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MircroRNAs in Innate Immunity; the Smart Regulatory Network

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ABSTRACT

MicroRNAs are regulatory elements at the post-transcriptional level that play a crucial role in all cellular and developmental processes. Numerous studies have demonstrated the substantial role of miRNAs in the development of immune cells, initiation of Toll-like receptors (TLRs) signaling, and production of cytokines in response to damaged-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). MiRNAs contribute to development and regulation of immune system and inflammatory processes by regulating the expression of specific genes. Cancer and autoimmune diseases can arise due to dysregulated expression of some miRNAs involved in innate immune processes. In this review, the key miRNAs influencing immune system response and inflammatory processes and their role in development of immune cells are discussed.

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Abbreviations

TLRs: Toll-like receptors; MyD88: Myeloid differentiation primary response 88; IRAK4: IL-1 receptor associated kinase 4; IRAK1/2: IL-1 receptor associated kinase ½; TRAF6: TNF receptor-associated factor 6; TAK1: Transforming growth factor-β-activated kinase-1; TAB2: Transforming growth factor-β-activated kinase 1 (TAK1)-binding protein 2; TAB3: Transforming growth factor-β-activated kinase 1 (TAK1)-binding protein 3; NF-κB : Nuclear factor kappa B; IKKα: inhibitory-κB kinase α; IKKβ: inhibitory-κB kinase β

Background

Any dysregulation in the immune system can cause disease or immune system dysfunction. Regulation of the immune system is a precise procedure in which many factors work together accurately. MiRNAs are small, single-stranded, non-coding RNA molecules containing 21–23 nucleotides. These molecules play a substantial role in gene expression and post-transcriptional regulation.

Innate immune system

The immune system is composed of innate and adaptive immune systems (1). The innate immune system serves as the primary defense barrier against pathogens (2). Innate immune cells, such as dendritic cells (DCs), natural killer (NK) cells, macrophages, and neutrophils recognize damaged-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs) (3). These PRRs include nucleotide-binding oligomerization domain-like receptors (NODs), C-type lectin receptors (CLRs), and Toll-like receptors (TLRs) (4). The structure of TLRs, the most well-known receptor in this category, comprises three domains: the extracellular domain, the Toll/interleukin-1 receptor (TIR) domain, and the transmembrane domain (5). Upon pathogen recognition by TLRs, several intracellular signaling pathways are activated. Two cascades are involved in this process: the MyD88-dependent pathway and the Toll/IL-1R domain-containing adaptor-inducing IFN-β (TRIF)-dependent pathway (6). Both pathways trigger nuclear factor kappa B (NF-κB) signaling, a critical component of the innate immune response (7). Innate immunity in epithelial cells and the regulatory roles of microRNAs and their interaction with TLRs on their surfaces are presented in the figure 1.

Functional activities of miRNA

MiRNAs have emerged as crucial regulatory elements of biological processes. They form intricate networks that regulate cellular differentiation, growth, homeostasis, and development (8-11). Dysregulation of miRNAs is associated with various diseases, particularly cancer (12). The binding of mature miRNAs to a seed region in the 3′UTR of mRNAs leads to the formation of a duplex (the base-pairing of six to eight nucleotides) at the 5′ end of the miRNA (13). This duplex facilitates the assembly of the RNA-induced silencing complex (RISC) with Argonaut 2 (Ago2), which triggers mRNA degradation, destabilization, or translation inhibition (14). A single miRNA can modulate the expression of multiple proteins by targeting several mRNAs. It is worth noting that a single mRNA sequence may contain seed regions for multiple miRNAs, potentially enabling the synergistic action of several miRNAs on protein production (15).

MiRNAs and immune system regulation

Numerous studies have highlighted that, miRNAs play a significant role in regulating immunological responses, including the development, maturation, activation, functioning, and differentiation of hematopoietic progenitor cells into either the lymphoid or myeloid lineages (16). MiRNAs have been shown to influence both innate and adaptive immune system regulation. The innate immune response, which serves as the trigger for inflammatory responses is also subjected to regulation by microRNAs (17, 18).

