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REVIEW

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# Regulatory role of microRNAs in virus-mediated inflammation

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## Abstract

Viral infections in humans often cause excessive inflammation. In some viral infections, inflammation can be serious and even fatal, while in other infections it can promote viral clearance. Viruses can escape from the host immune system via regulating inflammatory pathways, thus worsening the illness. MicroRNAs (miRNAs) are tiny non-coding RNA molecules expressed within diverse tissues as well as cells and are engaged in different normal pathological and physiological pathways. Emerging proof suggests that miRNAs can impact innate and adaptive immunity, inflammatory responses, cell invasion, and the progression of viral infections. We discuss some intriguing new findings in the current work, focusing on the impacts of different miRNAs on host inflammatory responses and virus-mediated inflammation. A better understanding of dysregulated miRNAs in viral infections could improve the identification, prevention, and treatment of several serious diseases.

**Keywords** Viral inflammation, Host microRNAs, Viral miRNAs, Respiratory infections, Immune responses

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## Introduction

Viruses have evolved methods to evade the host's immune system by manipulating specific biological mechanisms within the host cells [1]. One of the prominent tactics that viruses utilize to impair the host's innate immune response is through the use of small regulatory RNAs [2]. Small RNAs, particularly microRNAs (miRNAs), play a vital role in regulating host gene expression programs related to antiviral innate immunity genes [3]. MiRNAs have been recognized for their ability to regulate protein-coding genes by means of posttranscriptional repression, either by suppressing translation or promoting the degradation of mRNA [4]. MiRNAs have the ability to regulate the expression of the majority of protein-coding genes, resulting in a significant impact on regulatory networks [2]. The significant role of miRNAs in coordinating innate and adaptive immune respo1nses and inflammatory processes within various cell and tissue types has been well established [5].

Interestingly, viruses have been discovered to disrupt the regulatory role of host miRNAs while also encoding their own miRNAs to evade the host's immune response. Furthermore, viruses are capable of manipulating the host's transcriptional machinery for their own benefit, allowing them to produce viral miRNAs [6]. Despite the clearly defined role of viral miRNAs in evading the host immune response, the mechanisms by which virus-derived miRNAs function and elude the immune system's defenses remain incompletely understood [6]. In this review, we will explore how viruses can control inflammatory responses by altering host miRNAs and using viral miRNAs. Our aim is to provide insights on improving prevention and treatment methods for a range of viral infections.

## Role of inflammation in viral pathogenesis

Many innate immune system receptors are expressed either within or on the surface of the host cell. These receptors can recognize invasive viruses and their intermediaries employed in their reproduction. The best-studied types of innate immune receptors linked to viral infections are RIG-I (retinoic acid-inducible gene I), TLRs (Toll-like receptors), as well as NLRs (NOD-like receptors). Viral infections often activate TLRs which are capable of identifying intermediate double-stranded RNA and viral nucleic acids [7, 8]. In fact, the cytoplasmic RIG-I-like receptors are capable of recognizing viral genomic RNA or RNA encoded by genomic DNA, while the NLRs is able to recognize viral DNA genomes [9]. When many of these receptors are stimulated, they produce interferons (IFNs), pro-inflammatory cytokines (PICs), and signals that activates inflammation along with adaptive immunity. The network of intrinsic immune reactions set off by the initial viral entrance into a cell may affect how an infection develops. Many viruses stimulate innate immune cells like natural killer (NK) cells, macrophages, as well as dendritic cells, to generate anti-inflammatory mediators like transforming growth factor β (TGFβ) as well as interleukin-10 (IL-10). For instance, monocytes isolated from humans infected by human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus HCV were found to produce TGF-β and Il-10. For instance, dendritic cells (DCs), isolated from lymphocytic choriomeningitis virus (LCMV)- infected mice produced high amounts of Il-10 [8, 10]. The interaction between tnfplasmacytoid DCs (pDCs) and the virus present in the lungs was in favor of the anti-inflammatory effect [11]. This conclusion was supported because the elimination of pDCs prior to infection promoted inflammation inside the lungs after the respiratory syncytial virus (RSV) infection. When viruses can interfere with one or more of the host innate defense mechanisms, a more severe viral infection is more likely to occur [8].

Moreover, the adaptive immune system effector cells could also cause damage in the host tissues after their generation in reaction to viral infection. For example, T cells are capable of killing virus-infected cells and releasing harmful cytokines such as tumor necrosis factor alpha (TNF-α). The major cause of liver injury in some noncytopathic viral infections like HCV and HBV, is due to an attempt by host CD8 effector T cells to eradicate infected cells [8]. Different subtypes of CD4 T cells coordinate inflammatory responses to combat persistent viruses inside infected cells, and thereby can cause tissue damage. Infection with HIV, HCV, as well as influenza viruses might invoke TH17 cells to be a part of inflammatory response, although T helper 1 cells (TH1 cells) are more commonly involved [12]. In responses driven by TH17 cells, neutrophils are attracted to the infected area and secrete antimicrobial substances that can also cause tissue damage. However, in extreme cases of pulmonary RSV infection, TH2 cell responses may also occur [13]. Nevertheless, generally TH2 cells rarely participate in inflammatory responses to a viral infection.

An inflammatory reaction is started when an antibody links to one infected cell and activates the complement system. Alternatively, toxicity can also occur when IgG molecules bind to Fc receptors expressed on inflammatory and phagocytic cells, causing the release of inflammatory mediators [8]. If the viruses are still present and IgG continues to be generated, immune complexes can be deposited in the host tissue, leading to chronic conditions like nephritis, polyarteritis, or arthritis. The first diseases in which immune complex lesions were identified were LCMV infection, chronic HCV and HBV infection, and HIV infection-related idiotypic IgA nephropathy. The

pulmonary lesions observed in some children with RSV infection may be explained in part by a type I hypersensitivity reaction, because viruses like RSV produce antigens which can cause an IgE reaction [8, 14].

The blood-brain barrier (BBB) is a special semipermeable barrier which allows passage of a limited number of circulating host cells, respiratory gases, and specific metabolites, and physically isolates the central nervous system (CNS) from other body parts. The BBB can protect neuronal cells from systemic inflammation. Microglia resemble macrophage-like immune cells, and together with oligodendrocytes and astrocytes, are examples of glial cells, which protect and repair damaged neural tissue. They provide critical structural support for the neurons. The ability of microglial cells to affect immune responses is employed to control pathological inflammation [15, 16]. A number of viruses, including coronaviruses, picornaviruses, flaviviridae, and togaviridae can attack the central nervous system when it is weakened [16, 17]. Some viruses are confined within the surrounding tissue in the absence of an obvious entry point, before entering peripheral neurons or BBB micro vessels [16, 17]. Several viruses, such as West Nile virus (WNV), Japanese encephalitis virus (JEV), Zika virus (ZIKAV), as well as poliovirus are more likely to cross BBB and damage brain and spinal cord. Both WNV and JEV can lead to BBB disruption within the CNS. It has been suggested that the BBB is disrupted by PICs released via the infected endothelial cells, and not by the viruses themselves [8, 17]. Tissue damage is the result of either an excessive inflammatory reaction driven via PICs or CD8 cytotoxic T lymphocytes (CTLs), or by direct neuronal infections that activate the apoptosis in the neurons. Infected neurons release chemokines in order to attract white blood cells such as monocytes and lymphocytes. However, the CNS is characterized by a very fine line that must be drawn between "good" and "bad" immune responses. Viral eradication and survival are strongly influenced by the migration of CTLs expressing receptors for chemokines, such as CXCL9–11, CXCL2-4, CCL5, and their timing relative to the onset of infection. Through a Fas-Fas ligand (FasL)-mediated or a granzyme-perforin dependent mechanism, CTLs can kill host cells in order to carry out their antiviral function. Moreover, some PICs secreted during a viral infection could also result in the direct death of neuronal cells [16, 17].

Exogenous regulation of these inflammatory responses by disrupting or supplementing key regulators has been proposed as an anti-viral therapeutic measure, since a poorly controlled inflammatory response can have negative effects [16]. The advantages and disadvantages of various inflammation-related strategies are still under investigation. These approaches have been successfully used to treat some viral diseases, because they may protect the affected subjects without any direct effect on the virus life cycle. In addition, if inflammation-related approaches can be shown to be effective, they could reduce the morbidity and mortality caused by some viral infections, which have proven particularly challenging to treat, using conventional antiviral drugs or prophylactic vaccines.

## MicroRNAs and inflammation

### Biogenesis of microRNAs

Short endogenous non-coding RNAs known as microRNAs (miRNAs) control the translation along with stability of mRNAs. RNA polymerase II converts the miRNA gene into a primary miRNA (pri-miRNA) having a stem-loop structure, which is the initial stage of standard miRNA production. The Drosha microprocessor complex as well as DGCR8 endonuclease subsequently cleave the pri-miRNA for generating hairpin precursor miRNAs (pre-miRNA) of almost 70 nt in length [18]. Pre-miRNAs are transferred to the cytoplasm via exportin-5, where they're divided into miRNA duplexes by TRBP complexes (two strands) and Dicer [19, 20]. Consequently, the mature miRNA duplex is added to the RNA-induced silencing complex (RISC). This duplex must be further processed by cleavage or thermodynamic instability [21, 22]. The key element Argonaute 2 in the RISC complex guides mature miRNAs to their destination after strand selection, and then shortens the 3'-poly-A tail of each target complementary mRNA, or else cleaves the mRNA to destabilize it. The target mRNA-encoded protein experiences translational inhibition as a result of this whole process [21, 23].

### Role of microRNAs in the regulation of inflammatory responses

It was indicated that during inflammatory reactions, a number of miRNAs regulate gene expression at transcriptional level. At late stages of inflammatory transcriptional programs, numerous miRNAs can be activated. MiRNAs are governed similarly to protein-coding genes, according to recent research, but the timing of their synthesis and their type of activity may provide these short RNA molecules with special regulatory properties [24, 25]. Several proteins that are produced during inflammatory responses, are able to control miRNA processing. These include TGF-β-activated SMAD proteins and p68 RNA helicase, which is a part of the Drosha endoribonuclease complex. When ADAR (adenosine deaminase acting on RNA) is triggered via inflammation, double-stranded miRNA precursors can acquire mutations that alter the target selectivity of the miRNAs [26]. Many miRNA transcripts can be processed by tumor-suppressing protein

p53 that is increased throughout specific inflammatory responses. Moreover, the expression of Dicer as well as other biogenesis factors is suppressed by interferon-γ [27]. Each miRNA can undergo highly specific posttranscriptional processing. For instance, the processing of miRNA let-7 was controlled by the Lin28 RNA-binding protein [28]. It is unknown whether any other regulatory elements related to a single or to a handful of miRNAs are present throughout inflammation. Moreover, whether miRNA biogenesis regulates immune responses through any other pathways remains to be elucidated. MiRNAs could regulate inflammation mainly via changing expression of particular mRNAs within activated immune cells or bystander cells [29]. There are proofs that inflammatory responses can regulate miRNA biogenesis via changing the transcription, processing, or stability of precursor or mature miRNA transcripts [30]. MiRNAs are involved in both favorable and unfavorable regulatory mechanisms that control the initiation, propagation, and termination of inflammation. A positive feedback loop triggers a series of molecular mechanisms, which successfully repairs tissue damage and prevents the invasion of microbial pathogens. A negative feedback loop, which occurs only when inflammation is at its highest, should prevent potentially harmful results and maintain tissue homeostasis [31].

