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MicroRNAs in Allergy and Asthma

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Abstract microRNAs (miRNAs) are short, single-stranded RNA molecules that function together with the partner proteins and cause degradation of target mRNAs or inhibit their translation. A particular miRNA can have hundreds of targets; therefore, miRNAs cumulatively influence the expression of a large proportion of genes. The functions of miRNAs in human diseases have been studied since their discovery in mammalian cells approximately 12 years ago. However, the role of miRNAs in allergic disease has only very recently begun to be uncovered. The purpose of this review is to provide an overview of the functions of miRNAs involved in the development of allergic diseases. We describe here the functions of miRNAs that regulate Th2 polarization and influence general inflammatory and tissue responses. In addition, we will highlight findings about the functions of extracellular miRNAs as possible noninvasive biomarkers of diseases with heterogeneous phenotypes and complex mechanisms and briefly discuss advances in the development of miRNA-based therapeutics.

Keywords Allergy · Asthma · Atopic · Non-coding RNA · T cells · Dendritic cells · Epithelial cells · microRNA · Extracellular miRNA

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Introduction

The immune system is controlled by dynamic and multilevel regulation of gene expression in each involved cell type. microRNAs (miRNAs) constitute a group of gene expression regulators that post-transcriptionally fine-tune the expression of up to 50 % of genes [1, 2]. The growing number of studies demonstrates that miRNAs control the signaling pathways in every cell type, impact the development and phenotypic stability of immune cells, and regulate the strength of inflammation in tissues. Because of numerous biological functions of miRNAs, the expression modulation of this novel group of molecules may potentially be used for therapeutic purposes. The presence of quantifiable amounts of miRNAs in the body fluids suggests that miRNAs can potentially be used as noninvasive biomarkers to better distinguish endotypes of heterogeneous diseases, including asthma and other allergic diseases [3, 4]. Studies regarding the roles of miRNAs in allergic diseases have been emerging during the last 4 years, and the functions of miRNAs in the regulation and pathogenesis of these diseases are mostly uncharacterized [5, 6]. Here, we provide an overview of miRNAs that influence the development of allergic diseases or impact the strength of inflammation in affected tissues. In addition, we discuss the potential of miRNAs as biomarkers and targets of gene therapy.

miRNA Biogenesis and Mechanisms of Action

miRNAs are transcribed in the nucleus by RNA polymerase II as a part of longer transcripts by either independent promoters, as polycistronic transcripts, or embedded within the introns of protein-encoding genes. Similar to other genes, the expression of miRNA encoding sequences is controlled at the epigenetic level, during transcription, processing, nuclear export and degradation [5]. For maturation, miRNAs pass through

consecutive steps of processing that include cleavage by endonuclease Drosha-DGCR8 (DiGeorge syndrome critical region gene 8) in the nucleus, export to the cytoplasm by the Exportin-5–Ran-GTP complex and additional processing by the enzyme Dicer in the cytoplasm. Finally, one strand of the duplex is incorporated into the RNA-induced silencing complex (RISC), which contains the Argonaute 2 (AGO2) and glycine-tryptophan 182 kDa protein (GW182) [7, 8]. In mammalian cells, RISC-loaded miRNAs bind through partial complementarity of at least 6-8 nucleotides to the target mRNAs and thereby mediate repression of translation or induce mRNA degradation via initiation of deadenylation. miRNAs mainly interact with 3' untranslated regions (3'UTRs) of mRNA, where their binding is more efficient because of the lack of active translation [9].

miRNAs Regulate Immune Responses

A healthy immune system detects and eliminates pathogens very efficiently. However, excessive and inappropriate responses to pathogens, self-antigens, damaged cells, toxins, allergens or irritants can cause unreasonably strong inflammation and tissue damage as well as autoimmunity and allergic diseases [10–12]. Numerous studies have demonstrated that miRNAs impact both innate and adaptive immune responses. miR-21, miR-146a and miR-155 are among the most intensively studied immune system-related miRNAs. miR-21 is highly expressed in many cell types and regulates various immunological processes [13]. The expression of miR-21 is regulated by STAT3 and NF-κB [14]. In mouse macrophages, miR-21 has been shown to suppress inflammatory responses via targeting tumor suppressors and a proinflammatory protein, PDCD4, which promotes activation of NF-κB and controls production of IL-10 [15].

