AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Clinical Microbiology | Review

MicroRNAs in infectious diseases: potential diagnostic biomarkers and therapeutic targets

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SUMMARY MicroRNAs (miRNAs) are conserved, short, non-coding RNAs that play a crucial role in the post-transcriptional regulation of gene expression. They have been implicated in the pathogenesis of cancer and neurological, cardiovascular, and autoimmune diseases. Several recent studies have suggested that miRNAs are key players in regulating the differentiation, maturation, and activation of immune cells, thereby influencing the host immune response to infection. The resultant upregulation or downregulation of miRNAs from infection influences the protein expression of genes responsible for the immune response and can determine the risk of disease progression. Recently, miRNAs have been explored as diagnostic biomarkers and therapeutic targets in various infectious diseases. This review summarizes our current understanding of the role of miRNAs during viral, fungal, bacterial, and parasitic infections from a clinical perspective, including critical functional mechanisms and implications for their potential use as biomarkers and therapeutic targets.

KEYWORDS microRNA, viral infection, fungal infection, bacterial infection, parasite infection, biomarker

Editor Graeme N. Forrest, Rush University, Chicago, Illinois, USA

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The authors declare no conflict of interest.

Published 1 November 2023

INTRODUCTION

MicroRNAs (miRNAs) are evolutionally conserved short (18–25 nucleotides) non-coding RNAs that play vital roles in post-transcriptional regulation of gene expression. Since their discovery in 1993, over 1,900 miRNAs have been identified in the human genome and are thought to maintain homeostasis by regulating over 60% of human protein-coding genes (1, 2). miRNA synthesis begins in the nucleus with the transcription of miRNA genes by RNA polymerase II, producing ~80-bp-long primary miRNA (pri-miRNA) with a hairpin structure (3). pri-mRNA is processed into precursor miRNAs by two endonucleases, first in the nucleus by Drosha, and then further in the cytoplasm by Dicer, to form duplex intermediates of ~22 nucleotides (4, 5). After duplex unwinding, the passenger strand is degraded owing to a lack of biological function, and the remaining stabilized strand acts as a matured miRNA. The matured miRNA forms the microRNA-induced silencing complex (miRISC) together with the Argonaute protein and several other proteins (6). Assembly of the miRISC allows for sequence-specific targeting of mRNA 3′ untranslated regions, leading to reduced translation (6–8).

The discovery of miRNAs has brought another level of complexity to our understanding of gene regulation. miRNAs have been shown to play a critical role in maintaining various biological processes, such as immune cell development, differentiation, activation, proliferation, metabolism, apoptosis, and autophagy (9–15). Dysregulation of miRNA expression has been extensively studied in cancer, neurological and cardiovascular diseases, obesity, and autoimmune diseases (15–18). Additionally, some studies have suggested that miRNAs are key players in regulating the maturation and differentiation of immune cells, which ultimately influence both the innate and adaptive immune responses (19, 20). Some studies have explored the role of human miRNAs during the host immune response to viral, fungal, bacterial, and parasitic infections. For example, toll-like receptors (TLRs), a class of pattern recognition receptors (PRRs) that play an essential role in the innate immune response, have been shown to influence miRNA expression (21). Cell surface TLRs can induce miR-146 after a challenge with lipopolysaccharide (LPS), a common bacterial endotoxin, in a monocytic cell line (22). In this report, upregulated miR-146 downregulated cellular LPS sensitivity via negative feedback and prevented excessive inflammation caused by activation of the LPS-TLR pathway (22). In the adaptive immune response, miRNAs such as miR-155 can affect the generation of anti-viral antibodies and $CD4^+$ helper T and $CD8^+$ cytotoxic T-cell responses in viral infections (23). Thus, it is conceivable that miRNAs play an essential role in infectious diseases. This presents a significant opportunity for novel diagnostics and therapeutics in infectious diseases, particularly infections that pose challenges in timely diagnoses, such as invasive aspergillosis or BK virus (BKV) nephropathy. miRNA profiling has the potential to bridge these gaps as a diagnostic marker for some infectious diseases, similar to studies on oncotherapeutics (24).

To our knowledge, only a few reviews have comprehensively focused on the functions and characteristics of miRNAs in viral, fungal, bacterial, and parasitic infection. Here, we provide an overview of the roles of miRNAs in these infectious diseases. We also discuss the possibility of miRNAs as diagnostic tools for infectious diseases and their potential as new therapeutic targets for gene therapies utilizing miRNA mimics or inhibitors (25). It would be difficult to discuss miRNAs associated with viral, fungal, bacterial, and parasitic infections in a single review. This review focuses on hepatitis viruses [hepatitis C virus (HCV) and hepatitis B virus (HBV)], herpes viruses [herpes simplex virus (HSV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV)], respiratory syncytial virus (RSV), BKV, *Aspergillus* spp., *Candida* spp., *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Plasmodium falciparum*, and *Schistosoma japonicum*. These pathogens are important from a clinical point of view because of their epidemiological predominancy, high morbidity, and mortality particularly in immunocompromised patients, including solid organ and hematopoietic stem cell transplant recipients, limited treatment options, or lack of efficient diagnostic tools (26–39). For each pathogen, we present miRNAs

examined in clinical studies, common mechanisms of action, and potential for use as biomarkers.

miRNA AND INFECTION

miRNAs play an essential role when hosts are infected (40, 41) and can promote or inhibit infectious disease progression by regulating the immune system. Importantly, miRNAs can regulate the proliferation of causative organisms, such as the replication of viruses, and do not directly regulate the immune response (41). For example, some miRNAs regulate pathogen entry into a target cell by downregulating the expression of cell membrane receptor proteins (42, 43). Therefore, modulation of miRNA function could be applied as a therapeutic option. In addition, many miRNAs have been implicated in infectious processes whose functions still need to be well investigated; these have untapped potential for use as biomarkers for infection diagnosis or disease progression (44, 45).

Regarding host-encoded miRNAs, some miRNAs in tissues and experimental cell lines are upregulated or downregulated in patients with viral infections compared to those in control populations (42, 46–52). The reasons why these dysregulations occur have yet to be fully investigated for each miRNA. However, cascade responses caused by pathogenic components and crosstalk between pathogens and PRRs are considered to be associated with several host-encoded miRNAs (48, 53). For instance, miR-21 expression is activated during HCV infection through two signaling pathways: the PKCε/JNK/c-Jun pathway and the PKCα/ERK/c-Fos pathway (48). These pathways are stimulated by HCV viral components NS5A and NS3/4A complex, respectively. Thus, HCV viral proteins stimulate miR-21 expression in hepatocytes (48). In addition, viral attachment to PRRs of target cells can lead to upregulation or downregulation of each miRNA during viral infections. These kinds of mechanisms which cause dysregulation of miRNAs during viral infections are also likely to occur during fungal, bacterial, and parasitic infections. For example, changes in miRNA expression occur after *Aspergillus fumigatus* binds to PRRs such as TLRs and dectin-1 (45, 47). Subsequent to the changes in miRNA expression during infection, upregulated miRNAs inhibit expression of the target genes by post-transcriptional regulation of gene expression induced by the miRNAs (6, 8). In contrast, downregulated miRNAs promote expression of the target genes (6, 8). These fundamental roles of miRNAs are essential for understanding the relationships between infectious pathogens and miRNAs described in the following sections.

VIRAL INFECTION

Currently, there is a lack of highly effective active anti-viral agents against viruses such as EBV, RSV, and BKV. As a result, these viruses can cause serious illnesses, particularly in immunocompromised patients, including solid organ and hematopoietic stem cell transplant recipients (27–29, 54), and drug discovery remains challenging. For example, no anti-viral agents can treat and prevent post-transplant lymphoproliferative disease caused by EBV, a disease with high mortality (27, 55). In addition, anti-viral resistance is a concern in many viral infections, including HCV, HBV, HSV, and CMV, despite the development of effective anti-virals (26, 36–39). This is especially pertinent for resistant CMV, which can have single or multiple resistant mutations against available anti-CMV agents such as (val)ganciclovir, foscarnet, cidofovir, letermovir, and maribavir (36, 37). Therefore, new therapeutic targets for these viruses are required. Recently, a clinical study showed that a miRNA can be utilized as a therapeutic target during viral infection (56). This indicates that investigating miRNAs may help identify new therapeutic targets. The following section examines host-encoded miRNAs that are associated with HCV, HBV, HSV, EBV, CMV, RSV, and BKV infections. In addition, viral-encoded miRNAs and their influence on the pathogenesis of infectious diseases are reviewed.

Function and characteristics of host-encoded miRNAs during viral infections

Some of the most relevant host-encoded miRNAs associated with viral replication, viral entry into target cells, and immune functions by repression of the target genes are presented in Fig. 1 and Tables 1 to 4. The target genes of host-encoded miRNAs are generally the host genes. However, host-encoded miRNAs can also target viral genes such as miR-122 and miR-125, which target the S genes of HCV and HBV (Table 1) (57, 58). Herein, hepatitis, herpes and atypical viruses are discussed independently.

Host-encoded miRNAs during HCV and HBV infection

When a host is first infected, changes in miRNA expression occur (Fig. 1). We present examples of well-investigated molecular pathways involving human miRNAs in Fig. 1. These data were primarily obtained from *in vitro* studies.

Studies using human samples and/or human cell lines

In this section, we focus on miRNAs associated with HCV and HBV infection, which are mainly in studies using human samples and/or human cell lines. During HCV infection, miR-21 and miR-130a are upregulated in hepatocytes (48, 67). In contrast, miR-181a and miR-182 are downregulated in a $CD4^+$ T cell and a hepatocyte, respectively, during HCV infection (Fig. 1) (42, 51). Upregulated miRNAs generally repress the expression of their target genes (6, 8). For example, myeloid differentiation factor 88 and interleukin-1 receptor-associated kinase (*IRAK1*), which are the target genes of miR-21 in hepatocytes and associated with interferon-α (IFN-α) production, are repressed by upregulated miR-21 during HCV infection (Fig. 1) (48). As a result, the output of IFN-α decreases, which permits viral replication of HCV (48). In addition, upregulation of miR-130a during HCV infection represses interferon-induced transmembrane 1 (*IFITM1*), which is a target

