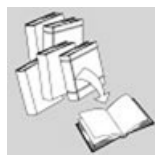


REVIEW



The role of microRNAs in respiratory viral infection: friend or foe?

Alireza Tahamtan¹, Christopher S. Inchley², Mona Marzban¹,
Masoumeh Tavakoli-Yaraki⁴, Majid Teymoori-Rad¹, Britt Nakstad^{2,3} and
Vahid Salimi^{1*}

¹Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

²Department of Pediatric and Adolescent Medicine, Akershus University Hospital, Lørenskog, Norway

³Institute of Clinical Medicine, University of Oslo, Oslo, Norway

⁴Department of Biochemistry, school of Medicine, Iran University of Medical Sciences, Tehran, Iran

SUMMARY

MicroRNAs (miRNAs) have emerged as a class of regulatory RNAs in host–pathogen interactions. Aberrant miRNA expression seems to play a central role in the pathology of several respiratory viruses, promoting development and progression of infection. miRNAs may thus serve as therapeutic and prognostic factors for respiratory viral infectious disease caused by a variety of agents. We present a comprehensive review of recent findings related to the role of miRNAs in different respiratory viral infections and discuss possible therapeutic opportunities aiming to attenuate the burden of viral infections. Our review supports the emerging concept that cellular and viral-encoded miRNAs might be broadly implicated in human respiratory viral infections, with either positive or negative effects on virus life cycle. Copyright © 2016 John Wiley & Sons, Ltd.

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INTRODUCTION

MicroRNAs (miRNAs) are small endogenous, non-coding RNAs, approximately 20–25 nt long. They are RNA-sequence-specific post-transcriptional regulators of gene expression [1]. miRNAs are expressed in a wide variety of organisms and originate in the nucleus as primary miRNA transcripts (~1000 nt), which are processed by the dsRNA-specific endonuclease Droscha into precursor miRNAs (pre-miRNA). The pre-miRNA (~70 nt) are transported to the cytoplasm, and further processed by Dicer into mature miRNAs. A single

strand of mature miRNA is incorporated into the RNA-induced silencing complex (RISC), which binds to the three prime untranslated region (3'-UTR) of target mRNA, and exerts direct effects by blocking the translational process or inducing mRNA degradation, and indirect effects by influencing methylation or targeting of transcriptional factors [2,3]. Over 2000 human miRNAs are currently recognized in the comprehensive miRNA database miRBase [4], and the function of many of these miRNAs in various biological processes including differentiation, proliferation, metabolism, and apoptosis is well established [1]. It is estimated that about 60% of human genes may be subjected to miRNA regulation. miRNA systems constitute complex combinatorial networks, where one miRNA may regulate many mRNA, and conversely, one mRNA may be regulated by several miRNAs [5].

Given the breadth of miRNA-mediated regulation of various biological process and immunity in mammals, the role of miRNAs has recently been highlighted in host–pathogen interactions [6–8]. Host–pathogen interaction is the most important

*Correspondence to: V. Salimi, PhD, Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. E-mail: vsalimi@tums.ac.ir; vahidsalimii@gmail.com

Abbreviations

microRNAs, miRNAs; nucleotide, nt; precursor miRNAs, pre-miRNA; RNA-induced silencing complex, RISC; three prime untranslated region, 3'-UTR; nuclear factor kappa B, NF- κ B; interleukin-1 receptor-associated kinase, IRAK; chemokine (C-C motif) ligand, CCL; nerve growth factor, NGF; tropomyosin-related kinase A, TrkA; severe acute respiratory syndrome-coronavirus, SARS-CoV; Middle East respiratory syndrome-coronavirus, MERS-CoV; OC43-coronavirus, OC43-CoV; very low-density lipoprotein receptor, VLDLR; human metapneumovirus, HMPV; virus-associated RNAs, VARNAs.

dynamic system in nature, and epigenetic modifications and post-transcriptional regulation through miRNA systems may provide an accessory source of fast-acting and readily available phenotypic variation that can be directly carried out by both host and pathogen selection pressures [9]. Over the past decade, our knowledge of miRNA processes in various biological systems and host–pathogen interactions has rapidly advanced, but the precise role of miRNAs in the host–pathogen interactions is still unclear [10]. A number of studies in recent years report differential expression and biological function of miRNAs in airway cells [11,12]. miRNAs play an important role in physiological and pathological aspects of airway cells including pulmonary development, immune function, fibrosis, and cancer [13,14]. In airway epithelial cells, miRNAs have been shown to affect numerous processes pertaining to respiratory pathogens, such as modulation of innate and adaptive immune responses, cell cycle progression, and apoptosis induction [7,15].

In this comprehensive review, we discuss recent findings that indicate an important role for miRNAs in various respiratory viral infections. We also discuss the putative significance of these effects on respiratory viral replication, viral cytopathogenicity, and the immune response. Identifying the role of miRNAs in respiratory viral infections may enhance our understanding of the mechanisms of infection and also indicate a potential future for miRNA-based therapies.

MICRORNA AND VIRUS INTERACTION

Viruses are obligate intracellular infectious agents that use the host cellular machinery to ensure their own fitness and survival. The success of viruses principally depends on their capability to efficiently use the host machinery to take advantage of basic biological processes [16–18]. miRNA systems have several features that make them ideal tools for virus propagation. They are potent post-transcriptional gene expression regulators. They are both small and non-antigenic and can modulate expression of several critical cellular pathways [19–21]. miRNA systems modulate viral replication and pathogenesis in several ways: (i) Host cell miRNAs can positively or negatively affect viral replication and pathogenesis as a result of their biological functions. (ii) Some viruses also encode miRNAs. Current evidence indicates that viral-encoded miRNAs target several cellular genes involved in cell proliferation and

survival, stress responses, and anti-viral response. (iii) Virus-encoded miRNAs may also regulate viral gene expression [21–27]. Thus, host-encoded miRNAs, virus-encoded miRNAs, and miRNA targets together form a novel regulatory system (miRNA system) between the host and the virus, which contributes to the outcome of infection [19,28].

Host cellular miRNA expression is profoundly altered following viral infection (Figure 1), which affects the viral life cycle including viral replication, immune responses, and infection outcome [22]. On the one hand, these changes could represent a host defense against infection and might therefore act to inhibit virus replication. On the other hand, changes in cellular miRNA may be induced by viruses to prepare a suitable environment for productive viral infection and/or latency [21]. Host cellular miRNAs may have direct effects on viral replication, through positive or negative interactions with viral genomes or other viral factors [29]. An miRNA system may also contribute to anti-viral host defense [30]. Evidence suggests that miRNA can positively or negatively regulate innate and adaptive immune responses [7]. Furthermore, host cell miRNAs have potential to regulate virus tissue tropisms [22]. Thus, miRNAs are utilized by viruses to invade host cells, replicate in host cell, evade host immune response, and establish and maintain virus latency [19,24].