MiRNAs and innate immunity cells

MiRNAs play crucial roles in certain mechanisms associated with the development and function of myeloid cells. The processes governing the development and function of myeloid cells are among the most well characterized biological functions in terms of miRNA regulation. Here we highlighted some miRNAs that are involved in regulating these processes.

MiR 155 and miR 146a are key regulators in controlling the development of macrophages and immunity. miR 155 is significantly induced in macrophages and dendritic cells by NF κB and activator protein 1 (AP 1) in response to a broad range of TLRs and cytokine signal (19, 20).

MiR-233 has been introduced as the first miRNA that changes the fate of granulocytes and contributes to their differentiation (21). Additionally, the growth of NK cells is modulated by miR-181 through inducing notch signaling (22).

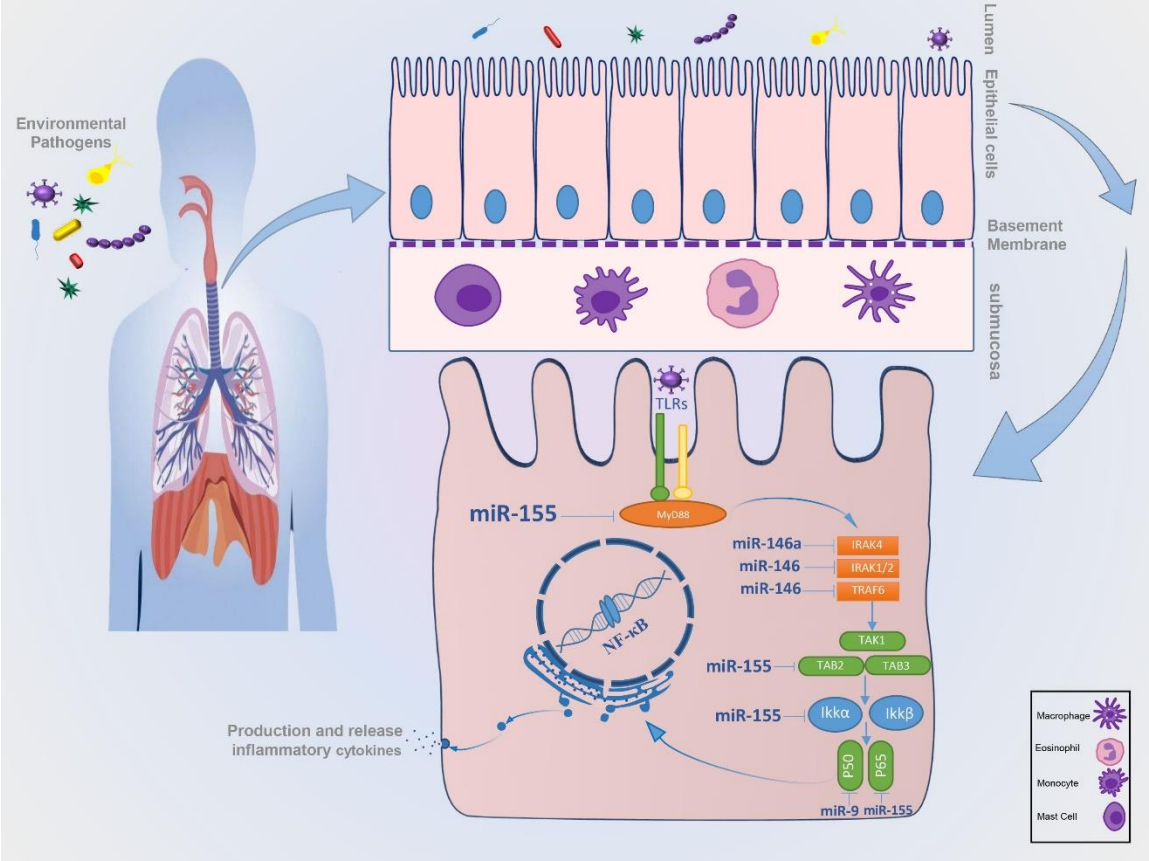

Figure 1. Innate immunity in epithelial cells and the regulatory roles of microRNAs. *TLRs on epithelial cells are activated by microbial stimuli (e.g., bacteria, viruses, and fungi). TLR activation establishes downstream signaling via the MyD88 adaptor molecule. On the other hand, involved IRAK4, IRAK1/2, and TRAF6, leading to the activation of TAK1, TAB2, and TAB3complexes. NF-κB signaling cascade is activated through IKKα, IKKβ, p50 and p56 and this induces expression of pro-inflammatory cytokines. Some miRNAs, such as miR-146a, miR-146, and miR-155, play critical roles in regulating immune response by targeting key components of the TLR signaling pathway. This regulation results in adjustment of inflammatory and immune responses. TLRs: Toll-like receptors; MyD88: Myeloid differentiation primary response 88; IRAK4: IL-1 receptor associated kinase 4; IRAK1/2: IL-1 receptor associated kinase ½; TRAF6: TNF receptor-associated factor 6; TAK1: Transforming growth factor-β-activated kinase-1; TAB2: Transforming growth factor-β-activated kinase 1 (TAK1)-binding protein 2; TAB3: Transforming growth factor-β-activated kinase 1 (TAK1)-binding protein 3; NF-κB : Nuclear factor kappa B; IKKα: inhibitory-κB kinase α; IKKβ: inhibitory-κB kinase β.*

Key miRNAs in innate immune system