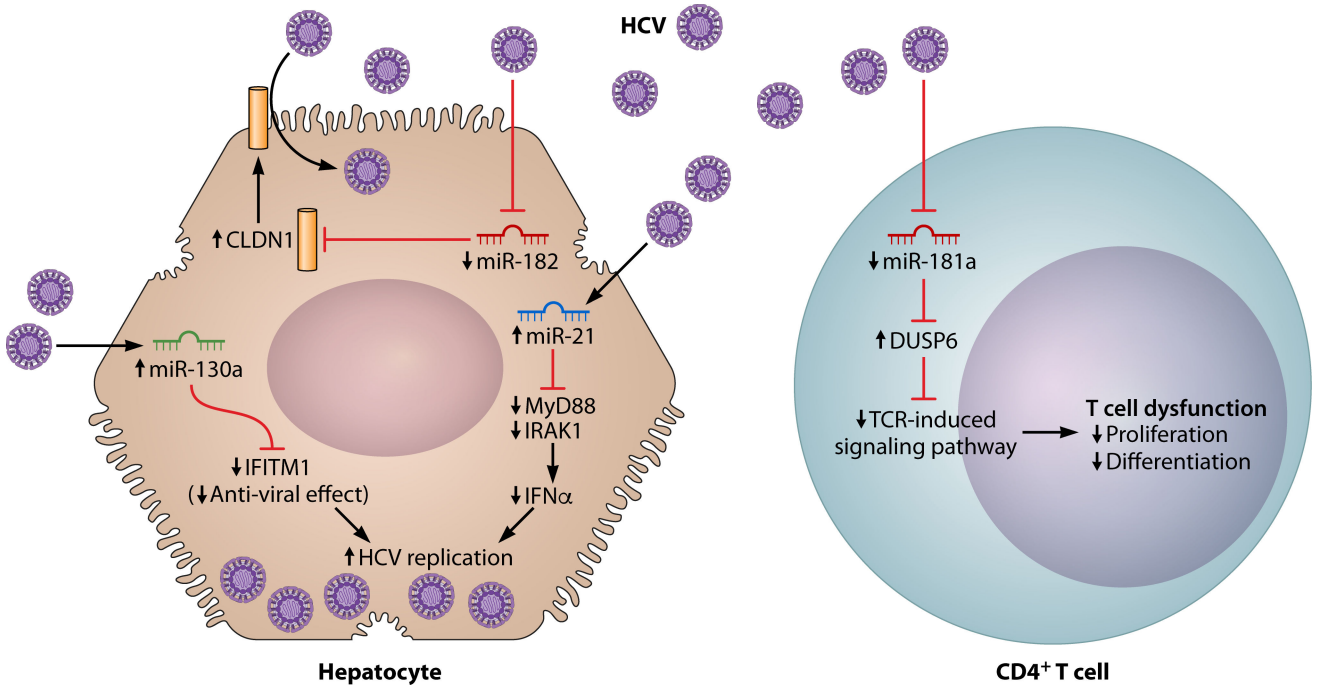

FIG 1 Functions of host-encoded miRNA during HCV infections. Illustrated here are examples of functional pathways of host-encoded miRNAs. Examples were chosen if they met the following criteria: (i) miRNA expression was compared to control populations or status without the infection; (ii) the target genes of the miRNA were identified in the study; (iii) the functional mechanisms reported had sufficient data; and (iv) the experiments were in human cell lines. In the left, miR-21 and miR-130a are upregulated and miR-182 is downregulated during HCV infection in a hepatocyte. In the right, miR-181a is downregulated during HCV infection in a $CD4^+$ T cell. Abbreviations: CLDN1, claudin-1; DUSP6, dual specific phosphatase 6; IFITM1, interferon-induced transmembrane 1; IFN, interferon; IRAK1, interleukin-1 receptor-associated kinase; MyD88, myeloid differentiation factor 88; TCR, T-cell receptor.

TABLE 1 Functions and characteristics of microRNA in HBV and HCV infection[a]

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
Host-encoded microRNA in HCV infection			
miR-122			
	Target sites (S1 and S2) of HCV RNA	Human *in vitro* study (57, 59) (Huh-7 cells, Hep 3B, and Huh-7.5 cells)	Stimulates viral replication
	OCLN	Human *in vitro* study (60) (Huh-7.5 cells)	Overexpression decreases HCV entry into hepatocytes.
	Not reported	Clinical study (61) (liver and blood samples)	Predicts therapeutic response to PEG-IFN/RBV + differentiation between healthy controls and chronic hepatitis C
	Not reported	Clinical study (56) (randomized, double-blind, placebo-controlled study) (blood samples)	miR122 inhibitor usage resulted in the reduction of HCV RNA without resistance.
miR-155			
	TLR3-dependent anti-viral pathway	Animal *in vitro* and human *in vitro* study (62) [liver (mice and humans) and blood (human) samples]	Increases hepatic expression in chronic HCV, decreases HCV viral load
	T-bet/Tim3 pathway	human *in vitro* study (63) [PBMCs (from patients and controls)]	miR-155 is downregulated and inhibits IFN-γ production in NK cells in chronic HCV infection.
	Not reported	clinical study (64) (blood samples)	Negative correlation with HCV Viral loads
miR-146			
(miR-146b-5p)	NF-κB signaling pathway	Human *in vitro* study (65) PBMCs (from patients and controls)	Suppression could induce an impaired immune response in monocytes and T cells.
(miR-146a)	Not reported	Human *in vitro* study (66) PBMCs (from patients and controls)	Regulates the immune responses correlate with cholesterol metabolism
miR-21			
	MyD88 and IRAK1	Human *in vitro* study (48) (Huh-7 and HEK293 cells)	Upregulated during HCV infection, increases HCV production by suppressing IFN-α production
miR-130a			
	IFITM 1	Human *in vitro* study (67) (liver samples and Huh-7 cells)	Upregulated during HCV infection, increases HCV replication
	ATG5	Human *in vitro* study (68) (Huh-7.5.1 cells)	Inhibits HCV replication
miR-27a			
	RXRα and ABCA1	Human *in vitro* study (69) (Huh-7.5 cells)	Inhibits HCV replication
miR-181a			
	DUSP6	Human *in vitro* study (51) [PBMCs (from patients and controls) and Huh-7 cells]	Downregulated during HCV infection in $CD4^+$ cells, resulting in their dysfunction
miR-182			
	CLDN1	Human *in vitro* study (42) (liver samples and Huh-7 cells)	Downregulated in HCV-infected patients, inhibits HCV entry into a target cell
miR-200c			
	OCLN	Human *in vitro* study (43) (liver samples and Huf7 cells)	Downregulated in HCV-infected patients, inhibits HCV entry into a target cell
miR-215			
	TRIM	Human *in vitro* study (70) (Con1b and Hub-7.5.1 cells)	Promotes HCV replication
miR-373			
	IRF5	Human *in vitro* study (71) (liver samples and Huh-7.5 and 293T cells)	Upregulated in HCV infection Inhibits replication of HCV
miR-196			

(*Continued on next page*)

TABLE 1 Functions and characteristics of microRNA in HBV and HCV infection[a] (*Continued*)

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
	Bach1	Human *in vitro* study (72) (9–13 cells and Huh-7.5 cells)	Inhibits expression of HCV
Host-encoded microRNA in HBV infection			
miR-122			
	Not reported	Human *in vitro* study (73) (liver samples and Huh-7 and HspG2 cells)	Upregulated in HBV-infected patients Inhibits HBV replication
	The core protein and polymerase of HBV	Human *in vitro* study (74) (HepG2 and HepG2.2.15)	Inhibits HBV replication
miR-125			
(miR-125b-5p)	LIN28B	Human *in vitro* study (75) (Con 1, HepG2, Huh-7, and HepG2.2.15)	Overexpression promotes HBV replication.
(miR-125a-5p)	HBV S gene	Human *in vitro* study (58) (HepG2 cells and Huh-7)	Interferes with the viral translation and downregulates expression of the surface antigen
(miR-125a-5p)	Not reported	Clinical study (76) (liver and blood samples)	Associated with severe disease progression (OR = 4.21 for histological activity index of >6 and OR = 3.12, for fibrosis score >2)
miR-17–92			
	HBV genome	human *in vitro* study (77) (HepAD38 cells)	Inhibition of miR-20a and miR-92a-1, both members of the miR-17–92 miRNA cluster, promotes HBV replication.
miR-122 and miR-130a			
	Not reported	Clinical study (78) (blood samples)	Can differentiate occult HBV infection from healthy controls, asymptomatic surface antigen of HBV carriers, and chronic hepatitis B (>0.87°F area under the curve)
miR-141			
	Sirt1	Human *in vitro* study (79) (HeLa/GFP-LC3, HepG2.2.15, and Huh-7 cells)	Inhibits HBV expression and replication
miR-146a-5p			
	XIAP	Human *in vitro* study (49) (blood samples and THLE-2 cells)	miR-146a-5p is upregulated in patients with chronic hepatitis B and HBV-expressing. hepatocytes. miR-146a-5p promotes HBV replication.
miR-185–5p			
	ELK1	Human *in vitro* study (80) (Huh-7 and HepG2.2.15)	Inhibits HBV gene expression and replication
miR-210			
	Not reported	Clinical study (81) (liver and blood samples)	Serum levels correlated with HBV DNA and hemoglobin antigen
miR-548			
	IFN-λ1	Human *in vitro* study (82) (blood samples, HepG2, and RD cells)	Downregulated in infected cells, it downregulates host anti-viral response.
(miR-548ah)	HDAC4	Animal and human *in vitro* study (83) (C57BL/6 mice, liver samples (from patients), HepG2.2.15, Huh-7, and 293T cells)	Promotes replication and expression of HBV
miR-802			
	SMARCE1	Human *in vitro* study (84) (liver samples, HepG2.2.15, and HepG2)	Upregulated in the HBV-associated hepatocellular carcinoma tissues; overexpression promotes HBV replication
miR-1231			
	HBV core gene	Animal and human *in vitro* study (85) PXB mice,	Upregulated in HBV infection Inhibits HBV replication

(*Continued on next page*)

TABLE 1 Functions and characteristics of microRNA in HBV and HCV infection[a] (*Continued*)

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
		liver (human and mice) and blood samples and HepG2	
miR-372/373			
	NFIB	Human *in vitro* study (86) (liver and blood samples, HepG2, and HepG2.2.15 cells)	Upregulated in infected liver tissues and human hepatic cell line Promote HBV expression

[a]ABCA1, ATP-binding cassette subfamily A member 1; ATG5, autophagy-related gene5; CLDN1, claudin-1; DUSP6, dual specific phosphatase 6; ELK1, ETS like-1; HDAC4, histone deacetylase 4; IFN, interferon; IRAK1, interleukin-1 receptor-associated kinase; IRF5; interferon regulatory factor 5; MyD88, myeloid differentiation factor 88; NFIB, nuclear factor I/B; OCLN, occludin; OR, odds ratio; PBMC, peripheral blood mononuclear cell; PEG-IFN/RBV, peginterferon/ribavirin; RXRα, retinoid X receptor alpha; SMARCE1, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily E, member 1.; Tim3, T-cell immunoglobulin and mucin domain proteins 3; TLR, toll-like receptor; TRIM, tripartile motif; XIAP, X-linked inhibitor of apoptosis.

gene of miR-130a, in hepatocytes (67). It promotes HCV replication by suppressing the anti-viral effect of IFITM1, which may be associated with the enhancement of neutralizing antibody and inhibition of cell entry of HCV (67, 130).

Similarly, downregulated miRNAs generally lead to overexpression of target genes. For instance, miR-181a is downregulated in $CD4^+$ T cells during HCV infection (51). The downregulation leads to the overexpression of dual specific phosphatase 6 (*DUSP6*), which is the target gene of miR-181a. *DUSP6* overexpression inhibits the proliferation and differentiation of T cells through T-cell receptor-induced signaling pathways. As a result, impairment of the global $CD4^+$ T-cell response (as these T cells were not confirmed to be HCV specific) can occur during HCV infection but through a downregulation mechanism (51). Therefore, reconstitution of miR-181a may restore the impaired immune response. Similarly, downregulation of miR-182 in hepatocytes during HCV infection leads to overexpression of the target gene claudin-1 (*CLDN1*) (42). Overexpression of *CLDN1* in hepatocytes enhances HCV endocytosis (Fig. 1) (42). In summary, these miRNAs are involved in the pathogenesis of HCV in terms of HCV replication, cell entry of HCV, and attenuation of immune response. Hence, these miRNAs may serve as important therapeutic targets.