There are several reports demonstrating that some viruses take advantage of cellular miRNAs by enhancing the expression of specific cellular miRNAs. This can enhance virus replication, apparently by down-regulating specific cellular mRNA targets with anti-viral potential [31–33]. Alternatively, viruses may use the miRNA system to limit their own replication in infected cells, allowing evasion of the host immune response, survival of infected cells, establishment of viral latency, and increased spread to other individuals in a population [34]. Furthermore, other studies indicate that viral gene products inhibit cellular miRNA expression [35]. Thus, viruses can induce certain cellular miRNAs that affect the virus life cycle positively and inhibit those that affect the virus life cycle negatively [29]. Interestingly, some viruses can propagate despite the presence of host cell-encoded inhibitory miRNA. Viruses may avoid inhibition by cellular miRNAs by several methods including: (i) blocking cellular miRNA biogenesis; (ii) inhibiting cellular miRNA function; or (iii)

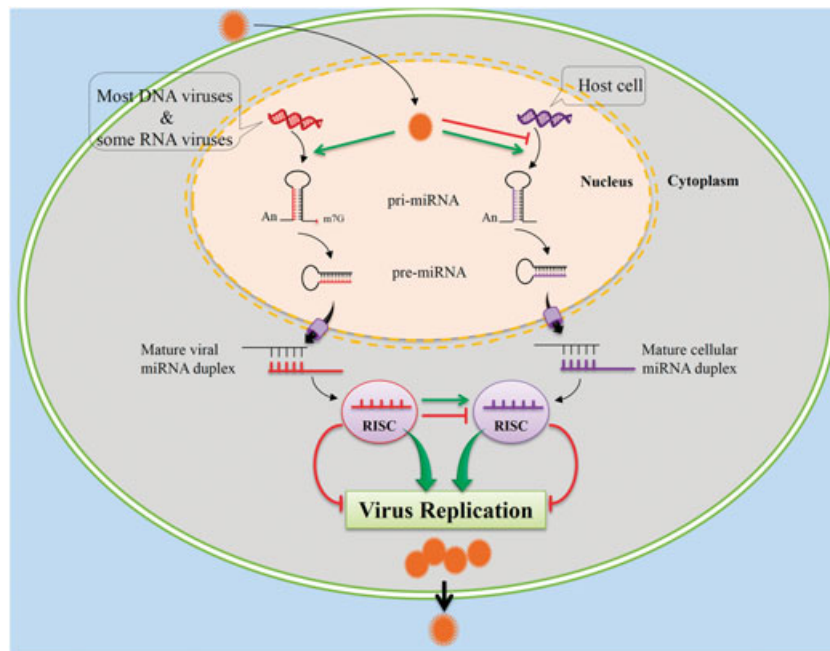


Figure 1. Following viral infection, host cells alter their microRNAs (miRNAs) expression as a defense against infection, while viruses can circumvent host defense and promote their own propagation by affecting host cellular miRNAs expression or by expressing their own miRNAs

evolving 3'-UTR sequences that miRNAs are unable to bind to because they are not complementary to miRNA, are too short, or have complex secondary structures that could restrict binding by RISCs [36]. However, some reports demonstrated that specific cellular miRNAs can negatively inhibit virus replication [37–39].

There are several ways in which the association of cellular and viral-encoded miRNAs with pathology and their targets can be identified [35]. Computational analyses (*in silico*) for predicting miRNAs and their targets are applied by most studies as the first step of a survey. However, computer-based predictions of miRNA-target interactions may or may not exist in reality and should be verified by *in vitro* and/or *in vivo* investigations, often involving addition and removal of miRNAs from a system. In recent years, rapid advances in next generation sequencing have been successfully incorporated to analyze miRNAs and their targets [40]. In addition, deep sequencing of small RNAs isolated from virus-infected cells may provide valuable information [41].

MICRORNAS AND RESPIRATORY VIRUSES

Respiratory viruses are the most common global health problem with morbidity and mortality worldwide [42]. Respiratory viral infections are

responsible for an enormous economic burden, precipitating considerable absence from school and work, large numbers of visits to clinicians, and also represent a major cause of exacerbations of chronic respiratory disease such as asthma and chronic obstructive pulmonary disease [43]. Viruses most commonly associated with respiratory infections are orthomyxoviruses, adenoviruses, paramyxoviruses, coronaviruses, picornaviruses, human bocavirus, and human herpesviruses [44]. The availability of effective vaccines against respiratory viral infections is limited, and other than the anti-influenza medications oseltamivir and zanamivir, no clinical anti-viral treatments for common respiratory viruses are available [45,46]. Novel anti-viral therapeutic approaches to prevent and treat respiratory viral infection are needed according to the WHO initiative Battle against Respiratory Viruses [47].

In recent years, significant progress has been made in understanding the molecular mechanisms underlying respiratory virus infection and host interaction. Identification and characterization of the miRNA expression profile following respiratory viral infection and its implication in viral infection is an important tool for understanding host–virus interaction, mechanisms of infection, and also therapy strategy development. Here, we

summarize the literature data on such host-respiratory virus implications in humans and discuss how these implications can be used as research tools or targets in the development of novel anti-viral therapeutics (Table 1).

RNA VIRUSES

Unlike DNA viruses, RNA viruses usually do not encode their own miRNA, and the reasons behind this discrepancy are debated theoretically [89]. The majority of RNA viruses replicate in the cytoplasm where they cannot access the nuclear enzyme Droscha, which is required for miRNA processing. Those RNA viruses, which do have access to the nucleus (e.g. influenza and HIV-1), may avoid encoding their own miRNAs because excision of a primary miRNA from RNA virus genome would induce cleavage and destruction of viral genome [20,27]. In addition, viruses that undergo short lytic replication cycles are less likely to encode miRNAs [22].

Influenza virus

Influenza virus is a common respiratory pathogen that primarily infects airway epithelial cells and leads to clinical outcomes ranging from mild upper respiratory infection to severe pneumonia [90]. The host cellular response, specifically miRNA dysregulation, is likely to play a critical role in influenza infection outcome [53,58]. Recent studies show distinct miRNA expression profiles in ill patients with influenza A (H1N1), that is, down-regulation of miR-29a, miR-29c, let-7g, miR-146b-5p, miR-150, miR-342-3p, miR-769-5p, miR-30b, miR-31, miR-361-3p, miR-362-3p, miR-342, miR-155, miR-210, and miR-192. These miRNAs are involved in the regulation of important biological pathways during virus infection, such as mitogen-activated protein kinase, epidermal growth factor receptor, and toll-like receptor signaling pathways [91]. Additional studies detected high expression of miR-299-5p and miR-335 in influenza patients [91,92]. In contrast, miR-765, miR-34b, miR-519e, miR-18a, miR-628-3p, miR-185, miR-576-3p, miR-519d, miR-28-5p, miR-26a, miR-1285, miR-665, and miR-30a were down-regulated in H1N1 patients, and interestingly, miR-576-3p could affect viral entry into cells by regulating AP1G1 expression [60]. Furthermore, miR-17, miR-20a, miR-106a, and miR-376c were significantly elevated in H7N9 patients [93].