MiRNAs have been demonstrated to regulate innate immune system and inflammatory responses, adaptive immune responses by controlling B and T cells' development. They also facilitate communication between immune system and local cells. They play a remarkable role in sustaining inflammatory reactions (23). Disruption of miRNA biogenesis through the removal of Dicer1, leading to reduced miRNA levels in macrophages, has been linked to decreased inflammatory cytokine production in response to innate immune activation by various TLR ligands. This highlights the essential role of certain miRNAs in shaping inflammatory responses (24). For instance, the expression levels of some miRNAs such as miR-21, miR-9, miR-146, miR-147, and miR-155 are upregulated during the infection-induced inflammatory responses in macrophages (25).

Moreover, mir-155, -146, -21, and -9 act as suppressors of TLR signaling by targeting the mRNAs of these genes at the posttranscriptional level (26). Here are some microRNAs that have substantial roles in regulating innate immune system.

MiR-146

MiR-146a is a critical regulator of various processes in the innate and adaptive immune systems, such as inflammation, differentiation, and the function of immune cells (25). NF-κB binds to the promoter of miR-146a to regulate its expression. Following the stimulation of TLRs, tumor necrosis factor receptors (TNFRs), IL1Rs, and receptor for advanced glycation end products (RAGE) are activated and both miR-146a and b are upregulated (24).

Genes like TNF receptor-associated factor 6 (TRAF6) and IL-1 receptor associated kinase 1 (IRAK1), which control TLRs and cytokine receptors are suppressed by miR-146. Consequently, the immune response is modulated by miR-146 (24).

MiR-155

TLR family can regulate miR-155 expression. Expression levels of miR-155 increases upon stimulation of TLR4, TLR8, and TLR9 (27, 28), while activation of TLR7 signaling inhibits miR-155 expression. Additionally, TLR3 signaling is modulated by miR-155 (29).

The MiR-155 is upregulated in TLR4/MyD88/NF-κB signaling pathway in the CD14+ monocytes that leads to the positive modulation of pro-inflammatory cytokines, oxidative stress, and proliferation rate in psoriasis patients (29). In addition, this microRNA plays a considerable role in regulating TLR signaling and the inflammatory response by targeting cytokine signal suppressor 1 (SOCS1), a negative regulator of TLR signaling (30). MiR-155 negatively regulates TLR signaling by targeting molecules such as TAB2, MyD88, IKKe, RIPK1, C/EBPb, eNOS, and NF-κB subunit p65, which are all involved in TLR signaling (24). In fibroblasts of synovial fluid in rheumatoid artritis, the expression of miR-155 is induced by TNF-α stimulation, which in turn inhibits IL-6-mediated JAK2/STAT3 activation (31).

