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MicroRNA 155 and Viral-Induced Neuroinflammation

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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.

Keywords

microRNAs; miR-155; neurotropic viruses; neuropathogenesis; neuroinflammation

2. Introduction

2.1 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 (2); however, they have since been further characterized as gene-repression elements that affect gene-expression profiles in more than 100 animal species (3).

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 (4). Pre-miRNAs and mirtrons are transported from the nucleus by Exportin 5 into the cytoplasm and processed by Dicer into

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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 (5). miRNAs are regulated in part by RNA-binding proteins that help determine the context in which miRNAs are available for target-gene repression (6).

Because miRNAs have been shown to target many important signaling proteins and transcription factors that govern immune processes and differentiation (7, 8), 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 (9, 10). 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.

2.2. miR-155

While miR-155 was originally identified as an oncogene in chicken lymphomas (11), subsequent work has revealed that it has myriad roles in regulating immune responses. miR-155 is overexpressed in some 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 (12–16) 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 (17–19), augments IFN-γ-dependent $CD4^+$ and $CD8^+$ T cell responses to tumors (20), contributes to the development of T regulatory cells (21, 22), and alters the $CD8^+$ T cell memory:effector ratio by skewing $CD8^+$ T cells toward an effector memory phenotype (23). Within immune cells, miR-155 represses a variety of immunoregulatory proteins that include signaling molecules such as SHIP1 (24) and SOCS1 (25), as well as transcriptional regulators such as Jarid2 (26), Ets1 (27, 28), PU.1 (29) and Fosl2 (30). Importantly, Moore et al. (31) showed that miR-155 drives myeloid cells toward an M1, or proinflammatory, phenotype. Several studies suggests 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 (10, 32–34). 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) (35, 36). Alejandro et al. (37) 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 (37) 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. (38) 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 (39), Alzheimer's Disease (40), alcohol-induced neuroinflammation (41), and amyotrophic lateral sclerosis (ALS) (42).

Not surprisingly, multiple reports identify miR-155 as important in mediating host responses to microbial diseases (43), including viral infections with members of the *Herpesviridae*, *Coronaviridae*, *Arenaviridae*, *Flaviviridae*, and *Retroviridae* families (discussed further below) (44–55). 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 (21, 47–51, 55). Below, we highlight several examples in which miR-155 influences inflammatory responses following viral infection of the CNS (Table 1).

3. miR-155 and neuroinflammation following CNS viral infection

3.1 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 (56). Occasionally, HSV spreads to the brain and causes a rare but life-threatening condition called herpes simplex encephalitis (HSE) (57). 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 (58). Lesions in the brain are believed to be caused by both the infection and the immune response to the infection (59). 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 (60).

Bhela et al. (48) 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 animals 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 (48), 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 (48). The number of CD8$^+$ T cells from HSV-infected *miR-155*$^{-/-}$ mice that produced TNF-α and/or IFN-γ in response to HSV-1 infection was reduced compared to CD8$^+$ T cells from WT mice. Furthermore, expression levels of homing molecules VLA-4 and CD44 on CD8$^+$ T cells from HSV-1-infected *miR-155*$^{-/-}$ mice were significantly reduced compared to cells from WT mice.

In a subsequent study, Bhela et al. (47) 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 subconjunctively 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 antagomir-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.

3.2 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 (61–65). 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 (66). NK cells are important in controlling immune responses to viruses, including MCMV (67). After infection, NK cells produce cytokines and lytic molecules that help control viral replication (68, 69). NK cells that express the Ly49H receptor, which recognizes glycoproteins on MCMV virions, secrete perforin and granzymes to specifically kill virally infected cells (70, 71). In addition, they proliferate to produce large numbers of virus-specific effector NK cells, and a small population of memory NK cells remains after the infection is cleared (67, 72, 73).

Zawislak et al. (55) showed that NK cell populations in naïve *miR-155*$^{-/-}$ mice demonstrated a more mature phenotype than NK populations in WT mice, indicating that miR-155 regulates NK cell maturation. The group generated mixed-bone-marrow-chimeric mice by reconstituting irradiated mice with equal numbers of bone marrow cells from