The virulence of influenza virus may be mediated in part by host cellular miRNAs via dysregulation of pathways critical for anti-viral immune responses [48]. Influenza infection up-regulates miR-29 expression, which is involved in regulation of both innate and adaptive immune responses through protection of A20 mRNA [32]. miR-29 acts as an RNA decoy to prevent HuR (human antigen R) from binding to the A20 3'-UTR and recruiting the RISC [94]. A20 is a deubiquitinating enzyme known to play an important role in terminating the anti-viral immune response by inhibiting nuclear factor kappa B (NF- κ B) and interferon regulatory factor pathways [95]. Influenza infection of A549 cells induces expression of miR-146a, also a negative regulator of NF- κ B [51]. Interestingly, one study showed that the zoonotic respiratory hendra virus induces miR-146a, which promotes viral replication by targeting ring finger protein 11 [33]. In a study by Huang, *et al.*, up-regulation of several miRNAs including miR-15b-3p, miR-24-2-5p, miR-331-3p, miR-124-3p, and miR-337-5p was demonstrated following H1N1 infection. These miRNAs participate in toll-like receptor and RIG-I-like receptor signaling pathways, and also regulate IL-1 β and TNF receptor-associated factor 3 [52]. Furthermore, miR-7, miR-132, miR-146a, miR-187, miR-200c, and miR-1275 accumulate in human lung cell lines in response to infection with two influenza A virus strains, A/Udorn/72 and A/WSN/33, causing down-regulation of anti-viral proteins such as interleukin-1 receptor-associated kinase (IRAK1) and mitogen-activated protein kinase 3 [53].

Virulence of highly pathogenic influenza viruses may be mediated in part by host cellular miRNAs. For example, the highly pathogenic H5N1 virus induces miR-141 shortly after infection, which suppresses the expression of transforming growth factor- β in lung epithelial cells [58]. Without sufficient transforming growth factor- β , the pro-inflammatory response might not be tightly controlled in cases of highly pathogenic H5N1 infection [96]. The 1918 pandemic influenza virus induces a distinct miRNA expression profile in mice compared with non-lethal influenza A/Texas/36/91, including down-regulation of miR-200a and up-regulation of miR-223; miR-223 is a negative modulator of neutrophil activation, and miR-200a has a role in the type I IFN response [59].

Table 1. miRNAs effects in respiratory viral infection

Virus	miRNAs	Effects	Reference
Influenza	miR-30 down-regulation and miR-223 up-regulation	Regulate apoptosis	[48]
	miR-29 up-regulation	Regulates apoptosis	[49]
	miR-4276 induction	Inhibits COX6C and caspase-9	[50]
	miR-29 up-regulation	Protects A20 mRNA	[32]
	miR-146a induction	Regulates immune response	[51]
	miR-15b-3p, miR-24-2-5p, miR-331-3p, miR-124-3p, and miR-337-5p up-regulation	Regulate anti-viral response	[52]
	miR-7, miR-132, miR-146a, miR-187, miR-200c, and miR-1275 expression	Regulate anti-viral response	[53]
	miR-106b, miR-124, and miR-1254 expression	Regulate human protease genes	[54]
	miR-24 down-regulation	Up-regulates furin mRNA	[55]
	miR-21 expression	Inhibits proliferation-suppressing factors	[56]
	miR-30 family down-regulation	Contribute to higher proliferation	[57]
	miR-141 up-regulation	Suppress expression of TGF- β	[58]
	miR-200a and miR-223 expression	Regulate neutrophil and IFN-I response	[59]
	miR-576-3p down-regulation	Regulates virus entry	[60]
	miR-323, miR-491, and miR-654 expression	Inhibit H1N1 influenza replication	[37]
RSV	let-7c expression	Inhibits M1 protein	[39]
	let-7f expression	Contributes to delayed viral clearance	[31]
	let-7i and miR-30b inhibition	Enhance viral replication	[61]
	miR-221 silencing	Enhance NGF and TrkA expression	[62]
	miR-125a down-regulation	Contributes to the virus immune evasion	[63]
Coronavirus	miR-17, miR-574-5p, and miR-214 up-regulation	Contribute to virus evade immune elimination	[64]
	miR-9 expression	Potentiates NF-kB activation	[65]
Rhinovirus	miR-128 and miR-155 expression	Contribute to the anti-viral activity against rhinovirus-1B	[38]
	miR-23b expression	Inhibits infections of minor group rhinoviruses	[66]
HMPV	miR-30a and miR-16 inhibition	Regulate host cellular response to HMPV virus infection	[67]
Adenovirus	miVARNAs expression	Targets cellular and viral genes	[68]
	miVARNAs expression	Inhibits human pre-miRNA	[69]
	miVARNAs expression	Down-regulates the TIA-1 expression	[70]
	miVARNAs expression	Down-regulates the HDGF expression	[71]
	miR-214 expression	Inhibits virus replication	[72]

Continues

Table 1. (Continued)

Virus	miRNAs	Effects	Reference
	miR-466 expression	Down-regulates the level of CAR protein	[73]
HCMV	miR-1, miR-34, miR-22, miR-365, miR-29, miR-145, and let-7 expression	Target Rb-dependent cell cycle and DNA replication mRNAs	[74]
	miR-US4-1 expression	Inhibits CD8 + T cell response	[75]
	miR-UL112 expression	Attenuates NK cell activity	[76]
	miR-UL148D expression	Targets the human chemokine CCL5	[77]
	miR-UL112-3p expression	Targets TLR2 and following signaling	[78]
	miR-UL112-1 expression	Down-regulates IL-32 expression	[79]
	miR-US25-1-5p expression	Inhibits viral replication	[80]
	miR-US25-2 expression	Reduces viral replication	[81]
	miR-200 family members expression	Targets the UL122 expression	[82]
	miR-US33 expression	Down-regulates virus replication	[83]
miR-UL112-1 expression	Decreases genomic viral DNA levels	[84]	
miR-UL112-1 expression	Down-regulates cellular BclAF1	[85]	
miR-UL112-1, miR-US5-1, and miR-US5-2 expression	Target multiple components of the host secretory pathway	[86]	
miR-UL70-3p and miR-UL148D expression	Target the pro-apoptotic genes	[87]	
HHV-6	miR-U86 expression	Targets the HHV-6A IE gene U86, thereby regulates virus lytic replication	[88]

miRNAs, microRNAs; TGF- β , transforming growth factor- β ; COX6C, cytochrome c oxidase VIC; NGF, nerve growth factor; TrkA, tropomyosin-related kinase A; NF- κ B, nuclear factor kappa B; HMPV, human metapneumovirus; HCMV, human cytomegalovirus; CAR, Coxsackie virus and adenovirus receptor; HDGF, hepatoma-derived growth factor.

Apoptosis is characteristic of influenza virus infection, and the mechanisms underlying this have advanced understanding of influenza virus replication [49,50]. According to Othumpangat, *et al.*, in the first hours after influenza infection, down-regulation of miR-4276 increases cytochrome c oxidase VIC expression, inhibiting viral replication by inducing the apoptotic protein caspase-9. However, after 6 to 9 h, this effect is completely reversed, thereby prolonging cell survival. This may suggest that influenza virus is able to induce miR-4276 and inhibit cytochrome c oxidase VIC and caspase-9 expression, thus promoting viral replication [50]. Recent studies have revealed that miR-29 family members are up-regulated during

influenza infection, especially miR-29c, which targets the anti-apoptotic factor B-cell lymphoma 2-like 2 contributing to virus-mediated apoptosis [49]. Furthermore, down-regulation of miR-30 family members and up-regulation of miR-223 during influenza infection lead to increased apoptosis [48].

