MicroRNA 155 and viral-induced neuroinflammation

Laura L. Dickey, Timothy M. Hanley, Thomas B. Huffaker, Andrew G. Ramstead, Ryan M. O’Connell *, Thomas E. Lane *

Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT 84112, United States

Abstract

MicroRNA (miRNA) regulation of gene expression is becoming an increasingly recognized mechanism by which host immune responses are governed following microbial infection. miRNAs are short, non-coding RNAs that repress translation of target genes, and have been implicated in a number of activities that modulate host immune responses, including the regulation of immune cell proliferation, survival, expansion, differentiation, migration, polarization, and effector function. This review highlights several examples in which mammalian-encoded miR-155 influences immune responses following viral infection of the CNS.

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1. Introduction

1.1. MicroRNAs (miRNAs)

miRNAs are short, non-coding RNA molecules that function to regulate gene expression at the post-transcriptional level by binding complimentary 3′ untranslated region (3′ UTR) sequences of target mRNAs, thereby repressing gene expression (1). miRNAs were first reported in the 1990s as regulatory sequences involved in C. elegans development (Lee et al., 1993); however, they have since been further characterized as gene-repression elements that affect gene-expression profiles in more than 100 animal species (Griffiths-Jones et al., 2006).

The majority of miRNAs are encoded within intron regions of genomes, and are transcribed by RNA polymerase II into primary transcripts referred to as pri-miRNAs. In the canonical miRNA pathway, pri-miRNAs are cleaved by an RNAase III-Drosha complex in order to yield pre-miRNAs. Alternatively, miRNA transcripts called mirtrons are produced independently of the RNAase III-Drosha complex (Kim et al.,...
Pre-miRNAs and mirtrons are transported from the nucleus by Exportin 5 into the cytoplasm and processed by Dicer into short (~22 nucleotides), double-stranded miRNA/miRNA molecules that subsequently form an RNA-induced silencing complex (RISC) with Argonaute and other proteins. In the RISC complex, one strand of the miRNA duplex functions to bind complementary sequences in the 3′UTR and thereby repress target genes, while the other strand is degraded (Dai and Ahmed, 2011). miRNAs are regulated in part by RNA-binding proteins that help determine the context in which miRNAs are available for target-gene repression (van Kouwenhove et al., 2011).

Because miRNAs have been shown to target many important signaling proteins and transcription factors that govern immune processes and differentiation (O’Connell and Baltimore, 2012; O’Connell et al., 2010a), it is not surprising that these molecules have important roles during immune responses to microbial infections, including those that affect the CNS. Infection of the CNS results in significant changes in miRNA expression profiles, many of which facilitate various aspects of immune processes (Dahm et al., 2016; Cardoso et al., 2016). It should be noted that there is a growing body of literature that discusses miRNAs encoded by viruses that influence viral pathogenesis; however, they are beyond the scope of this review. One miRNA that has gained considerable attention in recent years is mammalian-encoded miR-155, which numerous reports have implicated in regulating immune responses, including to neurotropic viruses. Here we provide a discussion of several examples in which miR-155 regulates neuroinflammation during viral infection of the CNS.

1.2. miR-155

While miR-155 was originally identified as an oncogene in chicken lymphomas (Tam et al., 1997), subsequent work has revealed that it has myriad roles in regulating immune responses. miR-155 is overexpressed in many mammalian hematopoietic cancers and is expressed by and functions within a variety of activated immune cell types, including B cells, macrophages, various T cell populations, NK cells, and dendritic cells (Vigorito et al., 2007; Haasch et al., 2002; O’Connell et al., 2007; Rodriguez et al., 2007; Taganov et al., 2006; Thai et al., 2007) to regulate cytokines, chemokines, and transcription factors important for mounting an optimal immune response. For example, miR-155 expression leads to increased production of IFN-γ and diminished expression of IL-2 by T cells (Banerjee et al., 2010; Das et al., 2013; Gracias et al., 2013), augments IFN-γ-dependent CD4+ and CD8+ T cell responses to tumors (Huffaker et al., 2012), contributes to the development of T regulatory cells (Lu et al., 2015; Kohlhaas et al., 2009), and alters the CD8+ T cell memory:effector ratio by skewing CD8+ T cells toward a memory phenotype (Almanza et al., 2010). Within immune cells, miR-155 represses a variety of immunoregulatory proteins that include signaling molecules such as SHIP1 (Trotta et al., 2012) and SOCS1 (Wang et al., 2010), as well as transcriptional regulators such as Jarid2 (Nakagawa et al., 2016), Ets1 (Zhu et al., 2011; Hu et al., 2013), PU.1 (29) and Foxl2 (Hu et al., 2014). Importantly, Moore et al. (2013) showed that miR-155 drives myeloid cells toward an M1, or proinflammatory, phenotype. Several studies suggest that expression of miR-155 by microglia is important in regulating expression of proinflammatory genes that subsequently influence neuroinflammation, primarily though the inhibition of SOCS1 and genes involved in microglial polarization such as IL-13R, SMAD2, and CEBPβ (Cardoso et al., 2016; Freilich et al., 2013; Ponomarev et al., 2013; Su et al., 2016). These and other studies have demonstrated that miR-155 is an important regulator of immune cell development and function.