Similar to miR-21, miR-146a is an antiinflammatory miRNA that has been shown to suppress the activation of NF-κB in numerous studies. miR-146a directly downregulates IL-1 receptor-associated kinase 1 (IRAK1), TNF receptor-associated factor 6 (TRAF6) [16], Relb, a member of the noncanonical NF-κB/Rel family [17], and caspase recruitment domain-containing protein 10 (CARD10, also known as CARD-recruited membrane-associated protein 3, CARMA3) [18]. *miR-146a-/-* mice have been shown to develop autoimmunity caused by the overactivation of STAT1 in Treg cells, which leads to increased IFN-γ production and an inability to suppress Th1 type responses [19–21]. Interestingly, constitutive ubiquitous overexpression of miR-146a also leads to autoimmunity. Mice with 2-6-fold overexpression of miR-146a in most of the tissues spontaneously develop autoimmune lymphoproliferative syndrome-like disease, most likely caused by reduced expression of Fas, and increased levels of serum IgG and double-negative T cells [22], which demonstrates that precise regulation of miR-146a expression is crucial for a healthy immune system.

In contrast to miR-21 and miR-146a, miR-155 acts mainly as a proinflammatory factor. miR-155 expression is induced upon vesicular stomatitis virus infection in macrophages, which promotes type I IFN signaling via targeting suppressor of cytokine signaling, SOCS1 [23]. Suppression of SH2 domain-containing inositol-5-phosphatase (SHIP1) by miR-155 causes activation of Akt kinase and upregulation of IFN response genes during the cellular response to LPS [24]. In addition, miR-155 directly represses BCL6, a transcription factor that attenuates NF-κB signaling, and this promotes atherosclerosis in mice [25]. miR-155 also functions in the development and activation of adaptive immune cells, including effector T cell subsets [26]. In addition, *miR-155*-deficient mice are defective in production of Th1 and Th17 cells and, therefore, are highly resistant to experimental autoimmune encephalomyelitis [27].

Numerous other miRNAs control innate and adaptive immune responses. miR-301a, miR-9, miR-147b and mir-125a have been implicated in regulating NF-κB [28], miR-10a, miR-17-92, miR-181a, miR-182 and miR-29a/b impact the differentiation and plasticity of T cells [29], and miR-17-92, miR-34a, miR-150, miR-181b, miR-125b and miR-217 influence the development and functions of B cells [30]. In the context of allergic diseases, it is especially interesting to study how miRNAs influence Th2 polarization, the suppressive capacity of Treg cells and Ig class switching in B cells.

miRNAs in Asthma

Dysregulated expression of several miRNAs has been found in the airways or lymphocytes of asthma patients and in different mouse models of asthma-like lung inflammation. For example, increased expression of miRNA-181a, miR-155, miR-150, miR-146a and miR-146b was detected in splenic CD4+ T lymphocytes of an ovalbumin (OVA)-induced mouse model of asthma [31]. In line with this observation, miR-155-deficient mice develop an altered inflammatory response with diminished eosinophilic inflammation, reduced eotaxin-2/CCL24 and periostin levels, and reduced Th2 cell numbers in the same mouse model [32•] Table 1. Interestingly, approximately 50 % of aging miR-155-deficient mice spontaneously develop asthma-like lung inflammation with elevated levels of certain Th2 type cytokines, and increased numbers of lymphocytes and macrophages, but similar counts of eosinophils compared to wild-type (wt) mice, [26], which indicates that miR-155 influences the development of asthma through multiple factors.

Several other miRNAs have been shown to modulate asthma-like lung inflammation in different mouse models. The expression of miR-126 is increased in the airways of mice

