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Regulation of innate receptor pathways by microRNAs

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The innate immune response provides the initial defense against infection. This is accomplished by families of pattern recognition receptors (PRRs) that bind to conserved molecules in bacteria, fungi and viruses. PRRs are finely regulated by elaborate mechanisms to ensure a beneficial outcome in response to foreign invaders. MicroRNAs (miRNAs) are a class of small non-coding regulatory RNAs that are emerging as important regulators in immune responses at the post-transcriptional level, through the inhibition of translation, or by inducing mRNA degradation. It has been shown that miRNAs have unique expression profiles in cells of the innate immune systems and play pivotal roles in regulating the signal pathways of innate receptors, including Toll-like receptors, RIG-I-like receptors and Nod-like receptors. We have summarized the recent literature providing new insights into the regulation of innate receptor pathways by miRNAs.

innate receptor, microRNA, immune regulation

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Germline-encoded pattern-recognition receptors (PRRs) are microbial sensors of the host innate immune system. They recognize components of foreign pathogens, referred to as pathogen-associated molecular patterns (PAMPs). Several families of PRRs have been characterized, including Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and Nod-like receptors (NLRs) [1]. At least 13 different TLRs (10 in humans and 13 in mice) have been identified [2]. All TLRs have an extracellular sensing leucine-rich repeat (LRR) domain, a transmembrane domain, and a highly conserved cytoplasmic Toll- and interleukin-1-(IL-1) receptor (TIR). PAMPs recognized by TLRs include three general categories of ligands: proteins; nucleic acids; and lipid-based elements derived from a wide range of microbes such as bacteria, viruses, parasites and fungi. Two additional families of innate receptors, RLRs and NLRs, have been described and join the TLRs as key pathogen sensors [3]. The RLR family contains RIG-I, MDA5, and LGP2 as memebers. These RLRs consist of two N-terminal caspase recruitment domains (CARDs), a central DEAD box helicase/ATPase domain, in addition to a C-terminal regulatory domain. RLRs recognize the double-stranded (ds) RNA generated as the replication intermediate of single-stranded (ss) RNA viruses, and the genomic RNA of dsRNA viruses [4]. NLRs are a group of intracellular microbial sensors that sense microbial products or the products of damaged cells, such as ATP and uric acid. NLRs are composed of a central nucleotide-binding domain and C-terminal leucine-rich repeats [5]. NLRs have been classified into four subfamilies with members such as NOD1, NOD2, NACHT, NALPs and IPAF. These PRRs have a critical role in both innate and adaptive immune responses [6].

Following the recognition of PAMPs, PRRs initiate innate immune responses by activating intracellular signaling cascades that lead to transcriptional expression of inflammatory mediators. These coordinate the elimination of pathogens and infected cells [7]. However, any dysregulation of this system leads to inflammatory diseases, autoim-

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mune diseases, or dissemination of pathogens. There is growing evidence to indicate that many molecules have been identified as positive or negative regulators of signaling for these innate receptors. For TLRs, these include membrane molecules (CD11b [8] and PECAM1 [9]), antigen presenting molecules (MHCI [10] and MHCII [11]), ubiquitin related proteins (Nrdp1 [12] and CHIP [13]), phosphatases (SHP-1 [14], SHP-2 [15], SHIP-1 [16] and PTP1B [17]), protein kinases (CaMKII [18]), endosome/lysosome-localized molecules (Rab7b [19,20], CLM [21]), a co-activator of gene transcription (β-catenin [22]), HSP70 [23], HSP70L1 [24], and NGF [25]. The regulation of RLR and NLR signal pathways has been extensively investigated recently [26,27]; however, the precise mechanisms of regulation remain to be fully elucidated.

