Recent insights and perspectives into the role of the miRNA-29 family in innate immunity (Review)

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Abstract. Innate immunity is the first line of defence against pathogenic microorganisms and is nearly universal among eukaryotes. The innate immune system is composed of various organs, cells and immune molecules. MicroRNAs (miRs) are a class of small non-coding RNAs (~22 nucleotides) that are widely involved in post-transcriptional regulation of proteins within the innate immune system through the recognition of seed sequences. The present review summarizes the role of the miR-29 family in innate immunity, with a focus on its specific functions in the differentiation of T cells, B cells, natural killer cells and macrophages, as well as the mechanisms by which the miR-29 family participates in innate immune signalling. Additionally, this review discusses how the miR-29 family helps the host combat infections by hepatitis B and C viruses, human immunodeficiency virus and influenza A virus through the regulation of specific signalling molecules. This comprehensive analysis of existing studies emphasizes the importance of the miR-29 family in maintaining immune balance and defence against pathogens.

Contents

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1. Introduction

Innate immunity, also known as natural or non-specific immunity, is the first line of defence against pathogenic microorganisms and is nearly universal among eukaryotes. The innate immune system encompasses various organs, cells and molecules (1-5). Pathogen-associated molecular patterns are recognized by the pattern recognition receptors of immune cells, which subsequently triggers the nuclear translocation of transcription factors and initiates transcription of type I interferons and inflammatory cytokines, thereby activating the innate immune response (1,6). MicroRNAs (miRNAs/miRs) participate in the initiation and regulation of innate immunity (7,8).

miRNAs are small non-coding RNAs, ~22 nucleotides long, synthesized by RNA polymerase II and processed by Drosha and Dicer into double-stranded miRNAs with overhangs (9,10). These miRNAs compose a mature RNA-induced silencing complex by interacting with the Argonaute protein family, utilizing a seed sequence of 2-8 nucleotides at the 5' end to match complementary mRNA sequences (11). Since they were first accidentally discovered in nematodes, miRNAs are now recognized as key regulatory factors that form complex regulatory networks in various biological processes, especially cell development, differentiation and homeostasis (12,13).

Members of the miR-29 family (miR-29s) have emerged as critical modulators of various biological processes, particularly immune responses (8,14). In *Homo sapiens*, miR-29a, miR-29b and miR-29c share the same seed sequences, with only a few base differences, as miR-29b-1/miR-29a are encoded by chromosome 7q32 and miR-29b-2/miR-29c by 1q23. Despite different precursor sequences, the mature forms of miR-29b-1 and miR-29b-2 are identical. The sequence, organization and expression patterns of miR-29s are conserved in vertebrates (11,15,16). Notably, miR-29a predominantly localizes to the cytoplasm, whereas miR-29b and miR-29c are primarily nuclear, with miR-29b localized to the nucleus in certain cells due to a hexanucleotide sequence (AGUGUU), but not HCT116 colorectal carcinoma cells (15,17,18).

The present review summarizes the expression and regulation of miR-29 family members in innate immune processes, highlighting their role in influencing innate immune effector cell differentiation, participating in innate immune Toll-like receptor (TLR) signalling pathways and IFN signalling pathways, and responding to pathogens (viruses). Collectively, this demonstrates the regulatory role of miR-29s in innate immunity from multiple perspectives, offering novel insights into their potential mechanisms in other diseases, as well as their implications for disease diagnosis, prognosis and therapeutic approaches (19-21).

2. Roles of miR-29s in the differentiation of innate immune effector cells

Innate immune effector cells arise from hematopoietic stem cells in the bone marrow, and they have the capacity to differentiate into various immune cells with self-renewal capabilities (22). Initially, these cells differentiate into early immune precursor lymphoid and myeloid progenitors. Lymphoid progenitors evolve into B, T and natural killer (NK) cells, while myeloid progenitors differentiate into monocytes, including macrophages and dendritic cells, in addition to granulocytes, such as neutrophils, eosinophils and basophils. Environmental factors and cytokines play critical roles during cell differentiation. For instance, highly purified resting splenic T cells were induced to proliferate in a short term assay by IL-7 in the presence of the comitogen, while IL4I1 limits B cell receptor (BCR)-induced B cell proliferation in IL4-I1KO mice (23,24). Specific transcription factors also play crucial roles in the differentiation of T and myeloid cells (25,26). Antigen stimulation is essential for the maturation and further differentiation of T and B cells (27). T cells mature in the thymus and B cells in the bone marrow, further differentiating into effector cells upon encountering specific antigens. Differentiated immune cells release cytokines that initiate and regulate innate immunity to recognize and eliminate pathogens. For instance, plasmacytoid dendritic cells (pDCs) secrete IFNs, which induce the expression of a range of interferon-stimulated genes in neighbouring cells, thereby establishing an 'antiviral state' that enhances cellular resistance to viral infection (28-30). miR-29s play a critical regulatory role across various layers of the immune system by influencing the differentiation, proliferation and function of T cells, B cells, NK cells and macrophages, thereby maintaining the appropriateness and balance of immune responses. Dysregulation of miR-29s is closely associated with the development of multiple immune diseases and tumours, indicating its potential value in disease prevention and treatment (Table I).