Table 1 The functions of miRNAs in allergic diseases

miRNA	Disease	Function	Targets
miR-126	Asthma	Silencing reduced allergic inflammation in an HDM-induced mouse model of asthma [33] and reduced eosinophilia in the mouse model of chronic airway inflammation [34]	?
miR-221	Asthma	Upregulated in OVA-induced mouse models of asthma,_ENREF_136 silencing reduces allergic inflammation [37]	Spred-2
miR-145	Asthma	Silencing reduced allergic inflammation in an HDM-induced mouse model of asthma [35]	?
miR-106a	Asthma	Silencing reduced allergic inflammation in an HDM-induced mouse model of asthma [36]	IL-10
let-7a	Asthma	Overexpression reduced allergic inflammation in an OVA-induced mouse model of asthma [48]	IL-13
		Intravenous administration of LNA inhibitors impeded AHR in a mouse model of asthma [46]	
miR-21	Asthma, allergic rhinitis, contact dermatitis, EoE	Overexpressed in lung-specific IL-13 expressing transgenic mice with induced allergic airway inflammation [41]	IL-12p35
		Overexpression reduced TLR2 agonist-induced lung inflammation in mice [43]	
		Increased levels of Th1 cytokines and reduced eosinophilia in an OVA-induced mouse model of asthma in miR-21-deficient mice [42]	
		Antenatal IgE production and development of allergic rhinitis [44]	
		Upregulated in contact dermatitis lesional skin [47]	
		Upregulated in EoE esophageal tissue [45•]	
miR-146a	Asthma?	Overexpressed in splenic CD4+ T lymphocytes [31]	?
		Reduced expression in CD8+ and CD4+ cells in patients under oral corticosteroid treatment [101]	
		Reduces cytokine-induced apoptosis in human bronchial epithelial cells [59]	
miR-375	EoE	Positive regulator of TSLP in human primary lung epithelial cells [52]	?
		Expression is modulated by IL-13 [46]	
		Downregulated in EoE esophageal tissue [45•]	
miR-133a	Asthma	Downregulation in mouse bronchial smooth muscle cells augmented airway contraction and hyperresponsiveness [61]	RhoA
miR-1	Asthma	Downregulated by VEGF in the lung endothelium, intranasal administration of miR-1 inhibited inflammatory responses to OVA, HDM and IL-13 overexpression Mpl [60]	Mpl
miR-155	Atopic dermatitis, asthma	Influences development of AD by downregulation of CTLA-4-negative regulator of T-cell activation [63]	CTLA-4
		Is required for Th2-mediated eosinophilic inflammation in the OVA-induced mouse model of asthma [32•]	PU.1
		miR-155-deficient mice spontaneously developed asthma-like inflammation in the lung and had increased levels of IL-4 and IL-5 in T cells [26]	c-Maf
miR-125b	CRS with nasal polyps	Upregulated in CRS with nasal polyps, influenced IFN-α/β production [68]	4E-BP1
miR-150	ACD	Nanovesicles containing miR-150 induced antigen-specific tolerance in ACD model in mice [84•]	

upon exposure to house dust mite (HDM). Inhibition of miR-126 expression using intranasal administration of miR-126 antagomir, which is a cholesterol-linked single-stranded RNA complementary to miR-126, abolished airway hyperreactivity (AHR), impaired Th2 responses and reduced allergic inflammation in an HDM-induced mouse model of asthma [33], and decreased eosinophilia in a mouse model of chronic airway inflammation [34]. Similarly, the inhibition of miR-145 [35] and miR-106a [36] had antiinflammatory effects on HDM-induced allergic airway disease in mice.

Increased levels of miRNA-221 were detected in the lung biopsies of mice subjected to an OVA-induced mouse model of asthma, whereas the inhibition of miR-221 reduced inflammation in the airways [37]. In agreement with this observation, miR-221, which is known to regulate the cell cycle of mast cells, is upregulated in mast cells by stimulation with IgE-allergen complexes and stem cell factor [38, 39].

The potential role of miRNAs in corticosteroid-resistant asthma is mostly unexplored. One of the initial studies in this area demonstrated a rapid change in miRNA levels in mouse lungs following LPS-induced inflammation; however, no influence of glucocorticoids was detected [33]. Another study demonstrated that the expression of miR-146a is reduced in CD8+ and CD4+ T cells from severe asthma patients with continuous oral corticosteroid treatment [34]. In agreement with this observation, the expression of miR-146a was shown to be suppressed by dexamethasone in splenic CD4+ T lymphocytes from the mice used in the OVA-induced mouse model of asthma [31].

Together, these studies demonstrate that miRNAs can either enhance or reduce the allergic inflammation in asthma and suggest that a complex network of miRNAs impacts the development of asthma and related inflammatory processes. Because asthma is a complex syndrome with heterogeneous

endotypes or phenotypes [3, 4], miRNAs as fine-tuners of gene expression may possibly contribute to the development of different forms of asthma, including corticosteroid-resistant asthma.