The expression of host genes required for influenza virus replication can be regulated by multiple cellular miRNAs, for example, miR-106b, miR-124, and miR-1254 regulate human protease genes (ADAMTS7, CPE, DPP3, MST1, and PRSS12) that are essential for influenza replication [54]. In addition, down-regulation of miR-24 with a concomitant up-regulation of furin mRNA has been demonstrated during the influenza H5N1 infection

in A549 cells. miR-24 regulates furin-mediated activation of influenza hemagglutinin precursor and subsequent production of fusion-competent virions in the host secretory pathway [55].

Some miRNAs play important roles in priming airway cells for repair and regeneration following influenza infection [97]. Elevated expression of miR-21 throughout repair and regeneration corresponds with increased cell proliferation in repairing lungs, because miR-21 targets proliferation-suppressing factors [56]. The miR-30 family was significantly down-regulated during repair consistent with increased expression of its main target p53, which promotes proliferation in recovering lung tissues [57].

While influenza virus can clearly take advantage of cellular miRNAs via their promotion or inhibition, it is also revealed that certain cellular miRNAs can inhibit replication of influenza viruses in infected cells [37,39]. miR-323, miR-491, and miR-654 inhibit replication of the H1N1 influenza A virus in MDCK cells by targeting the same conserved region in the influenza PB1 gene [37].

Furthermore, let-7c inhibits M1 protein expression of the H1N1 influenza A virus in A549 cells [39].

Overall, these results suggest that influenza respiratory infection induces or inhibits expression of certain miRNAs in airway cells that favor viral replication, pathogenesis, and also suppress anti-viral responses (Figure 2). Thus, cellular miRNAs associated with immune response, apoptosis, and protease genes could be the best candidates for development of miRNA-based therapies for influenza disease. However, caution must be taken due to the immunopathogenic character of influenza infection.

Respiratory syncytial virus

RSV is a leading cause of viral respiratory tract disease among infants and young children [98,99]. Worldwide, 33.8 million episodes of RSV-associated acute lower respiratory tract infections are estimated to occur in children <5 years of age [100]. In developed countries, the RSV-associated mortality rates are reported to be approximately three deaths per 100 000 in children younger than 1 year [101–104].

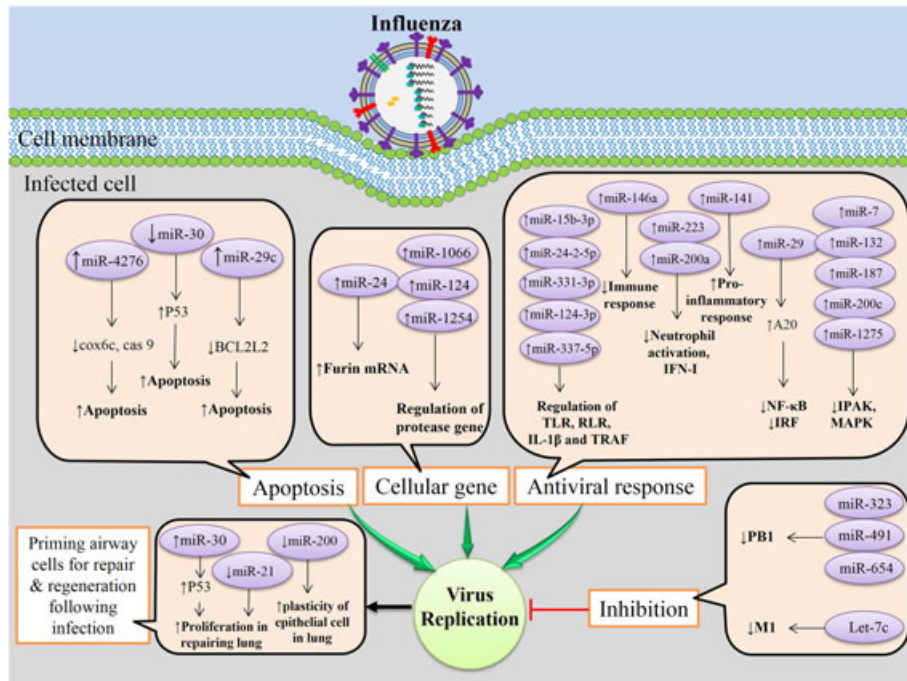


Figure 2. Influenza infection of airway epithelial cells induces or inhibits certain cellular microRNAs (miRNAs) expression in favor of viral replication, pathogenesis, and also suppress anti-viral responses. However, certain cellular miRNAs can inhibit replication of influenza in infected cells, and certain miRNAs play important roles in priming airway cells for repair and regeneration following influenza infection

RSV infection is a common example of viruses that modulate host miRNA expression to influence the outcome of the anti-viral host response and viral replication [7,15,105]. Distinct immune-associated miRNA expression profiles have been detected in the nasal epithelium of RSV-positive infants; down-regulation of miR-34b, miR-34c, miR-125b, miR-29c, miR125a, miR-429, and miR-27b, and up-regulation of miR-155, miR-31, miR-203a, miR-16, and let-7d were detected in these patients. In addition, miR-125a and miR-429 were down-regulated in mild disease, but not in severe disease, and the lack of down-regulation in severe disease may rationalize the observed differences in disease manifestations following RSV infection [63]. miR-125a regulates the expression of NF- κ B by suppressing the inhibitor protein A20, and chemokine (C-C motif) ligand (CCL5), an important cytokine in both innate and adaptive immune systems [106].

RSV infection of A549 cells induced let-7f, miR-24, miR-337-3p, miR-26b, and miR-520a-5p and repressed miR-198 and miR-59 expression. Let-7f expression was RSV G protein dependent, and its expression likely contributes to delayed viral clearance by targeting CCL7 and suppressor of cytokine signaling 3, which are involved in anti-viral response [31]. In another study, let-7b, let-7c, let-7i, and miR-30b were up-regulated on RSV infection of monocyte derived dendritic cells and human bronchial epithelial cells, and associated with IFN- β and/or NF- κ B activation. Interestingly, RSV nonstructural proteins NS1 and NS2 antagonized the up-regulation of let-7i and miR-30b, a process that may favor viral replication [61]. The miRNAs described in these studies have a number of experimentally confirmed targets that are associated with RSV replication and pathology. For example, an experimentally confirmed target of the let-7 family is IL-13, which appears to enhance the severity of disease [107].

RSV infection modifies the expression of critical neurotrophic factors and receptors such as nerve growth factor (NGF), and its cognate high-affinity receptor tropomyosin-related kinase A (TrkA), which prevents apoptosis by increasing expression of the anti-apoptotic Bcl-2 family members [108]. In human bronchial epithelial cells, high levels of intracellular miR-221 reduced NGF and TrkA expression, which favor the apoptotic death of infected cells, and attenuate virus infection. RSV infection reduces miR-221 expression, thus

interfering with the apoptotic death of infected cells by increasing NGF and TrkA expression and ultimately promoting viral replication [62].