T cells. In various T cell types, miR-29s play distinct regulatory roles, particularly by modulating different transcription factors and cytokines, thereby participating in the differentiation, maturation and functional regulation of T cell subsets (31,32). The importance of miRNAs in T cells was first noted in T cells with a Dicer deficiency, which displayed a preference for T helper (Th)1 polarization (33,34). Subsequent stages of immune function and development have confirmed the critical roles of miRNAs in T cells (7).

Upon antigen stimulation, thymic epithelial cells induce production of naive T cells, which then differentiate into various subtypes, most notably Th1 and Th2 cells (27). These cells are crucial for the regulation of immune responses to intracellular (Th1) and extracellular (Th2) attacks. A study published in 2011 revealed that miR-29a-deficient mice exhibit premature thymic involution and hypersensitivity to pathogen-associated signals, which is closely related to the direct targeting of interferon-α receptor (IFNαR) by miR-29a (35). Further studies reported that miR-29s are novel regulators of Th1 differentiation by targeting the transcription factors T-bet and EOMES of IFN-γ, thus influencing Th1 polarization (32,36-38).

miR-29s also play a critical role in the Th1 differentiation. In miRNA-deficient $CD4^+$ T cells, reduced expression of T-bet and EOMES, key transcription factors for T cell development, have been linked to the direct targeting of these factors by miR-29b (31,36,39). Additionally, miR-29s can target the IFN-γ mRNA and suppress the differentiation of Th1 cells. IFN-γ signalling can also promote the expression of miR-29s, forming a negative feedback loop that regulates IFN-γ expression (37). This suggests that miR-29b is essential for proper T cell maturation and function, and its dysregulation may impair immune responses.

Furthermore, miR-29s appear to play distinct roles in the differentiation and function of $CD8^+$ T cells, and are essential for the normal memory response of mature $CD8^+$ T cells; whereas cells deficient in miR-29s prompt the differentiation of naive $CD8^+$ T cells into short-lived effector cells with minimal stimulation, while simultaneously reducing differentiation of memory precursor effector cells (39).

NK cells. NK cells, a type of innate lymphocyte, are crucial for early host defences against infectious pathogens and have been used to monitor malignant transformation, including acute myeloid leukaemia and lymphomas (40-42). Similarly to T cells, miR-29b influences the maturation and function of NK cells by regulating key transcription factors, such as T-bet and EOMES, which are crucial for NK cell development. Dysregulation of miR-29b leads to the downregulation of these transcription factors, thereby impairing the normal development and function of NK cells. Particularly in leukemic mice, the direct targeting of T-bet and EOMES by miR-29b highlights its importance in maintaining NK cell homeostasis (43).

miR-29s are involved in maturation of NK cells through IFN-γ and related transcription factors, such as T-bet, EOMES and IFN-γ (43-45). Regulation of miR-29b has been shown to restore the population of intermediate $CD27^-CD11b^+$ NK cells *in vivo* (43). In acute myeloid leukaemia, activation of the aryl hydrocarbon receptor pathway upregulates miR-29b expression, which then inhibits the development and function of NK cells, thereby allowing evasion of the innate immune system in both mice and humans (46,47).

B cells. In cancer biology, the role of miR-29s in regulating cell cycle proteins has been noted in B-cell lymphoma, particularly mantle cell lymphoma (MCL). miR-29s target the 3'-UTR of CDK6 mRNA, inhibiting the expression of CDK6, a key regulator of cell proliferation (48). Downregulation of miR-29s in MCL leads to frequent overexpression of CDK6, contributing

Table I. Gene targets of miR-29s in the differentiation of innate immune cells.

Type of cell	Target	Function	(Refs.)
T cells	IFNαR	Raise the threshold for infection-associated thymic atrophy	(35,37,38)
	IFN-γ	Reduce Th1 differentiation	(32,85)
	T-bet, Eomes	Reduce Th1 differentiation; differentiate into short-lived effector cells with minimal stimulation	(31,36,39)
NK cells	bet, Eomes, IFN-γ	Restore intermediate $CD27^{-}CD11b^{+}$ NK cells *in vivo*	(43)
		Upregulation of miR-29b inhibits NK cell development in acute myeloid leukaemia	(46,47)
B cells	PTEN	Maintain B cell survival and proliferation	(51,52)
	AID	Regulate B cell survival and proliferation	(53)
	RAG1	Control B cell differentiation	(55,56)
Macrophages	NFIA, CD93, GPR85	Promote macrophage polarization to the M2 phenotype	(57)
	PI3K		(58)
	SOCS-1		(60,61)

miR, microRNA; IFN, interferon; IFNR, interferon receptor; SOCS-1, suppressor of cytokine signalling 1; T-bet, T-box expressed in T cell; Th1, T helper 1; NK, natural killer; AID, activation induced cytidine deaminase; RAG1, recombination activating 1; NFIA, nuclear factor 1 A-type; GPR85, G protein-coupled receptor 85.

to uncontrolled cell proliferation and the progression of the lymphoma (48). This highlights the tumour-suppressive role of miR-29s in preventing excessive cell growth in MCL. The use of a transgenic mouse model of chronic lymphocytic leukaemia (CLL) demonstrated that miR-29s play key roles in the production of B cells. In this model of overexpressing miR-29s in mouse B cells, 85% (34/40) of the mice exhibited an expanded $CD5^{+}$ B cell population, which is a hallmark of B-cell CLL (49). Subsequent studies have reported additional roles of miR-29s in B cell differentiation. The loss of miR-29ab1 leads to a global loss of cells in the spleen and thymus, which has profound effects on B cell differentiation (50). While mice deficient in miR-29a exhibit congenital defects in B cell activation and germinal centre formation (50).