For example, recent research has shown that miR-21 is crucial for reducing inflammation [32]. It is likely that miR-21 has an anti-inflammatory effect since its overexpression within macrophages decreased secretion of IL-6 whilst raising the IL-10 secretion [24, 31]. In one study, miR-21 has been discovered to have a substantial part in regulating the coordination of Th1 and Th2 responses. Treatment of DCs that were non-responsive to lipopolysaccharide (LPS) with miR-21, increased the production of IL-12. Similarly, the generation of IFN-γ has been increased via ovalbumin, while IL-4 production was decreased. This occurred when miR-21-deficient CD4 T cells were stimulated [33]. Considering the preventing effect of miR-21 on lipid buildup and LPS-induced inflammatory responses in macrophages, miR-21 could serve as a possible therapeutic strategy for the treatment of atherosclerosis [34]. Accordingly, when atherogenesis occurs, macrophages lacking miR-21, could promote endothelial inflammation [31]. In fact, overexpression of miR-21 is found to suppress the classical pro-inflammatory activation (M1) phenotype, while it enhanced the alternative anti-inflammatory activation (M2) phenotype of macrophage [35].

The production of miR-146a and miR-146b may function as a negative feedback loop to stop excessive inflammation, whilst reacting to pro-inflammatory stimuli [36, 37]. Several inflammatory disorders like lupus, psoriasis, rheumatoid arthritis, osteoarthritis, along with viral infection, were connected to low expression of these miRNAs [36, 37]. In fact, miR-146 transcription must be induced via nuclear factor κB (NF-kB), while JNK-1/2 as well as MEK-1/2 are then involved in post-transcriptional processing to produce mature miR-146 [38]. MiR-146a and miR-146b influence TLRs and their downstream effectors to control the inflammatory procedure. MiR-146a negatively controls IFN responses as well as adaptive immunity via selectively targeting adaptor protein (AP)-1 transcription factor, immune cell activation, IL-2 expression, and cytokine production [39, 40]. Moreover, adenosine deaminase 2, which has been reported to control diabetic retinal inflammation, was also suppressed by miR-146b [41].

The MIRHG155 gene, originally known as BIC (B-cell integrating cluster) encodes a pri-miRNA that is converted into miR-155. Several signaling pathways, including NF-kB, SMAD4, ISRE (interferon stimulated response element), IRFs (interferon-regulatory factors) as well as AP -1 are established to have binding sites in BIC gene, and it can regulate miR-155 expression whilst reacting to various cues [42]. Numerous works have indicated that miR-155 expression has been abnormally increased within various activated immune cells, thus demonstrating the critical part that miR-155 plays in immune response [43–45]. Several inflammatory stimuli, including TLR ligands, alarmins (e.g. IL-1), damage-associated molecular patterns (DAMPs), interferons, and pathogen-associated molecular patterns (PAMPs) are particularly sensitive to miR-155 in different cells, especially macrophage/monocytes [46]. Indeed, various signaling pathways can control miR-155 expression [46]. The anti-inflammatory protein IRF3 is found to regulate miR-155-3p along with miR-155-5p expression within astrocytes [47]. Moreover, it has been demonstrated that through inhibiting miR-155 expression, resolvin D1 can reduce inflammation during experimental corneal immunopathology [48]. In addition, in mice lacking Ets2, LPS-induced miR-155 expression was shown to be lower. Moreover, IL-10 suppressed the Ets2 gene to control miR-155 expression [49]. It is confirmed that the NF-κB-miR-155 along with NF-κB-miR-146a axis can collaborate in inflammatory responses to control the severity and length of inflammation. Thus, miR-146a-deficient mice were more prone to cancer, autoimmune illnesses, as well as inflammatory disorders. Interestingly, miR-146a-deficient cells expressed more miR-155, which can result in reduced pro-inflammatory phenotype [46]. Furthermore, NF-κB activity is controlled via a two-step system that combines the activity of miR-146a along with miR-155. NF-κB signaling is autoregulated during inflammation. In the initial twelve-hour period of an

inflammatory reaction, miR-155 quickly increases NF-κB. In addition, miR-155 targets SHIP1 and, through PI3K/Akt-dependent activation of the IKK signaling complex, creates a positive feedback loop for signal amplification. Furthermore, miR-146a inhibited IRAK1 and TNF receptor associated factor 6 (TRAF6), result in a negative feedback loop that reduced NF- κB activity in later stages of inflammation [50].

Recently, miR-149 was reported to control innate immune defense mechanisms. When miR-149 is increased in macrophages, it can decrease the MyD88 protein expression and the generation of inflammatory mediators, TNF-α, IL-6 as well as NF-kB in reaction to LPS stimulation or actual infection. Additionally, miR-149 inhibited STAT3-mediated signaling, which decreased inflammatory responses in the liver [51, 52]. Moreover, it has been established that tumor necrosis factor (TNF-α) downregulates miR-149 and subsequently promotes the expression of IL-6, Inducible nitric oxide synthase (iNOS), and matrix metalloproteinase −9 (MMP-9). In that context, it is shown that the transfection with a miR-149 mimic, can block this effect [53]. Several studies have connected osteoarthritis, a joint condition typified by uncontrolled inflammatory responses, to the downregulation of miR-149 [54]. These results are relevant to TNF-α-associated immune disorders, and may provide useful suggestions for possible future therapeutic approaches.

## Virus-mediated regulation of inflammatory pathways by host-derived miRNAs

Viral infections can alter host miRNA expression, which then affects host immune responses via transcriptional and translational mechanisms. Changes in miRNA expression can be a result of cell differentiation, cell cycle alteration, apoptosis, host immune signals, and antiviral defenses all of which can be affected by viruses. Severe viral infections often cause widespread inflammation and tissue damage. However, these inflammatory responses are required to rapidly control the initial infection, as well as to start the adaptive immune responses, which will finally stop viral replication. Various mediators or cell types involved in triggering the immune response, can also cause tissue damage and cell death at high concentrations or numbers. In addition, instead of providing protection, some mediators and signaling pathways have been linked to increased death and injuries in tissues. In order to lower the viral load and reduce disease severity, combination therapy with both antiviral and anti-inflammatory drugs is essential. In addition to being effective after the onset of symptoms, the optimized anti-inflammatory drugs can work in tandem with established antiviral drugs, thus decreasing the probability of subsequent bacterial infection, while not interfering with viral clearance mechanisms [55]. Therefore, it is critical to select the most effective therapeutic approaches and/or targets to reduce inflammation during viral infection. Because inflammation is a multifactorial phenomenon, the ability of miRNAs in regulating relevant genes at transcriptional as well as posttranscriptional levels could influence one or more pathways in the growth of viral illnesses. Each miRNA's ability to act on multiple genes opens the possibility of genetic interference with multiple disease mechanisms [56].

### Influenza virus

Influenza virus infections are in charge for excessive mortality and morbidity globally. The yearly influenza epidemics can cause about 500,000 deaths and almost 5 million cases globally in a bad year [57]. The viruses that cause influenza B Victoria, influenza B Yamagata, influenza A H1N1 (swine flu), and influenza A H3N2 (H3N2v), which are mostly limited to the respiratory system, are the most common reasons behind influenza infections in humans [58]. Numerous lines of evidence point to specific miRNAs acting as important regulators in development of influenza infections. For instance, Zhang et al. discovered that H1N1 infection increased miR-29c expression within A549 cells, which raised inflammatory as well as antiviral responses [59]. In addition, Podsiad et al. discovered that miR-155 could inhibit the IL-23/IL-17 signaling pathway, which leads to reduced bacterial clearance and increased mortality due to post-influenza pneumonia [60]. On the other hand, Guo et al. reported that H1N1 infection could cause significant cell damage by increasing cytokine production, decreasing viability, and inducing apoptosis. They found that inoculation with H1N1 virus reduced miR-4485 expression within A549 cells, while miR-4485 overexpression inhibited H1N1-induced cell damage [61]. Traber et al. showed that STAT3 could control the generation of chemokine CXCL5 (C-X-C motif ligand 5) that is necessary for neutrophil and macrophage recruitment to the lungs in pneumonia [62]. Small molecule inhibition of STAT3 reduced LPS-induced infiltration of inflammatory cells and macrophages within bronchoalveolar lavage fluid [63]. Guo et al. demonstrated that STAT3 has been a miR-4485 direct target gene. Downregulation of miR-4485 and cell damage induced by H1N1 virus were reversed by STAT3 silencing. They also found that the knockdown of STAT3 significantly reduced the activity of PI3K/mTOR/AKT pathway, suggesting that miR-4485 regulates the activity of STAT3-mediated pathways. Their study showed that STAT3 has been upregulated whilst miR-4485 has been downregulated, and that PI3K/

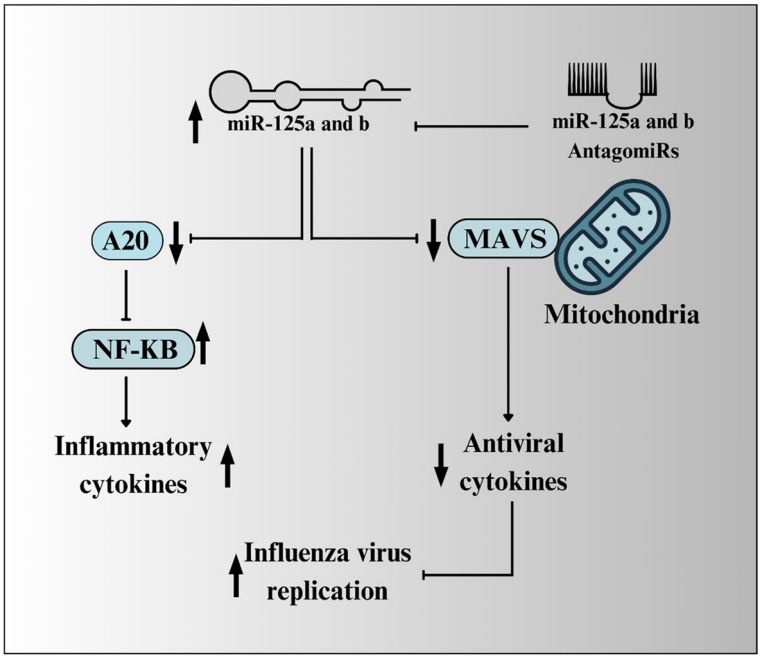


**Fig. 1** Regulation of inflammation by miR-125a/b throughout IAV infection. miR-125a/b increases inflammation and suppresses antiviral responses in COPD by inhibiting A20 and MAVS [66]

AKT/mTOR pathway's activation could increase damage induced by H1N1 infection in A549 cells [61].