MicroRNAs (miRNAs) are noncoding RNAs with pleiotropic effects that are dependent on post-transcriptional and translational regulation of gene expression. These miRNA-related effects are essential for organ development, cell differentiation, and tumor progression [28,29]. MiRNAs are short ssRNAs of about 22 nucleotides, which regulate the expression of target genes at the post-transcriptional level by binding to their 3′ untranslated regions (UTRs). Around 1000 miRNAs have been identified in the human genome; more than 30% of protein-coding genes are predicted to be regulated by miRNAs at the post-transcriptional and translational level as each miRNA can potentially target thousands of different mRNAs. The biogenesis of miRNAs involves two processing steps by two RNaseIII enzymes, Drosha and Dicer. This then results in repression by translational inhibition, mRNA cleavage, and mRNA decay initiated by miRNA-guided deadenylation [30]. An accumulation of evidence has shown that miRNAs are involved in PRR signaling of the innate immune system. In this review, we aim to provide an overview of the regulation of innate receptor pathways by miRNAs, and how miRNAs can be used in the development of therapeutics against immune diseases.

1 Regulation of TLR pathways by miRNAs

Following ligand binding, TLRs initiate innate immune responses by activating downstream intracellular signaling pathways via the adaptor MyD88 or the adaptor TRIF. This induces the production of proinflammatory cytokines and type I interferon [31]. Many signal molecules, such as adaptor proteins and kinases, transcriptional factors, regulatory molecules, and inflammatory cytokines in the TLR signal pathway are identified to be likely targets of miRNAs, especially the TLR-induced miRNAs [32].

TLRs mainly signal through the MyD88-dependent pathway, which is responsible for the production of proinflammatory cytokines, and the TRIF-dependent pathway, leading to the anti-viral effects of TLRs. Previous reports have shown that tolerance is established and sustained by the activities of miR-146a, -155, -145, -346, -223 and -199a, which are known to target key adaptors and kinases of the TLR signaling pathway. The miR-146 family is composed of two members, miR-146a and miR-146b. MiR-146a is one of the most prominent miRNAs induced by TLR signals through NF-κB activation, and then feeds back to suppress TLR-triggered NF-κB activation [33]. Like miR-146a, miR-155 is known to target the TAK1-binding protein 2 (TAB2), inhibiting the activation of TAK1, and hence NF-κB and MAPK, thereby acting as an anti-inflammatory agent [34]. Significant targets of miR-155 include IKKε, FADD and RIP-1 [35]. The MyD88 adaptor-like protein (MAL), which functions as a bridging adaptor for TLR2- and TLR4-mediated MyD88-dependent signaling and undergoes proteasomal degradation following TLR2 and TLR4 stimulation, has emerged as a target of miR-145 [36]. Bruton's tyrosine kinase (BTK) participates in the TLR4, TLR7–TLR8 and TLR9 signaling pathways required for NF-κB activation, and it has recently been shown that miR-346 is strongly induced by treatment with lipopolysaccharides (LPS). miR-346 has been shown to target Btk mRNA in synovial fibroblasts (FLS) of rheumatoid arthritis (RA) patients. Whether miR-346 in macrophages targets Btk mRNA needs to be further studied [37]. In macrophages, a decrease in miR-15a, -16, and -223 expression levels has been shown to correlate with an increase in IKKα protein expression, suggesting that these miRNAs could function as modulators of IKKα mRNA and protein expression [38]. Chen R et al. identified miR-199a as a regulator of IKKβ which is a major factor promoting a functional TLR-MyD88-NF-κB pathway to constitutively secrete proinflammatory/protumor cytokines [39]. A link between dysregulation of miRNAs and human brain disorders has become increasingly evident [40,41]. Recently, extracellular let-7 has been shown to activate the RNA-sensing TLR7 and induce neurodegeneration [42].