As described earlier, the primary action of miRNAs to repress gene expression is to bind a target sequence on the resultant mRNA and inhibiting its translation (6, 8). However, there are some exceptions. The most prominent exception is hepatocyte expression of miR-122 during HCV infection (131). miR-122 binds to two closely spaced target sites (S1 and S2) in the highly conserved 5′ untranslated region of the HCV genome, forming an oligomeric miR-122-HCV complex that protects against nucleolytic degradation or host innate immune responses (131–133). Here, miR-122 does not silence mRNA expression but stabilizes the pathogen genome and incites virus replication. This mechanism is clinically significant because the administration of miravirsen, a miR-122 inhibitor developed for patients with chronic HCV genotype 1 infection, showed a prolonged dose-dependent reduction in HCV RNA levels without evidence of resistance in a phase 2 clinical trial (56).

In HBV infection, upregulated miR-146a-5p in hepatocytes represses inflammatory genes [X-linked inhibitor of apoptosis (*XIAP*)] in the hepatocytes (49). miR-146a-5p overexpression promotes HBV replication through the autophagy pathway, which is mediated by XIAP in an *in vitro* model of HBV infection (49). Additionally, miR-802 is upregulated in hepatocytes in HBV infection (84). Upregulated miR-802 promotes HBV DNA replication and surface antigen of HBV (HBsAg) and HBeAg expression through the inhibition of SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily E, member 1 (*SMARCE1*), which is the target gene of miR-802, although the detailed mechanism of *SMARCE1* in the expression and replication of HBV remains largely unknown (84, 134). In this context, miR-146a-5p and miR-802 may be potential therapeutic targets for HBV infection.

During HBV infection, some host-encoded miRNAs target genes of HBV. For instance, the HBV genomic segment 3037–3065, which encodes amino acid residues 244–252 of

polymerase and 64–72 of HBsAg, is a direct target of miR-125a-5p (58). miR-125a-5p, which is expressed in the human liver, can downregulate the expression of HBV S gene via post-transcriptional regulation, thus reducing the amount of HBsAg (58). The downregulation of HBsAg probably inhibits HBV replication (135). Thus, delivery of synthetic miR-125a-5p mimics may be a therapeutic option for HBV infection.

In addition to mechanistic studies, host-encoded miRNAs have been investigated as biomarkers during viral infection. For instance, miR-125a-5p levels in liver tissue have been investigated as predictors of disease progression in HBV infection (76). More precisely, miR-125a-5p level in the liver tissue was able to predict histological activity index of >6 [odds ratio (OR) = 4.2; 95% confidence interval (CI), 1.1–16.4] and fibrosis score of>2 (OR = 3.1; 95% CI, 1.2–8.3) (76) in patients with chronic hepatitis B who were naïve to nucleoside analogs and interferon therapy.

Moreover, studies of other miRNAs associated with HCV and HBV infection, which have information of target genes and/or are investigated using human samples, are listed in Table 1. Apart from all the miRNAs written in the text and/or Table 1, well-designed functional studies were also performed by using human cell lines for miR-27, miR-130, and miR-491 in HCV infection, although they lacked detailed information of target genes (136–138).

Animal studies

In an animal study of chimpanzees, effectiveness of miravirsen (a miR-122 inhibitor) in HCV infection was demonstrated (139).

Host-encoded miRNAs during HSV, EBV, and CMV infection

Studies using human samples and/or human cell lines

In this section, we focus on miRNAs associated with HSV, EBV, and CMV infection, which are mainly in studies using human samples and/or human cell line. In HSV infection, miR-373 is upregulated in a HeLa cell line in HSV (50). In contrast, miR-649 is downregulated in a HeLa cell in HSV infection (52). Upregulated miR-373 represses interferon regulatory factor 1 (*IRF1*) in HeLa cells. Owing to the inhibition of *IRF1*, upregulated miR-373 facilitates HSV replication by suppressing the type 1 interferon response during HSV infection (50). Similarly, downregulation of miR-649 in HeLa cells during HSV infection leads to overexpression of the target gene mucosa-associated lymphoma translation gene 1 (*MALT1*) (52). *MALT1* overexpression inhibited HSV replication in a HeLa cell through activation of NF-κβ (52). Hence, miR-373 and miR-649 may be potential therapeutic targets in HSV infection.

EBV commonly infects with B cells and epithelial cells *in vivo* (140). In EBV-infected cells, some host-encoded miRNAs are associated with the pathogenesis of EBV infection by escaping the host immune systems and maintaining EBV in its latent phase (141). For example, miR-155 is induced by the oncogeneic latency gene expression program of EBV in B cells (91). miR-155 inhibits bone morphogenetic protein (BMP)-mediated lytic EBV reactivation in an EBV-positive B-cell line by suppressing multiple predicted target genes: *Drosophila* mother against decapentaplegic 1, *Drosophila* mother against decapentaplegic 5, human immunodeficiency virus type 1 enhancer-binding protein 2, CCAAT/enhancer-binding protein beta, runt-related transcription factor 2, and myosin X, all of which comprise the BMP signaling cascade (91). These results suggest that miR-155 can maintain EBV-infected B cells latent by suppressing the BMP signaling pathway conferring a survival advantage to EBV (91). Additionally, miR-429, which belongs to the miR-200 family, is associated with EBV reactivation in EBV-infected cells (92). Expression of miR-429 breaks the latency of EBV in both EBV-infected human epithelial and human B cells *in vitro* through inhibition of ZEB1 (92). *ZEB1* is a direct target of the miR-200 family and inhibits EBV reactivation (142–144). Hence, further understanding how host-encoded miRNAs involve a switching mechanism from latent to lytic reactivation of EBV might be helpful to develop a novel therapeutic strategy against EBV infection.

miR-100 and miR-101 are downregulated during CMV infection, although levels of most miRNAs do not change markedly in Medical Research Council cell strain 5 cells (104). These two miRNAs can inhibit CMV replication by repressing the mammalian target of rapamycin kinase (mTOR) pathway, including mTOR and raptor (104). mTOR and raptor are components of the mTOR protein translation initiation regulatory pathway, which is important for CMV replication under some conditions (145). mTOR is a predicted target of both miR-100 and miR-101 (104). In contrast, raptor is a predicted target of miR-100 (104). MiR-100 and miR-101, either alone or in combination, reduce the amount of infectious CMV *in vitro* (104). Thus, downregulation of miR-100 and miR-101 induced by CMV can assist its replication (104). In contrast, miR-221 is upregulated in human neural precursor cells in CMV infection (105). Subsequently, upregulated miR-221 suppresses replication of CMV by targeting suppressor of cytokine signal 1 (*SOCS1*) since the SOCS1 downregulation induced by miR-221 leads to type 1 interferon (IFN-α and IFN-β) production in CMV-infected cells (105). In this context, miR-100, miR-101, and miR-221 may be therapeutic targets of CMV.

In CMV infection, the utility of several miRNAs as biomarkers of CMV infection has been reported. For instance, plasma levels of miR-183–5p and miR-210–3p have been investigated as predictors of congenital CMV infection (44). According to this study, plasma levels of miR-183–5p and miR-210–3p were significantly higher in infants with congenital CMV infection than in controls (44).

Studies of other miRNAs associated with HSV, EBV, and CMV infection, which have information regarding target genes and/or are investigated using human samples, are listed in Table 2. Apart from all the miRNAs described here and/or Table 2, well-designed functional studies were also performed in human cell lines for miR-101–1 in HSV infection and miR-146a and miR-155 in EBV infection, although they lack detailed information of target genes (146–148).

Animal studies

In a mouse model, miR-132 and miR-155 were associated with HSV ocular infection (149, 150). In addition, miR-96, miR-141, miR-183, and miR-200 may be associated with the entry of HSV to target cells in a mouse model (151). Furthermore, miR-592, miR-1245b-5p, miR-150, miR-342–5p, miR-1245b-3p, and miR-124 were incorporated into regulation of the TLR pathway during HSV-2 infection in a guinea pig model (152). In CMV infection, function of miR-199a/214 cluster was investigated in a mouse cell line (153).

Host-encoded miRNAs during RSV infection

Although the number of host-encoded miRNAs which have been investigated in RSV infection is fewer than those in the hepatitis and herpes viruses listed in this review, some miRNAs contribute to pathogenesis of these infections (Table 3). These miRNAs have been investigated in studies using human clinical samples and/or human cell lines (Table 3). For example, miR-221 is downregulated in human bronchial epithelial cells during RSV infection (121). This leads to upregulation of the nerve growth factor-tropomyosin-related kinase A axis, which might be caused by upregulated relevant genes that are predicted targets of miR-221 (121). Upregulation of this axis takes advantage of RSV replication by inhibiting apoptotic death of infected cells (121). These findings suggest that miR-221 may be a therapeutic target for RSV infection. In fact, miR-221 transfection in human bronchial epithelial cells reduces RSV replication and infectivity (121).

Host-encoded miRNAs related to RSV infection are summarized in Table 3.

Host-encoded miRNAs during BKV infection

Some miRNAs contribute to pathogenesis of BKV infections and have been investigated in studies using human samples and/or human cell lines. We summarize these in Table 4. In BKV infection, miR-10b and miR-30a are downregulated in normal human renal tubule epithelial cells infected with BKV (125). In addition, these two miRNAs are

TABLE 2 Functions and characteristics of microRNA in herpes viral infection[a]

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
Host-encoded microRNA in HSV infection			
miR-101			
	ATP5B	Human *in vitro* study (87) (HeLa cells)	Inhibits HSV-1 replication
miR-23a			
	IRF1	Human *in vitro* study (88) (HeLa cells)	Promotes HSV replication
miR-138			
	ICP0 (viral gene)	Animal *in vitro* and *in vivo* studies and human *in vitro* study (89) [CD1 mice, Vero (monkey), 293T, HFF, and neuro-2A (mice) cells]	Suppresses HSV-1 lytic gene expression
miR-373			
	IRF1	Human *in vitro* study (50) (blood samples and HeLa cells)	Upregulated by HSV-1 infection in HeLa cells and patients with herpetic gingivostomatitis, promotes HSV1 replication
miR-649			
	MALT1	Human *in vitro* study (52) (HeLa cells)	Downregulated after HSV-1 infection, promotes HSV-1 replication.
Viral-encoded microRNA in HSV infection			
HSV-1 miR-H6			
	ICP4	Human *in vitro* study (90) (human limbal cells)	Inhibits HSV-1 replication and IL-6 expression in human corneal epithelial cells
Host-encoded microRNA in EBV infection			
miR-155			
	SMAD1, SMAD5, HIVEP2, CEBPB, RUNX2, and MYO10	Human *in vitro* study (91) (Mutu I and A549 cells)	Inhibits BMP-mediated EBV reactivation.
miR-429			
	ZEB1	Human *in vitro* study (92) (Rael, Akata, AGS-EBV, and AGS cells)	Can break latency of EBV
Viral-encoded microRNA in EBV infection			
miR-BART1			
	IL-12B	Human *in vitro* study (93) (MNCs/PBMCs, Raji,DG-75,and HEK293-based EBV producer cells)	Inhibits anti-viral $CD4^+$ T cells
(miR-BART1-3p and 5 p)	IFI30	Human *in vitro* study (94) (PBMCs and adenoids, Raji and HEK293-based EBV producer cells)	Reduces immune surveillance by virus-specific T cells
miR-BART15			
	NLRP3	Human *in vitro* study (95) ($CD14^{+VE}$and 293T cells)	Inhibits inflammasome activation in non-infected cells by transfer of the miRNA through exosomes.
miR-BART16			
	CREBBP	Human *in vitro* study (96)	Facilitates the establishment of latent EBV infection and promotes viral replication

(*Continued on next page*)

TABLE 2 Functions and characteristics of microRNA in herpes viral infection[a] (*Continued*)