MiR-223

MiR-223 serves as a crucial regulator of innate immune responses, controling myeloid differentiation and granulocyte functions (23). Upon activation of TLR9, binding of NF-κB to the miR-223 promoter is enhanced, leading to the upregulation of miR223. Conversely, miR-223 targets IκB kinase α expression, thereby reducing TLR9/NF-κB-mediated inflammation (32). Activation of innate immune responses and initiation of adaptive immunity require differentiation of monocytes into macrophages (33). During this process, the expression levels of miR-223, miR-15, and miR-16 decrease, a response induced by inflammatory stimuli like Phorbol 12-myristate 13-acetate (PMA) and bacterial lipopolysaccharides (LPS) (23).

Let-7

Certain studies have shown a connection between members of let-7 family and innate immune responses to the pathogenic infections and stress. Let-7 family members regulate TLR4 in order to modulate innate immune responses and level of inflammation in response to Pseudomonas aeruginosa or Helicobacter pylori infections (34-36). The activation of NF-κB and various genes involved in inflammation is controlled by TLR4. In addition, let-7 suppresses TLR4, thereby reducing innate immune response and inflammation during infection (37).

MiR-21

MiR-21 is one of crucial and significant regulators within the immune system. It negatively regulates TLR4 by targeting the pro-inflammatory tumor suppressor gene, PDCD4 (38). Furthermore, miR-21 plays a pivotal role in macrophage polarization (39). Circulating miR-21 can function as a ligand for TLR7 and TLR8 and then, subsequently leading to an increase in TNF-α and IL-6 production by macrophages (40).

MiR-9

MiR-9 is induced by TLR2, 4, 7, and 8, regulating the production of pro-inflammatory cytokines. It plays a key role in restoring homeostasis following immune activation through targeting NF-κB signaling (24). In the context of macrophage activation, CCL2 supports classical immune activation, where miR-9 downregulates Dusp6, potentially enhancing ERK-mediated signal transduction and leading to increased expression of proinflammatory genes (41). Furthermore, miR-9 targets JAK1 and inhibits the activation of the NLRP3 inflammasome in THP-1-derived macrophages (42). Thus, MiR-9 has dual functionality in both enhancing and suppressing innate immune responses.

MiRNAs in autoimmunity and infectious diseases

Considering the regulatory role of miRNAs in the innate immune system, the disorders of this system could be related to dysregulated expression of miRNAs (43). Due to their stability and abundance, miRNAs could be potential biomarkers for early diagnosing of cancer and cardiovascular disorders (44, 45). Some pathways including NF-κB dysregulation and interferon activation are involved in autoimmunity process (46).

Some animal and human studies have suggested that miRNAs may serve as a diagnostic biomarker or have therapeutic potential for infectious diseases and autoimmunity (47-50,51-53). MiRNAs have also be applied for evaluation of response to treatment in rheumatoid arthritis and Behcet disease (52,53) (tables 1 and 2).

Table 1. Animal studies indicating the role of miRNAs in infectious diseases and autoimmunity.

Animal model	MiRNA	Result	Year
Tuberculosis	miR-155	miR-155 up-regulated and key factor in immune response	2015 (47)
Zika virus Infection	miR-9	miR-9 up-regulated and induced microcephaly	2018 (48)
Keratitis induced by Fusarium solani	miR-223	MiR-223-3p regulates autophagy and and is associated with the inflammatory response	2022 (49)
Multiple sclerosis	Let-7	Let-7 directly target the cytokine receptors IL1R1 and IL23R, and negatively regulates Th17 cells differentiation	2019 (50)

MiRNA's therapeutic potential for different diseases

In the hippocampal tissue of rats with temporal lobe epilepsy (TLE), the expression levels of TNF-α and miR-155 are increased. Therefore, inhibition of the expression of miR-155 could prevent production of TNF-α (54).