There is increasing evidence that miR-155 influences neuroinflammatory diseases such as the human demyelinating disease multiple sclerosis. miR-155 was initially shown to influence neuroinflammation through the induction of myelin-reactive Th17 cells following induction of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis (MS) (Murugaiyan et al., 2011; O’Connell et al., 2010b). Alejandro et al. (Lopez-Ramirez et al., 2014) discovered that miR-155 is upregulated in neurovascular units in active MS lesions compared to normal-appearing white matter in MS patients. In addition, the group used the EAE model to show that miR-155 expression is dramatically increased in mice with hind-limb paralysis during the recovery phase, and that miR-155 regulates blood-brain-barrier (BBB) function. The latter finding is consistent with a study by Lopez-Ramirez et al. (2014) showing that miR-155 negatively regulates blood-brain-barrier permeability by targeting the cell-cell complex molecules annexin-2 and claudin1, as well as the adhesion components DOCK-1 and syntenin-1. In a recent study, Cerutti et al. (2016) also demonstrated that miR-155 regulates blood-brain barrier function by targeting adhesion molecules VCAM1 and ICAM1, thereby affecting monocyte and T cell adhesion to the brain endothelium. Roles for miR-155 during neuroinflammation have also been demonstrated in models of Parkinson’s Disease (Thome et al., 2016), Alzheimer’s Disease (Guedes et al., 2014), alcohol-induced neuroinflammation (Lippai et al., 2013), and amyotrophic lateral sclerosis (ALS) (Paris et al., 2013).

Not surprisingly, multiple reports identify miR-155 as important in mediating host responses to microbial diseases (Zeng et al., 2015), including viral infections with members of the Herpesviridae, Coronaviridae, Arenaviridae, Flaviviridae, and Retroviridae families (discussed further below) (Yao and Nair, 2014; Kaluzna, 2014; Gottwein, 2013; Bhela et al., 2015; Bhela et al., 2016; Diceny et al., 2016; Dudda et al., 2013; Lind et al., 2013; Lu et al., 2011; Martinez-Nunez et al., 2009; Napuri et al., 2013; Zawislak et al., 2013). Recently, miR-155 has been shown to tailor immune responses in models of viral-induced neurologic disease, and numerous mechanisms by which miR-155 controls immune responses following viral infection have been identified. For example, multiple studies have demonstrated that T cell responses are impaired in the absence of miR-155 during infection with certain neurotropic viruses (Lu et al., 2015; Bhela et al., 2015; Bhela et al., 2014; Diceny et al., 2016; Dudda et al., 2013; Lind et al., 2013; Zawislak et al., 2013). Below, we highlight several examples in which miR-155 influences inflammatory responses following viral infection of the CNS (Table 1).

2. miR-155 and neuroinflammation following CNS viral infection

2.1. Herpes simplex virus (HSV)

HSV infections generally result in surface lesions on skin, mucosa, and eyes. After primary infection, HSV establishes a life-long latent infection in neuronal tissues, although latent virus is periodically reactivated. While this process is not thoroughly defined, factors such as fever, UV exposure, increased viral load, stress, and host genetics have been implicated in HSV reactivation (Roizman and Whitley, 2013). Occasionally, HSV spreads to the brain and causes a rare but life-threatening condition called herpes simplex encephalitis (HSE) (Whitley et al., 1982). In adults, HSE is generally a result of reactivated infection with HSV-1 and results in focal hemorrhagic necrosis in the temporal lobe, whereas, in infants, HSE is more often the result of primary HSV-2 infection and manifests as diffuse brain involvement or multifocal lesions, often without hemorrhage (Whitley, 2006). Lesions in the brain are believed to be caused by both the infection and the immune response to the infection (Wang et al., 2012). Ocular infection of susceptible mice results in a T cell-mediated lesion in the cornea that can lead to encephalitis, and provides a useful model for studying the neuroinflammatory response to HSV infection (Lundberg et al., 2008).