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
		(EBV$^+$BL Jijoye, HEK293T, SNU-719, Mutu-1-cl3, and Mutu1 cells)	
miR-BART17			
	TAP2	Human *in vitro* study (94) (PBMCs and adenoids and Raji, HEK293-based EBV producer cells)	Reduces immune surveillance by virus-specific T cells
miR-BART6-3p			
	RIG-1	Human *in vitro* study (97) (HK-1, C666-1, BJAB, and B95.8cells)	miR-BART6-3p inhibits the EBV-triggered IFN-β response and facilitates EBV infection.
miR-BART18-5p			
	MAP 3K2	Human *in vitro* study (98) (BL2, Akata2A8, Akata2A8.1, BJAB, B95-8, and B95.8-LCL cells)	Inhibits EBV replication in B cells
miR-BART22			
	IL-12B	Human *in vitro* study (93) (PBMCs and adenoids, Raji, DG-75, and HEK293-based EBV producer cells)	Inhibits anti-viral CD4$^+$ T cells
miR-BART10			
	IL-12B	Human *in vitro* study (93) (PBMCs and adenoids, Raji, DG-75, and HEK293-based EBV producer cells)	Inhibits anti-viral CD4$^+$ T cells
miR-BART2			
	IL-12B	Human *in vitro* study (93) (PBMCs and adenoids, Raji, DG-75, HEK293- based EBV producer cells)	Inhibits anti-viral CD4$^+$ T cells
(miR-BART2-5p)	MICB	Human *in vitro* study (99) (293T, RKO, HeLa, 721.221, and BCBL1 cells)	Promotes escape recognition by NK cells
(miR-BART2-5p)	CTSB and LGMN	Human *in vitro* study (94) (PBMCs and adenoids and Raji, HEK293-based EBV producer cells)	Reduces immune surveillance by virus-specific T cells.
miR-BHRF1-2			
	IL-12B	Human *in vitro* study (93) (PBMCs and adenoids, Raji, DG-75, HEK293-based EBV producer cells)	Inhibits anti-viral CD4$^+$ T cells
	CTSB and IL-12B	Human *in vitro* study (94) (PBMCs and adenoids and Raji, HEK293-based EBV producer cells)	Reduces immune surveillance by virus-specific T cells
(miR-BHRF1-2-5p)	IL1R1	Human *in vitro* study (100) (LCLs and BJAB cells)	Inhibits IL-1 cytokine signaling
(miR-BHRF1-2-5p)	GRB2	Human *in vitro* study (101) (LCLs, BJAB, DLBCLs, and Mutu I cells)	Inhibition of miR-BHRF1-2-5p enhances BCR (B-cell receptor)-mediated EBV reactivation.
Host-encoded microRNA in CMV infection			
miR-155			

(*Continued on next page*)

TABLE 2 Functions and characteristics of microRNA in herpes viral infection[a] (*Continued*)

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
	Not reported	Clinical study (102) (blood samples)	Able to discriminate patients with CMV infection from patients without it in a kidney transplant setting
miR-200			
	UL122 (viral gene)	Human *in vitro* study (103) (Kasumi-3, fibroblast, and CD34+ hematopoietic projenitor cells)	Maintains CMV virus latency
miR-100 and miR-101			
	mTOR	Human *in vitro* study (104) (MRC-5, HeLa, and 293T cells)	Downregulated after CMV infection, inhibits CMV replication
miR-221			
	SOCS1	Human *in vitro* and animal (mice) *in vivo* study (105) (neural precursor cells and C57BL/6 mice)	Upregulated in CMV infection, inhibits CMV replication
miR-183 and miR-210			
	Not reported	Clinical study (44) (blood samples)	The plasma levels of miR-183–5p and miR-210–3p can discriminate congenital CMV from healthy control infants.
Viral-encoded microRNA in CMV infection			
miR-UL112			
	IL-32	Human *in vitro* study (106) (blood samples and HEK293 and MRC-5 cells)	Reduces IL-32 expression during human CMV infection
	MICB	Human *in vitro* study (107) (HFF cells and HeLa cells)	Inhibits NK cell cytotoxicity
(miR-UL112-1)	VAMP3, RAB5C, RAB11A, and SNAP23	Human *in vitro* study (108) (HEK293T, NHDF, and HeLa cells)	miR-UL112-1 inhibits pro-inflammatory cytokine secretion and facilitates formation of the VAC for efficient infectious virus production
(miR-UL112-3p)	ATG 5	Human *in vitro* study (109) (HFFs, HEK293T, and HeLa cells)	Inhibits autophagy
(miR-UL112-3p)	IKKα and IKKβ	Human *in vitro* study (110) (NHDF, HeLa, hAEC, THP-1, and 293T cells)	Inhibits the processing and presentation of the human CMV pp65 peptide to CD8+ T cells
(miR-UL112-3p)	TLR2	Human *in vitro* study (111) (HEK293T, NHDF, and THP-1 cells)	Reduces IL-32 expression during human CMV infection
(miR-UL112-5p)	ERAP1	Human *in vitro* study (112) (HEK293T cells)	Inhibits the processing and presentation of the human CMV pp65 peptide to CD8+ T cells
miR-UL148D			
	ACVR1B	Human *in vitro* study (113) (PBMCs and $CD34^+$ hematopoietic progenitor cells from healthy donors, HFFF2 fibroblast, and KG-1 cells)	Inhibits IL-6 production

(*Continued on next page*)

TABLE 2 Functions and characteristics of microRNA in herpes viral infection[a] (*Continued*)

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
IER5	Human and animal (murine) *in vitro* study (114) (Kasumi-3, HFF, and murine AFT024 cells)	Facilitates latent CMV infection	
RANTES	Human *in vitro* study (115) (HEK293T and HFF cells)	Reduces RANTES	
miR-US25			
(miR-US25-1-5p)	CD147	Human *in vitro* study (116) (HFF cells, U251 cells and HEK293 cells)	Inhibits Innate immune response
(miR-US25-2-3p)	eIF4A1	Human *in vitro* study (117) (MRC-5 cells)	Overexpression inhibits CMV replication
miR-US5			
	IKKα and IKKβ	Human *in vitro* study (110) (NHDF, HeLa, hAEC, THP-1, and 293T cells)	Inhibits pro-inflammatory cytokine production
(miR-US5-1 and −2)	VAMP3, RAB5C, RAB11A, SNAP23, and CDC42	Human *in vitro* study (108) (HEK293T, NHDF, and HeLa cells)	Inhibits pro-inflammatory cytokine production and facilitates formation of the VAC for efficient infectious virus production
miR-US22-5p			
	ATG 5	Human *in vitro* study (109) (HFFs, HEK293T, and HeLa cells)	Inhibits autophagy
miR-US29-5p			
	ATG 5	Human *in vitro* study (109) (HFFs, HEK293T, and HeLa cells)	Inhibits autophagy
miR-UL22A-5p			
	C-MYC	Clinical study (118) (blood samples)	Detection at baseline independently predicted the recurrence of CMV viremia upon discontinuation of anti-viral therapy among solid organ transplant recipients who diagnosed with CMV diseases (OR = 3.024, $P = 0.007$).
miR-UL148D, miR-US25-1-5p, and miR-US5-1			
	Not reported	clinical study (119) (Blood samples)	Plasma concentrations can discriminate pregnant women with adverse pregnancy outcomes associated with CMV from normal controls. (miR-US25-1-5p presented the largest area under the ROC curve (0.735), with a sensitivity of 68% and specificity of 71%.)

[a]ACVR1B, activin A receptor 1B; ATG5, autophagy-related gene5; ATP5B, ATP synthase subunit beta; BMP, bone morphogenetic protein; CEBPB, CCAAT/enhancer-binding protein beta; CREBBP, CREB-binding protein; CTSB, cathepsin B; eIF4A1, eukaryotic translation initiation factor 4A1; ERAP1, endoplasmic reticulum aminopeptidase 1; GRB2, growth factor receptor-bound protein 2; HIVEP2; human immunodeficiency virus type 1 enhancer-binding protein 2, ICP; infected cell polypeptide; IER5, immediate early response gene5; IFN, interferon; IFI30, IFN-γ-regulated thiol reductase; IKK, IκB kinase; IL, interleukin; IL1R1, IL-1 receptor 1; IRF1, interferon regulatory factor 1; LGMN, legumain; MALT1, mucosa associated lymphoma translation gene 1; MAP3K2, MAP kinase kinase kinase 2; MICB, major histocompatibility complex class I-related chain B; MRC-5, Medical Research Council cell strain 5; mTOR, mammalian target of rapamycin; MYO10, myosin X; NK, natural killer; NLRP3, NLR family pyrin domain containing 3; PBMC, peripheral blood mononuclear cell; RANTES, regulated on activation normal T-cell expressed and secreted; RIG-1, retinoic acid includible gene 1; ROC, receiver operating characteristic; RUNX2, runt-related transcription factor 2; SMAD1, *Drosophila* mother against decapentaplegic 1; SMAD5, *Drosophila* mother against decapentaplegic 5; SNAP23, synaptosome associated protein 23; SOCS1, suppressor of cytokine signaling-1; TAP2, transporter2; TLR, toll-like receptor; VAC, virion.

significantly decreased in specimens obtained from kidney transplant recipients with BKV nephropathy compared to those with a functional graft (125). Moreover, upregulation or downregulation of some genes [e.g., interleukin (*IL*)-*6*, *IL-8*, and tumor protein p53 inducible protein], which are predicted to be direct or indirect targets of miR-10b and miR-30a, may be induced by BKV nephropathy (125). These responses lead to evasion of the host immune response, nurturing the growth of BKV-infected cells, preventing apoptosis, induction of inflammation, and development of fibrosis (125), permitting BKV survival in the tissues. Thus, these miRNAs may be used as therapeutic targets (125).

Function and characteristics of viral-encoded miRNAs during viral infections

miRNAs are also encoded by several types of viruses that have dsDNA genomes, including adenoviruses, herpesviruses, and polyomaviruses (154). Thus far, viral-encoded miRNAs have not been identified in papillomaviruses or poxviruses (154). No viral-encoded miRNAs have been reported in RNA viruses (154).

Viral-encoded miRNAs are incorporated into the miRISC, and this miRNA complex interacts with the 3′ untranslated region of the host and viral-encoded mRNAs. This suppresses the expression of target genes either via translational repression or mRNA degradation (155). Remarkably, the functions of these viral-encoded miRNAs are similar to those of the host-encoded miRNAs as described above (141, 156). These viral-encoded miRNAs usually permit viral persistence and/or promote self-proliferation (141). In particular, viral-encoded miRNAs, which EBV and CMV encode, play an important role in achieving lifelong latency by evading the host immune systems (156, 157). Moreover, some evidence suggests that some viral-encoded miRNAs are active during latency, whereas others are more important during the productive replication phase (155). However, the detailed mechanisms underlying these different expression patterns in each phase remain unclear (155).

Viral miRNAs encoded by HSV, EBV, CMV, and BKV are described in Tables 2 and 4. These viral-encoded miRNAs inhibit target genes within the virus and its host cell (154). The functions of EBV- and CMV-encoded miRNAs have been investigated well in these four viruses.