With 3.23 million fatalities from chronic obstructive pulmonary disease (COPD) in 2019, it is the third most common reason behind mortality in the world. COPD is defined by emphysema, increasing inflammation in the airways, as well as diminished lung function [64]. IAV infection can worsen the symptoms in COPD patients. Hsu et al. reported that when mice having experimental COPD have been infected with IAV, they showed increased inflammatory cytokines but lower antiviral responses [65]. The expression levels of miR-125a and miR-125b were increased within IAV-infected cells. The group reported that levels of protein A20 were lower in IAV infection as well as in COPD, which led to increased NF-kB-mediated inflammation, because A20 is the inhibitor of NF-kB. Treatment with a selective antagonist of miR-125a/b lowered NF-kB activation, while increasing the release of I/III IFNs as well as reducing infection. MiR-125a and miR-125b both inhibit the induction of type I/III IFNs along with NF-kB, by directly targeting MAVS (mitochondrial antiviral signaling) and A20. They concluded that miR-125-mediated signaling lowered the expressions of MAVS and A20, thereby inducing excessive inflammation, and increasing the susceptibility of COPD patients to IAV infection (Fig. 1) [66]. Therefore, miRNAs could be used in the therapy of IAV infection, by improving antiviral immunity and protecting against excessive inflammatory reactions (Table 1).

#### SARS-CoV-2 virus

The SARS-CoV-2 coronavirus infection is to blame for 2019 coronavirus epidemic (COVID-19), and has resulted in over 623 million new cases along with 6.55 million mortalities globally until February 2021. Severe COVID-19 infections have a significant mortality rate and can result in lethal lung hypoxia and a cytokine storm. Apoptosis and necrosis can damage the alveolar epithelial and vascular endothelial cells causing tissue damage due to excessive cytokine production [113, 114].

The SARS-CoV envelope protein (E) is regarded as a virulence factor that supports pulmonary inflammation caused by SARS-CoV through several mechanisms [115, 116]. NF-kB-dependent proinflammatory responses can be triggered by the E protein [117]. The p38 mitogen-activated protein kinase (MAPK) signaling pathway is activated when the PDZ-binding motif of E protein interacts specifically with the PDZ domains of syntenin [118]. In addition, NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasomes and the secretion of IL-1β are triggered by Ca (2+) transport into infected cells. Acute respiratory distress syndrome (ARDS) etiology, includes this mechanism as a critical element, an extreme pulmonary inflammation suffered by SARS and COVID-19 patients who have severe disease [119, 120].

**Table 1** Virus-mediated regulation of inflammation by host and viral microRNAs

| miRNA/ expression | Viral infection | In vitro (cell type), in vivo (animal model), Human | Target of miRNA | Induction/ Inhibition of inflammation by miRNA | Results | Ref |
|---|---|---|---|---|---|---|
| miR-145-5p/ Down | IAV (H3N2) | In vitro (pHBEC) | - | Inhibition of inflammation | MiR-145-5p suppressed the NF-κB pathway, IL-1β and TNF-α expression during IAV infection. LncRNA TUG1 was upregulated in pHBECs cells infected with IAV, leading lead to airway inflammation by sponging miR-145-5p. | [67] |
| miR-221/ Down | IAV (H1N1) | In vitro (A549) | SOCS1 | Inhibition of inflammation | MiR-146a/b expression has been substantially decreased within IAV-infected A549 cells. | [68] |
| miR-4485/ Down | IAV | In vitro (A549) | STAT3 | Inhibition of inflammation | H1N1 infection downregulated miR-4485 in A549 cells, while overexpression of miR-4485 ameliorated A549 cell damage caused by H1N1 by inhibiting apoptosis, decreasing IL-6, TNF-α & IL-1β and increasing cell viability. | [61] |
| miR-590-5p/ Up | IAV (H3N2) | In vitro (A549) | IL-6R | Inhibition of inflammation | miR-590-5p contributed to IAV replication by suppressing IL-6 and interferons. | [69] |
| miR-302a/ Down | IAV | Human (throat swabs), In vitro | IRF-5 | Inhibition of inflammation | miR-302a suppressed IAV-induced cytokines and prevented a cytokine storm by targeting IRF-5. | [70] |
| miR-29c/ Up | IAV | In vitro (A549) | - | Inhibition of inflammation | IAV upregulated miR-29c thus inhibiting the expression of antiviral & proinflammatory genes by targeting A20 mRNA. | [59] |
| miR-125a and -b | IAV | Human (primary bronchial epithelial cells), In vivo (mice) | MAVS, A20 | Induction of inflammation | Overexpression of miR-125a/b increased proinflammatory cytokines by downregulating A20. Downregulation of miR-125a/b increased MAVS expression and anti-IAV responses. | [71] |
| let-7/- | SARS-CoV-2 | In vitro (HEK293T) | SARS-CoV-2 S and M proteins. | Inhibition of inflammation | let-7 inhibited SARS-CoV-2 replication & inflammatory cytokine expression. | [72] |
| miRNA-223/ Up | SARS-CoV-2 | In vivo (mice) | - | Inhibition of inflammation | Pro-inflammatory mediators NLRP3, CXCL2, and IL-6 were upregulated after miRNA-223-3p was inhibited in mice lungs. | [73] |

**Table 1** (continued)

| miRNA/ expression | Viral infection | In vitro (cell type), in vivo (animal model), Human | Target of miRNA | Induction/ Inhibition of inflammation by miRNA | Results | Ref |
|---|---|---|---|---|---|---|
| miR-140-5p/ Down | RSV | Human (PBMC, nasal mucosal), In vitro (BEAS-2B) | TLR4 | Inhibition of inflammation | TNFα, IL-1β, -6, -8, and overexpression of miR-140-5p have been all reduced. The IFNα-mediated downregulation of TNFα, IL-1β, IL-6, and IL-8 has been decreased by inhibition of miR-140-5p. Downregulation of miR-140-5p promoted RSV replication by targeting TLR4. | [74] |
| miR-146a/ - | RSV | In vitro (A549 & HEp-2), In vivo (mice) | TRAF-6 | Inhibition of inflammation | Ectopic expression of miR-146a suppressed RSV infection as well as reduced inflammatory cytokines by targeting TRAF-6 | [75] |
| miR-146a, miR-146b/ Up | RV | In vitro (pHBEC), In vivo (mice) | - | Inhibition of inflammation | miR-146a/b was significantly downregulated in RSV infection. miR-146a/b can promote expression of IFN response genes and suppress pro-inflammatory cytokines in HBECs and mouse airways during RSV infection. | [76] |
| miR-328-3p/ Up | HBV | In vitro (THLE-2), in vivo (mice) | FOXO4 | Induction of inflammation | HBV upregulated the expression of miR-328-3p via inducing the binding of STAT3 to its promoter in THLE-2 cells. miR-328-3p inhibited apoptosis, promoted proliferation as well as induced expression of pro-inflammatory cytokines by targeting FOXO4. | [77] |
| miR-130a/ Down | asymptomatic HBV carriers | In vitro (HepG2), In vivo (mice) | PGC1α and PPARγ | Induction of inflammation | miR-130a decreased HBV replication and activated NF-κB by targeting PGC1α and PPARγ. HBV attenuated inflammation and promoted immune tolerance by decreasing miR-130a and NF-κB activation in asymptomatic HBV carriers. | [78] |

**Table 1** (continued)

| miRNA/ expression | Viral infection | In vitro (cell type), in vivo (animal model), Human | Target of miRNA | Induction/ Inhibition of inflammation by miRNA | Results | Ref |
|---|---|---|---|---|---|---|
| miR-146a/ Up | HBV | Human (liver tissue), in vivo (mice) | CFH | Induction of inflammation | HBV increased the expression of miR-146a via inducing NF-κB binding to miR-146a promoter. miR-146a promoted HBV-related liver inflammation by targeting CFH. | [79] |
| miR-203a/ Up | HBV | In vitro (HepG2) | Rap1a | Induction of inflammation | HBV-HBx protein significantly raised the expression of miR-203a. miR-203a induced hepatic inflammation by targeting Rap1a. | [80] |
| miR-106a/ Down | Chronic HBV | Human (PBMC) | IL-8 | Inhibition of inflammation | miR-106a might have a substantial part in chronic HBV-inflammation by targeting IL-8. | [81] |
| miR-125a/ Up | HCV | In vitro (huh7) | TRAF6 & MAVS | - | HCV induced expression of miR-125a, and miR-125a promoted HCV replication. miR-125a modulated IFN signaling by targeting MAVS and TRAF6. | [82] |
| miRNA-449a and miRNA-107/ Down | HCV | Human (liver tissue), In vitro (primary human hepatocytes & HEPG2) | IL-6R & JAK1 | Inhibition of inflammation | HCV promoted CCL2 expression, inflammatory responses and fibrosis via activating the IL-6-mediated signaling cascade by downregulating miR-449a and miR-107 levels. | [83] |
| miRNA-34a/ Up | HIV-Tat protein | In vitro (BV-2), In vivo (mice) | NLRC5 | Induction of inflammation | By targeting NLRC5, HIV-1 Tat enhanced the production of miR-34a, which in turn caused the proinflammatory cytokines IL-1β and IL-6 to be upregulated in microglia. | [84] |
| miR-32/ Up | HIV-1 (Tat C) | In vitro (CHME3) | TRAF3 | Induction of inflammation | HIV-1 Tat C raised expression of miR-32 and the expression of inflammatory genes in microglial cells by targeting TRAF3. | [85] |
| miR-126-5p/ Up | chronic HIV-1 infection | Human (primary monocytes) | CYLD | Induction of inflammation | miR-126-5p substantially reduced CYLD during chronic HIV-1 infection, thus promoting monocyte inflammation by inducing pJNK2. | [86] |

**Table 1** (continued)

| miRNA/ expression | Viral infection | In vitro (cell type), in vivo (animal model), Human | Target of miRNA | Induction/ Inhibition of inflammation by miRNA | Results | Ref |
|---|---|---|---|---|---|---|
| miR-21/ Down | HIV | Human (monocytes) | IP-10 | Inhibition of inflammation | miR-21 inhibited inflammation mediated by monocytes in HIV-infected patients by targeting IP-10. | [87] |
| miR-146a/ | HIV | In vitro (primary human fetal microglial cells, U937) | CCL8/MCP-2 | Inhibition of inflammation | HIV increased expression of mir-146a, and inhibited the expression of the proinflammatory chemokine MCP-2. The brain's HIV-mediated chronic inflammation was maintained in part by mir-146a. | [88] |
| miR-155/ Up | JEV | In vitro (CHME3), In vivo (BALB/c mice) | PELI1 | Inhibition of inflammation | Through the upregulation of miR-155 in human microglial cells, JEV can inhibit the non-canonical NF-κB pathway and pro-inflammatory cytokines (TNF-α and IL-6). | [89] |
| miR-466d-3p/ Down | JEV (strain P3) | In vitro (mouse neuroblastoma cells) | IL-1β | Inhibition of inflammation | JEV NS3 protein contributed to the degradation of miR-466d-3p within neurons. Suppression of miR-466d-3p promoted JEV replication and induced IL-1β secretion. | [90] |
| miR-146a/ Up | JEV | In vitro (C8-B4) | - | Inhibition of inflammation | JEV promoted miR-146a and pro-inflammatory cytokines expressions in mouse brain. miR-146a negatively regulated pro-inflammatory cytokines, through a negative feedback loop in a JEV replication independent fashion. | [91] |
| miR-15b/ Up | JEV | In vitro (U251 & BV2), In vivo (mouse brain) | RNF125 | Induction of inflammation | miR-15b promoted proinflammatory cytokines and interferon type 1 by inhibiting RNF125. | [92] |
| miR-432/ Down | JEV | In vitro (CHME3) | SOCS5 | Induction of inflammation | The upregulation of miR-432 resulted in a rise in pro-inflammatory cytokines, specifically TNF-α and IL-6. JEV may use miR-432 downregulation to avoid host antiviral immune responses. | [75] |