Additionally, miR-29s have been found to regulate proliferation and apoptosis of mature B cells by targeting the PTEN mRNA, thereby controlling the PTEN-PI3K axis (51,52). ERK and MAPK are activated downstream in BCR signal transduction, which is crucial for the proliferation and survival of B cells during development and differentiation. Upon BCR engagement, miRNA-29s modulate the survival and proliferation of B cells through the NF-κB and RAS-MAPK signalling pathways (53,54). Moreover, miR-29c targets the RAG1 mRNA, which influences the variable, diversity and joining genes of pre-B cells, thereby controlling B cell differentiation (55,56).

Macrophages. Notably, miR-29s also play crucial roles in the differentiation of monocytes into macrophages and macrophage polarization. They regulate key transcription factors and signalling pathways to control monocyte differentiation, modulate macrophage subtype balance, and contribute to immune regulation and tissue repair. A study conducted in 2013 revealed that miR-29s facilitate the differentiation of monocytes into macrophages (57). Additionally, miR-29s can downregulate mRNA expression of nuclear factor 1 A-type (NFIA), CD93 and G protein-coupled receptor 85, potentially impacting differentiation of macrophage lineages. Moreover, miR-29s promote polarization of macrophages towards the M2 subtype. Further studies have shown that miR-29a mediates macrophage autophagy via the PI3K/AKT/mTOR pathway (58,59).

In inflammatory diseases such as atherosclerosis, miR-29s may alleviate inflammation and enhance anti-inflammatory effects by regulating macrophage polarization. miR-29a amplifies M2-like macrophage polarization and inhibits polarization of M1-like macrophages within atherosclerotic plaques. Additionally, suppressor of cytokine signalling 1 (SOCS-1), the target of miR-29a and a negative regulator of STAT6, appears to be crucial for macrophage polarization (60,61). Inhibition of the STAT6 pathway significantly suppresses polarization of macrophages into the M2 subtype, highlighting the complex regulatory roles of miR-29s in immune effector cell function and inflammation modulation.

3. Roles of miR-29s in the signalling of innate immunity

In innate immunity, miR-29s not only play a role in the differentiation of innate immune effector cells, but also in the signal transduction of the occurrence and development of innate immunity, the role of miR-29s is worth paying attention to (62). Innate immunity involves a complex and rapid signalling cascade, which starts from virus PAMP [such as lipopolysaccharides (LPS)] recognition by cell PRR (such as TLR and RLR) to cellular response measures such as the release of inflammatory factors, interferon and interferon stimulating factors. miR-29s are widely involved in the signalling cascade process. Next, the present review will systematically introduce miR-29s as a participant in classical innate immune signalling

pathways. Then the review will systematically introduce miR-29s as a participant in classical innate immune signalling pathways.

TLR signalling pathway. Toll-like receptors (TLRs) are pivotal in recognizing pathogen-associated molecular patterns (PAMPs), such as bacterial LPS and viral double-stranded RNA. This recognition activates signalling pathways that initiate immune responses, particularly through MyD88-dependent pathways, which drive inflammation (63,64). Although all TLRs can engage MyD88 to trigger inflammatory responses, they also elicit distinct immune responses tailored to different pathogens, thus bridging the innate and adaptive immunities (65,66). This process culminates in the activation of transcription factors, such as NF-κB, which promotes the expression of pro-inflammatory cytokines (63,66).

More and more findings have revealed that serum miR-29a can directly bind to TLR7 and TLR8, initiating the activation of dendritic cells and triggering the NF-κB pathway, which leads to the secretion of pro-inflammatory cytokines such as TNF-α and IL-6 (67,68). As TLR7 and TLR8 are key upstream components of the TLR signalling pathway, the interaction of miR-29a with these receptors places it at a critical juncture in immune activation (Fig. 1A).

miR-29s influence NF-κB signalling through various mechanisms. By inhibiting DNA methyltransferase (DNMT) activity, miR-29s promote the expression of cyclooxygenase-2 (COX2) and prostaglandin E2 (PGE2), which enhance NF-κB binding to the IFN-λ1 promoter, leading to increased IFN-λ1 expression. This highlights the involvement of miR-29s in both inflammation and antiviral responses (69,70).

Notably, miR-29s also target TNF receptor-associated factor 4 (TRAF4), a critical regulator in NF-κB signalling (71). This finding suggests that miR-29s downregulation in CLL can promote tumour progression by amplifying NF-κB activity through TRAF4. In macrophages, miR-29a promotes NF-κB activation by targeting Akt1, modulating the inflammatory response to bacterial LPS. This illustrates the role of miR-29a in regulating inflammation during bacterial infections (72-74).