Th2 Cell Polarization and miRNAs

A growing number of studies describe miRNA functions in the differentiation, phenotypic stability and plasticity of T cells [29]. Allergic diseases are characterized by the expansion of Th2 cells and development of IgE-expressing memory B cells and plasma cells that produce IgE antibodies specific to common environmental allergens [12]. The hallmark cytokines for Th2 cells are IL-4, IL-5 and IL-13. However, the Th1/Th2 balance is also influenced by the levels of Th1 cytokines such as IL-12 and IFN-γ [40]. Several miRNAs directly target either Th1 or Th2 type cytokines. miR-21 is the most highly upregulated miRNA detected in doxycycline-induced lung-specific IL-13 transgenic mice during OVA-induced allergic airway inflammation. Because miR-21 directly targeted IL-12p35, it was suggested that miR-21 might contribute to Th2 polarization during allergic airway inflammation [41]. Later, reduced lung eosinophilia and increased levels of IFN-γ were detected in OVA-challenged miR-21-deficient mice consistent with a miR-21 binding site on IL-12p35 [42]. miRNA-21 also inhibited innate immune responses in TLR2 agonist-induced lung inflammation in mice [43]. Clinical studies have demonstrated a correlation between reduced levels of miR-21 in mononuclear leukocytes from human umbilical cord blood samples and elevated antenatal IgE production in allergic rhinitis patients [44]. Additionally, the upregulation of miR-21 was observed in esophageal biopsies from patients with eosinophilic esophagitis (EoE) [45•]. EoE is characterized by very high IL-13 overproduction and strong Th2 type inflammation and eosinophilia in the esophagus; it can therefore be regarded as a model for Th2 type disease [46]. In addition, miR-21 is upregulated in the lesional skin from subjects with allergic responses to diphenylcyclopropenone (DPCP) in humans and in a dinitrofluorobenzene (DNFB)-induced contact dermatitis model in mice, in which Th17 and Th1 responses are dominant [47].

Ubiquitously expressed miRNA let-7 has been shown to influence the expression of IL-13 in lung epithelial cell-line A549. Indeed, intranasal administration of let-7 family miRNAs led to reduced IL-13 and AHR as well as resolution of allergic inflammation in an OVA-induced mouse model of asthma [48]. However, in another study, inhibition of let-7 miRNAs using intravenously administered locked nucleic acid (LNA) inhibitors hampered AHR in a mouse model of asthma instead of exacerbating the disease [49].

miR-155 might impact the Th1/Th2 balance and the development of allergic disease through its function in macrophages, in which miR-155 targets IL-13RA, SOCS1 and SHIP1. When miR-155 levels are reduced in differentiating macrophages, STAT6 is more activated, leading to the establishment an alternative pro-Th2 phenotype M2 of macrophages [50]. Opposite to miR-155, the increased levels of miR-375 promote the differentiation of Th2 cells in gut mucosal epithelial cells, in which miR-375 has been shown to be induced by IL-13. In the presence of miR-375, the elevated expression of key Th2 cytokines, thymic stromal lymphopoietin (TSLP) and resistin-like beta (RELMβ) [51•] was detected, which correlated with the suppression of the transcription repressor Kruppel-like factor 5 (KLF5). In agreement with these results, diesel exhaust particles, which are known to aggravate asthma, upregulated TSLP mRNA and miR-375 in primary human bronchial epithelial cells, whereas miR-375 was shown to be a positive regulator of TSLP [52]. In contrast to gut mucosal epithelial cells, miR-375 is downregulated by IL-13 in human esophageal squamous and bronchial columnar epithelial cells, which suggests that the regulation of miR-375 expression is complicated and cell type specific [45•].