The stimulation of TLRs delivers signals through adaptor molecules and kinases. Ultimately, activation of certain transcription factors in the nucleus is the key step to triggering target gene transcription. Targeting of transcription factors by miRNAs possibly has an impact on TLR-induced gene expression [43]. The most important transcription factor of the TLR signaling pathway, NF-κB, is present in the cytoplasm, in an inactive form, and is trapped by an inhibitor of NF-κB (IκB) proteins. Phosphorylation targets IκBs for ubiquitination and degradation, allowing NF-κB to be released into the nucleus and to bind to a response element, which starts transcription of the target genes. MiR-9, the TLR-responsive miRNA in the MyD88- and NF-κB-dependent pathways, is shown to directly target Nfkb1 mRNA and then control the NF-κB responses by feedback [44]. More recently, miR-210 has been shown to be induced by LPS and target Nfkb1 mRNA [45]. The signal transduc-

tion and activator of transcription (STAT)-mediated feedback loop amplifies signaling by cytokines, and enhances macrophage responses to microbial inducers like TLR ligands [46]. The expression of STAT3 is found to be modulated by both miR-17-5p and miR-20a, suggesting that miRNAs could potentially be used for immunotherapy against diseases by blocking STAT3 expression [47]. Peroxisome proliferator-activated receptor γ (PPARγ) belongs to the nuclear hormone receptor superfamily of ligand-activated transcription factors and originally has been characterized to be an important therapeutic target of chronic inflammatory diseases. Jennewein et al. recently provided evidence that LPS-induced miR-27b contributes to destabilization of PPARγ1 mRNA, suggesting that decreased PPARγ expression by miRNAs prolongs inflammation, thereby attenuating resolution of inflammation [48]. Moreover, the transcriptional co-repressor C/EBPβ is shown to be targeted by miR-155, and the transcriptional co-activator p300 is targeted by miR-132 [49,50].

In addition to directly regulating adaptor molecules and kinases, as well as transcription factors of the TLR signaling pathway, it is increasingly apparent that miRNAs can target the regulators of TLR signaling. MiR-21 is expressed in numerous cancers and has been well established as an 'onco-miR'. Furthermore, miR-21 is implicated as a central player in the inflammatory response. The tumor suppressor protein programmed cell death 4 (PDCD4), an inhibitor of translation by targeting eukaryotic translation-initiation factor 4F (EIF4F), which is required for the initiation of translation at the 5′ UTR of mRNA sequences, has been recently identified to be a key target of miR-21 during TLR4 signaling in macrophages [51]. Iliopoulos et al. found that miR-21 targets the PTEN tumor suppressor gene that functions through the Akt pathway, further underlining the significance of miR-21 in inflammation and cancer [52]. Notch1 has also been identified as a target of miR-146a in studies of the miR-146a–mediated repression of IL-12p70 production in TLR9-triggered DCs [53]. O'Connell et al. showed that Src homology-2 domain-containing inositol 5-phosphatase 1 (SHIP1) is a direct target of miR-155, and the repression of endogenous SHIP1 by miR-155 results in increased activation of the kinase Akt during the cellular response to LPS [54].

Activation of TLRs leads to the induction of inflammatory cytokines such as TNF, IL-6, IL-12, and IL-10, and chemokines such as MCP-1, MIP-1α, IP-10 and RANTES [55,56], thereby linking the innate and adaptive immune systems. Several miRNAs, such as miR-221, miR-125b and miR-939 have been found to target the 3′ UTR of TNF-α mRNA during LPS tolerance [57,58]. Recently, miR-365, miR-142-3p and let-7 were found to target Il6 mRNA, and reduced endotoxin-induced mortality. Lu et al. identified mIL-12p35 as a molecular target of miR-21, which probably contributes to polarization of T helper (T_h) cells, suggesting a key role for miRNAs in allergic lung inflammation [59]. More recently, miR-466l has been shown to up-regulate IL-10 expression in TLR-triggered macrophages [60]. Ma et al. found that miR-29 suppresses immune responses to intracellular pathogens by directly targeting IFN-γ [61].

2 Regulation of RLR pathways by miRNAs

The RLR sensors recognize the genetic material of RNA viruses in the cytoplasm of infected cells and induce inflammatory cytokines and type I interferons. Upon recognition, conformational changes within these sensors exposing the CARD domains of RIG-I and MDA5 are induced. They then then interact with the CARD-containing adaptor protein, IPS-1. IPS-1 localizes to the mitochondria and is required for downstream signaling to activate IKK-related kinases, TBK1/IKKi, which then activates IRF3/IRF7 and the subsequent transcription of type I interferons via TRAF3. Upon recruitment, IPS-1 also activates NF-κB through recruitment of TRADD, FADD, caspase-8, and caspase-10 [4].