**Table 1** (continued)

| miRNA/ expression | Viral infection | In vitro (cell type), in vivo (animal model), Human | Target of miRNA | Induction/ Inhibition of inflammation by miRNA | Results | Ref |
|---|---|---|---|---|---|---|
| miR-19b-3p | JEV | In vitro (U251 & BV2), in vivo (BALB/c mice) | RNF11 | Induction of inflammation | miR-19b-3p increased inflammatory cytokines by targeting ring finger protein 11 (RNF11). | [93] |
| miR-155/ Up | JEV | In vitro (BV-2, primary microglia cells), In vivo (BALB/c mice) | SHIP1 | Induction of inflammation | miR-155 induced inflammation by regulating the NF-κB pathway by targeting SHIP1 during JEV infection. | [94] |
| miR-301a/ Up | JEV | In vitro (CHME3 & BV2), In vivo (BALB/c mice) | NKRF | Induction of inflammation | JEV increased the expression of miR-301a and induced an inflammatory response via targeting NKRF and promoting virus-induced neuroinflammation. | [95] |
| miR-15/ Up | CVB3 | In vitro (H9c2) | NLRX1 | Induction of inflammation | Suppression of miR-15 promoted cell viability, reduced apoptosis, myocardiocyte injury, and the inflammatory responses induced by CVB3 infection by modulation of the NLRX1-mediated NLRP3 inflammasomes. | [96] |
| miR-425-3p/ Down | CVB3 | In vivo (mouse myocardial tissue) | TGF-β1 | Induction of inflammation | miR-425-3p has been downregulated in Coxsackievirus type B3-infected mice. Upregulation of miR-425-3p led to myocardial inflammation by inhibiting the TGF-β1/smad axis in Coxsackievirus type B3-infected mice. | [97] |
| miR-221/-222 | CVB3 (Viral myocarditis) | In vitro, in vivo (mice) | CXCL12 & ICAM1 | Inhibition of inflammation | The cardiac viral load was markedly elevated by downregulation of miR-221/-222, aggravating heart damage and inflammation. | [98] |
| miR-302/ Down | Enterovirus 71 | Human (PBMC), In vitro (HEK293T & RD) | KPNA2 | Inhibition of inflammation | miR-305 significantly downregulated IL-6, TNF-α, and CCL3 in EV71-infected cells by targeting KPNA2. EV71 increased cytokines levels by stimulating KPNA2 expression by inhibition of miR-302 expression. | [99] |

**Table 1** (continued)

| miRNA/ expression | Viral infection | In vitro (cell type), in vivo (animal model), Human | Target of miRNA | Induction/ Inhibition of inflammation by miRNA | Results | Ref |
|---|---|---|---|---|---|---|
| miR-124/ Up | Enterovirus 71 | In vitro (human rhabdomyosarcoma) | IL-6R, STAT3 | Inhibition of inflammation | miR-124 promoted EV71 replication by attenuating the antiviral activity mediated by IL-6R and STAT3. | [100] |
| miR-206/ Down | Enterovirus 71 | In vitro (U-251) | CCL2 | Inhibition of inflammation | Overexpression of miR-206 affected severe HEV71 encephalitis by downregulation of CCL2. | [101] |
| miR-146a/ Up | Dengue virus | In vitro (A549) | TRAF6 | Induction of inflammation | By targeting TRAF6, miR-146a boosted TNF-α and IL-6 in A549 cells infected with DENV2. The miR-146a-autophagy axis significantly regulated pro-inflammatory cytokines during dengue virus infection. | [102] |
| miR-146a/ Up | BoDV1 | In vitro (HMC3), In vivo (rats) | IRAK1 and TRAF6 | Inhibition of inflammation | miR-146a was significantly upregulated in BoDV-1 infected microglial cells (HMC3). miR-146a contributed to BoDV-1 survival in microglial cells via inhibiting the IRAK1/TRAF6/NF-κB signaling pathway. | [103] |
| miR-155/ - | West Nile virus | In vitro (SK-N-SH), In vivo (miR-155 knockout mice) | - | Induction of inflammation | miR-155 ameliorated lethal West Nile virus infection by promoting anti-viral cytokines and chemokines. | [104] |
| miR-221/ Up | HCMV | In Vitro (neural precursor cells) | SOCS1 | Inhibition of inflammation | HCMV infection decreased SOCS1 protein by upregulating miR-221 expression, thus suppressing inflammation. | [105] |
| miR-21/ | HSV | In vivo (mice) | - | Induction of inflammation | Downregulation of miR-21 improved HSV-induced Behçet's Disease (BD)-like inflammatory symptoms as well as decreased pro-inflammatory cytokines IL-17 as well as IL-6. | [106] |
| miR-146a/ Up | CHIKV | In vitro (primary human synovial fibroblasts) | TRAF6, IRAK1, IRAK2 | Inhibition of inflammation | MiR-146a inhibition reduced CHIKV replication. Overexpression of miR-146a reduced inflammatory cytokines (TNF-, IL-1, and IL-6), and promoted CHIKV replication. | [107] |

**Table 1** (continued)

| miRNA/ expression | Viral infection | In vitro (cell type), in vivo (animal model), Human | Target of miRNA | Induction/ Inhibition of inflammation by miRNA | Results | Ref |
|---|---|---|---|---|---|---|
| miR-146a/ Up | ZIKV/ NS1 | In vitro (HMC3) | STAT-1 & TRAF6 | Inhibition of inflammation | miR-146a downregulated STAT-1 & TRAF6 and led to inhibition of pNF-κBp65 & TNF-α. ZIKV-NS1 suppressed pro-inflammatory & antiviral responses by increasing miR-146a expression in human microglial cells. | [108] |
| miR-21-5p/ Up | CHPV | In vitro (CHME3) | PTEN | Induction of inflammation | The expression of miR-21-5p was significantly increased in CHPV-infected CHME3 cells. miR-21-5p induced NF-κB activity and pro-inflammatory responses throughout CHPV infection. | [109] |
| EBV-miR-BART11/ Up | EBV | In vitro (MKN-45, SGC-7901, THP-1) | FOXP1 | Induction of inflammation | Upregulation of EBV-miR-BART11 level induced gastric cancer cell progression and metastasis mediated by inflammation. | [110] |
| HSV-1 miR-H6 | HSV-1 | In vitro (HCE) | HSV-1-ICP4 | Inhibition of inflammation | In vitro, HSV-1 miR-H6 decreased IL-6 expression and HSV-1 multiplication in human corneal epithelial cells. | [111] |
| KSHV miRNAs (miR-K12-1, −3, −7, −9, and −11) | KSHV | In vitro (BCBL-1) | - | Induction of inflammation | KSHV miRNAs induced IL-6 along with IL-10 expression in macrophages by down-regulating C/EBPβ. | [112] |

Recently, Morales et al. aimed to elucidate the effect of host's miRNAs on protein E-mediated virulence. In mice infected via pathogenic SARS-CoV wild type (WT) or even attenuated mutant deficient in the E gene (SARS-CoV-ΔE), miR-223 might function as a regulator of lung inflammation [121]. In virulent SARS-CoV-WT infection, miR-223 levels were significantly higher than in an infection with attenuated SARS-CoV-ΔE. It was found that miR-223 could particularly target inflammasomes and the cystic fibrosis transmembrane conductance regulator (CFTR). Then, in viral lung infections, miRNA-223 might help to regulate excessive inflammation by suppressing pro-inflammatory cytokines as well as the NLRP3 inflammasomes in vivo. The CFTR transporter, which reduces edema, was noticeably increased in the lung of mice infected with virulent SARS-CoV-WT as a result of the suppression of miRNA-223-3p. At the histological level, miR-223-3p inhibition, decreased pulmonary edema, indicating that miRNA-223-3p could regulate SARS-CoV-induced inflammation [121]. Since miRNA-223 can target several host mRNAs involved in lung inflammation during SARS-CoV infection, it could be a viable treatment target in SARS-CoV infection.

There is evidence that the miRNAs Let-7c and Let-7a can inhibit IL-6 expression that is a typical pro-inflammatory cytokine induced via SARS-Cov-2 [122]. It is possible that up-regulation of Let-7 could reduce the SARS-CoV-2-induced cytokine storm by down-regulating inflammatory factors other than IL-6. To test this hypothesis, Xie et al. studied Let-7 and C1632 for their ability to reduce inflammation caused by SARS-CoV-2 [123]. They found that Let-7 which is a universally expressed miRNA within human cells, could target the S and M viral proteins thus preventing SARS-CoV-2 replication. Several inflammatory factors like IL-6, IL-8, IL-1, C-C motif chemokine ligand 2 (CCL2), granulocyte macrophage-colony stimulating factor )GM-CSF(, vascular endothelial growth factor α (VEGFα) and TNF-α, could all be simultaneously suppressed by Let-7. More importantly, Let-7 expression could be increased by the Let-7 stimulating factor C1632, which lowers viral replication as well as inflammatory cytokine secretion [123]. The effectiveness of C1632 in limiting SARS-CoV-2 replication along with lowering virus-induced inflammation via upregulating Let-7 might be therapeutically useful [123].

#### Respiratory syncytial virus

The RSV is a lipid-enclosed virus which is a member of genus Pneumoviridae and family Paramyxoviridae. The 15.2 kb single-stranded negative RNA genome of RSV has 10 genes that code for 11 different viral proteins. These include small hydrophobic protein (SH), an envelope protein, as well as two major surface proteins, fusion protein (F) along with glycoprotein (G). Serious RSV infections are characterized by substantial airway inflammation, and release and synthesis of multiple NF-kB-controlled chemokines and cytokines [124, 125]. TLRs, along with cytokine receptors like the IL-1 receptor, TNF receptor (TNFR), as well as pattern recognition receptors are examples of receptors that can be stimulated in activating NF-kB [126]. Overexpression of NF-kB-mediated inflammatory genes is most likely caused by persistent NF-kB activity after RSV infection [127, 128]. TLR4 has been indicated to have a significant part in controlling innate immune reaction to RSV infection [129]. RSV F protein can activate pattern recognition receptors CD14, TLR-4, and MD-2, which can activate the transcription factor NF-kB and raise pro-inflammatory cytokines [130]. However, it is still not completely known how TLR4 is regulated after RSV infection. According to a recent publication, miR-140-5p may function via Myeloid differentiation factor 88 (MyD88)/NF-kB pathway to target TLR4 as well as decrease inflammatory cytokines in acute respiratory distress syndrome [131]. Zhang et al. discovered that the amounts of miR-140-5p have been dramatically lower in peripheral blood and nasal mucosa specimens of RSV-infected individuals [74]. Moreover, exogenous expression of miR-140-5p has been discovered to substantially lower the pro-inflammatory cytokines, IL-1, IL-6, and IL-8 along with TNF-α. Moreover, the generation of TNF-α, IL-1, and IL-6, along with IL-8 has been substantially raised when miR-140-5p was inhibited. These outcomes recommend that the immune response to RSV is impaired by lower amounts of miR-140-5p within RSV-infected cells, probably because miR-140-5p targets TLR4 [74].

