sclerosis

MS is a neurodegenerative demyelinating disorder that often first presents in 20 to 40 year olds. There are four types of MS: relapsing-remitting MS (RRMS), the most common form, which consists of transient MS symptoms with periods of remission; secondary progressive MS, during which MS clinical signs steadily progress after an initial period of RRMS; primary progressive MS, which presents as immediate progression of MS clinical signs; and progressive relapsing MS, during which relapsing and progressive MS occur concomitantly (Mahad and others 2015). Although the exact etiology of MS remains unknown, neuroinflammatory processes appear to contribute to MS pathology. Chronic MS-related pathological neuroinflammation eventually evolves into a more neurodegenerative form at later stages. Different aspects of MS can be explored using specific experimental models: for instance, inflammatory pathology in MS is modeled using experimental autoimmune encephalomyelitis (EAE), which can be induced by immunization with CNS antigens (e.g., myelin-oligodendrocyte glycoprotein); the cellular and molecular determinants of demyelination and remyelination can be assessed using focal intraparenchymal injection of lysolecithin or ethidium bromide or by adding cuprizone in rodent chow (Ransohoff 2012).

As mentioned, although the molecular mechanisms that initiate MS pathology remain elusive, neuroinflammation likely causes or exacerbates MS pathology. Focally activated microglia demyelinate axons and help recruit monocytes, T cells, and B cells (Berard and others 2010; Hemmer and others 2015; Rawji and Yong 2013). T and B cells expand clonally and worsen inflammation (Obermeier and others 2011; Prineas and Graham 1981; Skulina and others 2004). Various T cell subsets influence MS/EAE outcomes: $CD8^+$ cytotoxic T cells, $Tbet^+$ T_h1 cells, $GATA3^+$ T_h2 cells, and ROR-γt^+ T_h17 cells can contribute to EAE pathology (Grifka-Walk and others 2015; Sie and others 2014; Sinha and others 2015) (although these cells can also have reparative properties). In contrast, $FOXP3^+$ regulatory T (T_{reg}) cells, which maintain tolerance to self-antigens and could thereby reduce neuroinflammation, likely have impaired regulatory activity during EAE (Nyirenda and others 2015). B cells also influence EAE outcomes through their ability to secrete antibodies, present antigens, and release cytokines. B cells may limit EAE onset, but worsen EAE progression by augmenting T cell activation and infiltration (Matsushita and others 2008; Pierson and others 2014). The early protective actions of B cells are carried out by a rare IL-10-producing regulatory B cell subset that can reduce neuroinflammation. Unfortunately, the benefit of this small endogenous B cell population is likely overwhelmed by inflammatory changes as the disease progresses (Matsushita and others 2008; Shen and others 2014; Zhang and others 2015).

The inflammatory basis for MS is highlighted by recent clinical developments. Indeed, a humanized antibody (ocrelizumab) for treating RRMS acts by binding to CD20 to deplete B cells (Barun and Bar-Or 2012; Sorensen and Blinkenberg, 2016); B cell depletion showed efficacy in the EAE model (Matsushita and others 2008; Weber and others 2010), and ocrelizumab has recently been approved by the US Food and Drug Administration as a therapy for MS. In phase 3 trials for RRMS, ocrelizumab reduced relapse rate by 46% compared to a gold standard treatment, IFN-β1a (Hauser and others 2017). Remarkably, ocrelizumab also effectively reduced symptoms of primary progressive MS, which currently has no standard treatment (possibly due to a more neurodegenerative, less inflammatory basis compared to RRMS) (Calabresi 2017; Montalban and others 2017).

Aging and Alzheimer's Disease

Neuroinflammation also contributes to age-related cognitive decline, AD, and other neurodegenerative conditions (Gomez-Nicola and Perry 2015). In the brains of aging animals and humans, inflammatory stimuli elicit an exaggerated response from microglia (Barrientos and others 2009; Frank and others 2010; Henry and others 2009; Streit and others 2004). Aged microglia are considered to be in a "primed" state; they express increased basal levels of immune receptors and host defense genes and are hypersensitive to immune stimulation (Hickman and others 2013; Fonken and others 2016c; Sierra and others 2007). For instance, aged rats injected with *Escherichia coli* have exaggerated and prolonged neuroinflammatory responses that correlate with a prolonged sickness response and related cognitive deficits. Although hippocampal microglia from aged rats do not exhibit elevated cytokines at baseline, they have increased expression of pattern recognition receptors and danger signals. Targeting HMGB1 with its competitive antagonist, Box-A, prevents age-related exaggerated neuroinflammatory and behavioral responses to infection (Fonken and others 2016a).

Similarly, neuroinflammation likely contributes to AD (Heneka and others 2015). In AD, misfolded and aggregated proteins (amyloid β oligomers) accumulate in the extracellular space; these complexes trigger inflammatory signaling in microglia by activating pattern recognition receptors such as toll-like receptors (TLRs) (Heneka and others 2015). As described above in the context of CNS injury, microglia in AD brain are activated; however, they are inefficient phagocytes and do not efficiently clear amyloid β oligomers (Heneka and others 2015).

Because these immune-reactive proteins are constantly deposited in AD brain and persist in the extracellular space indefinitely, the aggregates are associated with chronic neuroinflammation (Laske and others 2010; Lue and others 2001). This likely worsens the neurodegeneration and impaired cognition that is characteristic of AD (Holmes and others 2009; Jin and others 2008; Tarkowski and others 2003). Neuroinflammation also contributes to other chronic neurodegenerative disorders including amyotrophic lateral sclerosis, prion disease, and possibly Parkinson's and Huntington's diseases (see Gomez-Nicola and Perry 2015).

microRNA Production and Function

Transcription of miRNAs is usually mediated by RNA polymerase II and its associated transcription factors (Cai and others 2004; Lee and others 2004). As with production of protein-coding mRNAs, transcription of different miRNAs can be elicited by the same transcription factor. For instance, the canonical pro-inflammatory transcription factor NFκB increases expression of both pro-inflammatory (*miR-155*) and anti-inflammatory (*miR-124, miR-146a*) miRNAs (Doxaki and others 2015; Ma and others 2014), illustrating how miRNA induction can both elicit inflammation and provide negative feedback regulation of the inflammatory response (see below for more detail). Transcription of a miRNA gene produces miRNA primary transcripts (pri-miRNAs), which are several kilobases long and contain local stem-loop structures (Ha and Kim 2014).

Canonical miRNA biogenesis occurs in a multi-step process that involves the key processing proteins Drosha, DGCR8, and Dicer (Fig. 2) (Daugaard and Hansen 2017; Kim and others 2009). miRNAs also can be produced via alternative pathways that generate mature miRNAs independent of Drosha/DGCR8 and/or Dicer (see Daugaard and Hansen 2017).

For canonical miRNA biogenesis, the RNase type II protein, Drosha, along with cofactor DGCR8, form a microprocessor complex that recognizes specific motifs in the pri-miRNA (Gregory and others 2004; Han and others 2004; Kwon and others 2016; Lee and others 2003). Ultimately, the microprocessor complex defines the mature miRNA sequence to be used by cleaving at the stem of the hairpin structure then releasing a small RNA hairpin called the pre-miRNA (Lee and others 2002). Next, the pre-miRNA is exported to the cytoplasm by the nuclear transport receptor Exportin-5. Exportin-5 binds cooperatively to the pre-miRNA and a cofactor, GTP-bound Ran; once in the cytosol, GTP is hydrolyzed and the pre-miRNA cargo is released (Bohnsack and others 2004; Lund and others 2004).