Overall, these findings suggest that following RSV respiratory infection, an altered expression profile of distinct immune-associated miRNAs occurs in the airway cells that inhibit viral replication and preserve the airway epithelial barrier. However, the virus concurrently induces or inhibits the expression of other miRNAs that favor viral replication (Figure 3). These conflicting miRNA effects during RSV infection may provide treatment options in susceptible individuals. However, attempts to modulate RSV pathology in clinical practice should be made with caution as RSV immunopathogenesis is complicated and an early RSV vaccine candidate caused serious adverse events during natural RSV infection [109].

Coronaviruses

Coronaviruses can cause a wide spectrum of respiratory infections ranging from mild, upper respiratory tract infections to severe and life-threatening lower respiratory tract infections [110]. There are no *in vivo* studies regarding the role of miRNAs in coronaviruses infection, but the OC43 virus has been investigated *in vitro*, and severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV) were analyzed by *in silico* methods (Figure 4).

The coronavirus OC43 contributes to the common cold worldwide [112]. Coronavirus N protein is essential for replication and binds to genomic RNA to form a helical capsid. OC43 N protein potentiates NF- κ B activation by binding to its negative regulator miR-9. It is not clear whether NF- κ B activation is directly beneficial to viral replication, or whether this is an incidental effect that limits viral virulence. Compared with more pathogenic coronaviruses, reduced OC43 virulence with limited symptoms may promote contact between infected and non-infected individuals and thus promote spread of the virus within a population [65]. This novel mechanism of miRNA-binding to promote gene activity may provide insight into the mechanisms by which successful RNA viruses avoid the host immune system or cause pathology.

Severe acute respiratory syndrome-coronavirus is a novel coronavirus that threatened to cause a global pandemic of the severe acute respiratory

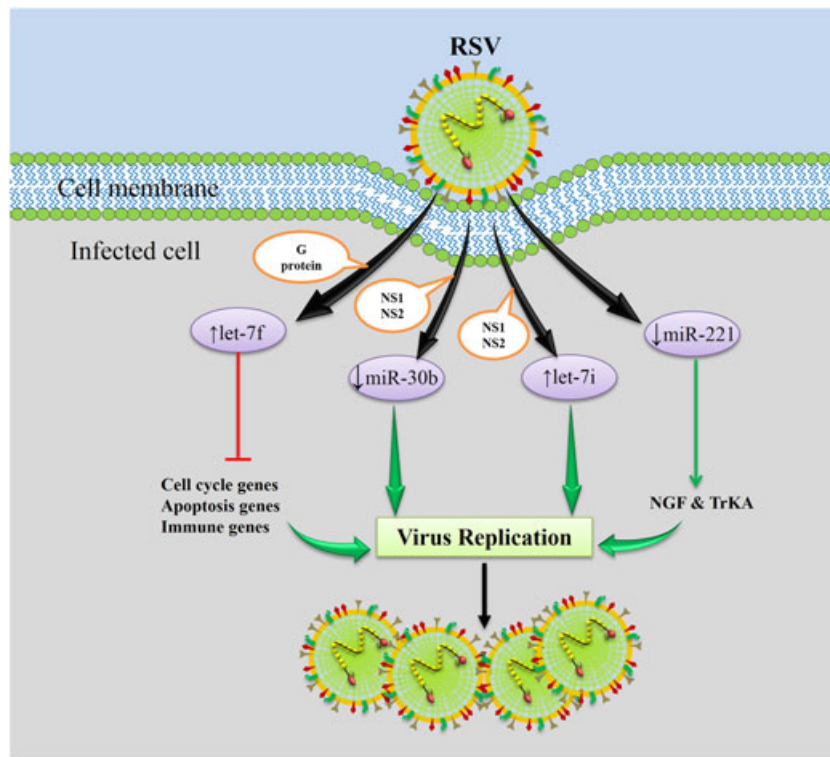


Figure 3. Following RSV respiratory infection, an altered expression profile of certain cellular miRNAs, specifically immune-associated miRNAs, occurs in order to inhibit viral replication and preserve the airway epithelial barrier; meanwhile, the virus induces or inhibits the expression of other miRNAs that favor viral replication. The RSV G protein enhances let-7f, the RSV NS1/NS2 proteins decrease miR-30b and enhance let-7i, and RSV infection decrease miR-221, which is an advantage for the virus

syndrome in 2002–2003 [113]. An *in silico* analysis of miRNA interactions with SARS-CoV mRNA suggested that the virus might suppress its own replication early during infection by up-regulation of miR-17, miR-574-5p, and miR-214. These host miRNAs target all four virulent viral proteins, spike (S), nucleocapsid (N), matrix (M), and envelope (E) [64]. Suppression of viral replication may aid evasion of immune surveillance until successful infection of other cells. These results demonstrate how SARS-CoV might alter host miRNA expression profile to its own advantage.

Middle East respiratory syndrome, caused by a novel human coronavirus MERS-CoV, has emerged recently [114]. An *in silico* analysis identified miR-628-5p, miR-6804-3p, miR-4289, miR-208a-3p, miR-510-3p, miR-18a-3p, miR-329-3p, miR-548ax, miR-3934-5p, miR-4474-5p, miR-7974, miR-6865-5p, and miR-342-3p as having significant sequence similarity to hairpin structures in the MERS-CoV genome, and they may thus down-regulate viral gene expression to inhibit viral replication [111].

This knowledge may help us to better understand host–virus interactions with the intention to develop new anti-viral therapies against MERS-CoV, a highly lethal respiratory disease.

Rhinoviruses

Rhinoviruses are members of the *Picornaviridae* family. Rhinoviruses cause respiratory infection in humans with severity ranging from the common cold to viral bronchiolitis, and exacerbations of asthma and chronic obstructive pulmonary disease [115]. Bondanese, *et al.* showed that cellular miRNAs miR-128 and miR-155 with putative sites in the rhinovirus-1B coding region can inhibit virus replication. miR-128 inhibition seemed to increase viral replication by inducing apoptosis. The detection of miR-155-mediated anti-viral activity in bronchial epithelial cells is very relevant because this miRNA has a central role in innate and adaptive immunity. As an example, miR-155 has been shown to target suppressor of cytokine signaling 1, an inhibitor of type I IFN signaling [38].

