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MicroRNAs Regulate Dendritic Cell Differentiation and Function

Marian L. Turner, Frauke M. Schnorfeil, and Thomas Brocker

MicroRNAs (miRNAs) are an important class of cellular regulators that modulate gene expression and thereby influence cell fate and function. In the immune system, miRNAs act at checkpoints during hematopoietic development and cell subset differentiation, they modulate effector cell function, and they are implicated in the maintenance of homeostasis. Dendritic cells (DCs), the professional APCs involved in the coordination of adaptive immune responses, are also regulated by miRNAs. Some DC-relevant miRNAs, including miR-155 and miR-146a, are shared with other immune cells, whereas others have been newly identified. In this review, we summarize the current understanding of where miRNAs are active during DC development from myeloid precursors and differentiation into specialized subsets, and which miRNAs play roles in DC function. The Journal of Immunology, 2011, 187: 3911–3917.

MicroRNAs (miRNAs) are an evolutionarily ancient class of endogenous small noncoding RNAs that posttranscriptionally regulate gene expression by binding to target mRNAs, thereby inhibiting their translation. Since the discovery of miRNAs less than two decades ago, hundreds have now been identified in mammals, and many of them are conserved across species. miRNAs are essential for development (1), and multiple examples of miRNA dysregulation leading to oncogenesis implicate miRNAs in the maintenance of homeostasis (2).

The generation of miRNAs proceeds via a specialized pathway involving the RNase Dicer that produces RNA duplexes of ∼21 bp in length, the mature miRNA (3). miRNA binding to target mRNAs silences gene expression by mRNA degradation or translational repression (4, 5). Gene expression regulation achieved by miRNAs is complex: >60% of all human protein coding genes are predicted to contain miRNA binding sites in their 3′ untranslated region (3′UTR) (6). Expression profiling has shown that distinct cell types express unique miRNA profiles, with changing patterns during cellular differentiation and malignant transformation (7). The degree of silencing achieved by an individual miRNA is relatively modest, leading to the idea that miRNAs fine-tune gene expression (5, 8). However, each miRNA may control the expression of hundreds of target genes (6), and miRNAs may have multiple miRNA binding sites, such that different miRNAs may regulate target genes coordinately or synergistically (9, 10). Furthermore, some of the primary gene targets of miRNAs are transcription factors, rendering miRNAs regulators of the regulators, or “micromanagers” (5). Importantly, in contrast to regulation by transcription factors, miRNAs are especially capable of inducing rapid changes in gene expression, which is of particular relevance during cellular responses to environmental cues (11).

More than 100 miRNAs are selectively expressed in cells of the adaptive and innate immune systems (12), and miRNAs are known to modulate hematopoietic lineage commitment (13). Multiple transgenic mouse strains have been made in which Dicer, an enzyme required for miRNA production, is specifically deleted in various cell types, thereby allowing analysis of the effect of loss of functional miRNAs. In the absence of Dicer, defective homeostasis and function have been observed in various T cell subsets (14-16), NK cells (17), and B cells (18). Functions of specific miRNAs in immune cells have also been documented. For example, loss of miR-155 leads to impaired responses to pathogens or immunization due to inhibited germinal center responses and altered Th cell subset polarization (19–21), whereas miR-181a regulates TCR signal transduction sensitivity (22, 23). Several miRNAs have been implicated in innate inflammatory responses, including miR-146a, miR-132, and miR-155, which are upregulated in monocytes in response to TLR activation (24). The role of miRNAs in lymphocyte and myeloid cell biology has been reviewed elsewhere (including 8, 25–27). Therefore, we will focus in this review on dendritic cells (DCs).

Some miRNAs are active in multiple immune cells, whereas for other miRNAs functions have been described in DCs only. DCs are cells of the myeloid lineage that are specialized in the uptake and presentation of Ags and, consequently, in the induction of adaptive immune responses via B and T cells. DC development proceeds from common myeloid progenitors in the bone marrow (BM), where common DC progenitors form.

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Abbreviations used in this article: BM, bone marrow; GSK3α/β, glycogen synthase kinase 3α/β; GRKs, G protein-coupled receptor kinases; iDC, immature DC; miRNA, microRNA; mDC, monocyte-derived DC; miRNA, microRNA; pDC, plasmacytoid DC; SOCS-1, suppressor of cytokine signaling 1; 3′UTR, 3′ untranslated region.