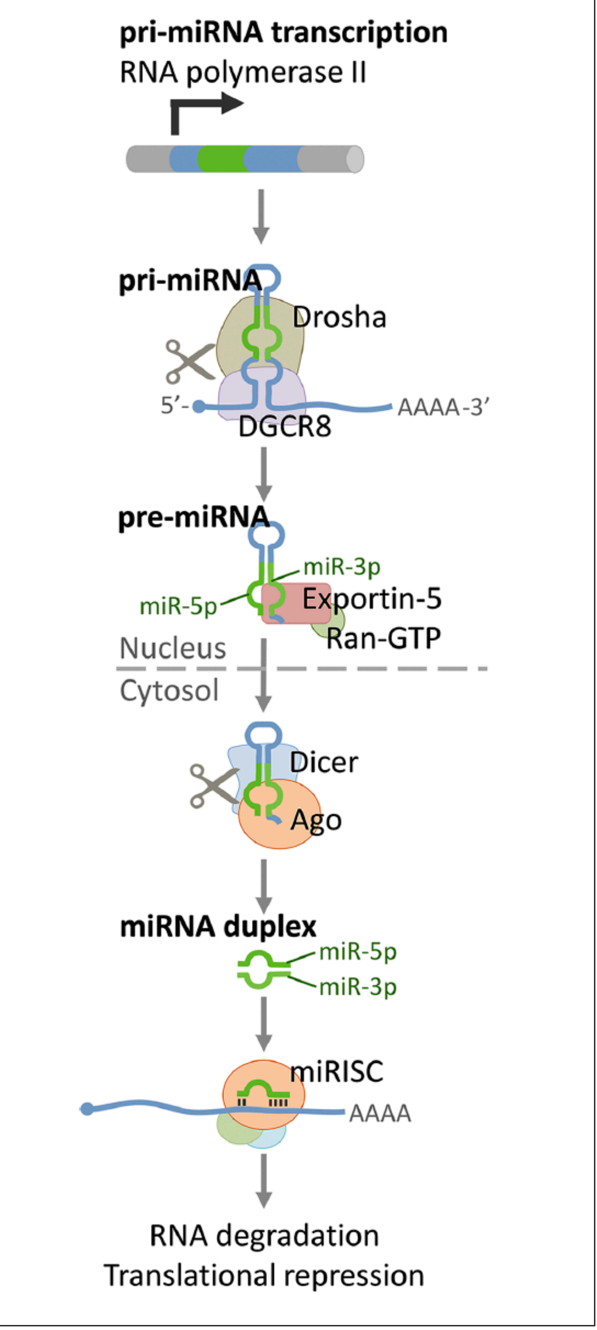

Figure 2. An overview of microRNA processing and function. Most miRNA primary transcripts (pri-miRNAs) are transcribed by RNA polymerase II. The pri-miRNA is loaded into the microprocessor complex, which consists of the proteins Drosha and DGCR8. Drosha cleaves the pri-miRNA to create a small hairpin RNA, the 70- to 90-nucleotide pre-miRNA. The pre-miRNA is bound by Exportin-5 (linked to Ran-GTP); then, the Exportin-5-miRNA complex is translocated to the cytosol. The pre-miRNA is then loaded into a protein complex including Dicer and Argonaute (Ago). Dicing the pre-miRNA results in a ~22 nucleotide long

(continued)

Figure 2. (continued)

miRNA duplex. The miRNA duplex consists of the miR-5p (e.g., miR-155-5p), which is the sequence that was closest to the 5′ end of the pri-miRNA; and the complementary miR-3p (e.g., miR-155-3p), which is the sequence that was closest to the 3′ end of the pri-miRNA. One of the strands (usually the more stable strand, which is often the -5p strand) is loaded into the Ago in the microRNA-induced silencing complex (miRISC). In animals, the miRNA seed sequence (5–7 nucleotides) binds with partial complementarity to sequences in the 3′ untranslated region of target mRNAs. The miRISC complex then directs these target mRNAs for degradation or translational repression. Bold text indicates miRNA species. Please see text for further detail and citations.

Next, the protein Dicer acts with cofactors to cleave the pre-miRNA into ~22 nucleotide miRNA duplexes (double-stranded RNA). The ~22 nucleotide RNA duplex is incorporated into an Argonaute protein (four members, Ago1–4, in humans) to create the miRNA-induced silencing complex (miRISC) (Chendrimada and others 2005; Iwasaki and others 2010). Based on relative stability, one strand of the duplex is released; the other remains in the miRISC to participate in miRNA-mediated inhibition of translation (Kwak and Tomari 2012). Although both strands are active and have knockdown potential, generally one strand is more prevalent and biologically relevant than the other strand due to differing stability/half-lives of each strand (Meijer and others 2014).

The miRNA in the miRISC helps target the complex to specific RNAs and dampens their expression through translational repression, mRNA decay, and mRNA deadenylation (Bartel 2009; Eichhorn and others 2014). In animals, miRNAs identify their target RNAs by partial complementary binding between the miRNA seed sequence—a sequence at positions 2 to 7 from the 5′ end—and regions in the 3′ untranslated region of the target RNA (Ameres and Zamore 2013; Daugaard and Hansen 2017). Although partial complementarity is one key mechanism of target recognition, nucleotides downstream of the seed sequence can also modulate RNA target recognition and other mechanisms of miRNA-mediated inhibition have been identified. It is clear that partial complementarity would enable an individual miRNA to modulate expression of hundreds of mRNAs, and at least one miRNA binding site exists in 30% to 80% of protein-coding genes (Friedman and others 2009; Lu and Clark 2012). Thus, miRNA-based regulation likely has roles in nearly all biological processes and pathologies (Bartel 2009; Cloonan 2015; Mendell and Olson 2012).

miRNA nomenclature is evolving; details on nomenclature are reviewed elsewhere (Budak and others 2016; Griffiths-Jones and others 2006). Briefly, miRNAs derived from a single duplex are distinguished by -5p and -3p suffixes (e.g., miR-124-5p for 5′ arm; miR-124-3p for 3′ arm), and a lettered suffix represents closely related mature miRNAs derived from distinct precursors or loci (e.g., miR-146a, miR-146b) (Budak and others 2016).

Mature miRNAs can have wide-ranging effects on the function and translation of other RNAs (Fig. 3a). As mentioned, each individual miRNA binds on average 200 mRNAs. Conversely, mRNAs can be bound by multiple miRNAs (Krek and others 2005; Tsang and others 2010). miRNAs often act by binding the 3′ untranslated region of target mRNAs, but they can also target sequences in the 5′ region or protein-coding domain (Ameres and Zamore 2013). Although individual miRNAs reduce translation/function of target RNAs, they generally do not completely shut down target RNA function. Instead, they act to dampen partially the function of these RNAs, although miRNAs acting in concert can have more profound effects (Cech and Steitz 2014). Furthermore, miRNAs can target other classes of noncoding RNA, including circular RNAs and long noncoding RNAs (Jeggari and others 2012; Millan 2017). Thus, miRNAs fine-tune output of the transcriptome.