Bhela et al. (2014) showed that miR-155−/− mice were significantly more susceptible to HSE than WT animals following ocular HSV-1 infection, and that this was concomitant with higher viral titers in brains, but not corneas. In addition, the degree of astrocytosis in WT mice was higher than in miR-155−/− mice. Numbers of virus-specific CD8+ T cells in draining lymph nodes were reduced in miR-155−/− mice compared to WT mice (Bhela et al., 2014), and transferring HSV-immune
CD8+ T cells from HSV-specific TCR transgenic mice into miR-155−/− mice rescued the knockout animals from lethal herpetic encephalitis, indicating that the increased disease susceptibility of miR-155−/− mice was due to impaired CD8+ T cell responses (Bhela et al., 2014). The number of CD8+ T cells from HSV-infected miR-155−/− mice that produced TNF-α and/or IFN-γ was significantly lower than that in WT mice, indicating that miR-155 is necessary for the expansion and differentiation of CD8+ T cells during chronic infection.

In a subsequent study, Bhela et al. (2015) showed that after ocular infection with HSV-1, CD4+ T cell accumulation in corneas was significantly decreased in miR-155−/− mice compared to WT mice, which corresponded with reduced lesion severity in either miR-155−/− mice or WT mice treated subconjunctivally with a miR-155 antagonist (antagomir-155). In addition, HSV-infected miR-155−/− mice exhibited decreased frequencies of Th1 and Th17 cells in lesions and lymphoid organs compared to infected WT mice, and this was likely due to miR-155-mediated promotion of CD4+ T cell proliferation. Local antagonism of miR-155 treatment after HSV-1 infection resulted in decreased CD4+ T cell and neutrophil infiltration to corneas, in addition to reduced expression of IL-1β, IL-6, IFN-γ, and IL-16. Furthermore, the group showed that expression levels of SHIP1 and IFN-γRα, which regulate IFN-γ expression and Th1 differentiation, respectively, were higher in activated CD4+ T cells from miR-155−/− mice compared to cells from WT mice during HSV-1 infection. These studies demonstrate an important role for miR-155-mediated regulation of T cell responses during HSV-1 infection.

2.2. Cytomegalovirus (CMV)

CMV is a common virus that infects persons of all ages. It is generally asymptomatic, but can cause disease in people with weakened immune systems and fetuses infected with the virus in utero. Infants born after congenital CMV infection can have neurological defects, including microcephaly, cerebral palsy, ocular problems, seizures, hearing loss, and cognitive deficiencies (Varani and Landini, 2011; Boppiana et al., 2013; Mussi-Pinhata et al., 2009; Pass et al., 2006; Anderson et al., 1996). Intraperitoneal inoculation of newborn mice with murine CMV (MCMV) provides a model that recapitulates the major characteristics of human CMV infection with regard to route of neuroinvasion, neuropathology, and immunopathology (Slavuljica et al., 2015). NK cells are important in controlling immune responses to viruses, including MCMV (Wei et al., 2014). Infection after reconstitution of irradiated mice with equal numbers of bone marrow cells from miR-155−/− mice compared to WT mice, which corresponded with reduced lesion severity in either miR-155−/− mice or WT mice treated subconjunctivally with a miR-155 antagonist (antagomir-155). In addition, HSV-infected miR-155−/− mice exhibited decreased frequencies of Th1 and Th17 cells in lesions and lymphoid organs compared to infected WT mice, and this was likely due to miR-155-mediated promotion of CD4+ T cell proliferation. Local antagonism of miR-155 treatment after HSV-1 infection resulted in decreased CD4+ T cell and neutrophil infiltration to corneas, in addition to reduced expression of IL-1β, IL-6, IFN-γ, and IL-16. Further, the group showed that expression levels of SHIP1 and IFN-γRα, which regulate IFN-γ expression and Th1 differentiation, respectively, were higher in activated CD4+ T cells from miR-155−/− mice compared to cells from WT mice during HSV-1 infection. These studies demonstrate an important role for miR-155-mediated regulation of T cell responses during HSV-1 infection.