In marine organisms, miR-29a also plays a role in immune regulation in marine organisms. In the pearl oyster, miR-29a targets the neuropeptide Y receptor type 2, resulting in the upregulation of IL-17 and NF-κB expression (75,76). This suggests that miR-29a can modulate immune responses in invertebrates, paralleling its role in vertebrates.

In the TLR signalling pathway, miR-29a regulates the immune-suppressive molecule B7-H3, which is highly expressed in tumours. By targeting the 3'UTR of B7-H3, miR-29a downregulates its expression, potentially enhancing the efficacy of immunotherapies for solid tumours (77-79). miR-29s influence the secretion of cytokines IL-12 and IL-23 in dendritic cells co-stimulated by NOD2 and TLR2, further emphasizing their broad role in immune modulation across various contexts (80).

IFN signalling pathway. The interferon (IFN) signalling pathway is a core component of the innate immune system, consisting of type I, II and III interferons, which plays critical roles in antiviral defence, immune regulation and cell cycle control (32,81,82). Upon binding to their specific receptors, interferons initiate the JAK-STAT signalling pathway, leading to the activation of transcription factors, particularly STATs, which subsequently induce the expression of interferon-stimulated genes (83,84). This process is essential for the proper execution of antiviral responses, immune regulation and the maintenance of homeostasis (Fig. 1B).

In immune responses, IFN-γ serves as a key factor in the differentiation of Th1 cells (36,37,85). Previous studies have shown that the expression levels of miR-29s are significantly downregulated in mice infected with Listeria monocytogenes or vaccinated with Bacillus Calmette-Guérin (32). miR-29s directly target IFN-γ mRNA, thereby suppressing IFN-γ production, which suggests that miR-29s play a crucial role in regulating Th1-mediated immune responses.

Furthermore, miR-29s exert regulatory effects at the interferon receptor level (35,86). For instance, miR-29a-deficient mice exhibit premature thymic involution and hypersensitivity to pathogen-associated signals, which is closely related to the direct targeting of interferon-α receptor (IFNAR) by miR-29a (35). Notably, in human host cells infected with respiratory syncytial virus (RSV), the RSV non-structural protein 1 (NS1) protein enhances miR-29a expression. Elevated miR-29a subsequently downregulates IFNAR1 expression, facilitating viral immune evasion (86).

At the downstream level of interferon signalling, several members of the JAK-STAT pathway are also regulated by miR-29s (60,87,88). In certain patients with oral cancer, elevated levels of miR-29a are observed in both cancer tissues and exosomes. miR-29a indirectly modulates STAT6 signalling by targeting the negative regulator SOCS-1, further influencing immune responses (60). In hepatocytes infected with hepatitis C virus (HCV), the downregulation of miR-29c increases the expression of its target gene, STAT3, contributing to antiviral effects (87). However, it is important to note that the upregulation of STAT3 is not solely due to miR-29c downregulation; factors such as the HCV core protein and oxidative stress also contribute to STAT3 induction.

These findings highlight that miR-29s play a critical role in the interferon signalling pathway at multiple levels, from interferon production and receptor regulation to downstream signalling.

4. Roles of miR-29s in innate immune responses against viral infections

Viruses are among the most common pathogens that trigger innate immunity, with viral RNA, DNA, spike proteins and other components serving as recognizable PAMPs. For miRNA, thymic deletion of Drosha results in reduced T lymphocytes, increased spontaneous secretion of inflammatory cytokines such as IFN-γ and IL-17A, and premature death in mice, while deletion of Dicer leads to embryonic lethality in mice (89-91). In the innate immune response, miR-29s are involved in the recognition of pathogens by innate immune cells and the release of immune factors and inflammatory mediators, which target pathogen mRNA, activate inflammatory response pathways, and induce of apoptosis and autophagy to rapidly clear pathogens and damaged host cells (92-94). During viral infections, dysregulation of miR-29s plays a dual role in modulating the proliferation of viruses by targeting both host and