In addition to their autocrine regulatory roles, miRNAs can be released to alter function of other cells nearby or throughout the body (Chen and others 2012; Hulsmans and Holvoet 2013) (Fig. 3b). miRNAs exist in the extracellular space in small vesicles (exosomes, shedding microvesicles, and synaptic vesicles) (Li and others 2015; Mitchell and others 2008; Valadi and others 2007) or protected in extracellular protein-miRNA complexes (e.g., with Ago2 or high-density lipoprotein) (Arroyo and others 2011; Vickers and others 2011). The miRNA repertoire in microvesicles can be significantly different from that in their parent cell, suggesting that specific miRNAs are selectively packaged into vesicles (Diehl and others 2012). These extracellular miRNAs likely affect health and pathology. For instance, inactivated endothelial cells secrete miRNA-containing exosomes to suppress monocyte activation (Njock and others 2015), and circulating adipose-derived exosomal miRNAs regulate target mRNAs in distant tissues to control metabolic function (Thomou and others 2017). Extracellular miRNAs may also act as DAMPs; for example, the miRNA *let-7b* can bind to TLR7 to elicit neurodegeneration (Lehmann and others 2012). Therefore, release of miRNAs during neuropathology could shape the inflammatory response, including modulation of cell phenotype, response intensity, and the balance between toxic or reparative effector functions.

microRNAs: Role in CNS Neuroinflammation

miRNAs (and other noncoding RNAs) were discovered only recently. As such, their functional roles in the context of neuroinflammation remain largely unknown (Fig. 4). Still, it is increasingly clear that miRNAs control inflammation initiation and maintenance (e.g., Liu and Abraham

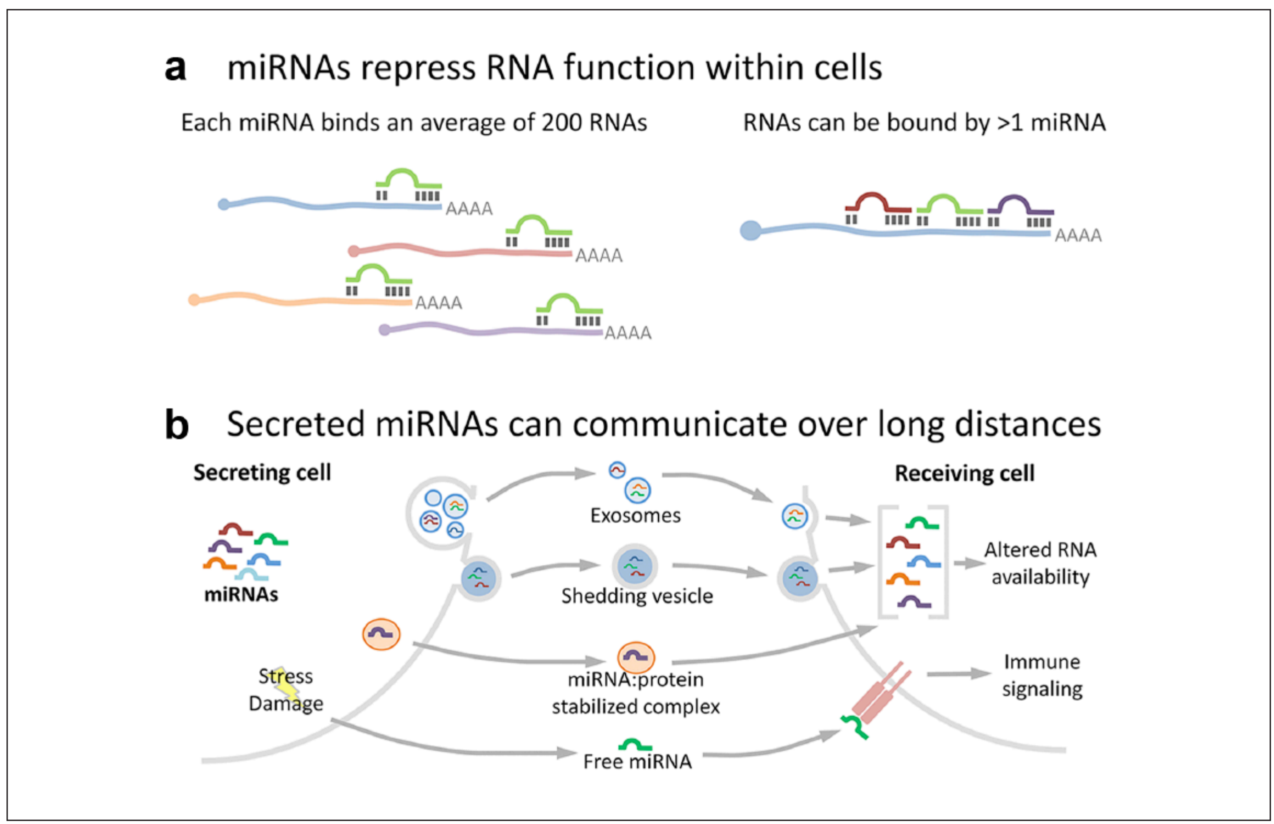

Figure 3. MicroRNAs dynamically regulate post-transcriptional function and translation of RNAs, both within the producing cell and between cells (intercellular communication). (a) MicroRNAs bind RNA sequences complementary to the miRNAs 6–7 oligonucleotide "seed sequence." miRNAs typically bind RNAs in the 3′ untranslated region, although they can bind in the 5′ region or in coding areas. Once bound, miRNAs cause RNA degradation or sequestration. The complexity of miRNA functions is highlighted by the fact that each miRNA binds an average of 200 RNAs (left), and individual RNAs can be bound by multiple miRNAs (right). (b) miRNAs can also be secreted/released to act over short or long distances in a paracrine manner. miRNAs from the secreting cell can be sorted and packaged into microvesicles (exosomes or shedding vesicles), which are then received by another cell by endocytosis or membrane fusion (miRNAs can also be packaged in synaptic vesicles; not shown). miRNAs can also be released in association with a protective protein (e.g., Ago2 or high-density lipoprotein); miRNA–protein complexes are stabilized for long periods in the extracellular space. Receiving cells can take up these secreted or released miRNAs, which regulate RNA availability and protein translation in that cell. In addition, cell stress, damage, or necrosis causes release of free miRNAs that bind to immune receptors to initiate inflammatory changes (e.g., *let-7b* binds to the immune receptor TLR7). In this manner, miRNAs act as short- or long-range communication cues that affect cell physiology throughout the body during health and pathology.

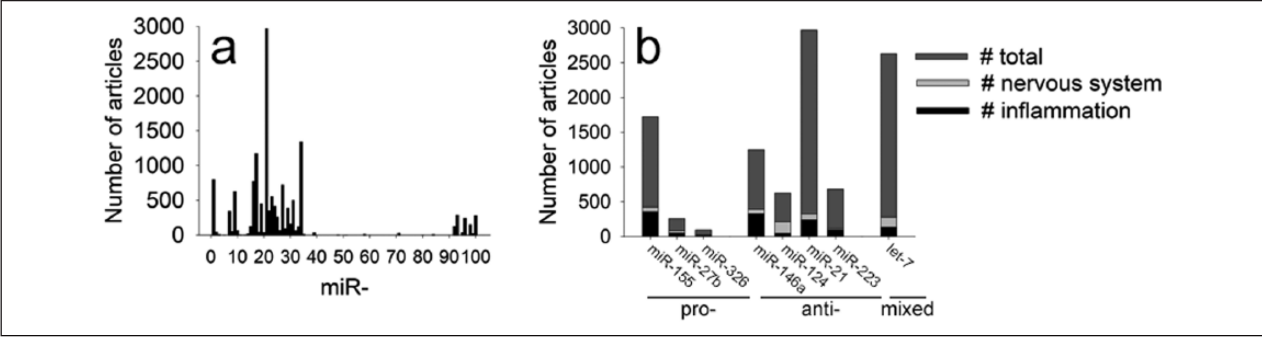

Figure 4. MicroRNAs remain understudied. (a) The number of articles (as of April 2017) for each miRNA from *miR-1* to *miR-100*. Many miRNAs have very few related published papers. (b) Published articles about miRNAs highlighted in this review, in the context of inflammation (black bar), the nervous system (light grey), and total papers (dark grey). Many of the top immunomodulatory miRNAs are understudied, highlighting that the miRNA-neuroinflammation field is in its infancy.