Several miRNAs can be induced by RIG-I signaling, and regulate viral replication through modulating the RIG-I pathway and the expression of type I interferon. miR-146a has been shown to regulate vesicular stomatitis virus (VSV) infection-triggered type I IFN production by negatively feeding back and targeting TRAF6, IRAK1 and IRAK2 [62]. The stimulator of IFN genes (STING) protein is a recently discovered adaptor protein that functions downstream of RIG-I and upstream of TBK1 and plays an important role in IFN-β production. Huang et al. found that endogenous STING could be regulated post-transcriptionally by miR-24 in IEC-6 cells [63]. Interferon-α (IFN-α) is a critical molecular mediator of pathogen-induced immune responses [64]. Recently, miR-466l has been demonstrated to directly target IFN-α expression through the 3′ UTR, and inhibit host antiviral innate immune responses in Sendai virus (SeV)- and VSV-infected macrophages and dendritic cells [65]. Li et al. recently found that miR-122 facilitates replication of hepatitis C virus (HCV) RNA and may partly counteract the anti-HCV effect of IFN-α [66]. MiR-29a has recently been identified to be critical for diminishing the sensitivity of the thymic epithelium in stimulating infection signals, protecting the thymus against inappropriate involution via miR-29a-mediated suppression of the IFN-α receptor [67]. Furthermore, using an in-depth analysis of miRNomes in resting and IFN-α-activated human natural killer (NK) cells, two abundant miRNAs (miR-378 and miR-30e) have been shown to be suppressed by IFN-α activation. They then directly target granzyme B and perforin [68].

Some viral miRNAs can regulate viral and/or host cell

gene expression. MiR-H2-3p, expressed by herpes simplex virus 1 (HSV-1), is now known to affect ICP0, a viral immediate-early transcriptional activator thought to play a key role in productive HSV-1 replication and reactivation from latency [69]. Liang et al. have recently found that miR-K12-11, encoded by Kaposi's sarcoma-associated herpesvirus (KSHV) is critical for the modulation of IFN signaling and contributes to maintenance of KSHV latency by targeting IKKε [70].

3 Regulation of NLR pathways by miRNAs

Ligation of NOD1 or NOD2 with related ligands activates MAPK- and NF-κB-signaling cascades, leading to the production of proinflammatory cytokines and chemokines. Other NLRs are involved in the assembly and activation of inflammasomes, which control the activation of caspase-1, and subsequent processing of IL-1β and IL-18 [71]. Haneklaus et al. identified that a highly conserved miR-223 targets the site of the NLRP3 3′ UTR and prevents accumulation of NLRP3 protein, and inhibits IL-1β production from the inflammasome. Furthermore, Epstein-Barr virus (EBV) can also take advantage of miR-BART15 to limit inflammation [72]. Bauernfeind et al. also found that miR-223 functions to control NLRP3 inflammasome activity [73]. It is possible there may be other miRNAs involved in the regulation of NLR pathways, but this requires further investigation.

4 Conclusion and perspective

The goal of inflammation is to resolve an injury and return the immune system to homeostasis. Many studies have focused on cellular and molecular networks that regulate inflammation, and recent breakthroughs have been made in understanding the roles of miRNAs in innate immunity. These miRNAs regulate innate receptor signaling pathways and ensuing cytokine responses at multiple epigenetic levels. Although the study of miRNAs has opened up many new areas in the regulation of innate receptor signaling, the mechanistic insight into the precise effects of miRNAs on TLR-, RLR- and NLR-mediated inflammatory responses are still lacking. In particular, how these miRNA networks collaborate together to optimize immune responses requires further elucidation. Future studies will illuminate the link between changes in miRNA levels and the onset of human inflammatory diseases. It is hoped this will lead to using miRNAs in diagnostics and therapeutics for the treatment of inflammatory diseases, autoimmunity, and cancers [74,75].

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