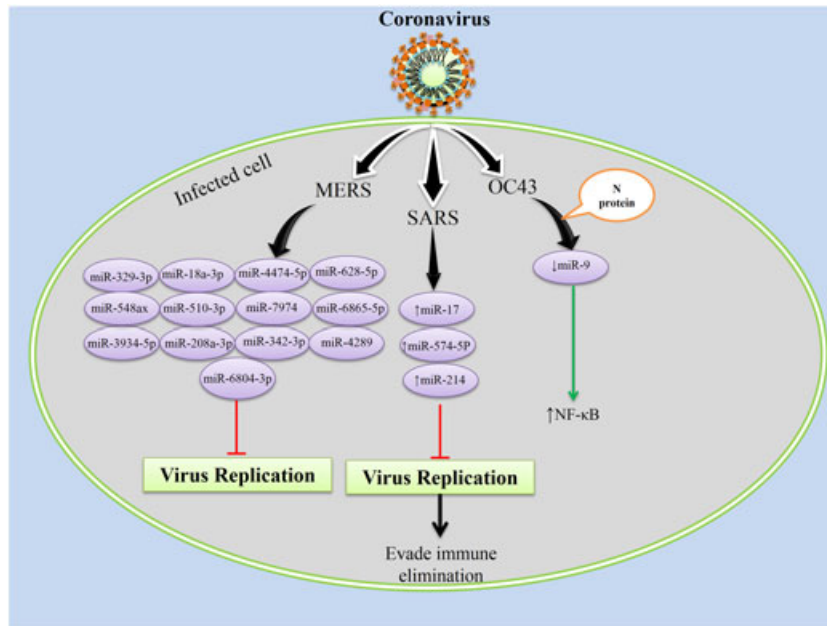


Figure 4. Coronaviruses interact with the host cell at the onset of infection and induces several changes in host cellular microRNAs (miRNAs) expression profile to their own advantage; severe acute respiratory syndrome-coronavirus (SARS-CoV) uses cellular miRNAs machinery to evade immune elimination [64]; in Middle East respiratory syndrome-coronavirus (MERS-CoV), host cells miRNAs would be an anti-viral therapeutic agent [111], and the N protein of OC43-coronavirus (OC43-CoV) causes potentiation of nuclear factor kappa B (NF- κ B) activation via binding to its negative regulator miR-9 [65]

A minor group of rhinoviruses including subtypes 1A, 1B, 2, 23, 25, 29, 30, 31, 44, 47, 49, and 62 commonly utilize the very low-density lipoprotein receptor (VLDLR) for entry into host cells, and cause disease more often than the major group. Recent evidence published by Ouda, *et al.*, showed that down-regulation of VLDLR by miR-23b is of significance for host defense against the minor group of rhinoviruses. miR-23b was induced by RIG-I-like receptor signaling resulting in suppression of respiratory infections caused by minor group viruses, specifically rhinovirus-1B through down-regulation of its receptor VLDLR [66]. In conclusion, these results suggest that miRNAs play an important role in human anti-viral responses against rhinovirus infection (Figure 5).

Human metapneumovirus

Human metapneumovirus causes acute respiratory disease in infants, the elderly, and immunocompromised individuals ranging from mild upper respiratory illness to more serious lower respiratory illness [117]. Limited literature is available regarding the role of miRNAs in human metapneumovirus

(HMPV) infection. Deng, *et al.* reported that host airway epithelial cells alter their miRNA expression profile upon HMPV infection as a defense mechanism against the virus. The HMPV M2-2 protein acted as a key viral protein that regulated host cell miRNA expression, specifically antagonizing miR-30a and miR-16 (Figure 5). Interestingly, M2-2-mediated miR-16 suppression was interferon dependent, whereas suppression of miR-30a was interferon independent [67].

The aforementioned data suggest a new way in which HMPV regulates the host cell response to infection. There are currently no licensed therapeutics or vaccines against HMPV. These and future studies may help the development of effective miRNA-based therapies.

DNA VIRUSES

Many DNA viruses encode their own miRNAs, because they generally replicate in the nucleus and have access to the canonical miRNA pathway (except poxviruses) [27]. Most DNA viruses establish long-term latent or persistent infections and take advantage of virus-encoded and host cell miRNAs

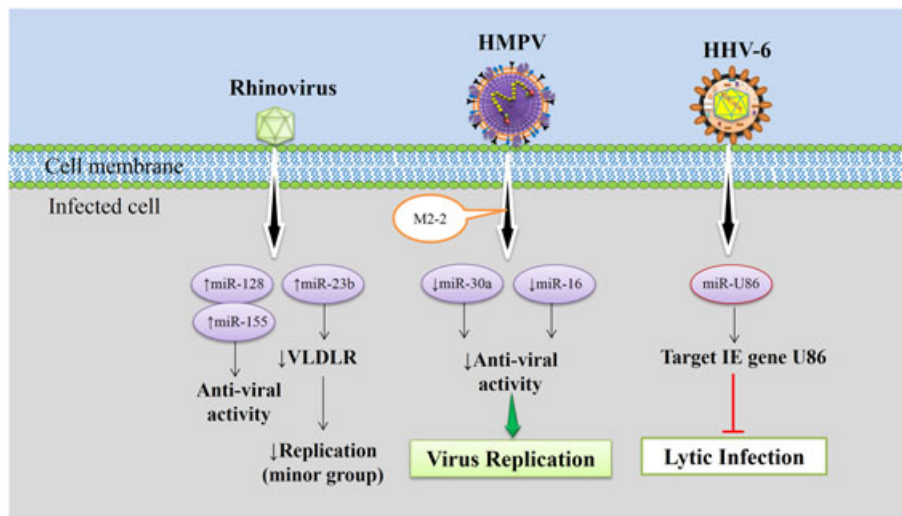


Figure 5. In rhinoviruses infection, cellular microRNAs play anti-viral responses against viruses [38], human metapneumovirus (HMPV) M2-2 regulates the host cell microRNAs response to infection [67], and HHV-6A miR-U86 targets the HHV-6A IE gene U86, thereby regulating virus lytic replication [116].

[22]. Because of the fact that viral miRNAs, unlike viral proteins, are non-immunogenic, viruses have developed their own miRNAs in order to escape and suppress both host innate and adaptive immune responses [118].

Adenoviruses

Adenoviruses cause mild to serious respiratory tract infections in many age groups [119]. Adenovirus infection has a great impact on cellular miRNA expression profiles [120,121]. A total of 44 miRNAs demonstrated high expression and 36 miRNAs low expression following adenovirus type 3 infection in human laryngeal epithelial cells [120]. A temporal study demonstrated dramatic changes in cellular miRNA expression patterns during the course of adenovirus type 2 infection in lung fibroblast cells; up-regulation of miR-22, miR-320, let-7, miR-181b, miR-155, miR-125, miR-27, and miR-191 and down-regulation of miR-21, miR-31, let-7 family, miR-30 family, and miR-23/27 cluster was detected. These miRNAs have been associated with host immune evasion and inflammatory responses, as well as in virus entry, replication, and propagation [121].

Adenoviruses encode a set of highly abundant miRNAs that are generated by Dicer-mediated cleavage of the larger non-coding virus-associated RNAs (VARNAs) I and II. VARNAs are dsRNA molecules similar in structure to cellular pre-miRNAs. They are

transported by exportin 5 into the cytoplasm, and processed to functional viral miRNAs (miVARNAs) [122]. miVARNAs actively target the expression of cellular genes involved in cell proliferation, DNA repair, or RNA regulation [68]. VARNAs are expressed at very high levels in adenovirus-infected cells and potentially inhibit human pre-miRNA via inhibition of nuclear export of pre-miRNA, competition for exportin 5 to facilitate their transportation, and inhibition of Dicer activity by direct binding to Dicer [69,123]. Adenovirus miVARNAs target cellular and viral genes that are important for the virus cell cycle. Hepatoma-derived growth factor inhibits adenovirus growth. However, the expression level of hepatoma-derived growth factor significantly decreased in response to miVARNAs under replication-deficient conditions, and this suppression was also observed during the early phase of viral infection under replication-competent conditions [71]. Adenovirus miVARNAs also target cellular genes involved in cell growth, gene expression and DNA repair. The TIA-1 (cytotoxic granule-associated RNA binding protein) is down-regulated at mRNA and protein levels in infected cells expressing functional miVARNAs and in transfected cells [70].