A pertinent example of immune-related functional changes associated with viral-encoded miRNAs has been observed in B cells during acute EBV infection. EBV-encoded

TABLE 3 Functions and characteristics of microRNA in RSV virus infection[a]

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
Host-encoded microRNA in RSV infection			
miR-24, miR-124, and miR-744			
	p38 MARK signaling pathway	Human *in vitro* study (120) (ATCC, MDCK, and Hep-2 cells)	Inhibits RSV infection
miR-221			
	NGF-TrkA axis	Human *in vitro* study (121) (human bronchial epithelial cells from donors)	Inhibits RSV replication
miR-34b/c-5p			
	Not reported	Human *in vitro* study (122) (HBE cells)	Downregulation of miR-34b/c-5p expression in airway epithelial cells in RSV infection is associated with increasing of mucus secretion.
miR155			
	SOCS1	Human *in vitro* and animal (mice) *in vivo* study (123) [Hep-2, A549, and HPAEpi cells, and MEFs (murine cells), and C57BL/6 mice]	Inhibits RSV replication
miR-125a and miR-429			
	Not reported	Clinical study (124) (nasal mucosa cytology specimens)	Discrimination between mild and severe RSV infection

[a]p38 MARK, P38 mitogen-activated protein kinase; NGF-TrkA, nerve growth factor-tropomyosin-related kinase A; SOCS1, suppressor of cytokine signaling-1.

miRNAs have been shown *in vitro* to inhibit the adaptive and innate immune systems of the host efficiently. miR-BART-1, miR-BART-2, and miR-BHRF1 were shown to suppress the human *IL-12B* gene expression (93). B cells are the principal cell target of EBV (158). As a result, IL-12 secretion from the infected B cells was decreased. Ultimately, this inhibited Th1 cell differentiation (93). Thus, these three miRNAs can inhibit the adaptive immunity of the host during EBV infection. In addition, miR-BART-2–5p represses the major histocompatibility complex class I-related chain B (*MICB*) gene in B cells after primary EBV infection. MICB is a receptor of natural killer (NK) cells. As a result, recognition of the infected B cells by NK cells is lost due to decreased cell surface expression of MICB protein on the infected B cells (99). Interestingly, one of the target genes of miR-UL112, which is a CMV-encoded miRNA, is also *MICB* gene in multiple human cell lines (107). miR-UL112 interferes with the recognition of infected human cells by NK cells by inhibiting the expression of MICBs during CMV infection (107). The other CMV-encoded miRNAs that inhibit host immune defense are presented in Table 2. In this context, inhibition of these viral-encoded miRNAs may be a therapeutic target for these viral infections.

In addition to therapeutic targets, some viral-encoded miRNAs may be useful as biomarkers. For example, in a study in which profiles of viral-encoded miRNA expression were analyzed in samples from a cohort of solid organ transplant patients with CMV disease, the identification of hcmv-miR-UL22A-5p at baseline independently predicted the recurrence of CMV viremia upon discontinuation of anti-viral therapy (OR = 3.024; 95% CI, 1.35–6.8) (118). Additionally, in a study analyzing kidney transplant patients with BKV DNAemia following transplantation, blood BKV-miR-B1-5p detection (cycle threshold value of bkv-miR-B1-5p was 31.9) provided a sensitivity of 100% and a specificity of 94.9% for the diagnosis of biopsy-proven BK virus nephritis. In this study, the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis was 0.97 (128). This miRNA may be an excellent tool for identifying patients at risk of BK virus nephritis, which is especially important because of the severe lack of accurate diagnostic markers for BK nephropathy (159, 160). We describe other candidate viral-encoded miRNAs as diagnostic biomarkers in Tables 2 and 4.

FUNGAL INFECTION

Over the last decade, as invasive fungal infections have risen in immunocompromised populations due to HIV, transplantation, and cancer, there has been renewed focus on reinventing anti-fungal therapy. As only a few classes of anti-fungal drugs are available, the emergence of resistance to single-drug classes and now multi-drug resistance significantly hampers patient management (161). In particular, *Candida auris* and cryptic species of *Aspergillus* are emerging concerns because of their multi-drug-resistant nature (32, 33, 162–164). Thus, newer therapeutic agents for highly resistant fungal infections are urgently required. In this context, miRNAs could become a treatment option, although the role of host miRNAs during fungal infections has not been extensively studied in humans. Furthermore, miRNAs may serve as useful diagnostic markers. The laboratory diagnosis of fungal infections such as invasive aspergillosis is often difficult due to the low sensitivity of culture and biomarkers, and consensus criteria have been used to tackle such limitations (165, 166). However, these criteria are not perfect, despite recent revisions (166). In this review, we focused on *Aspergillus* and *Candida* infections, which are the most common fungal infections.

Studies using human samples and/or human cell lines

Aspergillus fumigatus is one of the most ubiquitous airborne fungi that causes invasive aspergillosis in immunocompromised patients. Several miRNAs have been implicated in *Aspergillus* infection and have varying roles. One interesting role of miRNAs is that miRNAs can drive a negative feedback loop in inflammatory response. *In vitro*, one study demonstrated that *A. fumigatus* induces activation of the NF-κB and p38 mitogen-activated protein kinase pathways, mediated by TLR2, TLR4 and dectin-1, which contributed

TABLE 4 Functions and characteristics of microRNA in BK virus infection[a]

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
Host-encoded microRNA in BKV infection			
miR-10 and miR-30			
	Not reported	Human *in vitro* study (125) (RPTEC cells)	Controlled the expression of genes involved in evading the host immune response, nurturing the growth of BKV-infected cells, preventing apoptosis, induction of inflammation, and development of fibrosis
Viral-encoded microRNA in BKV infection			
BKV-miR-B1			
	Not reported	Human *in vitro* study (125) (RPTEC cells)	bkb-miR-B1-5p and bkv-miR-B1-3p showed a 1,000-fold increase in human tubular epithelium during BKV infection.
	Not reported	Clinical study (126) (blood and urine samples)	bkv-miR-B1-3p and bkv-miR-B1-5p levels in the urine might be able to detect viral replication (plasma BKV DNA) in kidney transplant recipients (the AUCs were 0.7928 and 0.7091, respectively).
	Not reported	Clinical study (127) (blood, urine, and cerebrospinal fluid samples)	bkv-miR-B1-3p and bkv-miR-5p in human plasma, urine, and cerebrospinal fluid might be able to detect suspected or severe BKV disease.
(bkv-miR-B1-5p)	Not reported	Clinical study (128) (blood samples)	Biomarker for BKV nephropathy and infection (sensitivity of 100.0% and specificity of 94.9%; the AUC was 0.97)
(bkv-miR-B1-5p)	Not reported	Clinical study (129) (blood and urine samples)	The urinary exosomal microRNA levels of bkv-miR-B1-5p and bkv-miR-B1-5p/miR-16 detect biopsy-proven BKVN. [The AUC was 0.989 for bkv-miR-B1-5p, 0.985 for bkv-miR-B1-5p/miR-16. The cut-off values for bkv-miR-B1-5p and bkv-miR-B1-5p/miR-16 were 5.9 log10 copies/mL (sensitivity, 100%; specificity, 98.5%) and 1.2 log10 copies/mL (sensitivity, 100%; specificity, 98.5%), respectively.]

[a]AUC, area under the curve.

to miR-146a upregulation in THP-1 macrophage-like cells (Fig. 2) (47). Upregulation of miR-146a inhibited *IRAK1* and tumor necrosis factor receptor-associated factor 6, the target genes of miR-146a, and the inhibition of these genes then led to suppression of the NF-κB pathway. The observed increase in IL-6 and tumor necrosis factor alpha (TNF-α) in the cells was later decreased via a negative feedback loop (Fig. 2) (47). While this study provided evidence that the pro-inflammatory cytokines IL-6 and TNF-α play a central role in regulating the inflammatory response to *A. fumigatus*, a plausible reason for this mechanism of regulation remains unknown (167). Our group has previously shown that naïve T cells from patients with invasive aspergillosis, but not those with mucormycosis, exhibit reduced responsiveness to IL-6; whether impaired IL-6 responsiveness and downstream Th17 responses observed in T cells from patients with *Aspergillus* infection are mediated through miRNA upregulation requires further study (168). The function of miR-146a requires further investigation because of its potential value as a therapeutic target for invasive aspergillosis. Interestingly, miR-146a was upregulated in THP-1 cells (a human leukemia monocytic cell line) through the dectin-1 signaling pathway after exposure to *Candida albicans* (169). miR-146a, in turn, decreased the production of dectin-1-induced cytokines (such as IL-6 and TNF-α) in THP-1 cells (169).

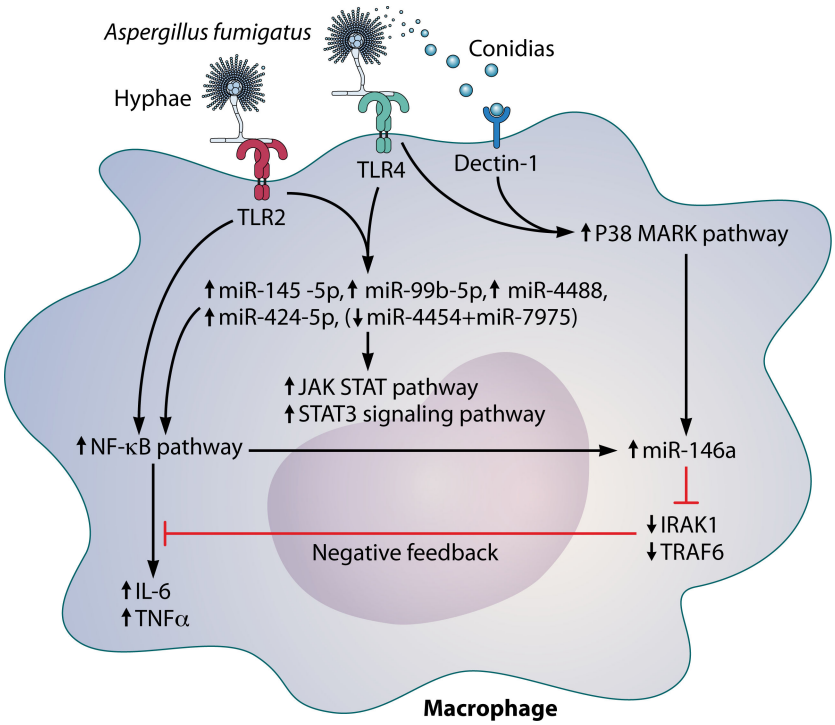

FIG 2 Regulation pathway and functions of miR-146a and its related pathways during *Aspergillus fumigatus* infection in a macrophage cell line. Abbreviations: IL-6, interleukin 6; IRAK1, interleukin-1 receptor-associated kinase; NF-κB, nuclear factor-kappa B; p38 MARK, p38 mitogen-activated protein kinase; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; TRAF6, TNF receptor-associated factor 6.

This function is quite similar to that observed after exposure to *A. fumigatus*. In contrast, the expression of miRNA-146a was downregulated in macrophages infected with *Candida glabrata* (170). This suggests that the mechanisms associated with miR-146a expression differ between other fungal species. In this context, the association between miR-146a and fungal infections has been relatively well investigated in human cell lines. However, the function of miRNAs other than miR-146a has yet to be well investigated during *Aspergillus* and *Candida* infection. We describe other functional miRNAs implicated in fungal infections that have been evaluated in studies using human samples and human cell lines in Table 5.