2.3. Lymphocytic choriomeningitis virus (LCMV)

LCMV is a rodent-borne arenavirus that causes mild meningitis or, rarely, meningoencephalitis in adults and more severe complications in fetuses and neonates, including acute hydrocephalus, fetal demise, birth defects such as microcephaly and intracranial calcifications, and chorioretinitis. Infections with LCMV are not generally fatal; however, post-infection neurological damage is possible. As with many diseases,
LCMV disease is caused by the combination of the viral infection and the host immune response to the virus (Bonthius, 2012).

Dudda et al. (2013) infected WT or miR-155−/− mice intravenously (i.v.) with LCMV and demonstrated that the levels of total and virus-specific CD8+ T cells were drastically reduced in miR-155−/− mice compared to WT mice at the peak of response. The group used adoptive transfer experiments to show that during LCMV infection, miR-155−/− CD8+ T cells exhibited decreased proliferation and increased levels of the apoptosis-marker AnnexinV compared to cells from WT mice. SOCS1 transcript and protein levels were inversely related to the cellular levels of miR-155 in CD8+ T cells. Furthermore, stimulation of effector CD8+ T cells isolated 8 days after LCMV infection resulted in limited phosphorylation of STAT5 in miRNA-155-ablated cells compared to WT cells, demonstrating impaired cytokine signaling in response to IL-2, IL-7, or IL-15 stimulation. This study identified a novel role for miR-155 in regulating cytokine production through SOCS1.

Lind et al. (2013) showed that after i.v. LCMV infection of WT or miR-155−/− mice, there was a dramatic reduction of virus-specific CD8+ T cells in splenocytes from miR-155−/− mice compared to WT mice. As multiple studies have demonstrated that miR-155 is required for optimal CD8+ T cell accumulation, the group hypothesized that the phenomenon could be due to interference in PI3K/Akt signaling. The PI3K/Akt signaling pathway is a highly conserved, tightly regulated signaling cascade that relays signals from activated cell-surface receptors, such as receptor tyrosine kinases and cytokine receptors, to downstream effectors that regulate transcription, protein synthesis, metabolism, growth, proliferation, and survival (Vanhaesebroeck et al., 2012). Previous studies have shown that miR-155 targets multiple steps in this survival pathway (Yamamoto et al., 2011). Lind et al. demonstrated that anti-CD3-stimulated CD8+ T cells isolated from WT mice demonstrated an increase in phosphorylated Akt Ser473; however, there was no increase in Akt Ser473 phosphorylation in stimulated CD8+ T cells from miR-155−/− mice (Lind et al., 2013), indicating that miR-155 mediates T cell survival by regulating the PI3/Akt signaling pathway.

Consistent with previous studies, Lu et al. (2015) used bone marrow chimeras to show that miR-155 is necessary for optimal CD4+ and CD8+ T cell accumulation after i.v. infection with LCMV-Armstrong, which results in acute disease, and that the effect was independent of miR-155 repression of SOCS1; however, the group demonstrated that SOCS1 repression by miR-155 was necessary for the expansion of virus-specific NK cells, as well as the maintenance of virus-specific CD8+ T cell levels after i.p. infection with LCMV Clone 13, which results in chronic infection. These results suggest that miR-155-mediated regulation of T cell expansion is context-specific. Taken together, these studies indicate that miR-155 influences multiple aspects of LCMV-mediated neuroinflammation.

2.4. Japanese encephalitis virus (JEV)

JEV is a mosquito-borne Flavivirus that targets the CNS and causes encephalitis, with the degree of virus-mediated neuroinflammation inversely correlated with positive clinical outcome. Japanese encephalitis has a high mortality rate (up to 30%) and is associated with moderate to severe post-infection sequelae in the majority of patients that survive the disease, including permanent cognitive deficits, behavioral changes, and neurological problems such as paralysis, recurrent seizures, and aphasia (Campbell et al., 2011; Ooi et al., 2008).

Work by Pareek et al. (2014) assessed the effects of miR-155 on JEV-associated inflammation in vitro. The authors overexpressed miR-155 in an immortalized microglial cell line, CHM3E, and showed that concomitant with reduced JEV replication, expression levels of IFN-β, interferon-stimulated genes, TNF-α, and IL-10 were decreased in cells overexpressing miR-155. In addition, interferon regulatory factor 8 (IRF8), complement factor H (CFH), and JEV-induced NF-κB downstream gene expression was attenuated in cells overexpressing miR-155. These findings suggest that miR-155 is important for regulating levels of cytokines and other pro-inflammatory molecules in response to JEV infection in microglia.