MiR-146a was reported to be a possible biomarker of sepsis as it was involved in the control of inflammation [132]. Since miR-146a regulates the inflammatory response in both acute lung injury and asthma, it has been considered as a reliable predictor of acute lung damage [133]. However, it is still unclear if miR-146a could contribute to lung damage caused by RSV infection. Stress-induced cytokine secretion has been substantially decreased by both miR-146a expression as well as TRAF-6 inhibition compared to the control group, suggesting that miR-146a has an influence on TRAF-6 in airway inflammation. Huang et al. examined the mechanisms underlying the impact of miR-146a upon RSV transmission [134]. In young rats, as well as in HEp-2 and A549 cells, miR-146a mimics were administered before exposure to RSV. RSV infection substantially decreased miR-146a levels in rat lung tissue, HEp-2, and A549 cells. A more rapid growth, overexpression of TRAF-6 and inflammatory cytokines, and activated JNK signaling pathway were observed in RSV-infected cells. In rats,

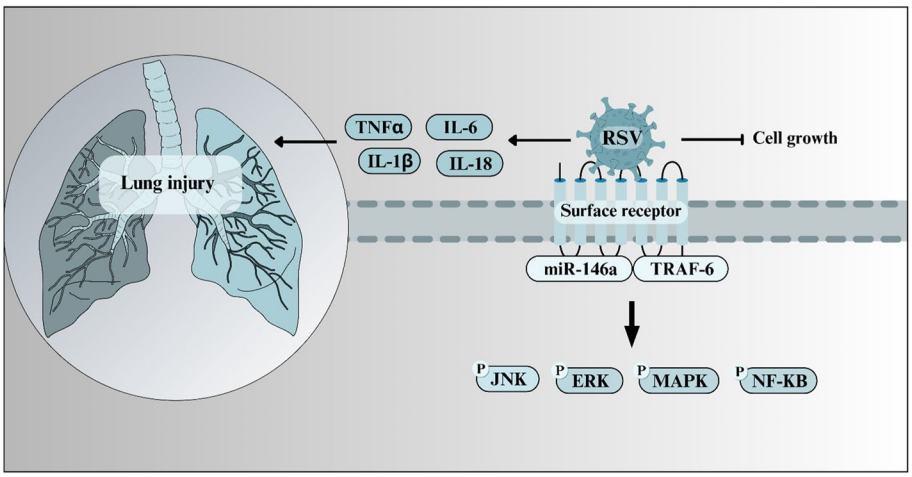


**Fig. 2** MiR-146a decreases inflammation-induced acute lung injury via regulating JNK/ERKMAPK signaling pathway and targeting TRAF-6 [134]

the lungs exhibited inflammatory infiltrates and worse pathology scores. The group confirmed that overexpression of miR-146a decreased IL-6 and TNF-α production. Furthermore, downregulation of TRAF-6 and suppressed the JNK/ERK/MAPK/NF-B signaling cascade resulted in inhibited lung damage caused by RSV infection. Similar results were obtained with HEp-2 and A549 cells. These results suggested that miR-146a could target TRAF-6 as well as regulating inflammatory pathways [134] (Fig. 2).

#### Viral hepatitis

Both HBV and HCV are two primary hepatotropic viruses responsible for chronic liver infections [135, 136]. Upon viral infection, the inflammasomes are activated in the liver cells, thereby chronic viral hepatitis frequently results in excessive liver inflammation. During this process, pro-inflammatory cytokines and type I interferons are processed and released by the inflammasomes, which function as a signaling hub [137]. Various cell types, including microglia, dendritic cells, epithelial cells, monocytes, macrophages, and fibroblasts are able to release CCL2 (referred to as monocyte chemoattractant protein 1) an 11 kDa cytokine of CC chemokine family [138, 139]. Individuals having chronic liver illnesses like alcoholic hepatitis as well as HCV infection, show increased liver inflammation along with elevated levels of CCL2 [140, 141]. It has been demonstrated that reduction of IL-6 and IL-6R complex, along with STAT3 in mice results in downregulation of CCL2 [142]. Cell proliferation and differentiation are tightly regulated via homodimeric bZIP transcription factor CCAAT/CEBPα [143]. A subpopulation of HCC patients shows higher CEBPα levels that can influence the expression of many genes like hepatocyte-specific miR-122, which has been implicated in hepatocarcinogenesis [144]. According to Sarma et al., patients with HCV-induced liver damage show increased miR-107 levels as well as lower miR-449a after infection. These changes affected parts of the IL-6R complex and regulated CCL2 expression [83]. Furthermore, they demonstrated how STAT3, CEBPα, and PU.1 could interact with one another to bind to the promoter and enhance CCL2 expression. Measurements of JAK1 and IL-6R expression in samples from HCV patients indicated that these markers were higher when expressions of miR-107 and miR-449a has been disrupted. This was linked to higher levels of PU.1 and STAT3, but not CEBPα. In vitro research with human hepatocytes, indicated that miR-449a along with miR-107 could target IL-6R and JAK1 expressions respectively, decrease IL-6 signaling, and modify STAT3 activation. Together, their findings unveiled a new gene regulatory system explaining how HCV-induced alterations within miRNAs (miR-449a and miR-107) could control CCL2 expression via triggering IL-6 signaling cascade, thus causing excessive inflammation and fibrosis [83].

Hepatocellular carcinoma as well as liver cirrhosis are often caused by HBV infection [145]. The HBV X (HBx) protein is a multipurpose protein which binds to host regulatory elements, causing inflammatory responses, and can eventually result in liver cancer and cirrhosis [146]. In one study, Wu et al. investigated how microRNAs could contribute to the inflammation caused by HBX [80]. Microarray technology was used to compare miR-203a expression in liver samples from individuals with and without HBV. They used HepG2 cells in vitro to overexpress HBx protein using a plasmid that encodes HBx. The obtained result indicated that the overexpression of HBx promotes miR-203a activity. Forced overexpression of miR-203a within HepG2 cells resulted in increased proliferation and suppressed apoptosis. In addition, it

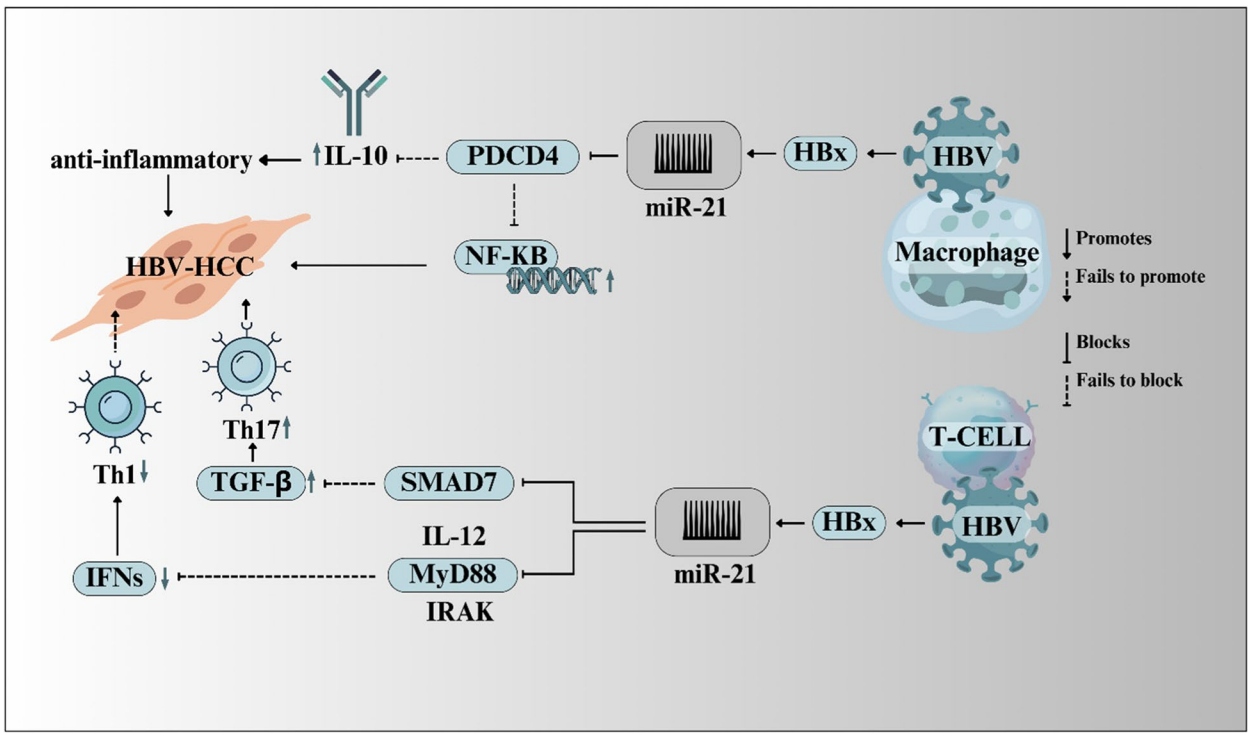


**Fig. 3** The function of HBV HBx protein-induced miR-21 in the regulation of inflammation during HBV infection and hepatocarcinogenesis [151]

was found that overexpression of miR-203a could shift cells from the G0/G1 stage to the G2/M stage. Upregulation of cytokines, such as IL-8 and IL-6 in HepG2 cells was noticeable following miR-203a overexpression, while TGF-β and IFN levels were downregulated. By using luciferase assays, protein mass spectrometry analysis, and real-time PCR, the target gene of miR-203a has been found to be Rap1a (member of RAS oncogene family 1a). Further investigation revealed that the PI3K/ERK/p38/NF-kB signaling pathway controlled these changes. Such outcomes recommend that HBV infection might increase the miR-203a expression, thus decreasing Rap1a expression and affecting the PI3K/ERK/p38/NF-kB signaling pathway, ultimately triggering inflammation associated with hepatitis [80]. Interestingly, the crucial inflammatory cytokine IL-8 was recently discovered to have a part in the development of HBV-induced chronic hepatitis B. (CHB). Earlier studies had demonstrated that HBV-encoded HBX regulatory protein could transactivate IL-8 promoter, and therefore increase its secretion [147]. It has been demonstrated that IL-8 expression in asthmatic bronchial epithelium is modulated by a variety of miRNAs, including miR-18a, miR-128, miR-27a, and miR-155 [148]. According to Dalbeth et al. miR-146a dramatically decreased IL-8 gene expression induced by MSU (monosodium urate) crystals. In addition, miR-106a is found to considerably suppress IL-8 expression at protein and mRNA levels [149]. Moreover, miR-106a was downregulated in human peripheral blood mononuclear cells (PBMCs) isolated from CHB patients. Considering the essential role of IL-8 in liver inflammation caused by HBV infection, inhibition of IL-8 by miR-106a might have a substantial effect on the progression of CHB [150].

The regulation of inflammatory pathways by miR-21 during HBV-associated HCC is shown in Fig. 3.