Regarding the application of miRNAs as biomarkers for the diagnosis of fungal infection, there are some clinical studies in which miRNAs were used as diagnostic markers for invasive aspergillosis. Gohir et al. reported that six miRNAs from bronchoalveolar lavage samples of lung transplant recipients were specific for the diagnosis of invasive aspergillosis, including four (miR-145–5p, miR-424–5p, miR-99b-5p, and miR-4488) that were upregulated and a pair (miR-4454 + miR-7975) that was downregulated. These six were found in patients with invasive aspergillosis but not in controls, who did not develop chronic lung allograft dysfunction or *Aspergillus* colonization after lung transplantation (45). This study reported that signaling from TLR2 and TLR4 might regulate these miRNAs, with downstream effects on the JAK-STAT and NF-κB pathways, both central to the intracellular immune response (Fig. 2). However, the detailed mechanisms and the consequences of this regulation remain unclear. Moreover, miR-142–3p, miR-142–5p, miR-26b-5p, and miR-21–5p in peripheral blood specimens showed significant overexpression associated with invasive aspergillosis in hemato-oncology patients with profound neutropenia (172), suggesting a potential role for these miRNAs as diagnostic biomarkers (Table 5). Some miRNAs might be helpful in *Candida* infection as diagnostic markers (Table 5); however, most have not been investigated well in clinical settings.

TABLE 5 Functions and characteristics of microRNA in fungal infections[a]

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
microRNA in *Candida* infection			
miR-129–5p, miR-132–3p, miR-212–3p, and miR-212–5p			
	Not reported	Human *in vitro* study (171) (dendritic cells from healthy volunteers)	These are induced by *Candida albicans* in dendritic cells.
miR-30–5p, miR-146a, and miR-210–3p			
	NF-κB signaling pathway	Human *in vitro* study (169) (THP-1 cells)	These expression levels are increased in human THP-1 cells after exposure of *Candida albicans*. Overexpression of miR146a significantly suppresses the production of IL-6 and TNF-α.
miR-146a			
	Not reported	Human *in vitro* study (170) (PBMCs)	The expression of miR-146a is downregulated in infected macrophages with *Candida glabrata*. The downregulated miR-146a might reduce pro-inflammatory cytokine production.
microRNA in *Aspergillus* infection			
miR-145–5p, miR-424–5p, miR99b-5p, miR-4488, and (miR-4454 + miR-7975)	JAK STAT and NF-κB signaling pathway	Clinical study (45) (BALF samples)	In the lung transplant recipients, a total of five miRNAs are found to be specific to invasive aspergillosis, including four (miR-145–5p, miR-424–5p, miR-99b-5p, and miR-4488) that were upregulated and the pair (miR-4454 + miR-7975) that was downregulated in the invasive aspergillosis group versus controls.
miR-21–5p, miR-26b-5p miR-142–3p, and miR-142–5p			
	Not reported	Clinical study (172) (blood sample)	These show significant overexpression due to invasive aspergillosis in hemato-oncology patients with profound neutropenia.
miR-191, miR-106, miR16-2, miR-26, miR-15, miR-20, miR-106, and miR-17			
	Not reported	Clinical study (173) (blood sample)	8 miRNAs (miR-191–5p, miR-106b-5p, miR-16-2-3p, miR-26a-5p, miR-15a-5p, miR-20a-5p, miR-106a-5p, and miR-17–5p) measured by quantitative RT-PCR had high discriminatory power (AUC >0.98 in ROC analysis), which could distinguish proven/probable IA from possible IA.
miR-129–5p, miR-132–3p, miR-132–5p, miR-212–3p, and miR-212–5p			
	Not reported	Human *in vitro* study (171) (PBMCs)	These are induced by *Aspergillus fumigatus* in dendritic cells.
miR-132			
	Not reported	Human *in vitro* study (174) (PBMCs)	miR-132 is induced by *Aspergillus fumigatus* but not by lipopolysaccharide in human monocytes and dendritic cells.
miR-146a			
	IRAK1 and TRAF6	Human *in vitro* study (47) (THP-1 cells)	Downregulates the level of TNF-α and IL-6 through the NF-κB signaling pathway in THP-1 macrophage-like cells challenged with *A. fumigatus*.

[a]AUC, area under the curve; BALF, bronchoalveolar lavage fluid; IL, interleukin; IRAK1, interleukin-1 receptor-associated kinase; NF-κB, nuclear factor-kappa B; PBMC, peripheral blood mononuclear cell; ROC, receiver operating characteristic; TNF-α, tumor necrosis factor alpha; TRAF6, tumor necrosis factor receptor-associated factor 6.

Animal studies

Several miRNAs have been investigated in animal cell lines or animal *in vivo* studies. For instance, miR-125a, miR-146, miR-155, and miR-455 are upregulated by heat-killed *C. albicans* in macrophages of mice (175). miR-29a-3p and miR-23b-3p are downregulated during *Aspergillus* exposure, and they regulate genes involved in innate responses to viable *A. fumigatus* in a mouse model (176).

BACTERIAL INFECTION

In the following section, we focus on miRNAs during *Staphylococcus aureus* and *Pseudomonas aeruginosa* infection because these two pathogens often cause complicated and life-threatening infections (30, 31). Furthermore, drug resistance such as methicillin-resistant *Staphylococcus aureus* and multi-drug-resistant *P. aeruginosa* make approaches to therapy very difficult. Therefore, investigating miRNAs during these infections is essential for developing new therapeutic options, in addition to new anti-microbial agents. An overview of functions and characteristics of miRNAs implicated in these infections and their target genes is provided in Tables 6 . In *S. aureus* and *P. aeruginosa* infections, most studies investigating miRNAs include animal experiments with or without human cellular experiments. Thus, we discuss the miRNA identified in both types of studies in this section and in Table 6.

miR-15b-5p, miR-24, miR-155, and miR-223 have been associated with diabetic foot ulcers, osteomyelitis, pneumonia, and wounds caused by *S. aureus* (46, 177, 178, 181). These studies were primarily performed by using animal cell lines and/or animal models (46, 177, 178, 181). Interestingly, some of these miRNAs have been investigated for therapeutic applications in animal models. For instance, miR-223 was highly expressed during the inflammatory phase of *S. aureus*-infected wound sites in mice (46). A known target of miR-223 is IL-6, so the secretion of IL-6 from neutrophils was potentially decreased by the high expression of miR-223 at the wound sites. Support for the important role of miR-223 is illustrated by the delayed healing of the infected sites, as neutrophil-derived IL-6 was positively linked to *S. aureus* clearance (187). Furthermore, topical miR-223 antisense oligodeoxynucleotides (ODNs) in *S. aureus*-infected wild-type wounds markedly improved wound healing compared to that in control wounds (wild-type wounds without miR-223 antisense ODNs) in an animal experiment (46). This result suggests that miR-223 antisense ODNs could be utilized for wounds associated with *S. aureus* infection in a clinical setting.

Regarding *P. aeruginosa*, miR-155 and a miR-183/96/182 cluster were associated with the pathogenesis of pseudomonal keratitis (182, 184). According to previous studies (182, 184), the severity of the keratitis may be decreased if these miRNAs are inactivated. Therefore, these miRNAs could be considered as new therapeutic targets. In addition, the miR-183/96/182 cluster and the miR-302/367 cluster have been found to influence macrophage function and subsequent bacterial clearance during *P. aeruginosa* infection (183, 186). In other words, some miRNAs were directly associated with innate immune responses during *P. aeruginosa* infection. Furthermore, miR-302/367 cluster expression was significantly increased after *P. aeruginosa* respiratory infection in a mouse model (186).

Additionally, NF-κB, which inhibits mitophagy in macrophages, was identified as a target gene of the miR-302/367 cluster in the same study (186). Mitophagy, the selective autophagy to eliminate damaged mitochondria, is a highly conserved cellular self-digestion and catabolism critical for maintaining cellular homeostasis (188). Various microbial components modulate this process, thereby affecting the innate immune response to infection (189). In this study, ongoing mitophagy was associated with the clearance of *P. aeruginosa* in the macrophages (186, 190). Therefore, overexpression of the miR-302/367 cluster promotes the clearance of *P. aeruginosa* in macrophages through mitophagy by inhibiting the target gene (*NF-κB*) expression (186). Although details of how *P. aeruginosa* accesses the mitochondria and impacts mitophagy induction require further

TABLE 6 Functions and characteristics of microRNA in bacterial infections[a]

Type of miRNAs	Target gene/pathway	Study type	Function and characteristics of miRNA
microRNA in *Staphylococcus aureus* infection			
miR-15b-5p			
	IKBKB and WEE1	Animal *in vivo* and human *in vitro* study (177) (porcine wound infection model, HaCaT cells, and skin samples from patients)	Responsible for defective DNA repair, may delay healing of wound in diabetic foot
miR-24			
	Chitinase3-like1	Animal *in vitro* and human *in vitro* study (178) [MC3T3-E1 cells (mouse cell line) and Blood from patients]	Downregulated in blood of osteomyelitis, protective against worsening of osteomyelitis
miR-128			
	MyD88	Animal *in vivo* and *in vitro* study (179) (BALB/C mice and RAW264.7 macrophages (mouse cell line)]	Increase expression in *S. aureus* infection. reduces the secretion of IL-6, IL-1β, and TNF-α
miR-142			
	Not reported	Animal *in vivo* study (180) (mouse skin wound model)	Necessary for *S. aureus* clearance at skin wound sites
miR-155			
	IL-17 pathway	Animal *in vivo* and human *in vitro* study (181) (BAL from patients and C57BL/6 mice)	Treatment with miR-155 antagomir improves lung bacterial clearance by 4.2-fold compared with control.
miR-223			
	IL-6 and Pclo	Animal *in vivo* and human *in vitro* study(46) (mouse wound model, skin sample from patients, and HL-60 cells)	miR-223 is the most highly expressed during the inflammatory phase at wound sites. miR-223 antisense oligodeoxynucleotides in S. aureus-infected wild-type mice's wounds markedly improved the healing of them.
microRNA in *Pseudomonas aeruginosa* infection			
miR-183/96/182 cluster			
	Not reported	Animal *in vivo* and human *in vitro* study (182) (129 S2/BL6-mixed mice, human corneas sample, and human PBMCs)	Inactivation of the miR-183/96/182 cluster decreases the severity of *P. aeruginosa*-induced keratitis because it decreases expression of pro-inflammatory neuropeptides in the cornea.
	DAP12 and Nox2	Animal *in vivo* and *in vitro* study (183) [129 S2/BL6-mixed mice and RAW64.7 cells (mice cell line)]	Knockdown of miR-183/96/182 cluster results in decreased production of multiple pro-inflammatory cytokines in response to *P. aeruginosa* or lipopolysaccharide treatment in macrophage-like RAW264.7 cells.
miR-155			
	Not reported	Animal *in vivo* and human *in vitro* study (184) (C57BL/6 mice and corneal samples)	Upregulated during infection, may enhance keratitis
miR-301b			
	c-Myb	Animal *in vivo* and *in vitro* study (185) [C57BL/6J mice, MLE-12 cells (mice),	Suppression of miR-301b elevates levels of neutrophil infiltration, thereby alleviating symptoms caused by *P. aeruginosa* infection in mice.

(*Continued on next page*)

TABLE 6 Functions and characteristics of microRNA in bacterial infections[a] (*Continued*)

Type of miRNAs	Target gene/pathway	Study type	Function and characteristics of miRNA
		and MH-S cells (mice)]	
miR-302/367 cluster			
	NF-κB	Animal *in vivo* and *in vitro* study (186) [C57BL/6J mice, MLE-12 cells (mice), and MH-S cells (mice)]	Upregulated after *P. aeruginosa* infection.

[a]DAP12, DNAX activation protein of 12kDa; IKBKB, inhibitor of nuclear factor kappa B kinase subunit beta; IL, interleukin; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-kappa B; Nox2, NADPH oxidase 2; PBMC, peripheral blood mononuclear cell; Pclo, presynaptic cytomatrix protein; TNF-α, tumor necrosis factor alpha.

investigation, it is apt to consider both miRNAs and host mitophagy as potential targets for therapy against *P. aeruginosa*-associated infection.