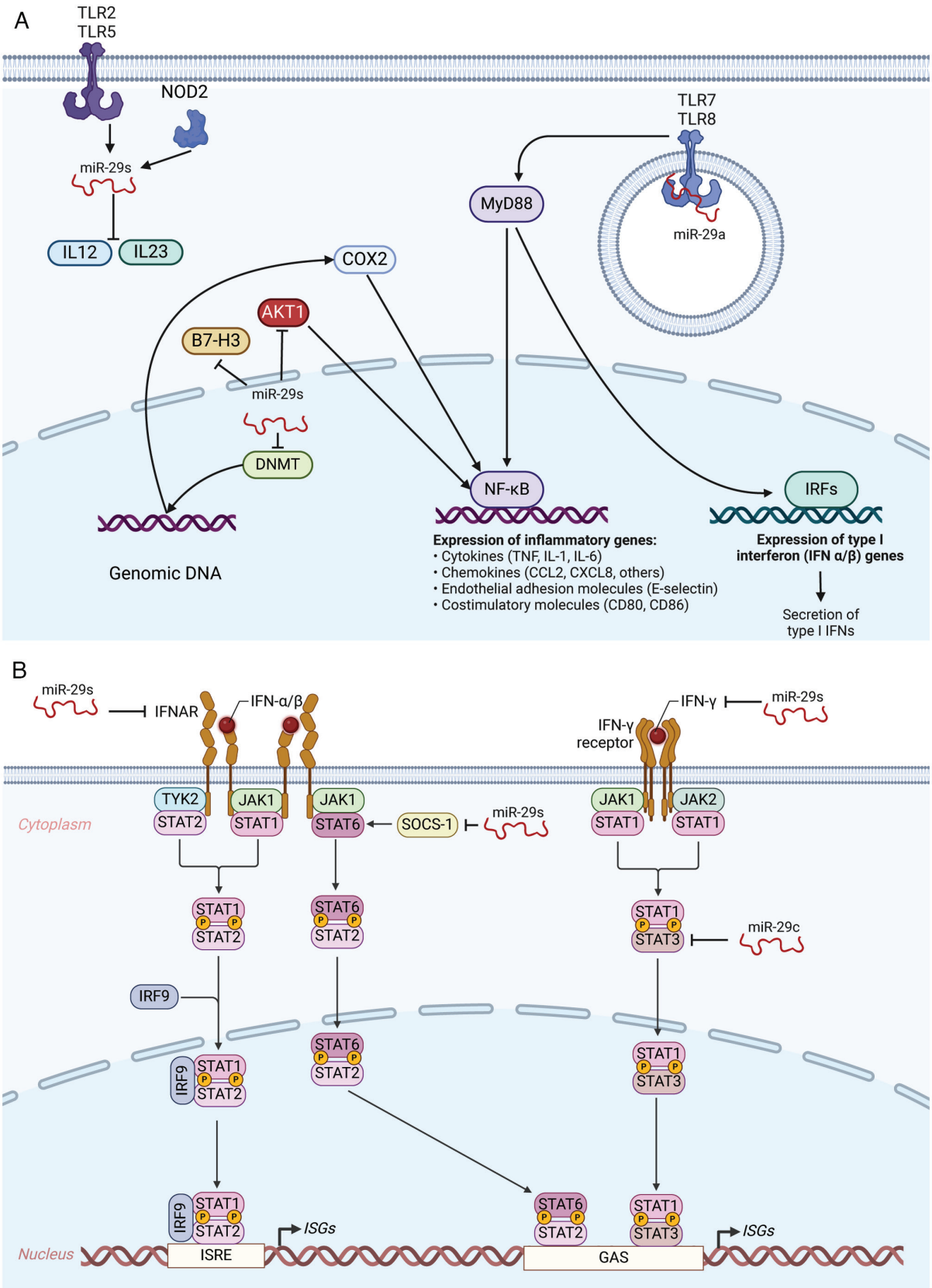

Figure 1. Mechanisms of miR-29s in the signalling of innate immunity. (A) Within the TLR signalling pathway, miR-29a interacts with TLR7 and TLR8, inhibiting the binding of MyD88 to TLR7/TLR8 and subsequent signal transduction. Additionally, miR-29s directly target and inhibit DNMT, B7-H3 and AKT1. The reduction of DNMT promotes the expression of COX2, which in turn facilitates the binding of NFκB to transcriptional genes. AKT1 binds directly to NFκB, enhancing the binding of NFκB to transcriptional genes. TLR2, TLR5 and NOD2 stimulate the formation of miR-29s, which can then directly target and reduce inflammatory cytokines such as IL12 and IL23. (B) Within the IFN signalling pathway, miR-29s directly target and reduce the translation of IFNαR and IFN-γ. Downstream of IFNR, miR-29s target the STAT6 inhibitor SOCS-1, increasing the levels of STAT6. Furthermore, miR-29c targets STAT3. miR, microRNA; TLR, Toll-like receptor; MyD88, DNMT, DNA methyltransferase; COX2, cyclooxygenase-2; NOD2, nucleotide binding oligomerization domain containing 2; IFN, interferon; IFNR, interferon receptor; SOCS-1, suppressor of cytokine signalling 1; P, phosphorus; ISRE, interferon stimulated response element; GAS, gamma-activated sequence.