### HIV infection

The family Retroviridae includes members of the lentivirus genus, such as HIV. At the present time, over 50% of patients infected with HIV throughout the world are taking combination antiretroviral therapy (cART). Moreover, CNS issues, often referred to as NeuroHIV, continue to affect people with HIV infection regardless of the capability of cART to reduce viremia. One of the nine HIV-1-encoded viral proteins which has attracted much interest, is HIV-1 transcriptional transactivator (Tat) that has the ability to damage CNS cells [152]. Also, HIV-1 Tat causes neuroinflammation via increasing viral replication within latently infected cells and by activating glial cells [153]. In the CNS and different tissues, transcription factor NF-kB controls the transcription of some inducible miRNAs like miRNA-34a. Pro-inflammatory cytokines can be secreted in response to elevated NF-kB activity, and this can cause neurodegeneration and cancer [154,

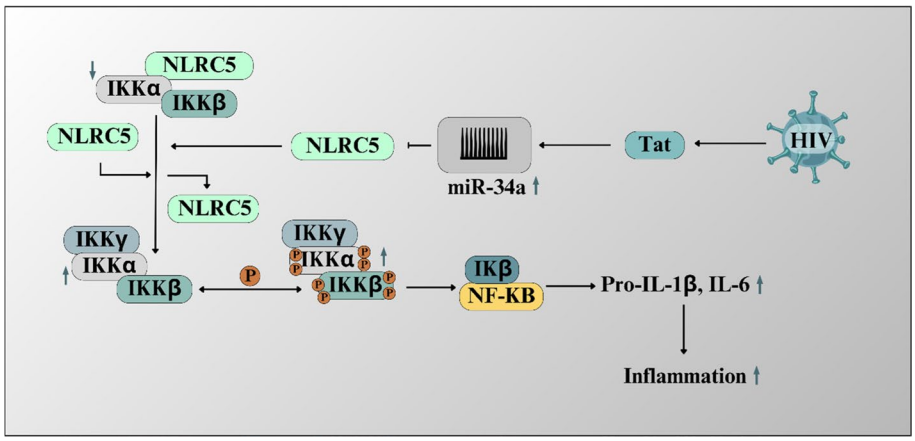


**Fig. 4** HIV Tat-induced miR-34a induces microglial inflammation by increasing level of IL-1β and IL-6 by targeting NLRC5 [84]

155]. Increased miRNA34a signaling has been correlated with the occurrence of neurological, neuroimmunological, neuroinflammatory, or neurodegenerative diseases in several studies [154, 156]. Periyasami et al. discovered that miR-34a has been raised in a dose and time-dependent manner when mouse microglia have been treated with HIV-1-Tat, while NLRC5-a (NOD-like receptor caspase recruitment domain having 5), a repressor of NF-kB signaling, was concurrently decreased [84]. When primary microglia from mice were transfected with miRNA-34a mimics, NLRC5 expression was markedly reduced, which increased p65 NF-kB expression, whereas, cells transfected with a miR-34a inhibitor produced more NLRC5. This suggests that the downregulation of NLRC5 via miR-34a and activation of NF-kB signaling can occur during HIV1-Tat-mediated microglial activation, while miR-34a inhibition prevented HIV-1 Tat from activating microglia. Therefore, the miR-34a-NLRC5-NF-kB axis could act as an important mechanism of HIV-1 Tat-mediated microglial activation. Overall, HIV-1 Tat upregulates miR-34a expression, that targets NLRC5 and promotes the generation of pro-inflammatory cytokines including IL-1 and IL-6 in microglia (Fig. 4) [84]. There are 2 subtypes of HIV-1 called HIV-1 B and HIV-1 C, which generate slightly various forms of Tat protein called Tat B and Tat C. It has been discovered that human microglial cells treated with HIV-1 Tat C upregulated miR-32 gene expression more than Tat B. It has been found that miR-32 bound to 3'UTR of TRAF3 to inhibit its expression, leading to increased expression of inflammatory genes within microglial cells [85].

Microglial cells secrete a range of chemokines as well as cytokines in response to HIV infection, especially monocyte chemoattractant proteins (MCPs). The primary nuclear receptor for macrophage-tropic HIV-1 is CCR5 (R5), among a range of chemokine receptors [157, 158]. In primary human fetal microglia infected with HIV-1, the expression of miR-146a has been determined, and it has been identified that miR-146a raised as the infection developed [159]. They discovered that overexpression of miR-146a before HIV-1 infection limited the production of MCP-2 within infected cells, and identified CCL8/MCP-2 mRNA to be a direct target for miR-146a. By analyzing the miR-146a expression along with MCP-2 in HIV-1 infected brain tissue, an inverse relationship was found between the level of miR-146a and the expression of its target gene MCP-2 [159]. Because MCP-2 is a powerful CCR5 ligand, the fact that miR-146a can inhibit its expression raises the possibility that the miR-146a/MCP-2 axis could be involved in controlling of viral shedding in brain. Production of the pro-inflammatory chemokine MCP-2 is generally inhibited by HIV-mediated upregulation of miR-146a, thereby maintaining chronic brain inflammation in HIV encephalitis [159].

The inflammatory cytokines overproduced in HIV-infected patients include IFN-γ, TNF-α, IL -18, as well as interferon-inducible protein 10 (IP-10) [160]. IP-10 is a pro-inflammatory chemokine linked to inflammatory disorders, immune system dysfunction, and the formation of tumors [161]. In HIV infection, increased blood levels of IP-10 were linked to both accelerated disease progression as well as persistent immune system activation [160, 162]. Prior research has shown that IP-10 can promote HIV multiplication while impairing T and NK cell activity [163, 164]. This explains how regulating IP-10 expression in HIV infection could prevent inflammation and slow the development of the disease. It was found that HIV-1 infection activated IP-10 synthesis by MDA5/Rig-I or TLR7/9-dependent mechanisms [165]. Although IP-10 is known to be upregulated in HIV infection, the exact mechanism is still unknown. Wu et al. investigated whether miRNAs that targeted IP-10 could decrease

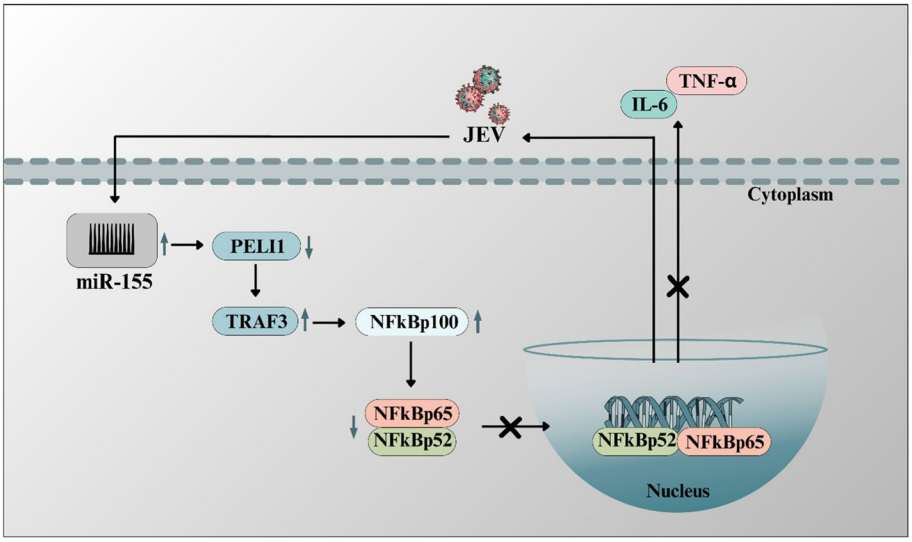


**Fig. 5** Japanese Encephalitis Virus (JEV) suppresses inflammation within microglial cells through the inhibition of the non-canonical NF-κB pathway through regulating miR-155 expression [91]

IP-10 levels in monocytes [166]. Their findings suggested that miR-21 might prevent monocytes from secreting IP-10, and that monocytes isolated from HIV-positive individuals had lower levels of miR-21. The increased synthesis of ISG15 (interferon-stimulated gene 15) may help to explain why alterations in miR-21 expression had no impact on IP-10 secretion in macrophages. Their data indicated that miR-21 could regulate IP-10 levels, shedding some light on the molecular control of IP-10 [166].

#### Japanese encephalitis virus

The Japanese encephalitis virus (JEV) is a positive-stranded encapsulated RNA virus, and a member of Flaviviridae family. JEV is a neurotropic virus that attacks the CNS as well as causing severe inflammation within the brain [94, 167]. When JEV infection occurs, pro-inflammatory cytokines are released, the BBB is disrupted, and CNS infiltration by T and B lymphocytes, DCs, along with NK cells occurs, especially at periphery, which worsens the inflammation [94, 167].

The E3 ubiquitin ligase family includes the pellino proteins PELI1, PELI2, and PELI3 [168, 169]. Pellino proteins can cause pro-inflammatory and antiviral responses in response to cell damage such as that found in neuropathic pain [168, 169]. The MAPK/NF-kB signaling cascade has been linked to PELI1 in chronic constriction injury (CCI) [170]. PELI1 controls NF-kB signaling as well as TRAF3 degradation [171]. Rastoghi et al. found that in microglial cells, miR-155 expression was dramatically higher 24 h after JEV infection. JEV replication increased upon miR-155 overexpression, while it was lower after miR-155 suppression. Inhibition of miR-155 reduced JEV infection and IL-6 level, which suggests a role for miR-155 during inflammation. Moreover, these findings demonstrated that JEV boosted the miR-155 expression, which within human microglial cells targeted PELI1 to block non-canonical NF-kB signaling along with pro-inflammatory factors like TNF-α and IL-6 (Fig. 5) [172].

Another study investigated the role of miR-146a in regulation of neuroinflammation caused by JEV infection [91]. The obtained result, demonstrated that the miR-146 and pro-inflammatory cytokines (TNF-α, IFN-β, IL -1b, IFN-α and IL-6) are upregulated in the brains of BALB/c mice and in cultured mouse microglial cells (C8-B4) following the JEV infection. They discovered that miR-146a had negative regulatory impacts on TNF-α, IL-1b, IFN-β, IL-6, and IFN-α in C8-B4 cells. Therefore, TNF-α, IL-1b, IFN-β, IL-6, and IFN-α were upregulated when miR-146a was downregulated. Such outcomes recommend that miR-146a can regulate inflammation during JEV infection, and could be involved in JEV infection-related seizures [91].