Cell type	miRNA	Function	Key validated RNA targets
Microglia	*miR-155*	Pro-inflammatory polarization, neurotoxicity	*Socs1*
	miR-124	Anti-inflammatory polarization, EAE protection	*C/ebpa*
	let-7 family	Dampens activation, neuroprotective	*Caspase-3*
Astrocyte	*miR-155*	Increased activation	*Socs1*
	miR-146a	Reduced activation	*Traf6*
	miR-21	Reduced activation	--
	let-7 family	Differentiation	--
Macrophage	*miR-155*	Pro-inflammatory polarization, neurotoxicity	*Ship1, Socs1, IL13ra1*
	miR-27b	Pro-inflammatory polarization	*PPARg*
	miR-124	Anti-inflammatory polarization, deactivation	*Stat3, C/ebpa, Tlr6, Myd88, Tnfa, Tace*
	miR-146a	Reduced activation	*Irak1, Traf6*
	miR-21	Anti-inflammatory polarization	*Pdcd4, IL12p35, Smad7*
		Pro-inflammatory polarization	*Stat3*
	miR-223	Anti-inflammatory polarization	*Nlrp3*
		Reduced suppressor cell activity	*Stat3*
	let-7 family	Anti-inflammatory polarization	*C/ebpd, IL6, Tlr4*
	Extracellular *let-7, miR-21*	DAMP that binds TLR7 to boost inflammation	N/A
Neutrophil	*miR-223*	Reduced activation	*IL6*
Dendritic cell	*miR-155*	Dendritic cell-mediated T cell activation	--
	miR-21	Restricts T cell activation	*IL12p35*
	miR-223	Reduced activation	*C/ebpb*
		Increased activation of Th17	--
T cell	*miR-155*	Th1 and Th17 polarization, EAE pathology	--
	miR-326	Th17 differentiation, EAE pathology	*Ets1*
	miR-124	T cell deactivation, EAE protection	--
	miR-21	Limits Th1 and Th17 polarization	Via reduced dendritic cell *IL-12p35*
		Increases Th17 polarization, EAE pathology	*Smad7*
	let-7 family	Th1 and Th17 differentiation	*IL10*
B cell	*miR-155*	Reduced activation and antibody production	*Pu.1*

Figure 5. Key miRNAs with regulatory roles in inflammatory cells. Immunomodulatory miRNAs, their functions, and validated RNA targets for each cell type are summarized. Please see text for citations. –, no RNAs identified; N/A, not applicable.

2013). Here, we consider the roles of specific pro- and anti-inflammatory miRNAs in neuroinflammation (Fig. 5).

Pro-Inflammatory miRNAs in Neuroinflammatory Disorders

miR-155. *miR-155-5p* is a pro-inflammatory miRNA that is uniquely positioned: it has been widely studied in inflammation, and its published potent pro-inflammatory actions across immune cell types are unparalleled by any other miRNA. *miR-155*'s role in inflammation was first identified in 2005 when its expression was found to be elevated in human B cell lymphoma (Eis and others 2005; Kluiver and others 2005). Subsequent studies showed that *miR-155* is required for typical B cell function and cytokine production (Thai and others 2007). Similarly, *miR-155* is critical for effective responses of macrophages and T cells. In macrophages, *miR-155* is upregulated by TLR ligands and by the pro-inflammatory cytokine IFN-γ (O'Connell and others 2007; Tili and others 2007). Key validated anti-inflammatory RNA targets of *miR-155-5p* include the inositol phosphatase *Ship1* (O'Connell and others 2009), the transcription factor *Cebpb* (Worm and others 2009), the STAT1 suppressor *Socs1* (Cardoso and others 2012; Lu and others 2009a), and the anti-inflammatory receptor *IL-13Rα1* (Martinez-Nunez and others 2011). Thus, induction of *miR-155* may release an endogenous anti-inflammatory "brake," resulting in increased inflammation. Indeed, using microarrays, our group found that activation of inflammatory signaling in *miR-155* KO macrophages was significantly blunted (Jablonski and others 2016). In macrophages from *miR-155* knockout mice stimulated with IFN-γ + LPS, that is, stimuli that elicit consistently strong inflammatory cascades in macrophages, 66% fewer genes were up- or downregulated (vs. media-treated; WT: 1989 genes, KO: 671 genes) via these activating stimuli (Jablonski and others 2016). These data suggest that

miR-155 critically regulates inflammatory signaling in macrophages.

miR-155 is a key pro-inflammatory miRNA, so removing or inhibiting *miR-155* should improve damaging aspects of neuroinflammation. Our group found that *miR-155* deletion was neuroprotective and improved histological and functional outcome measures in an experimental SCI model (Gaudet and others 2016b). In a novel co-culture model, *miR-155* KO macrophages improved growth and survival of wild-type neurons, particularly under inflammatory conditions. Interestingly, *miR-155* KO neurons also had improved intrinsic growth capacity, suggesting that *miR-155* inhibition could also affect axon growth and plasticity independent of its effects on macrophages. In vivo, *miR-155* KO mice with SCI showed enhanced neuroprotection and axon regeneration, and expedited locomotor recovery (Gaudet and others 2016b). In separate studies, our group reported that *miR-155* deletion reduced pathology in other diseases or disorders exacerbated by inflammation: *miR-155* KO mice had reduced anxiety- and depressive-like symptoms (Fonken and others 2016b) and reduced diet-induced obesity (Gaudet and others 2016b).

A pro-inflammatory role for *miR-155* has been observed in several other neuropathologies. In MS patients, *miR-155* is robustly upregulated in brain lesions (Junker and others 2009) and serum (Paraboschi and others 2011). In a rodent MS model (EAE), *miR-155* deletion (O'Connell and others 2010) or *miR-155-5p* inhibition (even after disease onset; Murugaiyan and others 2011; Zhang and others 2014) are neuroprotective and attenuate neurologic impairment. In EAE using *miR-155* KO or inhibitor-treated mice, induction of cytotoxic T cells, regulatory T_h17 cells, and dendritic cell-induced T cell activation are reduced (Murugaiyan and others 2011; O'Connell and others 2010; Zhang and others 2014). Endothelial *miR-155* regulates blood-brain barrier permeability to worsen EAE (Lopez-Ramirez and others 2014). Furthermore, a recent study suggests the involvement of *miR-155-3p* in EAE pathology (Mycko and others 2015). After ischemic stroke in mice, *miR-155-5p* inhibition (intravenous, beginning 48 hours postocclusion) reduced pro-inflammatory processes (Pena-Philippides and others 2016) and improved neuroprotection, brain perfusion, and functional recovery (Caballero-Garrido and others 2015). *miR-155* upregulation may be pathological in a mouse model of AD (Guedes and others 2014). Finally, in a mouse model of amyotrophic lateral sclerosis (male and female $SOD1^{G93A}$ mice), *miR-155* deletion/inhibition improved survival, likely by reducing the inflammatory potential of microglia (Butovsky and others 2015; Koval and others 2013).