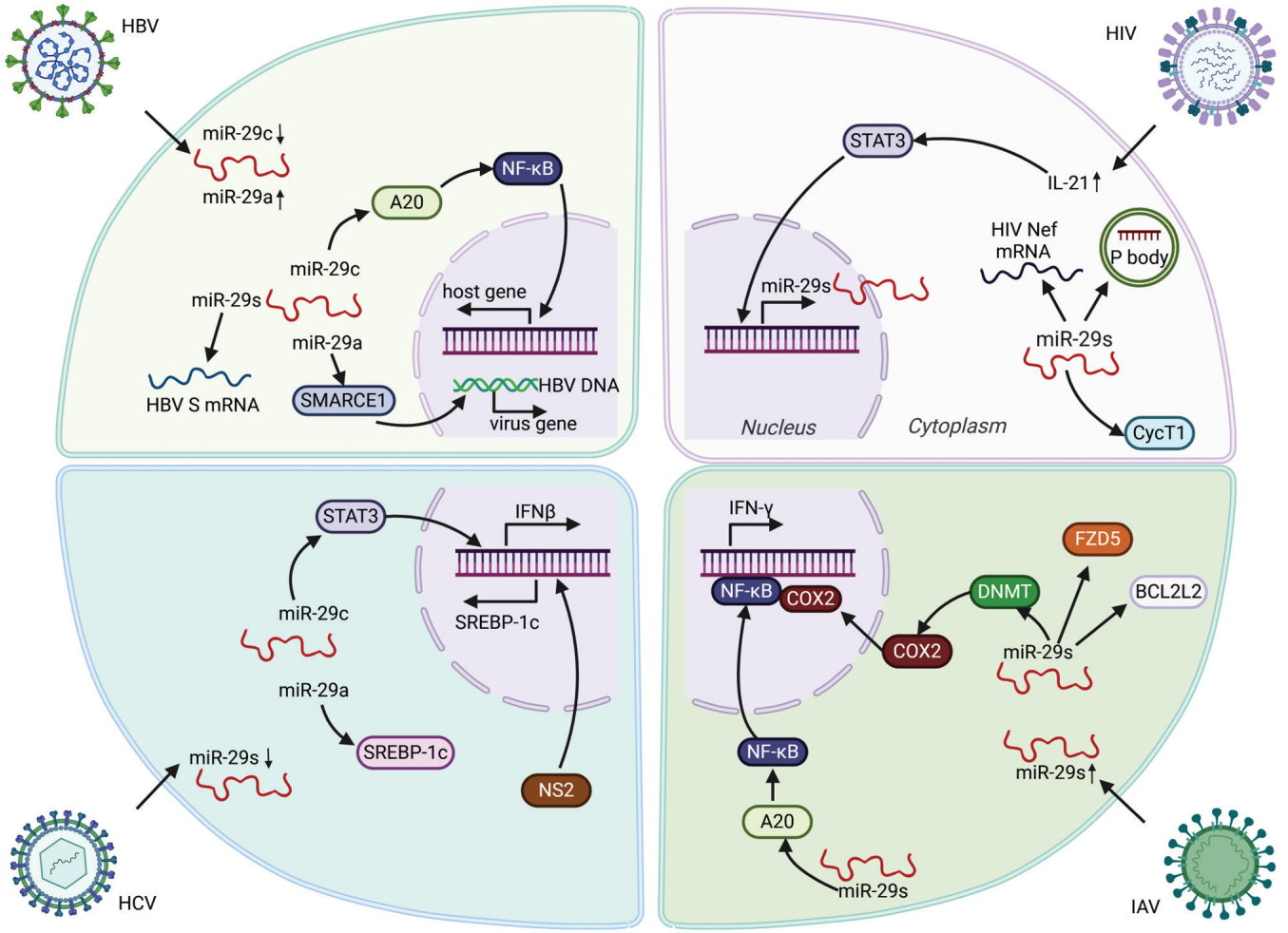

Figure 2. Mechanisms of miR-29s in viral infection. In HBV infection, miR-29c is downregulated while miR-29a is upregulated. Downregulation of miR-29c decreases targeting of A20, which increases transcription of host antiviral genes, whereas upregulation of miR-29a reduces viral gene transcription by targeting SMARCE1. In HIV infection, upregulation of IL-21 promotes the expression of miR-29s, which target the HIV Nef gene, facilitate P-body formation and target host genes to inhibit viral proliferation. In HCV infection, downregulation of miR-29s leads to the upregulation of host STAT3 and SREBP-1c. In IAV infection, upregulation of miR-29s stabilizes A20 mRNA, inhibits DNMT activity and regulates levels of BCL2L2 and FZD5. miR, microRNA; HBV, Hepatitis B virus; SMARCE1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1; HIV, Human immunodeficiency virus; SREBP-1c, sterol regulatory element-binding protein 1-c; IAV, influenza A virus; DNMT, DNA methyltransferase; FZD5, Frizzled-5.

viral genes during infection (Fig. 2). This activity can either promote or inhibit the proliferation of viruses, depending on the specific interactions and regulatory mechanisms involved.

Hepatitis B virus (HBV). HBV is a hepatotropic DNA virus that has been identified as a key risk factor for hepatocellular carcinoma (HCC) in epidemiological studies (95,96). As compared to controls, miR-29c is significantly downregulated in HBV-related HCC cell lines and HBV-infected transgenic mice. In HBV-infected HCC cells, miR-29c targets A20, a critical regulator of inflammation and immunity, thereby exerting a tumour-suppressive effect (97). In HepG2.2.15 cells, overexpression of miR-29c significantly inhibits HBV DNA replication, suppresses cell proliferation and induces apoptosis. In chronic HBV infection, serum levels of miR-29s are negatively correlated to the stage of liver fibrosis and necroinflammatory grading (98). In the context of HBV infection, miR-29c targets the HBV S gene and inhibits the expression level of S protein significantly in sperm embryos of patients with HBV (99).

Conversely, miR-29a expression is upregulated in HepG2.2.15 cells infected with HBV and directly regulates SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1 (SMARCE1) to promote HBV replication. SMARCE1 is known to inhibit HBV replication by binding to the core promoter of the virus (92,100). Moreover, high expression of miR-29a-5p (the passenger strand of miR-29a-3p) is significantly associated with shorter time to recurrence and overall survival of patients with HBV-related HCC after resection (101).