Investigating the impacts of JEV infection upon the miRNA expression profiles of microglia have shown that miRNAs, such as miR-301a can serve in the modulation of inflammatory responses [173]. MiR-301a has been indicated to regulate the autoimmune demyelination activity of Th cells and Th17 differentiation [174]. In JEV infection, miR-301a was found to be essential for controlling antiviral IFN-b response via inhibiting the production of IFN regulatory factor 1 (IRF1) as well as suppressor of cytokine signaling (SOCS). Hazara et al. confirmed that overexpressed miR-301a in JEV-infected human and mouse microglial cells, suppresses NKRF,

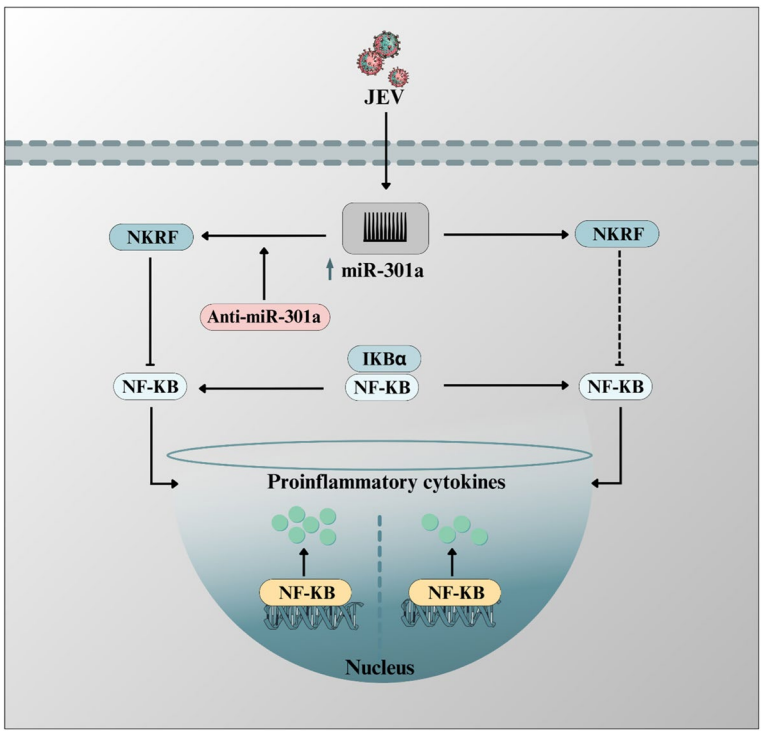


**Fig. 6** Japanese Encephalitis Virus (JEV) promotes inflammatory response via inhibiting NKRF production through upregulating the expression level of miR-301a [95]

the NF-kB inhibitory factor, and prevents NF-kB activation [175, 176]. Furthermore, it has been demonstrated that miR-301a knockdown in JEV-infected microglial cells elevated the NKRF expression, conforming the role of JEV-induced miR-301a in downregulating NKRF [95]. The miR-301a-mediated suppression of NKRF increased inflammation by promoting NF-kB nuclear translocation. However, when NKRF was overexpressed and miR-301a was inhibited, the nuclear accumulation of NF-kB decreased to baseline values. This study established that while JEV infection stimulated the M1 phenotype of microglia with increased proinflammatory cytokines, it reduced the M2 phenotype, which reduced the inflammatory response. Moreover, in vivo inhibition of miR-301a in the mouse brain restored expression of NKRF while decreasing neuronal cell death, inflammation, and microglial activation. Therefore, the NKRF production could be inhibited by JEV-induced miR-301a expression, and this may be employed to mitigate virus-induced neuroinflammation (Fig. 6) [95].

It has been established that JEV downregulating miR-432, results in upregulation of suppressor of cytokine signaling 5 (SOCS5) in CHME3 cells [177]. As a member of the suppressor of cytokine signaling (SOCS) protein family, SOCS5 has a negative impact on the ability of infected cells to respond to viruses [178]. Overexpression of miR-432 results in suppression of SOCS5 which in turn increases the phosphorylation of signal transducer and transcription activator 1 (STAT1) showed increased phosphorylation at Y-701 amino acid. This resulted in both increased ISRE activity along with increased proinflammatory cytokines' expression. Moreover, miR-432 overexpression boosted the production of the inflammatory cytokines TNF-a and IL-6. As a result, miR-432 overexpression promoted the shedding of viral particles into the culture supernatant along with a powerful antiviral milieu within the cells, both of which led to reduced viral replication within the cells. Overall, JEV infection resulted in miR-432 downregulation and SOCS5 upregulation that helped the virus to escape from the cellular immune antiviral response [177]. This microRNA-mediated strategy is used by JEV to evade cellular immunity and promote its pathogenesis.

### Coxsackie virus

Coxsackievirus group B type 3 (CVB3) is a member of the Picornaviridae family, and the main cause of viral myocarditis (VMC) [179]. VMC can result in myocardial damage through inducing an overactive host immune response [180]. Despite recent discoveries, there is currently no recognized therapy for VMC, and its pathogenesis is not well understood. The mechanism

underlying the immune response and excessive inflammation to VMC infection is yet to be elucidated [181].

NLRX1, a member of the NLR family, is found to be associated with several cancer, inflammatory, and neurodegenerative diseases [182]. However, the involvement of NLRX1 and its role in VMC remain unknown. It is established that during viral infection, NLRX1 suppresses the inflammation and innate immune response [183, 184]. Tong et al. investigated the implication of miR-15–NLRX1 axis in VMC development. In that context, they infected H9c2 cells with CVB3 which resulted in upregulation of miR-15 expression. In fact, knockdown of miR-15 reduced the levels of LDH, CK-MB, and cTn-I in CVB3-infected cells. Moreover, miR-15 knockdown increased cell survival, reduced apoptosis, and decreased the expression level of IL-1, IL-6, and IL-18 [96]. The expression of NLRP3 as well as caspase-1 p20 was also downregulated by miR-15 blockade, which considerably decreased the activation of the NLRP3 inflammasomes. Inhibition of NLRX1 suppressed NLRP3 inflammasomes and reversed the protective effect of miR-15 suppression versus CVB3-induced cardiac cell damage. Overall, the findings showed that CVB3-induced myocardial cell damage and inflammation were abrogated by miR-15 suppression [96].

Various cytokines (IL-1, IFN-γ , TNF-α, TGF-β, and IL-6) are secreted via different cells in reaction to viral infection and are responsible for causing myocardial damage [185]. Studies of cardiac hypertrophy and heart failure have shown that TGF-β is the major cause of fibrosis in both diseases [186]. In a viral myocarditis model in mice, TGF-β expression has been increased in CVB3-infected hearts [187]. Recently, Li et al. found that mice with viral myocarditis had decreased expression of miR-425-3p within their myocardial tissues [97]. In mice with myocarditis, the miR-425-3p overexpression gene alleviated the pathological symptoms, reduced cardiomyocyte death, boosted Bcl-2 expression, and decreased the levels of inflammatory markers and increased cardiac function and survival. They discovered that miR-425-3p can target TGF-β1, and indicated that miR-425-3p overexpression suppressed the expression of TGF-β1, p-smad2/smad2, as well as p-smad3/smad3. In fact, miR-425-3p overexpression could prevent apoptosis in CVB3-HL-1 cells, while the addition of TGF-β1 could counteract this effect according to in vitro studies. Overall, their outcomes indicated that miR-425-3p overexpression decreased cardiac inflammation as well as cardiomyocyte death in mice having viral myocarditis, and increased their survival by blocking the TGF1/smad axis [97].

**Enteroviruses**

The positive single-stranded RNA virus HEV71, also referred to as human enterovirus 71, is a member of the Picornaviridae family and Enterovirus genus [188]. A chemokine cascade involving overexpression of IL-8, CCL2, and CXCL10 has been reported to trigger the immune responses occurring after HEV71 infection [189]. CCL2 levels have been shown to be linked with the intensity of HEV71 encephalitis [190]. An alternative classification system of chemokines has been provided based on the miRNA-mediated regulation of chemokines, and has e wide range of variety for each chemokine. For instance, in macrophages of atherosclerotic lesions CCL2 is upregulated, while in inflammatory macrophages, CCL2 is expressed by miR-155 [191]. Zhang and colleagues have established that miR-206 is downregulated in severe HEV71 encephalitis. On the other hand, CCL2 is found to be upregulated during the transition between mild and severe HEV71 [101]. They also found that through targeting the 3'-UTR of CCL2, miR-206 can reduce the CCL2 expression in the human brain. Altogether, suggests that the severity of HEV71 encephalitis might be worsened by upregulation of CCL2 and downregulation of miR-206 [101].

IL-6 is one of many cytokines and proinflammatory mediators that can be expressed during EV71 infection [192, 193]. These cytokines and proinflammatory mediators (i.e., IL-6, IL-10, and COX-2) could stimulate STAT3 activity [194]. For example, IL-6 may bind to IL-6R by promoting STAT3 phosphorylation and activating downstream STAT3 signaling. The EV71 virus induced the activation of the MAPK, NF-kB, along with platelet-derived growth factor receptor (PDGFR) signaling pathways within neurons, thus upregulating the COX-2 expression [195]. Besides COX-2, STAT3 can also be activated by upstream signaling molecules including EGFR/PDGFR and NF-kB [194]. These findings collectively imply that STAT3 is involved in EV71 infection. In the traditional Janus kinase (JAK)-STAT3 signaling pathway, the major activators of STAT3 are IL-6, CNTF, IL-11, IL-27, IL-10, IL-22, along with other cytokines like TNF-α, IFN-α, and IFN-λ [196]. The life cycles of several viruses like varicella-zoster virus (VZV), SARS-CoV, HCV, and HBV are all affected by STAT3 [197]. Chang et al. found that after EV71 infection, miR-124 is upregulated while p-STAT3 and STAT3 levels were decreased [100]. MiR-124 was initially found to be a crucial regulator of the biological activity of microglia within the spinal cord and brain [198]. Current studies suggest that miR-124 play a substantial part in controlling immunity and inflammation [199]. Further studies have revealed that miR-124 can promote infection by EV71. Based on the collected data, they concluded that the antiviral

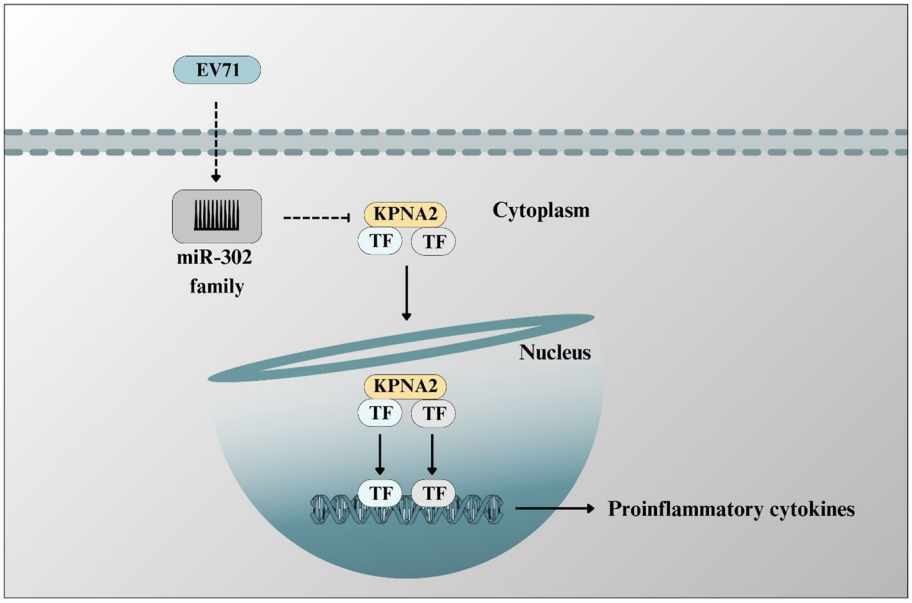


**Fig. 7** Enterovirus 71 (EV71) induces production of inflammatory cytokines by regulating KPNA2 expression by suppression of the miR-302 cluster [99]

activity of STAT3 against EV71 could be inhibited by virus-induced miR-124. It is likely that EV71-induced miR-124 could target the host STAT3 pathway and IL-6R thus mediating immune evasion [100].