Overall, *miR-155* (*miR-155-5p* in particular) is a critical pro-inflammatory miRNA that is commonly upregulated in inflammatory and neurological disorders. In fact, no other miRNA has been identified that has such profound pro-inflammatory effects. Therefore, *miR-155* inhibition or removal—perhaps in combination with an anti-inflammatory miRNA or other reparative factor—could be explored as a therapy for various neurological disorders.

Other Pro-Inflammatory miRNAs. Although *miR-155* is the most studied pro-inflammatory miRNA, other miRNAs also are known to be pro-inflammatory. *miR-27b* targets an anti-inflammatory transcriptional activator, PPAR-γ; in human macrophages, this interaction blocks the induction of an anti-inflammatory phenotype. Inhibiting *miR-27b* also limits inflammatory signaling. For example, *miR-27b* inhibition reduces the ability of LPS to increase macrophage production of inflammatory cytokines including IL-6 and TNF-α (Jennewein and others 2010); this likely occurs by de-repression of PPAR-γ, which normally dampens pro-inflammatory network activation (Lee and others 2012; see also Zhou and others 2012). PPAR-γ expression is dysregulated in SCI (McTigue and others 2007), MS (Klotz and others 2005), and AD (Sastre and others 2006), suggesting the possibility that PPAR-γ levels in neurologic disorders could be altered by *miR-27b*. Accordingly, *miR-27b* expression increases in several neuroinflammatory disorders; *miR-27b* is upregulated in $CD4^+$ T cells of MS patients (Guerau-de-Arellano and others 2011) and in the brain of Alzheimer's patients (Cogswell and others 2008). Therefore, inhibiting *miR-27b* could be a viable strategy for ameliorating neuroinflammation.

miR-326 has been implicated in MS pathology. *miR-326* expression in leukocytes correlated with disease severity in MS patients and in mice with EAE (Du and others 2009; Honardoost and others 2014). *miR-326* drives differentiation of IL-17-producing T_h17 cells, which worsen MS pathology. Conversely, silencing *miR-326* reduced EAE pathology (Du and others 2009). The role of *miR-326* in other inflammatory and neurologic disorders remains unclear.

With the exception of *miR-155*, which has broad pro-inflammatory effects in an array of immune cell types (including microglia [Cardoso and others 2012] and astrocytes [Tarassishin and others 2011]), there are few other examples of key pro-inflammatory miRNAs in the literature. Future studies will help clarify whether *miR-155* is the major pro-inflammatory miRNA, or whether there are additional miRNAs with similarly potent pro-inflammatory activities.

Anti-Inflammatory miRNAs in Neuroinflammatory Disorders

miR-124. *miR-124* is expressed most robustly in the nervous system and has predominantly anti-inflammatory effects (Sempere and others 2004). *miR-124* can have

anti-inflammatory actions in macrophages via the cholinergic anti-inflammatory pathway and the vagus nerve. The vagus nerve acts on splenic T cells, which produce acetylcholine that binds the α7-nicotonic acetylcholine receptor on macrophages to promote anti-inflammatory polarization (Rosas-Ballina and others 2011). Within these macrophages, *miR-124* drives anti-inflammatory polarization by reducing *Stat3* (and downstream IL-6) and TNF-α converting enzyme (and downstream TNF-α). In macrophages, *miR-124* is upregulated in response to anti-inflammatory cytokines IL-4 and IL-13 and is necessary for regulating the expression of genes associated with the anti-inflammatory macrophage phenotype (i.e., increased CD206 and Ym1; decreased CD86, iNOS, and TNF) (Veremeyko and others 2013). These anti-inflammatory effects of *miR-124* could be via translational repression of the transcription factor *Cebpa* and/or the cytokine receptor *IL6R* (Hatziapostolou and others 2011; Ponomarev and others 2011). Interestingly, *miR-124* is also upregulated in macrophages by pro-inflammatory stimuli (MyD88-dependent), and acts as a brake on inflammation (Ma and others 2014). *miR-124* gain-of-function also improved survival in a model of sepsis (Sun and others 2013b). Thus, *miR-124* has a critical anti-inflammatory role in macrophages. Overexpressing *miR-124* in T cells caused them to develop an effector phenotype that was protective in a mouse glioma model (i.e., T cells activated by *miR-124* help clear glioma) (Wei and others 2013); however, this *miR-124*-elicited effector T cell response could be damaging in neuroinflammatory conditions.

miR-124 also appears to have protective effects in EAE. In adult mice, *miR-124* was expressed in microglia, but not peripheral monocytes or macrophages (Ponomarev and others 2011). *miR-124* overexpression in microglia reduced induction of pro-inflammatory TNF-α and nitric oxide (Louw and others 2016). Similarly, overexpressing *miR-124* in macrophages transformed them into more quiescent cells, likely by targeting *C/ebp*-α (Ponomarev and others 2011). During EAE, microglial *miR-124* was downregulated. Peripheral *miR-124* administration, either prior to or after EAE onset, deactivated macrophages and T cells, and improved neurologic outcomes (Ponomarev and others 2011).

In rodent models of stroke, most studies show a neuroprotective role for *miR-124. miR-124* delivery, particularly at acute postinjury times, was neuroprotective and polarized CNS macrophages toward an anti-inflammatory phenotype (Doeppner and others 2013; Hamzei Taj and others 2016; Sun and others 2013a). However, *miR-124* also may have a detrimental role in stroke pathology; cerebral *miR-124* knockdown in rats (24 hours prior to occlusion) reduced infarct size and boosted neurologic outcomes (Zhu and others 2014). It is possible that different experimental models or timing of *miR-124* delivery could explain these divergent results. Regardless, serum exosome concentrations of *miR-124* have been identified as a biomarker that predicts the incidence and severity of acute ischemic stroke (Ji and others 2016).

miR-124 may also benefit other neurologic disorders. In AD, *miR-124* expression may be downregulated in hippocampus of humans with AD (Lukiw 2007) and this coincides with an increase in the potentially damaging BACE1 protein. Reducing BACE1 activity could dampen Aβ secretion, and *miR-124* appears to downregulate BACE1 expression (Fang and others 2012). Similarly, *miR-124* overexpression was neuroprotective in a *Drosophila* model of AD (Kong and others 2015). In mouse peripheral neuropathic pain models, intrathecal infusion of *miR-124* relieved hypersensitivity (Willemen and others 2012). Future studies will further reveal potential anti-inflammatory effects of *miR-124* and its neuroprotective actions in the context of neurotrauma, ALS, and AD.

miR-146a and miR-146b. *miR-146a* acts as a negative regulator of inflammation. *miR-146a* is induced by NFκB activation and feeds back on this pathway by inhibiting translation of *IRAK1* and *TRAF6* mRNAs. Accordingly, *miR-146a* is upregulated in various neurological conditions, suggesting that cells are compensating for pathological inflammation and attempting to restore homeostasis. For instance, in MS patients, *miR-146a* and *miR-146b* were upregulated in peripheral blood mononuclear cells compared to controls (Fenoglio and others 2011). This may represent a compensatory anti-inflammatory response; *miR-146a* expressed by brain endothelia reduces NFκB activation and T-cell adhesion (by targeting NFκB pathway activators *RhoA, Nfat5, IRAK1*, and *TRAF6* (Wu and others 2015), which could limit immune cell infiltration and neuroinflammation during pathology.

miR-146a has been studied in other preclinical models involving neuroinflammation. In a rat model of stroke, *miR-146a* was found to increase oligodendrogenesis by targeting *IRAK1* (Liu and others 2017). *miR-146a* is also protective after ischemia-reperfusion injury in other tissues including myocardium (Wang and others 2013), liver (Jiang and others 2014), and intestine (Chassin and others 2012) (all through reducing *IRAK1* and/or *TRAF6* translation). In temporal lobe epilepsy, *miR-146a* is increased in astrocytes (Aronica and others 2010). In a spared-nerve injury mouse model of neuropathic pain, overexpressing *miR-146a-5p* inhibited TRAF6-JNK-CCL2 signaling in astrocytes to limit neuropathic pain (Lu and others 2015).