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Upon leaving the BM, multiple subsets of DCs develop, which differ depending on their location, migratory capacity, phenotype, and function. A current classification system (28, 29) suggests that there are at least five types of DCs, as follows: two distinct types of conventional DCs (cDCs), CD11b+-like and CD8α+-like, which are specialized in priming of CD4+ and CD8+ T cells, respectively; skin-resident Langerhans cells (LCs), which are thought to have immunoregulatory functions; plasmacytoid DCs (pDCs), which specialize in antiviral defense via IFN-α/β production; and monocyte-derived inflammatory DCs, which are induced in response to infections and possess microbicidal activity. In this review, we describe how miRNAs regulate branch points during DC development and differentiation and how miRNAs influence the inflammatory capacity of DCs by tuning mature DC function.

How important are miRNAs in DCs?

Mutations in Dicer are associated with multiple human malignancies, including ovarian and lung cancers (30, 31). In mice, knocking out Dicer specifically in various immune cells has shown that the generation of T, B, and NK cells is impaired in the absence of the enzyme, implying that miRNAs are crucial for the development of these cells. However, a DC-specific (CD11c-driven) knockout of Dicer showed no apparent immune phenotype and only slightly reduced miRNA levels in splenic and lymph node cDCs (32). Given that the average miRNA 1/2 of several weeks in mice, showed increased turnover of DCs, however, which have a 1/2 of several weeks in mice, showed increased turnover and apoptosis, altered surface receptor expression, and a block in the maturation process when lacking Dicer, which rendered them unable to efficiently prime CD4+ T cells (32). Thus, although future attempts to study the global effect of loss of miRNAs in DCs would require an approach other than eliminating Dicer action, the observations in LCs suggest that miRNAs are critical for DC homeostasis and the hallmark Ag presentation and costimulation functions of DCs. The following sections describe specific aspects of DC development and function that are regulated by miRNAs, and these miRNAs are summarized in Table I and Fig. 1.

miRNA expression patterns in DCs

A common approach to identifying potential roles of miRNAs is to first characterize the expression levels of miRNAs in cells of interest and then assess whether the absence or overexpression of these miRNAs alters cell function. Multiple studies have performed miRNA expression profiling at various stages of DC development and differentiation. Two studies investigated differences in miRNA expression in human monocytes and monocytes differentiated in vitro into immature DCs (34, 35), and several overlapping miRNAs were identified in both studies, including miR-25, miR-93, miR-106a, and miR-106b in monocytes, and miR-21, miR-342, and miR-422b in immature DCs. Lu et al. (35) extended their analysis by activating DCs to induce maturation, and three other comparative profiles of human immature and mature DCs have been performed (36–38). Expression of miR-155 and miR-146a was associated with maturation in all four studies. However, the profiles also revealed multiple nonoverlapping miRNAs. miRNA expression profiles have also been reported from human cord blood hematopoietic progenitor cells differentiated into interstitial DCs or LCs in vitro (39) and on murine BM-derived DCs differentiated into pDCs and cDCs (40). Many of the specific miRNAs that act during DC development, differentiation, and function, as described in this review, were identified following these expression profile analyses.

miRNA regulation of DC development

Notch/Wnt signaling is important in DC development (41), and this pathway can be influenced by miRNA action. Hashimi et al. (34) analyzed miRNA expression profiles in human monocyte-derived DCs (MDDC) over multiple days of differentiation and identified miR-21 and miR-34a as being of interest. Treatment of monocytes with miR-21 or miR-34a inhibitors partially stalled MDDC differentiation, an effect that was enhanced upon inhibition of both miRNAs. Target gene analysis revealed miR-21 and miR-34a to coordinately regulate expression of the genes WNT1 (coding for the Wnt-1) and JAG1 (coding for the Notch ligand Jagged-1). Importantly, whereas mRNA expression of WNT1 and JAG1 was found to increase during MDDC differentiation, protein

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Table I. Summary of the miRNAs involved in regulating DC differentiation and function, as discussed in the text