In cystic fibrosis (CF), increased expression of miR-146a reduced the IL-6 production in macrophages, which could enhance the inflammatory responses of miRNAs in the macrophages. In particular, IL-6 production by CF macrophages in response to Lipopolysaccharide (LPS) stimulation appears to be the result of increased simultaneous of pro-inflammatory activities of miRNAs. This dysregulation leads to decreased or increased TLR signaling (55).

The association between the expressions of miR-451 and the IL-6R gene were investigated in RKO colon cancer cells and Hela cervical cancer cells. It was found that miR-451 reduced the expression of IL-6R mRNA and protein in these cells. miR-451 suppressed cancer cell growth and angiogenesis by reducing IL-6R gene expression (56).

Treatment of mice models of both acute hepatitis and NASH by miR-233 anolog (miR-223 3p) resulted in reducing of liver inflammation (57).

Injection of MRX34, a liposomal mimic of microRNA-34a (miR-34a), in combination with oral dexamethasone premedication was beneficial in patients with advanced solid tumors (58). Anti-miR-122 miravirsen found to be effective for treating patients with hepatitis C virus (HCV) (59).

Conclusion and Future Perspective

Numerous studies have highlighted the role of miRNAs in regulating inflammatory and immune responses. The question of whether inflammation triggers the expression of specific miRNAs or if dysregulation of miRNA expression initiates the inflammatory response remains unclear (60).

MiRNAs serve as valuable biomarkers for diagnosis due to their accessibility and high specificity (44,45). Several studies have explored the effects of miRNAs on molecular pathogenesis of various diseases by manipulating their expression levels. The expression of miR-146a and miR-155 plays a significant role in the repolarization mechanisms of M1 (TNF-α, IL-6) and M2 (MGL-1) macrophages, influencing the secretion of inflammatory factors. Inhibitors of miR-146a and miR-155 in human alveolar macrophages have been shown to increase TNF-α and IL-6 levels while decreasing mGluR-1 (MGL-1) expression in pneumonia patients compared to healthy individuals (61). Moreover, upregulation of miR-146 (via transfection of miR-146 mimics) led to a decrease in IL-6 and TNF-α expressions by disrupting the TLR4/ NF-κB signaling pathway, resulting in improved ovarian function in mice (62).

Table 2. Clinical studies indicating the role of miRNAs in autoimmunity and evaluation of response to treatment.

Disease	Medication	miRNA	Result	Year
Autoimmune Premature Ovarian Insufficiency	-	miR-21	Low expressions of miR-21 and Peli1 were detected in autoimmune POI mice model and patients.	2020 (51)
Rheumatoid Arthritis	Green tea extract	miR-125b miR-146a	miR-146a and miR-125 b expression levels could significantly predict clinical responses to green tea therapy.	2015 (52)
Behcet's Disease	Curcumin in nanocarrier	miRNA-181, miRNA-25 miRNA-326	Nanocurcumin supplementation decreased expression of miRNA-155, miRNA-181, miRNA-326 significantly and showed favorable effects in improving inflammatory factors and disease activity.	2022 (53)

MiR-21 has been shown to mitigate inflammation, cardiac dysfunction, and maladaptive remodeling post-myocardial infarction by targeting kelch repeat and BTB (POZ) domain containing 7 (KBTBD7) and inhibiting p38 and activation of NF-κB signaling (63).

Drawing from past and current research, miRNAs have been solidified as pivotal regulators of immune system and inflammatory processes. With an extensive comprehension of miRNAs functionality, there is a promising outlook for their utilization as biomarkers in both diagnosis and therapy in the near future.

Declaration

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Conflicts of interest/Competing interests

The authors declare no conflict of interest.

Authors' contributions

FT and HKA contributed to data collection and manuscript drafting. MH involved in reviewing, editing, and final approval. MV involved in conception, design, reviewing, and final approval of the manuscript. All authors approved the final version for submission.

Ethical Consideration

Not applicable.

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