NFκB directly induces both anti-inflammatory *miR-146a* and pro-inflammatory *miR-155*, so the expression of

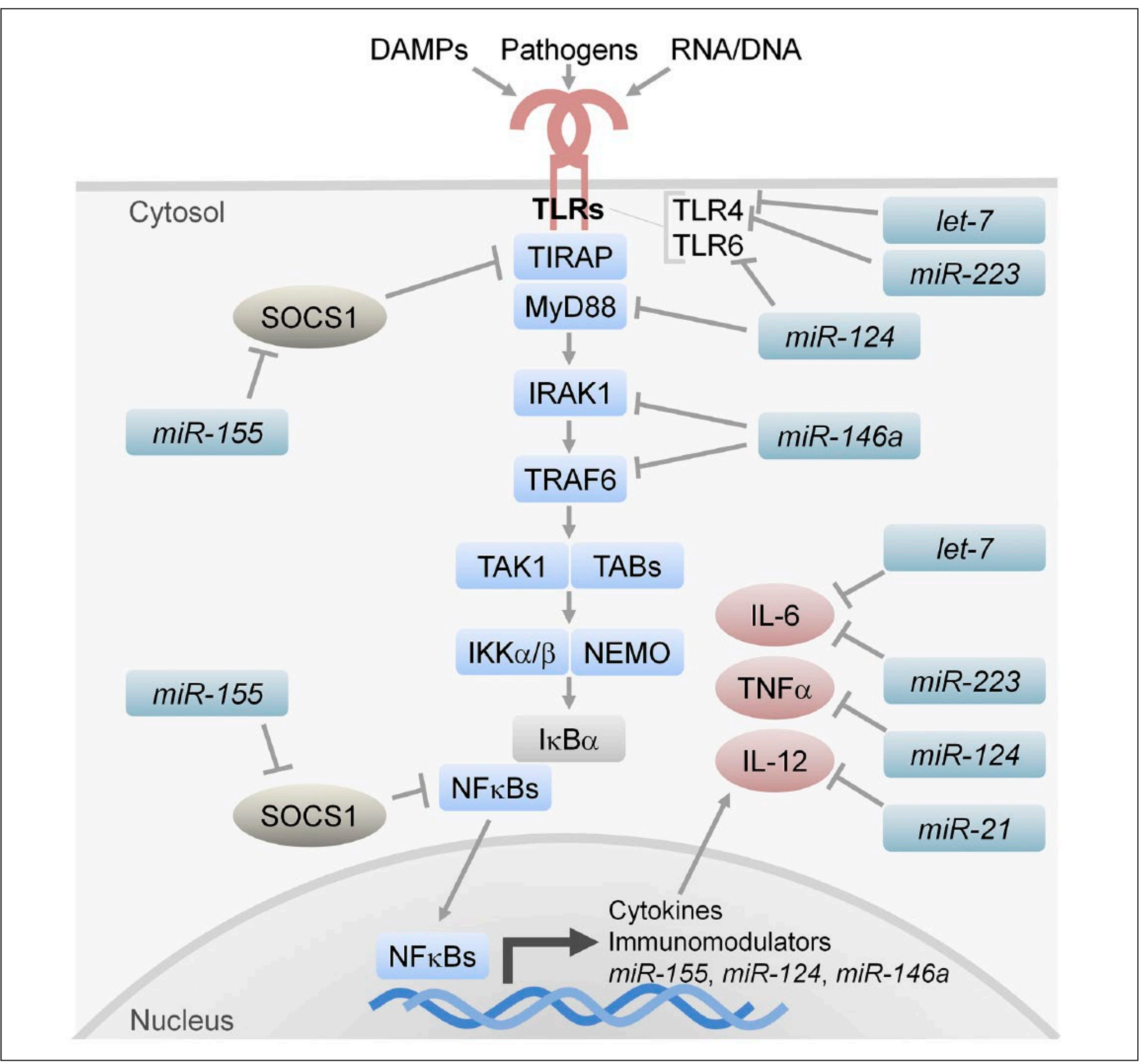

Figure 6. miRNAs both amplify and dampen inflammatory signaling pathways, such as the NFκB pathway. The NFκB signaling pathway is shown as an example of inflammatory signaling. TLR activation by binding of DAMPs, pathogen-associated molecular patterns, or extracellular RNA/DNA activates MyD88-dependent intracellular signaling, resulting in nuclear translocation of NFκB transcription factors p65 and p50. NFκBs upregulate both pro- and anti-inflammatory miRNAs. Pro-inflammatory miRNAs, such as *miR-155* (left side), reduce mRNA availability of factors that inhibit activation of this inflammatory pathway. These pro-inflammatory miRNA pathways can amplify pro-inflammatory signaling cascades. Anti-inflammatory miRNAs (right side) reduce mRNA availability of inflammatory receptors, signaling mediators, and cytokines. These anti-inflammatory miRNAs provide a negative feedback mechanism and act as a "brake" on inflammation. Blue, signaling mediators; grey, inhibitory binding partner; beige-gold, inhibitor of signaling; red, pro-inflammatory cytokines; turquoise, miRNAs.

these miRNAs is often considered in parallel. It is interesting that NFκB-dependent transcription involves activation of two miRNAs with such divergent roles (Fig. 6).

miR-21. *miR-21* is another anti-inflammatory miRNA that could effectively modulate neuroinflammation. *miR-21* is upregulated in activated immune cells, including neutrophils, dendritic cells, monocytes/macrophages, and T cells (see Sheedy 2015). In mouse bone marrow–derived macrophages and human blood monocytes, *miR-21* is induced by LPS downstream of TLR4-MyD88-NFκB signaling. *miR-21* directly targets *Pdcd4*; PDCD4 participates in pro-inflammatory signaling by increasing IL-6 and decreasing IL-10 (by preventing a Twist2-c-Maf-IL-10 transcriptional cascade)

(Sheedy and others 2010; van den Bosch and others 2014). The importance of PDCD4 is highlighted by the fact that more *Pdcd4* KO mice survive a potentially lethal LPS dose (a model of sepsis) (Sheedy and others 2010). Conversely, survival times are decreased in *miR-21* KO mice challenged with LPS-induced peritonitis (Barnett and others 2016). There is some evidence for a pro-inflammatory role of *miR-21* in macrophages. *miR-21* KO macrophages are better able to adopt an anti-inflammatory phenotype; this may be due to de-repressed expression of the *miR-21* target *Stat3* (Wang and others 2015).

miR-21 has several additional targets that are relevant to neuroinflammation. *miR-21* targets *Smad7*, thereby de-repressing TGF-β signaling (Barnett and others 2016). *miR-21* targets *Spry1* to boost MAP kinase signaling (Thum and others 2008). *miR-21* also affects differentiation of other immune cells, including T cells and dendritic cells. *miR-21* directly targets *IL-12p35*, a subunit of the cytokine IL-12 (Lu and others 2009b). IL-12 drives T_h1 cell differentiation and production of the T_h1 cytokine IFN-γ. Dendritic cells that are deficient in *miR-21* express higher IL-12 levels, and *miR-21* deficiency enhances T_h1 and T_h17 cell responses (Lu and others 2011). Others have shown that *miR-21* is required for T cells to develop a T_h17 phenotype (Murugaiyan and others 2015).