Conversely, cellular miRNAs may play a role in anti-adenovirus replication by regulating virus gene expression. It was shown that cellular miR-214 inhibits adenovirus replication by regulating the translation of viral E1A protein, which is key

to the activation of other adenovirus genes, while inhibition of miR-214 increases the productive efficiency of the virus [72]. Lam, *et al.* showed that cellular miR-466 can effectively down-regulate human Coxsackie virus and adenovirus receptor protein expression [73]. Furthermore, a subset of cellular miRNAs including miR-1, miR-34, miR-22, miR-365, miR-29, miR-145, and let-7 was shown to coordinately target retinoblastoma-dependent cell cycle and DNA replication mRNAs to restrict proliferation [74].

Taken together, these results suggest that miVARNA-mediated silencing can represent a novel mechanism used by adenoviruses to control cellular or viral gene expression, and are potential therapeutic targets. The actions of cellular miRNAs may also be exploited to combat adenovirus infection (Figure 6).

Human cytomegalovirus

Human cytomegalovirus (HCMV), a DNA virus, infects a broad range of human cell types and disrupts cellular processes through a variety of mechanisms. For example, HCMV uses several of its

own encoded proteins to disrupt the MHC class I pathway [124] and the fine balance between a beneficial and a destructive immune response [82], and uses several of its own encoded miRNAs to disrupt a variety of cellular pathways such as TLR2/IRAK1/NF- κ B signaling [125]. This virus therefore induces a complex and diverse pathogenesis, and is an opportunistic pathogen causing lung infection in immunocompromised individuals [126]. Host cell miRNA expression levels may determine the cellular site of HCMV infection. As an example, host miR-200 family members target the HCMV protein UL112 resulting in repression of this viral protein, and cells permissive for lytic HCMV replication demonstrate low levels of these miRNAs [127]. However, HCMV can also selectively alter the expression of some cellular miRNAs to help its own replication [128]. For example, significant up-regulation of miR-96, miR-182, and miR-183 have been observed following infection [77]. A study by Fu, *et al.*, indicated that expression of host miRNAs may be affected by latent HCMV; at least 49 miRNAs were differentially expressed;

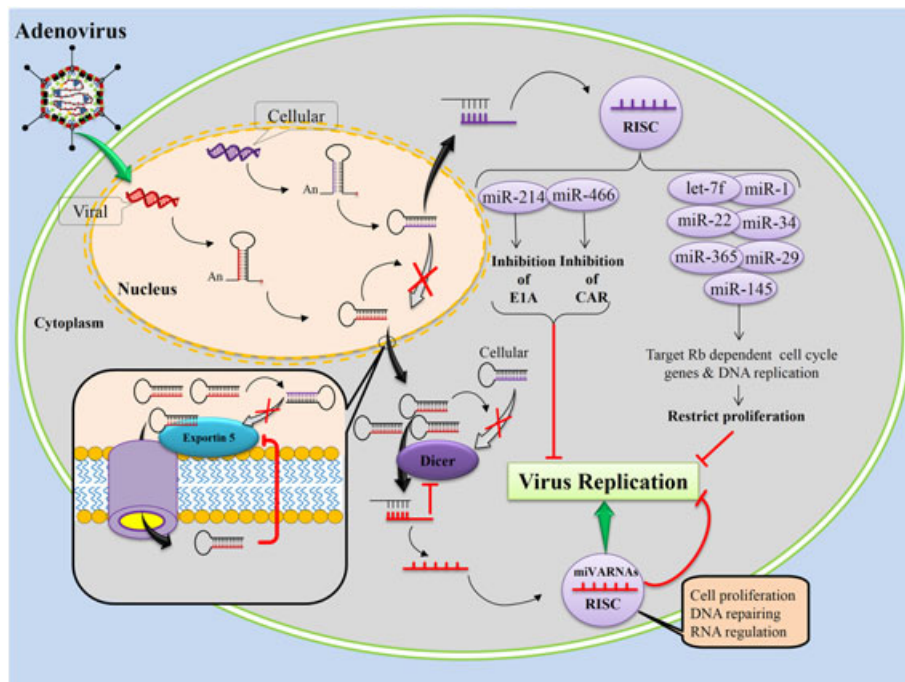


Figure 6. Adenovirus encodes viral miRNAs (miVARNAs) that potentially inhibit human pre-microRNA (miRNA) via inhibition of the nuclear export of pre-miRNA, competition for the exportin 5, and inhibition of Dicer activity by direct binding of Dicer. The miVARNAs are able to target cellular and viral genes that are important for the virus cell cycle. Adenovirus miVARNAs target cellular genes involved in cell proliferation, DNA repairing, and RNA regulation. However, cellular miRNAs may play a role in anti-adenovirus replication by regulating virus gene expression.

39 were up-regulated and 10 were down-regulated accordingly [76]. In addition, HCMV encodes its own miRNAs that target both viral and cellular genes in order to regulate viral replication, viral latency, cell survival, and anti-viral immunity (Figure 7) [79].

Human cytomegalovirus has miRNAs that help escape and suppress both host innate and adaptive immune responses [118]. HCMV-encoded miR-UL148D modulates host immune response by directly targeting the mRNA of human chemokine CCL5 [78]. HCMV miR-UL112 attenuates NK cell activity by inhibition of type I IFN secretion [75], down-regulation of IL-32 expression [129], and TLR2 targeting, causing significant modulation of the downstream signaling pathway (TLR2/IRAK1/NF- κ B) [125]. HCMV may evade CD8⁺ T-cells by altering MHC class 1 antigen expression; HCMV miR-US4-1 targets the endoplasmic reticulum aminopeptidase 1, a key step in the MHC class I antigen-processing pathway [80]. Furthermore, HCMV expresses miR-US25-2 and, in addition, increases cellular miR-17p expression, both of which target tissue inhibitor of metalloproteinase 3. Reduced tissue inhibitor of metalloproteinase 3

expression following HCMV infection reduces signaling via the MHC class I-like ligand MICA [81].