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Verified Targets in DCs</th>
<th>Expression in DCs</th>
<th>Action in DCs</th>
<th>References</th>
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<td>let-7i</td>
<td>SOCS-1</td>
<td>Expressed upon maturation</td>
<td>Regulates DC maturation and cytokine profile</td>
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<tr>
<td>miR-21</td>
<td>JAG1</td>
<td>Increasingly expressed during differentiation</td>
<td>Allows DC differentiation from monocytes</td>
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<td>miR-34a</td>
<td>JAG1, WNT1</td>
<td>Increasingly expressed during differentiation</td>
<td>Allows DC differentiation from monocytes</td>
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<td>miR-146a</td>
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<td>Constitutively expressed in LCs</td>
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</tr>
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<td>miR-148 family</td>
<td>c-Fos, KPC1, SOCS-1, TAB2, PU.1, DC-SIGN</td>
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<td>62</td>
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<td>miR-155</td>
<td>IRAK4, IRAK5</td>
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<td>miR-221</td>
<td>p21/1</td>
<td>Expressed in immature cDCs</td>
<td>Promotes survival of immature DCs</td>
<td>35, 40</td>
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<td>miR-222</td>
<td></td>
<td>Expressed in cDCs</td>
<td>Regulates pDC/cDC fate decisions</td>
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levels decreased, suggesting that miR-21 and -34a act to translationally repress Wnt-1 and Jagged-1, permitting MDDC differentiation. Hashimi et al. (34) postulate that miRNA-based regulation provides an additional level of control of Wnt-1 and Jagged-1 expression that does not interfere with transcription factor control, thus allowing other genes that are subject to regulation by mutual transcription factors to be expressed normally.

Lu et al. (35) identified miR-221 as being highly upregulated in immature DCs upon differentiation from human monocytes, and found p27kip1, a known target of miR-221 in mast cells (42), to be progressively inhibited during DC differentiation. p27kip1 is an inhibitor of cell cycle progression, and regulation of DC apoptosis by p27kip1 has been previously observed (43). The authors found higher levels of p27kip1 protein and moderately increased apoptosis in immature DCs when miR-221 was silenced, thereby suggesting that miR-221 contributes to the survival of immature DCs following their differentiation from monocytes.

miRNA activity in DC subset differentiation and specialization

Following development from bone marrow precursors, multiple DC subsets form, and miRNAs have been found to regulate the generation and specialized function of these subsets (Fig. 1A).

The bifurcation of pDCs and cDCs is an important checkpoint in DC differentiation, as the two subsets play functionally different roles, with pDCs in many ways resembling cells of the lymphoid lineage (44). In mice, the miRNA expression pattern of pDCs is more closely related to that of T cells than to cDCs (40). For example, several members of the miR-17∼92 cluster are more highly expressed in pDCs than in cDCs (40), and miR-17∼92 miRNAs are also highly expressed in lymphocyte progenitors (45). Also, the miR-23a/24/27a cluster is twice as highly expressed in cDCs than in pDCs (40), and this miRNA cluster has been reported to inhibit lymphopoiesis and positively regulate myelopoiesis (46). It is not yet clear whether the expression of these, or other, miRNAs imparts specific functions to these subsets, but it appears that miRNAs are involved in determining pDC/cDC fate decisions, as inhibition of miR-221 or miR-222 using antisense oligonucleotides skewed the balance of pDC and cDC differentiation from BM-derived DC precursors in favor of pDCs (40).

In LCs, a particular miRNA appears to play a role not in the differentiation of the subset, but in the cells' intrinsic specialization. miR-146a is ∼6-fold more highly expressed in LCs than in interstitial DCs generated in vitro from human granulocyte/myeloid progenitor cells (39). miR-146a expression increases upon cell activation in monocytes (24), but not upon activation in LCs, suggesting expression may be constitutively high in LCs (39). Gene target analysis found binding sites for PU.1 and C/EBPα in the miR-146a promoter, and both of these transcription factors have previously been implicated in LC differentiation (47, 48). High levels of PU.1 are thought to affect high miR-146a levels in LCs (39). miR-146a has been proposed to be an anti-inflammatory miRNA: it is induced by NF-κB in response to TLR signal-
ing in macrophages and, in turn, functions in a negative feedback loop and silences the TLR signaling components IL-1R–associated kinase (IRAK)1, IRAK2, and TNFR-associated factor 6 (24). When interstitial DCs, which naturally express low levels of miR-146a, were transduced with ectopic miR-146a and stimulated through TLR2, downstream signaling molecules were less strongly activated and the DCs produced less IL-12p40 and TNF-α (39). Thus, whereas the signal inhibition role of miR-146a in LCs is similar to that in macrophages, in LCs the miRNA is not part of a negative feedback loop in response to stimulation, but is constitutively high. The authors propose that expression of miR-146a in LCs might prevent inappropriate LC activation by environmental TLR ligands.