Reducing or blocking *miR-21* is beneficial in EAE. In mouse T cells, *miR-21* increased in T_h17 cells and promoted their differentiation by targeting *Smad7*. Adoptively transferring T_h17 cells that were polarized in the presence of *miR-21* inhibitor, or systemically inhibiting *miR-21* (using anti-miR-21) prior to disease onset, ameliorated EAE neurologic symptoms (Murugaiyan and others 2015). *miR-21* expression also associates with disease progression in human MS. In $CD4^+$ T cells, *miR-21* was upregulated in cells from patients with RRMS (Fenoglio and others 2011), but was downregulated in cells from patients with secondary progressive MS (Sanders and others 2016). Thus, *miR-21* has detrimental roles in EAE by driving T_h17 cell differentiation; however, *miR-21* likely has divergent roles in MS that vary by cell type and disease type/progression.

In contrast with its role in EAE, *miR-21* has anti-inflammatory functions in other diseases with prominent neuroinflammatory cascades. Bhalala and others (2012) overexpressed *miR-21* or a *miR-21* sponge (a synthetic RNA that contains several complementary binding sites to the seed region of a miRNA of interest; a dominant-negative method) specifically in astrocytes. They found that overexpressed *miR-21* reduced astrocyte hypertrophy in the traumatically injured spinal cord. Conversely, a *miR-21* sponge boosted SCI-induced astrocyte hypertrophy—but also increased axon sprouting into a glial scar that normally blocks axon growth. In another SCI study, intrathecal mini-pump administration of a *miR-21* antagomir in rats exacerbated intraspinal pathology and limited spontaneous recovery of function (Hu and others 2013). After TBI, *miR-21* is a biomarker for severe injury (Di Pietro and others 2017) and overexpressing *miR-21* improves blood-brain barrier maintenance, angiogenesis, and neuroprotection, as well as functional recovery (Ge and others 2014; Ge and others 2015). *miR-21* overexpression also indirectly (via reduced microglial toxicity) and directly protected cultured cortical neurons from apoptosis caused by oxygen and glucose deprivation (Buller and others 2010; Zhang and others 2012), suggesting that increasing *miR-21* could be therapeutic after stroke. In the context of aging, *miR-21* upregulation is a biomarker of aging (Olivieri and others 2012), and in mouse neurons, treatment with Aβ protein reduces *miR-21* (Schonrock and others 2010). Although these preliminary data on miR-21 in aging are promising, the function of miR-21 in aging, AD, and other neurodegenerative diseases is not well characterized.

Overall, *miR-21* has predominantly anti-inflammatory and neuroprotective effects that could benefit neurologic diseases with toxic neuroinflammatory cascades. However, it is clear that *miR-21* also can have detrimental effects in MS and other inflammatory conditions, highlighting the importance of understanding how potential miRNA therapeutics can affect the phenotype of different cell types in a specific neuroinflammatory disorder and disease stage.

miR-223. *miR-223* has anti-inflammatory properties in peripheral immune cells. In macrophages, *miR-223* drives typical anti-inflammatory macrophage phenotype (Deiuliis and others 2016; Ying and others 2015; Zhuang and others 2012). *miR-223* in macrophages limits translation of *Nlrp3* mRNA, which encodes a key component of the NLRP3 inflammasome (Bauernfeind and others 2012; Haneklaus and others 2012). *miR-223* may also reduce inflammatory signaling in neutrophils (Li and others 2017) and dendritic cells (Zhou and others 2015). In T cells, *miR-223* was upregulated in patients with rheumatoid arthritis and *miR-223* impaired activation of a protective IGF-1/IL-10 axis (Lu and others 2014).

miR-223 is understudied in the nervous system; however, existing data indicate that *miR-223* both positively and negatively affects neuroinflammatory cascades. *miR-223* reduced neurotoxicity after global ischemia and excitotoxic injury by enhancing the degradation of mRNA encoding glutamate receptors (Harraz and others 2012). A *miR-223* antagonist may reduce SCI pathology by improving neuroprotection and angiogenesis (Liu and others 2015), although more studies are required. In EAE, *miR-223* deletion in mice reduced dendritic cell activation of T_h17 (but not T_h1) cell differentiation, improved myeloid-derived suppressor cell activity, and enhanced

neurologic function (Cantoni and others 2017; Ifergan and others 2016). *miR-223* was significantly upregulated in CD4$^+$ T cells from patients in the relapse-remitting phase of MS, suggesting a possible role in positively regulating pathogenic cascade that contributes to RRMS (Hosseini and others 2016). Reduced serum *miR-223* may be a hallmark of AD (Jia and Liu 2016), although the function of *miR-223* in AD and other neurodegenerative disorders remains unclear.

miRNAs with Pro- and Anti-Inflammatory Actions: The Let-7 *Family*

The *Lethal-7* (*let-7*) miRNA is conserved across species (from *C. elegans* to humans) (Reinhart and others 2000), and was the first miRNA to be identified in humans (Pasquinelli and others 2000). In humans and mice, nine mature *let-7* miRNAs exist and each has distinct nucleotide sequences, but all contain highly conserved seed regions (Lee and others 2016). *Let-7* family members generally elicit cell differentiation and are tumor suppressors (Lee and others 2016).

Let-7 miRNAs modulate inflammation. Increasing *let-7* expression in macrophages promotes differentiation into an anti-inflammatory phenotype, likely by reducing expression of the transcription factor *C/ebp-δ* (Banerjee and others 2013). Other key mRNA targets of *let-7* include the inflammatory cytokine *IL6* (Schulte and others 2011), and the highly conserved pattern recognition receptor, *Tlr4* (Teng and others 2013). *Let-7* provides negative feedback to limit inflammatory activation; however, it is downregulated by NFκB activation (Schulte and others 2011). NFκB drives transcription of the RNA-binding protein Lin28, which inhibits *let-7* (Iliopoulos and others 2010). IL-6 translation is therefore disinhibited; IL-6 signaling can activate STAT3-dependent NFκB transcription, thereby closing a positive inflammatory feed-forward loop that amplifies inflammation. In dendritic cells activated by LPS, *let-7* inhibits *Socs1*, which promotes dendritic cell maturation and their ability to drive T cell proliferation (Kim and others 2013; Zhang and others 2011). *let-7* may also limit self-renewal of memory T cells (Almanza and others 2010), suppress CD4$^+$ T cell activation, promote T cell anergy (Marcais and others 2014), and inhibit T_h17 cell differentiation (Zhang and others 2013). In the CNS, *let-7* limits microglial activation (Cho and others 2015) and promotes differentiation of cultured glial progenitor cells into astrocytes (Shenoy and others 2015).

In neuroinflammatory disorders, *let-7* has some protective roles. After ischemic stroke, overexpression of *let-7* reduced poststroke neurotoxicity and improved neurologic outcomes, an effect that might be caused by *let-7*-mediated reduction of caspase-3. These effects were also associated with reduced microglial activation (Ni and others 2015). After T10 transection SCI, *let-7* was increased in the lumbar spinal cord (Liu and others 2010), although the biological effects of *let-7* induction remain undefined.