miR-155$^{-/-}$ (CD45.1) and WT (CD45.2) mice. The percentage of *miR-155*$^{-/-}$ NK cells in the peripheral blood was significantly lower than that of WT NK cells by 11 weeks post reconstitution, suggesting that NK cell homeostasis is impaired in the absence of miR-155. The group co-transferred WT and *miR-155*$^{-/-}$ NK cells into *Rag2*$^{-/-}$ × *Il2rg*$^{-/-}$ mice (deficient in NK, B, and T cells) and showed that while there were no differences in proliferation rate, *miR-155*$^{-/-}$ NK cells showed decreased survival compared to WT NK cells. Seven days post intraperitoneal (i.p.) MCMV infection of mixed-bone-marrow-chimeric mice, *miR-155*$^{-/-}$ NK cells were significantly reduced compared to WT NK cells, indicating that miR-155 is important for the expansion of effector NK cells during MCMV infection. In addition, upon adoptive transfer of equal numbers of purified WT or *miR-155*$^{-/-}$ Ly49H^{+} NK cells into Ly49H-deficient mice, the percentage of Ly49H^{+} NK cells in each group at defined points post-MCMV infection was determined. There were significantly higher numbers of long-lived, memory WT NK cells compared to *miR-155*$^{-/-}$ NK cells, and the ratio of WT:*miR-155*$^{-/-}$ NK cells increased steadily from 15 days post-infection (p.i.) to 45 days p.i., suggesting that miR-155 is necessary for robust memory NK cell generation in the context of MCMV infection. The group further showed that miR-155 targets Noxa and SOCS1 to regulate NK cell responses to MCMV infection. These findings suggest that miR-155 is important in shaping NK cell responses during MCMV infection.

3.3 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 (74).

Dudda et al. (50) 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. (51) 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 (75). Previous studies have shown that miR-155 targets multiple steps in this survival pathway (76). Lind et al. demonstrated that anti-CD3-stimulated $CD8^+$ T cells isolated from WT mice demonstrated an increase in phosphorylated Akt Ser^{473}; however, there was no increase in Akt Ser^{473} phosphorylation in stimulated $CD8^+$ T cells from *miR-155*$^{-/-}$ mice (51), indicating that miR-155 mediates T cell survival by regulating the PI3/Akt signaling pathway.

Consistent with previous studies, Lu et al. (21) 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.

3.4 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 (77, 78).

Work by Pareek et al. (79) assessed the effects of miR-155 on JEV-associated inflammation *in vitro*. The authors overexpressed miR-155 in an immortalized microglial cell line, CHME3, 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. (80) reported that miR-155 is upregulated within the CNS of mice infected i.v. with JEV, and subsequent *in vitro* experiments demonstrated that microglial 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.

3.5 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 (81–84). 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 (85–87). 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 (88)]. 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 (81, 89).

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. (90) 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. (91) 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 (92), and is also expressed on both macrophages and microglial cells (93–95). Martinez-Nunez et al. (53) 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. (54), 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 and colleagues (96) 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 or M1 phenotype (31). M1-polarized macrophages are refractory to HIV-1 infection (97) and are associated with decreased viral production (98), 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.

3.7 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 (99, 100). $CD4^+$ and $CD8^+$ T cell infiltration controls viral replication during acute infection (101–103); 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 (104–110).

Dickey et al. (49) 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 (Figures 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 (Figure 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 (49). In addition, CTL activity was diminished in *miR-155*$^{-/-}$ $CD8^+$ T cells compared to those WT cells, arguing that miR-155 has a role in influencing antiviral T cell responses (Figure 1D) (49). Adoptive transfer experiments revealed that virus-specific $CD4^+$ and $CD8^+$ T cells from *miR-155*$^{-/-}$ mice exhibited impaired migration to the CNS of JHMV-infected *RAG-1*$^{-/-}$ mice. Previous studies have shown that expression of both CXCR3 and CCR5 promote migration of virus-specific T cells into the CNS of JHMV-infected mice (111–114). Surprisingly, Dickey et al. (49) showed that surface

expression of CXCR3 was decreased on $CD8^+$ T cells isolated from *miR-155*$^{-/-}$ mice compared to those from WT mice (Figure 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.

4. Conclusions

This review highlights various mechanisms by which miR-155 regulates inflammatory processes 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 cytokine production, $CD8^+$ T cell-mediated cytotoxicity, astrogliosis, 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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Highlights

- MicroRNAs can silence the expression of target genes
- MicroRNA 155 is important for immune cell homeostasis and effector functions
- MicroRNA 155 regulates many aspects of immune responses to viral infections of CNS