miRNAs in DC maturation and function

Activation of naive DCs by pattern-recognition receptor engagement involves the upregulation of several surface markers, most importantly MHC II and the costimulatory molecules CD80, CD86, and CD40 (49). To enhance their Ag presentation capacity, activated DCs stabilize peptide-loaded MHC molecules on their surfaces and start to secrete cytokines that polarize adaptive immune responses to allow effective targeting of the specific pathogen. The impact of individual miRNAs on DC maturation is described in the following sections.

miR-155

One of the miRNAs that has been most often implicated in the adaptive immune system is miR-155, which is expressed upon activation of B cells, T cells, and macrophages (12). miR-155 upregulation also appears to be a defining feature of DC maturation: increased miR-155 expression is observed upon maturation of multiple subsets of mouse and human DCs in response to various TLR ligands, TNF-α, and IFN-α (35, 50, 51). The extent to which miR-155 expression changes on DC maturation is dramatic: 50- to 130-fold induction after LPS treatment of human MDDCs has been recorded (36, 52). Not only is miR-155 characteristic of DC maturation, it also appears to be necessary for the optimal function of mature DCs, as DCs lacking miR-155 fail to effectively activate T cells (19). Rodriguez et al. (19) found similar levels of MHC II and CD86 on the surface of LPS-activated murine BM-derived miR-155–deficient DCs, which at the same time showed impaired ability to activate T cells. However, Dunand-Sauthier et al. (50) showed similarly impaired CD4+ T cell activation by activated miR-155–deficient DCs, but reported significantly decreased DC surface levels of MHC II, CD40, and CD86. This was accompanied by lower levels of secreted IL-12p40, IL-12p35, and TNF-α, although other cytokines were secreted at normal levels. Another report shows identical levels of CD40, CD80, CD83, CD86, and MHC II in LPS-matured BM-derived DCs from wild-type or miR-155 knockout mice (35). Thus, it is not yet precisely clear which aspects of the DC maturation phenotype are regulated by miR-155. However, it does appear that miR-155 is involved in DC maturation, but not development, as numbers of CD8α+ cDCs, CD8α− cDCs, and pDCs are not altered in mice lacking miR-155 (50).

Multiple targets of miR-155 in DCs have been identified. The transcription factor PU.1 regulates the expression of a number of myeloid genes, including the DC-specific C-type lectin DC-SIGN (53). Increasing expression of miR-155 during DC maturation resulted in decreased PU.1 protein levels and a concomitant reduction in DC-SIGN mRNA (52). Consequently, the DCs exhibited an impaired capacity to bind the fungus Candida albicans. Pathogen binding of DC-SIGN can also influence Th cell subset polarization (54), and it is possible that miR-155 plays a role in this process as well.

KPC1 is another verified gene target of miR-155 (35). KPC1 recognizes and polyubiquitylates the cell cycle regulator p27kip1, leading to its degradation (55). This appears to impart in miR-155 a role in DC apoptosis regulation, and, indeed, overexpression of miR-155 inhibits KPC1 and enhances p27kip1 expression in DCs, leading to apoptosis (35). The authors suggest that miR-155 acts as a tumor suppressor gene in DCs, in contrast to its oncogenic role in other cells and tissues (35).

Suppressor of cytokine signaling 1 (SOCS-1), an inhibitor of JAK/STAT signaling, is regulated by miR-155 in regulatory T cells (56). In DCs, miR-155 deficiency leads to derepression of SOCS-1, thereby causing reduced IL-12p70 cytokine production in mature DCs (35). In contrast, overexpression of miR-155 in mature DCs enhanced IL-12p70 expression, leading to higher levels of IFN-γ being secreted by cocultured NK cells (35).

c-Fos, a component of the multifunctional dimeric transcription factor AP-1, is another direct target of miR-155, and upregulation of miR-155 upon DC maturation results in c-Fos silencing (50). Transduction of miR-155–sufficient DCs with c-Fos inhibited their proinflammatory cytokine expression and T cell activation capacity, mirroring the effect of loss of miR-155 (50). The authors suggest that c-Fos–containing AP-1 complexes repress DC maturation, and miR-155 targeting of c-Fos alleviates this and allows maturation to proceed.