Paradoxically, *let-7* can also contribute to neuropathology. During insult or in neurodegenerative disease, *let-7* can be released by dying neurons into the extracellular space, where it acts as a DAMP (Coleman and others 2017; Lehmann and others 2012). Extracellular *let-7* can act as a ligand for TLR7, an endolysosome-localized receptor that binds to extracellular-derived single-stranded RNA (which is found at low levels under healthy conditions) (Kawai and Akira 2010). When bound, *let-7*:TLR7 elicits microglia and macrophage activation and propagates neurotoxicity. The increased expression of TLR7 and binding by *let-7* indicates tissue damage or infection and immune cell activation. In fact, elevated *let-7* has been proposed as a biomarker in MS (Gandhi and others 2013), stroke (Huang and others 2016a), and AD (Lehmann and others 2012). In EAE, *let-7* was found to drive pathogenic T_h1 and T_h17 cell differentiation to worsen disease by targeting *IL-10* mRNA (Guan and others 2013). In a newt model of tail/spinal cord regeneration, *let-7* is downregulated; application of a *let-7* mimic prevents tail regeneration, likely by reducing the effectiveness of the ependymal response to amputation (Lepp and Carlone 2015).

Thus, it appears that *let-7* acts within immune cells to promote both anti- and pro-inflammatory actions, whereas extracellular *let-7* may worsen neuroinflammatory conditions. The *let-7* miRNA family remains underexplored in the context of several neurological conditions. Future studies could reveal whether the role of *let-7* as a DAMP is specific to a selected set of miRNAs (e.g., *miR-21* also binds TLR7; Yelamanchili and others 2015), or whether all/most miRNAs released during cell stress act as DAMPs and similarly activate immune cells.

Future Directions: Manipulating Immunomodulatory microRNAs to Improve CNS and Peripheral Nervous System Neuroinflammatory Pathologies

Several strategies can be used to reveal the functional importance of miRNAs. Deletion of essential miRNA machinery components Dicer, Drosha, or DGCR8 has been used to establish broad functional roles of miRNAs in health and disease. For instance, *Dicer* conditional deletion in developing parvalbumin-expressing dorsal root ganglion neurons prevents maintenance of proprioceptive cell fate and peripheral connectivity (O'Toole and

others 2017); deletion of *Dicer* in forebrain neurons predisposes mice to neurodegeneration in adulthood (Hébert and others 2010); and *Dicer*-deficient T cells show reduced differentiation capacity and preferentially differentiate into inflammatory T_h1 cells (Muljo and others 2005). These results indicate that miRNAs play a critical role in cell development, cell fate, and cell survival. However, there are caveats to strategies relying on deletion of these miRNA regulators: Dicer, Drosha, and DGCR8 have functions that are independent of regulating miRNA processing, so deleting these key genes will have pleiotropic effects that limit physiologic and therapeutic relevance (i.e., removing all miRNAs, even in a single cell type, could have wide-ranging effects that preclude therapeutic relevance) (Macias and others 2013). For example, *Dicer*-null embryonic stem cells lack both miRNAs and small interfering RNAs, Drosha cleaves and thereby destabilizes mRNAs and long noncoding RNAs, and DGCR8 also influences levels of other small RNAs. Regardless, complementing these studies with microarrays and follow-up research on newly identified functional miRNAs can be powerful. For example, *Dicer* conditional deletion in mature mouse oligodendrocytes caused demyelination, neuroinflammation, and shortened lifespan; using miRNA microanalysis combined with target prediction analyses of 3′ UTRs, *miR-219* and its target RNA *ELOVL7* were identified as novel mediators controlling oligodendrocyte physiology (Shin and others 2009). There are several in silico target prediction algorithms that can reveal potential miRNA-target interactions and networks (Steinkraus and others 2016).

Once a miRNA of interest is recognized, then specific gain- and loss-of-function experiments can be completed. In particular, several unique loss-of-function strategies can be used to identify key biological effects of miRNAs. In addition to typical mutagenesis (KO of specific miRNA; though there can exist miRNA redundancy), more therapeutically relevant competitive miRNA inhibitors (e.g., antimiRs, antagomirs, LNA-based antimiRs, and sponges) or miRNA response element blockers (i.e., a blocker that spans the miRNA binding site on a specific RNA to physically prevent miRNA binding) can be used to test the necessity and downstream mechanisms of action for a given miRNA (see Steinkraus and others 2016). Thus, coordinating bioinformatic predictive approaches with robust biological readouts and functional assays will facilitate discovery of relevant new miRNA targets.

In studying miRNAs, one must take into account several considerations. First, a miRNA labeled as a "biomarker" of inflammation suggests its potential involvement in the disease process, but the effects of the miRNA could be pro- or anti-inflammatory and could be indicative of an ongoing pathological response or, conversely, an attempt to restore homeostasis (e.g., *miR-155, miR-146*, and *miR-21* are all upregulated by LPS stimulation, yet have divergent roles). Second, there remain innumerable understudied miRNAs; examining existing microarray databases, profiling-based strategies, and other data could provide clues regarding undiscovered immunomodulatory miRNAs. Third, of the studied miRNAs, it is likely that most have other as yet unidentified roles. This is expected, since ongoing research is often biased by previous findings. For instance, our group found that *miR-155*—which had known roles in cancer and inflammation—also regulated axon growth (Gaudet and others 2016b), susceptibility to obesity (Gaudet and others 2016a), and anxiety- and depressive-like symptoms (Fonken and others 2016b). Fourth, miRNAs can have hundreds of "predicted" targets; however, it is important to determine whether these miRNA-RNA interactions are valid and have biological relevance. Conversely, it could be useful to work "backwards" to identify potential immunomodulatory miRNAs; that is, one could identify an inflammatory mRNA that they would like to downregulate, then use prediction algorithms to determine putative miRNAs that would bind to that inflammatory mRNAs. Finally, it is important to consider the double-edged sword of modulating miRNAs: by binding several mRNAs, they may act as intrinsic combinatorial therapies, but such coregulation could also have unintended consequences. For instance, *miR-21* has beneficial effects in several neuroinflammatory disorders (SCI, TBI, ischemia, and aging), but *miR-21* also worsens EAE (Murugaiyan and others 2015), binds TLR7 to act as a DAMP (Yelamanchili and others 2015), and is an oncogene (Medina and others 2010).

Conclusions

Thousands of published articles discuss the roles of miRNAs in the nervous system, yet microRNA research is still in its infancy. New genomic loci for noncoding RNAs continue to be discovered, increasing the complexity in our models of post-transcriptional regulatory networks. Furthermore, evidence that miRNAs can be delivered between cells—even over long distances—suggests that these small RNAs can communicate physiologic status and alter function of cells throughout the body.

Given that miRNAs have important intra- and intercellular roles, it is clear that they could control aspects of neuroinflammation. Indeed, as discussed above, miRNAs with roles in pro-inflammatory (*miR-155, miR-27b, miR-326*), anti-inflammatory (*miR-124, miR-146a, miR-21, miR-223*), and mixed immunomodulatory (*let-7* family) responses regulate neuroinflammation in rodent models of neurologic trauma and disease. Undoubtedly, other

miRNAs exist that have immunomodulatory function, but remain to be revealed and/or tested in the nervous system. It is remarkable that the miniscule seven-nucleotide miRNA-RNA interaction can have such wide-ranging cellular and physiologic functions.

Identifying miRNA-based strategies that improve neurological disorders could be useful, since miRNAs target multiple RNAs and act as intrinsic combinatorial modulators. Therapeutic modulation of miRNAs in CNS disorders is in clinical trials for glioblastoma (Christopher and others 2016), underscoring the clinical potential of these small molecules. Thus, revealing therapeutically relevant immunomodulatory miRNAs could lead to novel therapies that dampen neuroinflammation and improve outcomes in neurological disorders.

Declaration of Conflicting Interests

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