Thounaojam et al. (2014) reported that miR-155 is upregulated within the CNS of mice infected i.v. with JEV, and subsequent in vitro experiments demonstrated that microbial cells are a source of miR-155. Locked nucleic acid (LNA)-mediated repression of miR-155 minimized inflammatory responses to JEV infection by promoting increased SHIP1 expression and thereby decreasing downstream expression of the inflammatory cytokines and chemokines IFN-β, TNF-α, MCP-1, and IL-6 in mouse brains. In addition, repressing miR-155 led to the downregulation of TBK-1, IRF-3/7, and NF-κB phosphorylation. Furthermore, the group showed that inhibition of miR-155 resulted in decreased JEV-induced microglial activation and neuronal death, as well as improved survival and clinical symptoms, indicating that miR-155 may be a therapeutic target for virus-mediated inflammation. It is unclear why this study yielded seemingly different results from the previous study with regard to cytokine production; however, it is possible that the parameters of their model systems were responsible for miR-155 having different effects under varying conditions. For example, the study by Pareek et al. employed CHEM3 cells in vitro, while Thounaojam et al. studied inflammatory responses in vivo in the CNS of mice. Because miR-155 is known to mediate inflammatory mechanisms in a variety of cell types, it is likely that its net effect on JEV-induced inflammation is context dependent.

2.5. Human immunodeficiency virus type-1 (HIV-1)

HIV-1 enters the CNS shortly after infection and causes demonstrable CNS pathology within a few months in untreated individuals, most often manifested as minor neurocognitive or neuromotor impairment as assessed by neurological testing (Heaton et al., 2010; Antinori et al., 2007; Lentz et al., 2009; Meyerhoff et al., 1999). Autopsy studies of recently infected and presymptomatic HIV-positive individuals demonstrate encephalopathic changes within the brain, characterized by subtle gliosis, perivascular lymphocytic cuffing, microglial activation, perivascular macrophage accumulation, and multinucleated giant cells (Bell, 1996; Anthony et al., 2003; Tomlinson et al., 1999). The spectrum of HIV-1-induced CNS disease, referred to as HIV-associated neurocognitive disorder (HAND), includes encephalitis, metabolic encephalopathy, motor disorders, neurocognitive dysfunction, and dementia [reviewed in (Clifford and Ances, 2013)]. HAND is thought to be the result of persistent HIV-1 infection of the CNS with the release of toxic viral products, including gp120, Tat, and VPR, in addition to immune activation of CNS-resident microglia and macrophages. Rarely, HIV-1-infected individuals may also experience T-cell-mediated immune reconstitution inflammatory syndrome (IRIS) in the CNS following initiation of antiretroviral therapy. Although the incidence of HIV-associated dementia has decreased with the introduction of effective anti-retroviral therapy, the majority of HIV-1-infected individuals will experience clinically evident neurologic dysfunction during the course of the illness (Heaton et al., 2010; Tozzi et al., 2007).

Within the CNS, HIV-1 primarily infects microglial cells and perivascular macrophages, leading to the establishment of a reservoir for persistent virus production. Recent studies have demonstrated that miR-155 alters HIV-1 replication by targeting both host and viral factors involved in HIV pathogenesis. Swaminathan et al. (2012) showed that miR-155 is upregulated in macrophages in response to TLR3 stimulation, concomitant with a post-entry block to infection with HIV-1, as measured by increased late reverse transcription products and decreased integrated proviral DNA. The miR-155-mediated HIV-1 post-entry block was associated with decreased expression of factors involved in trafficking and/or nuclear import of HIV-1 pre-integration complexes, such as ADAM10, Nup153, and LEDGF/p75, all of which are targets of miR-155.

Ruelas et al. (2015) showed that miR-155 contributes to transcriptional silencing of HIV-1 in T cells by targeting host factor TRIM32, an
E3 ubiquitin ligase that activates NF-kB and drives HIV-1 transcription and associated inflammatory responses.