Human immunodeficiency virus (HIV). HIV is a single-stranded RNA virus that primarily targets $CD4^+$ T cells. As of 2022, ~39 million people globally were living with HIV (https://aidsinfo.unaids.org/). A growing body of research suggests that miRNAs, particularly miR-29a, inhibit HIV-1 replication both *in vivo* and *in vitro* (93,102-105). Both miR-29a and miR-29b directly target the HIV-1 Nef mRNA, thereby inhibiting translation of the Nef protein, a critical component of HIV (103). Additionally, miR-29a enhances

binding of HIV-1 gag mRNA to endogenous P-bodies, which facilitates mRNA degradation (104). IL-21 produced by $CD4^+$ T cells is a significant immune modulator and facilities the production of miR-29s during HIV infection through the STAT3 pathway. Serum levels of IL-21 are reduced in patients with HIV-1, suggesting that the IL-21-miR-29s axis may be involved in resistance to HIV-1 infection (102,106). However, during the latent period following HIV infection, which can be as brief as several months or up to 15 years, the virus is not cleared from the host cell. Mediation of RNA interference against HIV-1 by cellular miRNAs is limited. The extensive secondary structure of HIV RNA can resist binding by host miRNAs, thereby facilitating viral replication (107).

HCV. HCV, an RNA virus belonging to the *Flaviviridae* family, is a leading cause of chronic liver diseases and cirrhosis. In most patients with acute HCV infection, miR-29s are consistently downregulated. An *in vitro* study showed that levels of miR-29s were decreased in HCV-infected Huh7.5 cells, while overexpression of miR-29s reduced HCV RNA levels (94). The HCV NS2 protein has been linked to steatosis and increased transcription of the lipogenic transcription factor sterol regulatory element-binding protein 1-c (SREBP-1c). Targeting SREBP-1c by miR-29a contributes to lipid metabolism and inhibits HCV replication (108). Furthermore, downregulation of miR-29c in Huh7 cells infected with the HCV isolate JFH-1 was associated with upregulation of mRNA and protein expression of the transcription factor STAT3, which is directly targeted by miR-29c (87). This interaction enhanced the I-IFN pathway and suppressed viral replication.

Influenza A virus (IAV). IAV is an enveloped single-stranded negative-sense RNA virus that primarily targets respiratory epithelial cells, causing symptoms ranging from mild upper respiratory infections to severe pneumonia. The miR-29 family plays an antiviral role in IAV infection by targeting the 3'-UTR of BCL2L2 mRNA. BCL2L2 is an anti-apoptotic factor that inhibits translation and promotes IAV-mediated apoptosis of the host cell (109). Epigenetic modifications mediated by miR-29s have been reported in various diseases. Moreover, miR-29s can induce the expression of COX2 and PGE2 by inhibiting DNMT activity. COX2 enhances IFN-λ1 expression by facilitating the binding of NF-κB to enhancers in the IFN-λ1 promoter (69). Notably, inhibition of miR-29c significantly accelerates viral replication, while overexpression has no effect (110). Additionally, miR-29s target Frizzled-5, a positive regulator of the non-classical Wnt-Ca^{2+} signalling pathway, to inhibit IAV infection (111). Activation of the Wnt-Ca^{2+} pathway increases expression of IAV mRNA. During IAV infection, members of the miR-29 family, particularly miR-29c, are upregulated. Also, miR-29s enhance the abundance of A20, a negative regulator of the NF-κB signalling pathway, thus inhibiting RIP1-mediated NF-κB activation, thereby exerting an antiviral effect. Intriguingly, miR-29s can act as an RNA decoy to stabilize A20 mRNA independent of the seed sequence, prevent binding of human antigen R to the A20 3'-UTR and recruit the RNA-induced silencing complex, thereby protecting A20 mRNA (112).

In addition, changes in miR-29s have been reported during other viral infections. In COVID-19 infection, the levels of miR-29a exhibit significant variations at different stages of infection, although these changes differ across various studies (113,114). In patients recovering from Japanese encephalitis virus infection with sequelae, the expression level of miR-29b is significantly elevated (62,115). In the case of human T-lymphotropic virus 1 (HTLV-1), the upregulation of miR-29c in serum may serve as a novel potential biomarker for HTLV-1 diagnosis (116). Notably, in human host cells infected with RSV, the RSV NS1 protein enhances the expression of miR-29a. The subsequent elevation of miR-29a downregulates IFNAR1 expression, thereby facilitating viral immune evasion (86). Following Epstein-Barr virus infection, miR-29a is upregulated, which targets and reduces B-cell lymphoma and Burkitt's lymphoma levels (117). Apart from roles in viral infections in humans, miR-29s also exert antiviral effects in other animals. Porcine reproductive and respiratory syndrome virus (PRRSV), a positive-strand RNA virus of the *Arteriviridae* family, infects pigs. Transcript levels of miR-29a are increased in pig peripheral blood mononuclear cells following PRRSV infection both *in vitro* and *in vivo* (118). In the early stages of viral infection, miR-29ab might promote PRRSV replication through AKT3 (119). Bovine viral diarrhoea virus (BVDV) causes an endemic viral disease of cattle in North America and is considered a major pathogen worldwide. In Madin-Darby bovine kidney cells infected with BVDV strain NADL, miR-29b directly targets the 3'-UTR of genes associated with apoptosis (caspase-7 and NAIF1) and autophagy (ATG14 and ATG9A), thereby inhibiting BVDV replication. Additionally, during BVDV infection, decreased methylation of the promoter region of host miR-29b leads to upregulation of miR-29b expression and subsequent inhibition of BVDV replication (120-122).