Analysis of signaling pathways in activated DCs following miR-155 silencing revealed six of nine top-ranked pathways to contain IL-1, a proinflammatory cytokine (36). IL-1β and caspase-1 expression were higher in miR-155–silenced activated DCs. Extension of this analysis showed concomitant upregulation of miR-155 expression and downregulation of inflammatory genes upon DC maturation, suggesting an anti-inflammatory role for miR-155 (36). Target gene identification and reporter gene expression analysis revealed TAB2, an adaptor protein in the TLR/IL-1 pathway, to be a direct target of miR-155 (36). The authors propose that miR-155 and miR-146a act together to form a negative feedback control loop on IL-1 signaling in stimulated DCs: miR-155 via targeting TAB2 (and possibly also Pellino-1) and miR-146a via targeting TNFR-associated factor 6 and IRAK1 mRNAs (36). Thus, miRNAs might also act to limit the production of inflammatory cytokines at later stages of DC activation.

miR-155 and its star-form partner miR-155* are also highly upregulated upon TLR stimulation of human pDCs (51). Star-form miRNA strands are miRNA partner strands that are rarely loaded into the silencing complex (57). Zhou et al. (51) found that the two miRNAs played opposing roles in regulating IFN-α/β expression by pDCs: at early stages after activation miR-155* suppression of its target gene, IRAK1, enhanced cytokine production, whereas at later stages miR-155 suppression of TAB2 inhibited cytokine production. This is an interesting example of fine-tuning of cellular behavior by
miRNA action. From the one pre-miRNA transcript, two miRNAs are formed; one of these accumulates rapidly and then degrades, acting quickly to facilitate the functional outcome of pDC stimulation (cytokine secretion), whereas the other accumulates more slowly and stays active, operating to prevent potentially damagingly high levels of cytokines.

These data combine to suggest that upregulation of miR-155 is necessary for controlling the expression of multiple genes that operate coordinately to allow DC maturation and regulate mature DCs’ survival and cytokine production. However, it appears that miR-155 can also control late stages of mature DC function by rendering DCs less capable of cytokine production and pathogen binding.

**miR-221**

As described above, miR-221 expression increases upon differentiation of DCs from monocytes, leading to low levels of p27kip1 in immature DCs, and thereby contributing to immature DC homeostasis. However, upon DC maturation, miR-221 is downregulated and p27kip1 levels correspondingly increase (35). Increased p27kip1 expression is reinforced by the indirect action of miR-155 on DC maturation, via KPC1 (35). It is worth noting that these effects of maturation-associated miRNAs on enhancing p27kip1 in DCs contrast with the behavior of p27kip1 in macrophages, in which the protein is downregulated in response to mitogenic stimulus (58).

**let-7i**

let-7 was one of the first miRNAs to be identified, and its family members are highly conserved across species. let-7i is upregulated in response to LPS-induced rat DC maturation, and it appears to be necessary for normal DC maturation, as inhibition of let-7i in immature BM-derived DCs leads to lower surface expression of the costimulatory molecules CD80 and CD86 and reduced production of proinflammatory cytokines upon DC activation (59). Zhang et al. (59) showed that a population of CD86+ tolerogenic DCs forms when immature BM-derived DCs are transfected with a let-7i inhibitor prior to LPS-induced maturation, and that this results in the preferential formation of regulatory T cells in vivo in vitro cell cocultures. SOCS-1, which is also targeted by miR-155 (see above), was identified as a direct target of let-7i. It is interesting to note that let-7i induction was seen in response to DC activation through TLR4, but not through TLR2, 3, or 5.