PARASITIC INFECTION

The World Health Organization reported 241 million cases and 627 thousand deaths from malaria in 2020 (191). Analogously, it is estimated that at least 230 million people are infected with schistosomes, the pathogen responsible for schistosomiasis (192). Among the parasites that cause malaria or schistosomiasis, *P. falciparum* and *S. japonicum* cause the most severe clinical syndromes and/or pathogenicity, respectively (34, 35). To date, effective vaccines against malaria and schistosomiasis have not been established, limiting the prevention of these infections (192, 193). Furthermore, drug resistance to therapeutic agents, including artemisinin-resistant *Plasmodium*, is a serious concern (193). Regarding schistosomiasis, there is no clear evidence of praziquantel resistance yet, even after its extensive use in many endemic countries. However, such resistance can be experimentally induced; thus, the threat of emerging resistance caused by mass monotherapy remains (192). Hence, investigating miRNAs associated with these parasitic infections is necessary to identify new therapeutic options. Investigations of miRNAs in malaria and schistosomiasis have primarily focused on *P. falciparum* and *S. japonicum* (194), including animal studies and/or human *in vitro* studies (Tables 7 and 8). In this review, host-encoded miRNAs that are associated with *Plasmodium falciparum* and *Schistosoma japonicum* were examined. In addition, influence of parasite-encoded miRNAs on the pathogenesis of parasitic diseases is reviewed. miRNAs associated with strongyloidiasis were excluded from this review due to the limited data available.

Function and characteristics of host-encoded miRNAs during parasitic infection

Some host-encoded miRNAs are associated with pathogenesis of *P. falciparum* and *S. japonicum* infection. Herein, we discuss host-encoded miRNAs associated with *P. falciparum* and *S. japonicum* infection separately because they have different characteristics in terms of target cells and functional mechanisms.

Host-encoded miRNAs during P. falciparum infection

Studies using human samples and/or human cell lines with or without an animal experiment

miRNAs investigated in malaria infections caused by *P. falciparum* are mostly intraerythrocytic (see Table 7). Approximately 100 human (host-encoded) miRNAs have been identified in matured erythrocytes, which is of particular importance in that these cells lack a nucleus and transcription/translation machinery (222). Thus, the miRNAs found in matured erythrocytes primarily act on mRNA synthesis elsewhere (i.e., within the parasite). When merozoites of *P. falciparum* invade erythrocytes, genetic material between the host erythrocytes and *Plasmodium* species is exchanged (223). Infection

TABLE 7 Functions and characteristics of microRNA in malaria caused by *Plasmodium falciparum*[a]

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
Host-encoded microRNA in *P. falciparum* infection			
miR-146a			
	Not reported	Clinical study (195) (blood sample)	May be associated with protection in pregnant women
	Not reported	Clinical study (196) (blood sample)	No major role in the development of cerebral malaria
miR-150			
	Not reported	Clinical study (197) (blood sample)	Differentiation between fatal and non-fatal malaria
miR-150–3p and miR-197–5p			
	pfApricon (gene of malaria)	Human *in vitro* study (198) (human erythrocytes and HEK293T cells)	Inhibits virulence of *P. falciparum*
miR-155			
	Not reported	Human *in vitro* and animal (mice) *in vivo* study (199) (human blood sample)	Can reduce vascular leak in cerebral malaria
miR-223			
	Not reported	Human *in vitro* study (200) (human RBCs)	Negatively regulates *P. falciparum* along with miR-451 and let-7i *in vitro*
miR-451 and let-7i			
	mRNA of *P. falciparum* (not specified)	Human *in vitro* study (200) (human RBCs)	Associated with host protection
miR-451			
	Var gene of malaria	Human *in vitro* and animal (mice) *in vivo* study (201)	Inhibits the parasite virulence factor pfEMP1
miR-4497			
	Not reported	Clinical study (202) (blood sample)	Discriminate severe malaria from uncomplicated malaria
let-7a-5p			
	Not reported	Clinical study (203) (blood sample)	Discrimination between healthy control and *P. falciparum* infection

[a]Studies in mouse models of cerebral malaria using *Plasmodium berghei* ANKA, which causes cerebral malaria in mice, are included in this table because the cerebral malaria is a significant complication caused by *P. falciparum* in human. Abbreviations: pfEMP1, *P. falciparum* erythrocyte membrane protein 1.

allows the transfer of human miRNAs and Argonaute proteins, which are needed to form the miRISC, from the erythrocyte into the parasite cytoplasm (201, 223). As a result, some of these host-encoded miRNAs can bind the mRNAs of *P. falciparum*, inhibiting the translation of *P. falciparum* genes (224). This process has been observed in a previous *in vitro* study, where a subset of erythrocyte miRNAs, miR-451 and let-7, translocated into the parasite and negatively regulated *P. falciparum* (200). Moreover, these miRNAs are integrated into essential parasite mRNAs and via impairment of ribosomal loading, resulting in translational inhibition (200). In a more recent study, miR-451 was reported to repress the *P. falciparum* erythrocyte membrane protein 1 (pfEMP1), an important virulence factor produced by *P. falciparum*, by inhibiting the var gene encoding pfEMP1 (201). These miRNAs may confer innate resistance to malaria (200, 201).

Interestingly, miR-451 and let-7i were highly enriched in hemoglobin AS (sickle cell trait) erythrocytes and HbSS (sickle cell disease) erythrocytes, compared to HbAA (normal) erythrocytes (200, 225). Thus, the enrichment of these miRNAs in HbAS and HbSS erythrocytes might explain why those with sickle cell disease are resistant to malaria (200). In this context, miR-451 and let-7i could be utilized as therapeutic targets for *P. falciparum*. In addition, two erythrocytic miRNAs, miR-150–3p and miR-197–5p, have been reported to inhibit *P. falciparum* growth and invasion by targeting the apicortin gene (198).

Interestingly, some miRNAs may play an essential role in the pathogenesis of cerebral malaria. Cerebral malaria is the most common and severe neuropathological manifestation of malaria caused by *P. falciparum* in humans (224). In an *in vivo* experimental model of cerebral malaria (mice infected with *Plasmodium berghei*), survival was significantly improved in miR-155$^{-/-}$ mice compared to that in wild-type littermate mice (199). The improved survival was associated with preservation of blood-brain barrier integrity and reduced endothelial cell activation (199).

To supplement this evidence, pre-treatment with an antagomir of miR-155 reduced vascular leakage in an *ex vivo* endothelial microvessel model of cerebral malaria (199). Therefore, miR-155 may be an important therapeutic target to prevent cerebral malaria, although a target gene of miR-155 has not yet been identified. We report additional miRNAs associated with *P. falciparum* infection in studies using clinical samples and cell lines with or without animal experiments in Table 7.

Several miRNAs have been clinically explored for their application as biomarkers for the diagnosis or evaluation of parasitic infection (Table 7). For example, let-7a-5p was significantly upregulated in the blood of *P. falciparum*-infected patients compared to uninfected patients (control) ($P = 0.01$), with the area under the ROC curve equal to 0.82 ($P = 0.003$) (203). Thus, let-7a-5p could help identify *P. falciparum*-infected patients, although its sensitivity and specificity warrant confirmation (203). Similarly, plasma concentrations of miR-150 were higher in adult cases of fatal cerebral malaria than those of non-fatal cerebral malaria (median relative expression level 25.4 versus 8.5, $P = 0.003$) (197). Thus, miR-150 has the potential to discriminate between fatal and non-fatal adult cerebral malaria, and it should be explored further (197).

Animal and bioinformatic studies

In a mouse model experiment and bioinformatic analysis, miR-19a-3p, miR-19b-3p, miR-142–3p, and miR-223–3p were found to be involved in several pathways relevant to cerebral malaria (226). In addition, miR-451a and miR-223–3p may make the most notable contribution to the pathogenesis of *P. falciparum* based on a bioinformatic analysis (227).

Host-encoded miRNAs during S. japonicum

Most studies investigating miRNAs in *S. japonicum* infection include an animal experiment with or without a human cellular experiment. Thus, we discuss miRNAs identified in both types of studies in this section and in Table 8. In schistosomiasis caused by *S. japonicum*, many eggs are permanently lodged in the intestine or liver (192), providing an antigenic stimulus for the immune response, which leads to granuloma formation and hepatic fibrosis (35, 192). Hepatic fibrosis is associated with high morbidity and mortality in schistosomiasis (228), and many miRNAs have been explored in this setting (Table 8). For instance, miR-96 and miR-351 have been recognized as pro-fibrotic miRNAs (206, 213). They were found to be upregulated in hepatic stellate cells during the chronic progressive phase of the schistosomiasis, leading to repression of *Drosophila* mother against decapentaplegic 7 (SMAD7) and the vitamin D receptor (VDR), which were their direct targets, respectively (206, 213). Repression of these proteins promoted hepatic stellate cell activation and the release of IL-13 and the transforming growth factor beta 1 (TGF-β1). SMAD7 and VDR are antagonists of the TGF-β1/SMAD pathway, and activating these proteins normally inhibits pro-fibrosis responses (35, 206, 213).

An anti-fibrotic miRNA, miR-203–3p, has also been identified. miR-203–3p has been found to target IL-33 directly in hepatic stellate cells during a murine model of *S. japonicum* infection (212). Lowered levels of miR-203–3p lead to increased expression of IL-33 from hepatic stellate cells, which promotes the expansion and IL-13 production of hepatic group 2 innate lymphoid cells (ILC2s) (212). As a result, hepatic fibrosis pathology progressed through the activation of hepatic stellate cells by IL-13 from ILC2s (212). Elevation of miR-203–3p in the liver through recombinant adeno-associated virus 8 infections was found to protect mice from lethal infection (212). In this context, inhibition

TABLE 8 Functions and characteristics of microRNA in the schistosomiasis caused by *Schistosoma japonicum*[a]

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
Host-encoded microRNA in *S. japonicum* infection			
miR-21			
	SMAD7	Animal (mice) *in vitro* and *in vivo* study (204) (mouse hepatic stellate cells, hepatocytes, and Kupper cells)	Upregulated, pro-fibrotic
miR-92a-2–5p			
	TLR2	Animal (mice) and human *in vitro* and animal (mice) *in vivo* study (205) (NIH/3 T3 embryonic fibroblasts and 293T cells)	Anti-fibrotic
miR-96			
	SMAD7	Animal (mice and rats) and human *in vitro* and animal (mice) *in vivo* study (206) (HSC-T6, HEK293 and mouse primary hepatic stellate cells)	Upregulated, pro-fibrotic
miR-142			
	WASL	Animal (mice) *in vivo* study (207)	Suppresses infection
miR-146b			
	STAT1	Animal (mice) *in vivo* study (208)	Upregulated, inhibits differentiation of macrophages to M1 cells
miR-148a			
	PTEN	Animal (mice) *in vitro* and *in vivo* study (209) (RAW264.7cells and NCTC clone 1469 cells)	Regulates cytokine production in macrophages
miR-155			
	FOXO3a	Human *in vitro* study (210) (LX-2 cells)	Anti-fibrotic
miR-182–5p			
	TTP	Animal (mice) *in vivo* and human and animal (mice) *in vitro* study (211) (HL7702, AML12 and U937 cells)	Decreased in mice liver, pro-fibrotic
miR-203–3p			
	IL-33	Animal (mice) *in vitro* and *in vivo* study (212) (mouse HSCs, hepatocytes, and Kupper cells)	Downregulated, anti-fibrotic
miR-351			
	VDR	Animal (mice) *in vitro* and *in vivo* study (213) (mouse HSCs, hepatocytes, and Kupper cells)	Pro-fibrotic, initial downregulation during infection followed by upregulation
miR-454			
	SMAD4	Human *in vitro* and animal (mice) *in vivo* study (214) (LX-2 cells)	Anti-fibrotic
miR-92a-3p, miR-146a-5p, and miR-532–5p			