The results of these studies emphasize the wide-range of antiviral effects of miR-29s in different animal models through multiple pathways, suggesting significant potential for therapeutic exploitation.

5. Roles of miR-29s in various diseases

Over the past 2 decades, the roles of miR-29s in various diseases have been extensively reported. In osteoarthritis, overexpression of miR-29b inhibits TGF-β1-induced SMAD2/3/4 signalling, thereby suppressing the initiation of chondrogenesis, while miR-29a/b directly targets COL1A1, which is essential for human chondrocyte differentiation (123-127). In osteoporosis, miR-29s act as positive regulators of osteoblast differentiation and mineralization of the extracellular matrix (128-130). In fibrotic diseases, miR-29s have been implicated in fibrosis of the heart, liver, lungs, kidneys and skin by upregulating the expression levels of proteins involved with the extracellular matrix (131-134). In most cancers, such as non-small cell lung cancer, glioblastomas, neuroblastomas and genitourinary tumours, miR-29s are generally downregulated. Moreover, miR-29s inhibit tumour invasion and proliferation by inhibiting translation of specific proteins and promote apoptosis of cancer cells by targeting various anti-apoptotic genes (135-137).

6. Discussion

The present review summarizes the roles of miR-29 family members in the differentiation of innate immune effector cells, innate immune signalling pathways and responses to pathogens, highlighting the multifaceted involvement of miR-29s in innate immunity. However, current studies primarily focus on the roles of miR-29s in individual signalling pathways, specific effector cells or single viruses, lacking comprehensive and multidimensional analysis. Looking ahead, it will be important to investigate whether the mechanisms of miR-29s in innate immunity are also relevant in other diseases and whether their target genes are shared across different pathological contexts. The non-targeting mechanisms of miR-29s, particularly the nuclear-specific accumulation of miR-29b, also warrant further exploration.

The subcellular distribution and abundance contribute to the functional diversity of miR-29s. For example, miR-29a is primarily located in the cytoplasm, while miR-29b exhibits a nuclear-cytoplasmic ratio of 4.45 in nasopharyngeal carcinoma (5-8F) cells. Although predominantly localized to the nucleus for regulation of specific genes, the overall abundance of miR-29c is relatively low (17). The abundances of miR-29a, b and c are significantly higher in $CD44^{hi}$ cells than $CD44^{low}$ cells, with miR-29a being more abundant than miR-29b and c, despite concurrent transcription of miR-29a with miR-29b-1 and miR-29c with miR-29b-2 (138). Thus, in innate immunity, the cellular distribution and concentration of miR-29 family members may influence disease onset and progression.

Alterations to miR-29s levels have been reported in patients with HBV-associated HCC, HCV-related cirrhosis and HIV/HCV co-infection, suggesting potential roles in various viral infections (139). Notably, miR-29s interact differently with the A20 protein during IAV and HBV infections, which may reflect the distinct biological characteristics of the viruses, as IAV is an RNA virus that targets respiratory cells, while HBV is a DNA virus that primarily infects liver cells (97,112). The variation in mechanisms regulated by miR-29s during these infections might be related to the intrinsic functions of the A20 protein, which serves as an anti-inflammatory ubiquitin-editing enzyme. These findings highlight the complexity of host cell responses to different viruses and underscores the need to consider both pathogen specificity and unique host responses for the development of antiviral therapies.

The antiviral effects and differentiation of immune cells mediated by miR-29s are predominantly due to RNA interference, with only a minimal role in transcriptional repression. However, it remains unclear whether miR-29s also exert non-canonical effects. For example, miR-328 can act as a decoy by binding to regulatory RNA-binding proteins, thereby preventing inhibition of mRNA translation (140). A previous study reported that nuclear miR-709 inhibits the maturation of miR-15a and miR-16-1 through direct interactions with primary transcripts (141). Furthermore, increasing evidence suggests that exosomal miR-29s also play various roles in disease onset and progression. For example, exosomal miR-29a alleviates systemic sclerosis and exosomal miR-29a derived from tumour-associated macrophages promotes proliferation and immune evasion of ovarian cancer cells (142). Hence, exosomal miR-29s can also serve as diagnostic and prognostic biomarkers of various diseases.

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Authors' contributions

XY conducted the literature review, organized and analysed the collected data, and was the major contributor in drafting the manuscript. JW provided assistance in reviewing and summarizing specific sections of the manuscript. SY and FY provided overall guidance on the structure and intellectual content of the review. SY contributed to the manuscript writing, particularly the discussion section, and was also involved in guiding the revisions of the manuscript. FY also critically revised the manuscript for important intellectual content and supervised the review development and finalization process. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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