Some HCMV-encoded miRNAs suppress virus replication and lytic infection, which could help the virus to establish or maintain latent infection. It has been reported that HCMV miR-US25-1-5p was highly expressed during lytic and latent infections, and inhibited viral replication [83]; HCMV miR-US25-2 reduces viral replication by targeting the RNA helicase eIF4A1, which is a requisite for translation of viral mRNA [130], and HCMV miR-US33 negatively influences virus replication, possibly by suppression of the HCMV gene US29 [84] or cellular syntaxin 3 expression [131]. Premature expression of HCMV miR-UL112-1 during infection resulted in a significant decrease in genomic viral DNA levels, suggesting a functional role for miR-UL112-1 in regulating the expression of genes involved in viral replication [85]. Finally, HCMV encodes latency-associated CMV-IL-10, a homologue for cellular IL-10 associated with latent infection. Latency-associated CMV-IL-10 has been shown to suppress miR-92a, resulting in up-regulation of its target CCL8. The mechanisms for both miR-92a suppression and how CCL8 up-regulation might

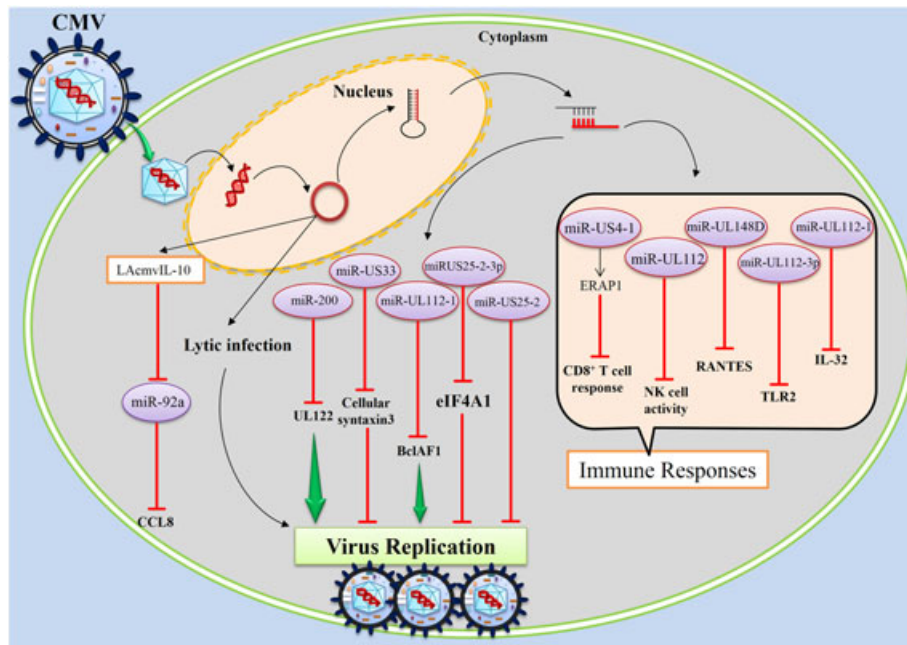


Figure 7. Human cytomegalovirus, a DNA virus, encodes its own microRNAs, and human cytomegalovirus microRNAs target both viral and cellular genes in order to; first regulation of viral replication, second regulation of viral latency infection, and third regulation of cellular anti-viral immunity.

promote latent infection are unclear, but seem to be associated with increased immune-regulatory cellular IL-10. These results provide insight into how HCMV can alter host gene expression [86].

Human cytomegalovirus-encoded miRNAs do not only suppress virus lytic replication but can also enhance virus replication. For example, HCMV-restricting cellular BclAF1 is down-regulated late in infection by HCMV-encoded miR-UL112-1 to promote virus production [87]. Furthermore, multiple HCMV-encoded miRNAs coordinately regulate reorganization of the secretory pathways responsible for controlling cytokine secretion and facilitate formation of the viral assembly compartment for efficient infectious virus production. In this aspect, HCMV-encoded miRNAs such as miR-UL112-1, miR-US5-1, and miR-US5-2 target multiple components of the host secretory pathways, including VAMP3, RAB5C, RAB11A, SNAP23, and CDC42 [132]. Additionally, HCMV employs its miRNA repertoire to counter cellular apoptosis and autophagy, particularly the mitochondrial-dependent intrinsic pathway of apoptosis. The pro-apoptotic genes MOAP1, PHAP, and ERN1 are identified as potential targets for miR-UL70-3p and miR-UL148D, respectively [133]. Finally, a viral intergenetic non-coding RNA element, composed of highly conserved sequences throughout HCMV clinical strains, selectively degrades the cellular miR-17 family members of the miR-17-92 cluster and accelerates virus production [134].

Overall, these results suggest that identification and characterization of the HCMV-encoded miRNAs that are expressed during lytic and latent infection are crucial to understanding their roles in HCMV persistence, pathogenesis, and disease. Knowledge of host and viral miRNAs expressed during HCMV infection can thus provide a precise insight into viral pathogenesis and may help researchers to develop new therapeutic approaches.

Human herpesvirus 6

HHV-6, a DNA virus in the betaherpesvirus sub-family, is associated with several human diseases. Complications of acute respiratory tract infection such as pneumonia and sinusitis in young children are associated with HHV-6 as is limbic encephalitis following hematopoietic stem cell transplantation. In addition, HHV-6 salivary gland replication and

subsequent secretion in saliva is the epidemiologically proven source of transmission [88,135]. As discussed previously, herpesvirus-derived miRNAs play considerable roles in modulating both cellular and viral gene expression, thereby facilitating a suitable environment for productive viral infection and/or latency. Like other human herpesviruses, HHV-6 encodes its own miRNAs, promoting efficient viral infection [116,136]. An miRNA encoded by HHV-6A (miR-U86) targets the HHV-6A IE gene U86, thereby regulating lytic replication, as revealed by growth analyses of mutant viruses (Figure 5) [116]. However, HHV-6B encodes at least four pre-miRNAs at two positions within the genome in an antisense orientation related to predicted HHV-6B-specific genes [136]. These data suggest that HHV-6, like other herpesviruses, encodes its own miRNAs, but the precise function of these miRNAs in HHV6B requires further investigation.

CONCLUSIONS

This comprehensive review attempts to highlight the role of miRNAs in replication as well as pathogenesis of respiratory viral infections. miRNAs modulate a variety of cellular processes by regulating multiple targets, promoting or inhibiting the development of viral infection [29]. Increasing evidence regarding disrupted miRNA expression and function following viral infection makes them promising targets for therapeutic interventions [137]. The development of miRNA-based therapy for respiratory infection is less advanced compared with other viral infections, such as hepatitis C. Improved knowledge on the cross-talk between host cells and viruses should increase our understanding of the molecular basis for viral pathogenesis and may enable us to develop better therapeutic strategies [23].

Therapeutic modulation of miRNAs can be achieved through miRNA inhibitors to disrupt miRNA function or miRNA mimics to increase miRNA function [138]. The application of miRNA-based therapies is in its beginning, and important difficulties remain. A significant barrier to miRNA-based therapy is the development of essential pharmaceutical strategies for targeted delivery to specific sites with minimum toxicity [139,140]. In support of this, novel nanotechnologies and delivery methods are under development for efficient and effective delivery [140,141].

Alongside the critical role of miRNAs in the regulation of viral respiratory infection and their potential to be targeted by new therapeutics, caution must be taken because excessive inhibition or overexpression of miRNAs might predispose patients to cellular abnormalities, impaired immunity, or even cancer. The relevance of miRNAs in viral infection has been proven broadly; however, the exact role of each miRNA on viral pathogenesis

remains to be determined, and future studies are warranted. Enhancing the knowledge on miRNAs may open opportunities to use them in clinical practice in order to develop more accurate and powerful diagnostic and therapeutic strategies.

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