**miR-142-3p**

Production of IL-6 occurs upon DC maturation, and a recent finding showed that miR-142-3p directly targets the 3’UTR of the IL-6 gene in DCs (60). Repression of miR-142-3p in murine BM-derived DCs led to enhanced IL-6 expression both in immature DCs and following LPS activation, although this did not alter the ability of DCs to stimulate T cells in a MLR. However, miR-142-3p seems to be important in the response to endotoxin-induced septic shock. Wild-type mice exposed to lethal levels of LPS survived longer when treated with miR-142-3p, whereas IL-6 knockout mice did not exhibit this protection from sepsis (60). IL-6 can act as either a pro- or anti-inflammatory cytokine; in the case of sepsis, expression of endogenous IL-6 can protect from endotoxin-induced mortality (61). Although miR-142-3p silencing in these experiments was not restricted to DCs, DCs are major producers of the cytokines that characterize sepsis, and it is likely that miR-142-3p regulation of IL-6 production by DCs was pertinent to these results.

**miR-148 family**

Members of the miR-148 family (miR-148a, miR-148b, and miR-152) are upregulated upon DC stimulation by LPS, and their overexpression leads to reduced MHC II surface expression on DCs, inhibition of DC secretion of some proinflammatory cytokines, and reduced DC-mediated CD4+ T cell expansion (62). Correspondingly, MHC II expression, cytokine production, and CD4+ T cell proliferation increased when LPS-stimulated DC cultures were treated with miR-148 family inhibitors. The 3’UTR of the gene encoding calcium/calcmodulin-dependent protein kinase II (CaMKIIα) contains a target sequence for miR-148a, miR-148b, and miR-152, and a luciferase reporter gene system identified CaMKIIα to be a direct target for downregulation by these miRNAs. CaMKIIα, an effector of calcium signaling, is an important regulator of DC maturation (63), and thus, it appears that miRNAs play a role in regulating this arm of functional DC maturation as well.

**Conclusions**

DC biology is one of many frontiers in the expanding field of miRNA research, but some trends in miRNA regulation of DCs have already emerged. It appears that miRNAs act in multiple circumstances to keep a check on the inflammatory capacity of DCs. This is seen via the actions of let-7i, miR-142-3p, miR-146a, the miR-148 family, miR-155, and miR-155* in regulating cytokine production in response to DC activation, and as an inherent characteristic of LCs via constitutive miR-146a expression. We also see that miRNAs regulate checkpoints of DC differentiation: miR-21 and miR-34a are necessary for DC differentiation from monocytes, and miR-221 and miR-222 control pDC and cDC cell fates.

These studies are likely to represent just the beginning of our understanding of miRNA functions in DCs. Plenty of untapped information remains in the numerous miRNA expression profiles that have been generated with various DC populations. Validation studies have to date primarily focused on miRNAs for which functions had previously been identified, but expression analyses of DCs at various developmental stages have revealed many other miRNAs that are at least as differentially expressed, yet remain uncharacterized.

It is not only interesting to identify those miRNAs that function in DC biology, but also to consider how the rapid regulation of gene expression that is achieved by these molecules in DCs impacts on adaptive immune responses. The finding that mRNA expression in DCs is associated with both proinflammatory and anti-inflammatory responses (Fig. 1B) implies that multiple miRNAs may act in a tightly balanced tandem to regulate the signals transmitted by DCs to other cells of the immune system. The cooperative behavior of miR-155 and miR-155* in pDCs also shows that sequential miRNA expression may influence both DC activation and subsequent contraction of immune responses (51), suggesting that further analysis of the temporal regulation of DC-relevant miRNAs is warranted.

DCs help to orchestrate pathogen-specific immune responses by secreting appropriate cytokines and influencing CD4+ T cell
subset differentiation. This review summarizes how many miRNAs regulate DC cytokine production. The finding that let-7 inhibits SOCS-1 expression in DCs in response to DC activation by LPS, but not by other TLR ligands, is an indication that miRNA expression may contribute to tailoring immune responses to pathogens. The ability of miRNAs to impart DCs with both pro- and anti-inflammatory, and even tolerogenic, capacities also raises the possibility that miRNAs are involved in the discriminative responses to pathogenic and commensal bacteria by the gut immune system. Finally, in addition to providing further insights into immune regulation, an enhanced understanding of miRNA biology in DCs may also reveal novel molecular origins of immune dysfunction or malignancies.

Disclosures

The authors have no financial conflicts of interest.

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ciprofloxacin resistance factors in Langerhans cell commitment.