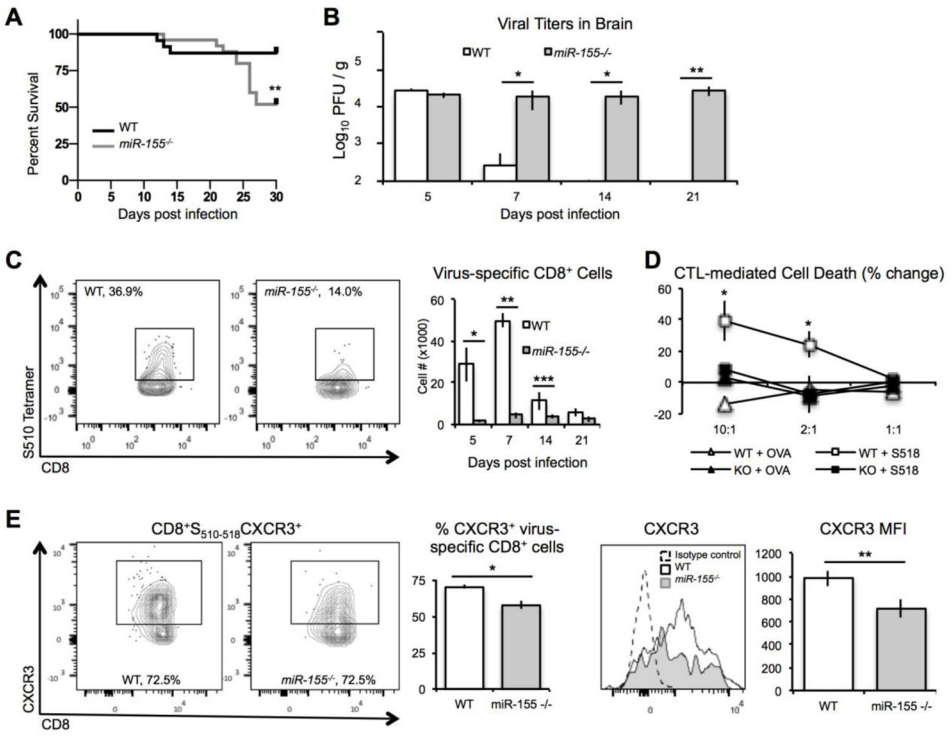

Figure 1. miR-155 regulates T cell accumulation and antiviral activity in response to JHMV infection

(**A**) JHVM-infected *miR-155*$^{-/-}$ mice demonstrated greater mortality than WT mice, concomitant with impaired ability to clear virus from brain (**B**). (**C**) Virus-specific CD8^{+} T cell accumulation in brains of JMHV infected mice was impaired in *miR-155*$^{-/-}$ mice. Virus-specific *miR-155*$^{-/-}$ CD8^{+} T cells exhibited diminished CTL activity in response to peptide stimulation (**D**), as well as decreased levels of CXCR3 expression (**E**).

Table 1

Mechanisms of miR-155-mediated regulation of neuroinflammation.

Virus	Mechanisms of miR-155-mediated regulation of neuroinflammation
Herpes simplex virus	Modulates disease severity and viral load in CNS Regulates accumulation of $CD8^+$ T cells Affects number of $CD8^+$ T cells that produce TNF-α and/or IFN-γ Necessary for optimal expression of homing molecules VLA-4 and CD44 Important for Th1 and Th17 cell accumulation in lymph nodes and spleens Promotes $CD4^+$ T cell proliferation Regulates expression of IL-1β, IL-6, IFN-γ, and IL-16 Regulates levels of SHIP1 and IFN-γRα in activated $CD4^+$ T cells
Cytomegalovirus	Critical for expansion of effector NK cells Regulates survival of NK cells Necessary for optimal memory NK cell generation Targets Noxa and SOCS1
Lymphocytic choriomeningitis virus	Necessary for optimal $CD4^+$ and $CD8^+$ T cell responses Necessary for optimal $CD8^+$ T cell proliferation Necessary for optimal $CD8^+$ T cell survival by interfering with PI3/Akt pathway Regulates cytokine signaling by targeting SOCS1 Targets SOCS1 to regulate expansion of virus-specific NK cells Targets SOCS1 to regulate maintenance of virus-specific $CD8^+$ T cells during chronic infection
Japanese encephalitis virus	Mediates disease severity Regulates expression of IFN-β, TNF-α, IL-10, MCP-1, IL-6, IRF-3/7, IRF-8, CFH, and TBK-1 Negatively regulates SHIP1 expression Contributes to JEV-induced microglial activation and neuronal death
Human immunodeficiency virus	Regulates HIV post-entry infectivity in macrophages Decreases expression of ADAM10, Nup153, and LEDGF/p57 Targets TRIM32 to decrease NF-κB activation Decreases expression of DC-SIGN; blocks gp120 binding to dendritic cells
Murine hepatitis virus	Regulates disease severity and virus clearance Necessary for optimal $CD4^+$ and $CD8^+$ T cell accumulation Necessary for optimal T cell production of IFN-γ Regulates CXCR3 expression on CD8+ T cells Necessary for optimal CTL activity Necessary for optimal $CD4^+$ and $CD8^+$ T cell migration to CNS