The mechanism by which macromolecules, including transcription factors, move from the cytoplasm to nucleus is called nucleocytoplasmic transport, and is conserved across all species. During such procedure, a nuclear localization signal (NLS) must usually be present in a cargo molecule. Through the action of importin proteins that bind to the NLS specifically, cargo proteins can cross the nuclear pore complex, which connects the cytoplasm to the nucleus [200]. Importin 1 is a component of the importin family, which acts as a nucleocytoplasmic transporter, and is also known as karyopherin 2 (KPNA2) [201]. However, there are not many studies discussing the relationship between viral infections and KPNA2. In one example, the ORF6 protein of coronavirus was found to bind to KPNA2 and disassemble STAT1 complex inside nucleus, leading to severe acute respiratory syndrome [202]. Peng et al. discovered that the miR-302 cluster directly targeted KPNA2, thereby preventing the production of proinflammatory cytokines triggered by EV71 infection. KPNA2 regulated JNK1/JNK2, p65, and p38 nuclear translocation that in turn regulated the expression of cytokines stimulated by EV71 infection [99]. In general, the expression of the miR-302 cluster was inhibited via EV71 to increase KPNA2 expression (Fig. 7) [99]. When KPNA2 interacts with such transcription factors, this leads to the translocation of JNK1, JNK2, as well as p38 from the cytoplasm into nucleus, which in turn stimulates the secretion of inflammatory cytokines. Details of some other relevant studies are summarized in Table 1.

## Virus-mediated regulation of inflammatory pathway by virus-derived miRNAs

### EBV-microRNA-BART11-mediated inflammation

A double-stranded DNA virus called Epstein-Barr virus (EBV) replicates in the human oral epithelium (lytic phase) and spreads via saliva. Sarcomas and cancers, including lung, breast, salivary gland, and gastric cancers, have all been associated with EBV [203–205]. How EBV promotes gastric cancer (GC) has been studied in detail [206, 207]. Viral elements that regulate the pathogenesis and development of these EBV-associated malignancies include viral proteins and viral miRNAs (EBV miRNAs) [203].

However, not much is known about the connection between viral miRNAs and GC. According to Song et al. EBV promoted inflammation-induced carcinogenesis by expression of the viral miRNA EBV-miR-BART11, which subsequently downregulated forkhead box protein P1 (FOXP1) [208]. This process promoted the development of tumor-associated macrophages (TAMs) in the host. Cytokine expression and tumor-promoting properties of TAMs were both decreased when FOXP1 was inhibited. The same researchers investigated the impacts of EBV-miR-BART11 upon epithelial-mesenchymal transition (EMT) along with metastasis in GC cells via focusing on FOXP1, an important human tumor suppressor

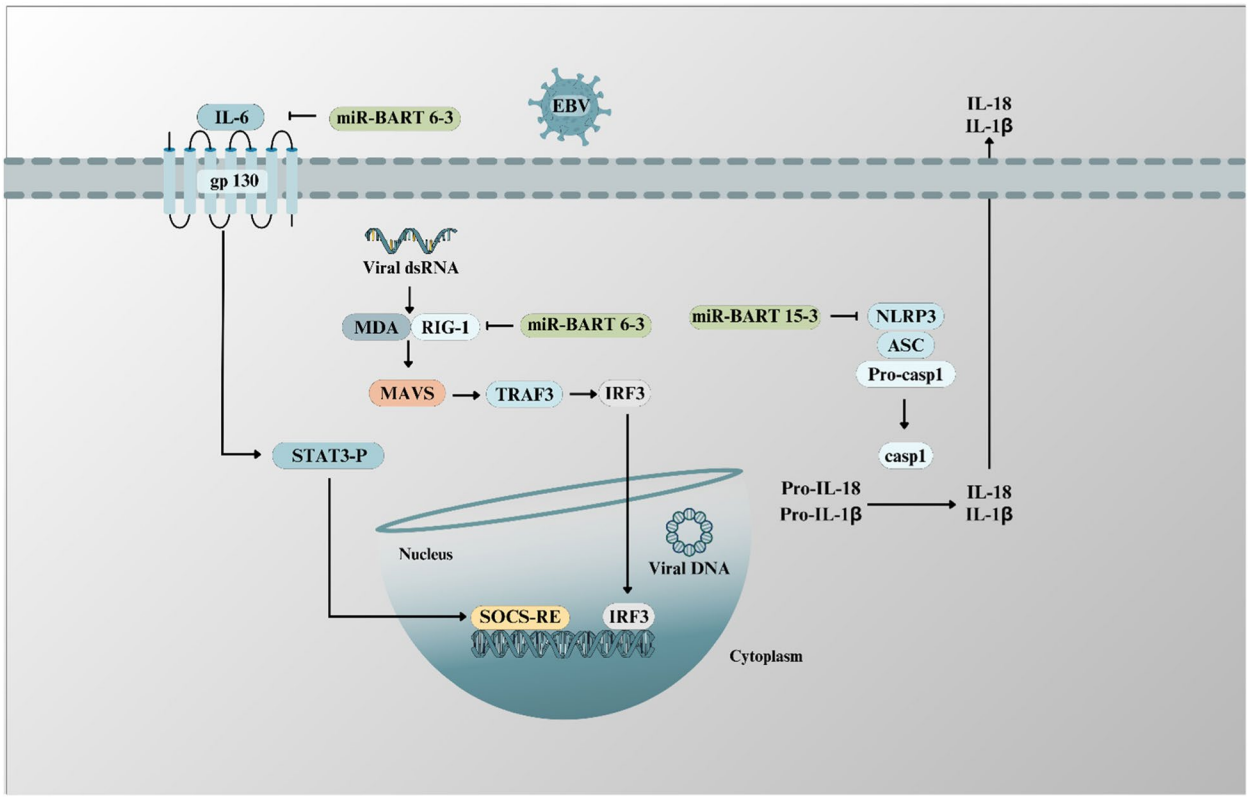


**Fig. 8** Regulation of immune responses and inflammation by EBV-encoded miRNAs [209]

gene [110]. Their findings indicated that increased EBV-miR-BART11 can downregulate FOXP1 in both GC tissues and cell lines. The FOXP1 downregulation could lead to cancer cells to release IL-1, IL-6, and 1 L-10, and in patients with GC this would lead to a worse prognosis. Moreover, TAMs from conditioned media promoted phenotypic changes and expression of EMT-related molecules in GC cells. Additionally, EMT changes were significantly promoted in GC cells cultured in a conditioned medium from TAMs infected with EBV-miR-BART11-containing lentivirus. In contrast, GC cells cultured in a conditioned medium from TAMs infected with FOXP1-encoding lentivirus exhibited little or no EMT change. Taken together, the upregulation of EBV-miR-BART11 level induces gastric cancer cell progression and metastasis mediated by promoting inflammation [110] (Fig. 8).

#### HSV encoded-miR-H6-mediated inflammation

The most common herpes simplex virus is HSV-1, a linear double-stranded DNA virus which mostly affects neuronal and epithelial cells. For a successful HSV-1 infection, the following processes must occur: viral DNA replication, virus assembly, and virus shedding. The infected cell 4 polypeptide (ICP4) is an immediate early (IE) protein needed for efficient transcription of the early as well as late HSV-1 viral genes, and for allowing the HSV-1 replication cycle to proceed [210]. HSV-1 reactivation after a period of latency is supported by ICP4. ICP4 appears to be regulated by latency-associated transcripts (LATs) at the posttranscriptional level [211]. Several cell types are prevented from producing viruses when the ICP4 gene is inhibited [212]. The pleiotropic cytokine IL-6 has been linked to the immunological response to HSV-1. IL-6 can exert anti-inflammatory and pro-inflammatory activities depending on context [213]. At least 21 distinct miRNAs, including miR-H1 and miR-H6, are encoded by the HSV-1 genome. These miRNAs are placed upstream of the LAT (latency-associated transcript) promoter [214]. ICP4 interacts with RNA polymerase II-associated transcription factors to downregulate IE-genes in lytic HSV-1 infections, while at the same time upregulating early and late genes and repressing the LAT-promoter to silence LAT production [215, 216]. Duan et al. investigated how miR-H6 could affect HSV-1 replication as well as the generation of IL-6 in herpes simplex keratitis, a disease where HSV-1 infection can result in corneal blindness [111]. They found that in human retinal pigment epithelial cells and human corneal epithelial (HCE) cells, miR-H6 reduced HSV-1 infection and downregulated ICP4 protein. They concluded that

the virus could trigger IL-6, and that the miR-H6-mediated reduction of IL-6 generation within HSV-1-infected HCE cells could explain the inhibitory activity of ICP4 in virus infections [217]. MiR-H6 mimics could inhibit the production of IL-6 following the HSV-1 infection within HCE cells. Because miR-H6 can both prevent viral replication and suppress inflammation caused by IL-6, it may be possible to treat HSV by regulating the expression of viral miRNAs [111].

#### HHV-8 (human herpesvirus 8) encoded miRNAs

The enveloped virus known as HHV-8 (human herpesvirus 8) is a member of Rhadinovirus genus of the Herpesviridae family [218]. HHV-8 can cause KS (Kaposi's sarcoma), a cancer that affects the skin and mucosal surface. Factors involved in both the lytic and latent stages of the virus life cycle are involved in pathogenesis of KS [218, 219]. According to the available evidence, cytokines like IL-10 and IL-6 could have a substantial part in the pathogenesis of HHV-8-related cancers by suppressing T-cell activation along with promoting tumor cell growth and angiogenesis [220, 221]. Further research linked specific genes encoded via the HHV-8 genome, including the viral glycoprotein vOX2, to IL-6 production by macrophages and monocytes [222]. Although the HHV-8 genome encodes 25 mature miRNAs (KSHV miRNAs) [223], only a few studies have been performed to determine whether HHV-8 miRNAs can regulate cytokine expression. One of these works has been conducted by Qing et al. [112]. They showed that macrophages and myelomonocyte cells preferentially secreted IL-10 and IL-6 after HHV-8 infection. They also found that the HHV-8 miRNAs (miR-K12-1, -3, -7, -9, and −11) could target the C/EBP-β isoform LIP and induce macrophages to secrete IL-6 and IL-10 [112]. How these HHV-8 miRNAs could be utilized to boost immune responses or block other HHV-8-induced cancer-promoting pathways by preventing HHV-8-macrophage interactions, requires additional research.

## Conclusion

Thanks to tremendous advances in miRNA research, a deeper understanding of the processes that underpin the reaction of the innate immune system to viral pathogens could now be expected. Our knowledge of the cell physiology and immunology of viral infections has grown substantially over the past 10 years due to studies on the role of miRNAs in viral pathogenesis. It has been found that a large amount of miRNAs are engaged in the regulation of inflammation in viral infections. These miRNAs are mostly derived from the host cells, but a few of them are encoded by the viral genome itself. Viral infections are extremely complex since a single miRNA could regulate various targets involved in distinct stages of infection. The precise processes behind the control of miRNAs in viral encephalitis, myocarditis, respiratory infections, and neuroinflammation need to be further investigated. To further comprehend these complex networks, future research should examine the potential effects of distinct host and viral miRNAs on diverse targets that may influence the host response to viral infections as a whole.

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