Recent reports suggest that miR-155 is able to interfere with HIV-1 spread within the CNS by regulating expression of DC-specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGN) on monocytes and monocyte-derived dendritic cells. DC-SIGN has been shown in a number of studies to be involved in HIV-1 spread through a mechanism known as trans-infection (Geijtenbeek et al., 2000), and is also expressed on both macrophages and microglial cells (Soilleux et al., 2002a; Soilleux et al., 2002b; Garcia-Vallejo et al., 2014). Martinez-Nunez et al. (2009) demonstrated that overexpression of miR-155 leads to the downregulation of cell-membrane levels of DC-SIGN by repressing the transcription factor PU.1, thereby decreasing the ability of the HIV-1 surface glycoprotein gp120 to bind the surface of dendritic cells. This study is supported by research by Napuri et al. (2013), who showed that cocaine-mediated miR-155 repression resulted in increased infectivity in monocyte-derived dendritic cells, concomitant with increased expression of DC-SIGN.

In addition to regulating cellular factors involved in HIV-1-mediated inflammatory processes, miR-155 has a direct impact on HIV-1 infection of CNS target cells. Whisnant et al. (2013) reported that miR-155 binds to the HIV-1 genome in the region of the viral infectivity factor (vif) gene and is capable of decreasing viral gene expression in experimental systems. Beyond the mechanisms described above, it is likely that miR-155 controls HIV neuroinflammation via other pathways. As discussed previously, miR-155 plays a role in the polarization of macrophages and microglial cells to the classically proinflammatory M1 phenotype (Moore et al., 2013). M1-polarized macrophages are refractory to HIV-1 infection (Cassol et al., 2009) and are associated with decreased viral production (Cassola et al., 2013), so it stands to reason that miR-155 activity will prove to be important in controlling multiple aspects of HIV-1 infectivity and innate immune responses to the virus.

2.6. Mouse hepatitis virus

Intracerebral inoculation of the neurotropic JHM strain of mouse hepatitis virus (JHMV) provides a model for examining host immune responses that control viral replication and modulate neuroinflammation within distinct cell lineages present in the brain (Bergmann et al., 2006; Lane and Hosking, 2010). CD4+ and CD8+ T cell infiltration controls viral replication during acute infection (Marten et al., 2001; Phares et al., 2012; Plaisted et al., 2014); however, virus clearance is incomplete, and animals that survive the acute disease develop an immune-mediated demyelinating disease that is governed by both T cells and macrophages (Cheever et al., 1949; Perlman et al., 1999; Stohlman et al., 2002; Wang et al., 1990; Sorensen et al., 1980; Houtman et al., 1995; Houtman and Fleming, 1996).

Dickey et al. (2016) recently reported that genetic silencing of miR-155 in JHMV-infected mice results in increased disease severity concomitant with increased mortality and decreased ability to clear virus (Fig. 1A and B). CNS infiltration of both total and virus-specific CD4+ T cells and CD8+ T cells of infected miR-155−/− mice was reduced compared to WT mice (Fig. 1C). T cell antiviral function was also dramatically impaired in miR-155−/− mice infected i.p. with MHV. IFN-γ secretion...
by CD4+ and CD8+ T cells in response to viral peptides was significantly reduced in infected miR-155−/− mice compared to infected control animals (Dickey et al., 2016). In addition, CTL activity was diminished in mice (Glass and Lane, 2003a; Glass and Lane, 2003b; Glass et al., 2001; Stiles et al., 2006). Surprisingly, Dickey et al. (2016) showed that surface expression of CXCR3 was decreased in CD8+ T cells isolated from miR-155−/− mice compared to those from WT mice (Fig. 1E); however, there were no differences in CXCR3 expression on CD4+ T cells between WT or miR-155−/− mice, nor were there differences in homing receptor CCR5 on WT or miR-155−/− T cells. These findings suggest that regulation of homing receptor expression by miR-155 likely occurs via more than one mechanism. Taken together, these studies show that miR-155 is important in mediating T cell responses to virally-induced demyelinating disease.

### 3. Conclusions

This review highlights various mechanisms by which miR-155 regulates inflammatory responses in response to viral infections in the CNS. Currently, miR-155 is known to influence virally induced neuroinflammation by regulating CD4+ and CD8+ T cell accumulation, NK cell maturation and expansion, T cell cytotoxic production, CD8+ T cell-mediated cytotoxicity, astroglisis, macrophage polarization, expression of receptors necessary for viral entry, and expression of viral proteins. As miRNA-virus pathogenesis interactions are an emerging concept in neuroimmunology, it is likely that in the coming years, many additional mechanisms by which miR-155 regulates virally induced CNS inflammation will be discovered.

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