(*Continued on next page*)

TABLE 8 Functions and characteristics of microRNA in the schistosomiasis caused by *Schistosoma japonicum*[a] (*Continued*)

Type of miRNAs	Target gene/pathway	Study type	Functions and characteristics of miRNA
	Not reported	Clinical study (215)	Differentiation between no fibrosis and fibrosis grade
miR-146a-5p, miR-150–5p, Let7a-5p, and Let-7d-5p			
	Not reported	Cinical study (216)	Differentiation between fibrotic grades
Parasite-encoded microRNA in *S. japonicum* infection			
Sja-miR-1			
	SFRP1	animal (mice) *in vivo* and human and animal (mice) *in vitro* study (217) (LX-2 cells and mouse primary HSCs)	Anti-fibrotic
Sja-miR-71a			
	SEMA4D	Animal (mice) *in vivo* and human *in vitro* study (218) (LX-2 cells)	Anti-fibrotic
Sja-miR-124			
	sjDDX1 and sjPOLE2	Animal (mice) *in vivo* study (219)	Reduces hepatic egg number Decreases inflammatory cell infiltration
Sja-miR-125b and Sja-bantam			
	PROS1, CLMP, and FAM212B	Animal (mice) *in vitro* and animal (mice and rbits) *in vivo* study (220) (RAW264.7cells and NCTC clone 1,469 cells)	Increases macrophage proliferation and TNF-α production
Sja-miR-2162			
	TGFBR3	Human and animal (rats) *in vitro* and animal (mice) *in vivo* study (221) (LX-2 cells and HSC-T6 cells)	Pro-fibrotic

[a]CLMP, CXADR-like membrane protein; FAM212B, family with sequence similarity 212 member B; FOXO, forkhead box O; IL, interleukin; PROS, protein S; PTEN, phosphatase and tensin homolog; SFRP1, secretion of frizzled-related protein 1; sjDDX1, *S. japonicum* DEAD-box ATP-dependent RNA helicase 1; sjPOLE2, *S. japonicum* DNA polymerase 2 subunit 2; SMAD, *Drosophila* mother against decapentaplegic; STAT1, signal transducer and activation of transcription 1; TGFBR3, transforming growth factor beta regulator 3; TLR, toll-like receptor. TTP, tristetraprolin; VDR, vitamin D receptor; WASL, Wiskott-Aldrich syndrome protein.

of the pro-fibrosis miRNAs and/or induction of anti-fibrosis miRNAs could be explored for the prevention of hepatic fibrosis caused by *S. japonicum*. We describe other miRNAs that are not directly associated with fibrosis but are associated with *S. japonicum* infection in Table 8.

Several miRNAs have been explored clinically regarding the application of miRNAs as biomarkers for diagnosis or evaluation of *S. japonicum* infection (Table 8). For instance, miR-146a-5p and miR-150–5p isolated from the blood could moderately distinguish mild hepatic fibrosis (up to grade I) from severe (grades II and III), with AUC of 0.66, $P = 0.0005$ and 0.68, and $P < 0.0001$, respectively, in schistosomiasis caused by *S. japonicum* (216).

Function and characteristics of parasite-encoded miRNAs during parasitic infection

miRNAs are encoded by almost all eukaryotic parasites, including *Schistosoma* spp., *Clonorchis* species, *Fasciola* species, and *Echinococcus* species (229). However, neither miRNAs, Dicer, nor Argonaute proteins are encoded in the genome of *Plasmodium falciparum* (222, 230, 231). Parasite-encoded miRNAs can suppress host and parasite-encoded mRNA (229). These characteristics are similar to those of viral-encoded miRNAs, described in the viral section of this review.

One pertinent example in schistosomiasis caused by *S. japonicum* is the promotion of hepatic fibrosis by parasite-encoded miRNAs sja-miR-1 and sja-miR-2162, which are found in hepatic stellate cells (217, 221). Sja-miR-1 represses the secretion of frizzled-related protein 1 directly in hepatic stellate cells (217), which leads to the activation

of wingless and INT-1/β-catenin, a pro-fibrosis pathway (232, 233). Additionally, sja-miR-2162 directly inhibited transforming growth factor beta regulator 3 in hepatic stellate cells, providing negative feedback to allow for increased TGF-β signaling, which also promoted hepatic fibrosis (221). Thus, these miRNAs may be therapeutic targets. Inhibition of these miRNAs alleviated hepatic fibrosis caused by *S. japonicum* in a mouse model (217, 221). Moreover, sja-miR-124 might play an important role in this infection, but through targeting a gene in *S. japonicum* itself. Overexpression of sja-miR-124–3p in infected mice was found to reduce hepatic egg number, produce smaller egg liver granulomas, and diminish inflammatory cell infiltration (219). The target genes of sja-miR-124–3p are *S. japonicum* DEAD-box ATP-dependent RNA helicase 1 (*sjDDX1*) and DNA polymerase 2 subunit 2 (219). In addition, RNA interference-mediated sjDDX1 silencing in mice resulted in 24.6% worm reduction rate and 18.4% egg reduction rate (219). This reduction in egg number is significant as schistosome eggs induce the pathology caused by schistosomiasis (192). These findings suggest that sja-miR-124–3p can decrease the hepatic damage caused by *S. japonicum*.

We present other *S. japonicum*-encoded miRNAs with therapeutic potential in Table 8.

FUTURE DIRECTIONS OF miRNA

Although the human genome encodes 25,000 genes, it is estimated that only 600 disease-modifying protein drug targets exist (234), and only some proteins can be targeted or modulated by a drug molecule. Therefore, the focus of target selection has shifted to other macromolecules, such as RNAs (25). Recently, RNA-targeted therapy has been developed rapidly (25, 235). One of the miRNA modulation strategies is using anti-sense oligonucleotide agents such as miRNA mimics and miRNA inhibitors (25). miRNA mimics are double-stranded RNA molecules that imitate endogenous miRNA duplexes (236) and induce gene silencing in the same manner as miRNAs, thus resulting in the downregulation of the target protein (25). Furthermore, antimir oligonucleotides, which belong to miRNA inhibitors, are antisense-like oligonucleotide analogs of various types perfectly complementary to the mature miRNA guide strand. miRNA inhibitors (237), including antimir oligonucleotides, induce selective upregulation of one protein population by binding to and inhibiting the target miRNA (25). These techniques have been applied to the production of miRNA drugs, which is a term to define drugs targeting miRNAs. To date, 10 miRNA drugs for various diseases, including infectious diseases, have been in clinical trials (238). A major concern is that an miRNA has the potential to bind to off-target genes, as one miRNA generally has multiple target genes (238–240). Regarding the 10 miRNA drugs in clinical trials, the target genes of each miRNA drug ranged from 30 to 250 (238). Because of its toxicity, no miRNA drug has been used in phase 3 clinical trials and has been approved for clinical usage (238). Thus, the developing of drugs targeting miRNAs may be complex because miRNAs regulate many genes other than the main target gene. The development of target cell-specific and/or target gene-specific miRNA drugs may be required to minimize these concerns.

miRNAs have also been evaluated for their potential as biomarkers of infection, specifically for diagnostic purposes. Both host-encoded and viral-encoded miRNAs have been evaluated in clinical studies (44, 45, 102, 118, 128). Only 4 of the 19 studies (Tables 1 to 8) which evaluated miRNAs as biomarkers reported sensitivity and specificity (61, 119, 128, 129). Ideally, multiple large clinical cohort studies in different patient populations are required to assess the robust sensitivity and specificity in diagnosing a specific infectious disease. However, none of the four studies were large. Thus, sensitivity and specificity which are reliable in specific clinical settings, have yet to be reported in most of these previous studies.

Moreover, to our knowledge, a standard assay to measure an miRNA as a biomarker, including commercially available ones, has yet to be established. The data from the studies reviewed in this paper are mainly obtained from assays developed *de novo* by a research institution. In this context, validation of these or new standardized assays

in large multi-center cohort studies and/or prospective studies is needed to verify the effectiveness of these miRNAs as biomarkers.

To explore the use of miRNAs as potential biomarkers of disease, it is necessary to establish robust detection methods. Northern blots are the gold standard for detecting miRNAs. However, this method is time-consuming and cannot be used to detect trace amounts of miRNAs. Over the past decade, commonly used technologies such as next-generation sequencing (NGS), microarrays, and quantitative reverse transcription PCR (RT-qPCR), along with emerging technologies such as NanoString nCounter Platform, have been used to detect and quantify miRNAs (241, 242). NGS is widely used for both the identification and quantification of miRNAs, and it allows for detection of miRNAs present in very low quantities. However, it has the disadvantage of being relatively expensive (243). Microarrays are one of the most commonly used high-throughput method for detection of miRNAs. Microarrays detect miRNAs through hybridization of the miRNAs to the target probe. They are used to identify known miRNAs and have limited potential for identifying new miRNAs (244). In clinical laboratories, the most frequently used method for detection of specific miRNAs is RT-qPCR because equipment required to run the assays is widely available, and a wide variety of commercial kits exist for detection of miRNA using RT-qPCR (245). The NanoString nCounter system is a new technology that enables direct quantification of individual miRNAs without the need for amplification or reverse transcription (246). The ability to detect and quantify miRNAs without amplification allows it to provide absolute quantification, which reduce potential bias (247). However, this method requires specialized equipment which is not widely available.

Adding further complexity to the practical utility of using miRNA as a biomarker is the availability of other nucleic acid-based molecular targets. Direct comparisons between miRNAs and other established biomarkers, such as microbial cell-free DNA (mcfDNA) obtained from the blood or urine of patients, have yet to be investigated. While mcfDNA can be used to identify causative pathogens at the species level (through sequencing) (248), miRNAs cannot. However, mcfDNA may have less utility in cases of infection by RNA viruses that lack DNA (248). In these contexts, miRNAs may be able to supplement the knowledge gained from mcfDNA testing by providing additional information about the infection severity or treatment response.

CONCLUDING REMARKS

In summary, the role of miRNAs in infectious diseases is emerging rapidly. The miRNAs reviewed are related to immune function and have diagnostic, prognostic, and therapeutic potentials. Their diagnostic potential is largely untapped in infectious diseases where the current molecular diagnostic tool is not perfected or requires a constellation of other clinical criteria, such as invasive mold infections. Although a few miRNAs have been developed and translated into clinical trials, only one miRNA has been evaluated in infectious disease (miravirsen for HCV) (56). Since miRNAs are extensively incorporated into the pathogenesis of infections and immune response, further studies elucidating the mechanistic functions of miRNAs will permit the development of additional targeted therapeutics. Nevertheless, we are only at the beginning of discovering the full potential of miRNA diagnostics and therapeutics in infectious disease.

ACKNOWLEDGMENTS

The authors declare no conflicts of interest related to this study. The authors alone are responsible for the content and writing of this article.

S.H. conceived ideas for this review. M.K. and S.K. wrote the primary draft of the manuscript. W.G., J.F.C., and S.H. revised the manuscript. All the authors approved the final version of the manuscript.

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