Several studies demonstrating the impact of miRNAs on the expression levels of proinflammatory cytokines suggest that many other miRNAs can affect the Th1/Th2 balance. For instance, IL-10-induced miR-187 negatively regulates TNF-α, IL-6 and IL-12p40 production in TLR4-stimulated monocytes [53], and miR-155 functions as a positive regulator of IFN-γ production through direct targeting of the inositol phosphatase SHIP1 in human NK cells [54, 55]. These data suggest that numerous miRNAs are involved in regulating the Th1/Th2 balance and may therefore play a role in the development of allergic diseases.

miRNAs in the Lung Tissue Cells

Disease-related changes in lung alveolar epithelial cells, endothelial cells, fibroblasts and bronchial smooth muscle cells play an important role in asthma. Already the initial expression profiling studies of different lung epithelial cell lines and tissue resident cells suggested that miRNAs are part of the regulatory network involved in tissue responses to asthma. miRNAs have different expression profiles in airway smooth muscle cells, alveolar epithelial A549 cells, bronchial epithelial Beas2B cells, bronchial fibroblasts and alveolar macrophages [56]. In epithelial cells from asthmatic patients, 66 miRNAs were shown to be differentially expressed, and pathway analysis indicated that the putative targets of these miRNAs encode disease or inflammation-related proteins such as TNF-α, IL-8, Cox2, IL-6 and AQP4 [57]. IL-1β-induced miR-146a has been shown to reduce the levels of the proinflammatory chemokines IL-8 and CCL5 (also known as RANTES) in human alveolar A549 epithelial cells [58]. In

addition, miR-146a might contribute to tissue remodeling in the lungs because it has been shown to reduce cytokine-induced apoptosis of human bronchial epithelial cells [59].

Several very recent and interesting studies describe the functions of miRNAs in lung endothelial cells and smooth muscle cells. The lung-specific overexpression of vascular endothelial growth factor (VEGF) was shown to decrease miR-1 expression in the lung endothelium, whereas intranasally delivered miR-1 inhibited inflammatory responses to OVA, HDM and IL-13 overexpression. In the same study, VEGF blockade, as well as knockdown of MPL, a miR-1 target myeloproliferative leukemia virus oncogene, inhibited Th2-mediated lung inflammation, demonstrating that VEGF controls lung Th2 inflammation via miR-1 and MPL [60]. Downregulation of miR-133a is responsible for the increased expression of a small GTPase RhoA that leads to an augmented contraction and hyper-responsiveness of bronchial smooth muscle cells in a mouse model of allergic asthma [61]. miR-140-3p modulates bronchial smooth muscle cells through indirect mechanisms involving activation of p38 MAPK and NF-κB in humans [62]. These studies together demonstrate that the increased activation of proinflammatory pathways, altered expression of tight junction proteins and other changes observed in the epithelial cells, smooth muscle cells and endothelium of patients with asthma may also be partially attributed to underlying aberrant miRNA expression.

miRNAs in Atopic Dermatitis, Allergic Contact Dermatitis and Chronic Rhinosinusitis

Only a few studies describe miRNA functions in atopic dermatitis (AD), allergic contact dermatitis (ACD) and chronic rhinosinusitis (CRS). miR-155 has been shown to be overexpressed in the skin from AD patients, mainly because of the infiltrating immune cells. miR-155 was reported to influence the development of AD through downregulation of cytotoxic T lymphocyte-associated antigen (CTLA)-4, a negative regulator of general T cell activation that also plays an important role in allergen tolerance [63, 64]. miRNA profiling of human skin challenged with diphenylcyclopropenone [47] and skin from mice subjected to a mouse model of contact dermatitis revealed that the same miRNAs, miR-21, miR-142-3p, miR-142-5p and miR-223, were upregulated in both humans and mice.

The enhanced expression of miR-203 and miR-146a [65] and reduced levels of miR-125b [66] have been found in the psoriatic skin. miR-125b acted as a suppressor of keratinocyte proliferation, most likely via direct targeting of fibroblast growth factor receptor 2 (FGR2) [66]. Similar to psoriasis, Th1 type inflammatory responses are dominant in ACD and become important in the chronic phase of skin inflammation in AD [67], suggesting that miR-203, miR-146a and miR-125b might have a role in AD and ACD as well. Interestingly, miR-125b was also upregulated in eosinophilic CRS with nasal polyps. miR-125b overexpression influenced IFN-α/β production, most likely through the suppression of eukaryotic translation initiation factor 4E (EIF4E)-binding protein 4E-BP1 in airway epithelial cells [68]. These initial studies demonstrate that miRNAs are involved in the regulation of allergic inflammation in the skin and sinonasal epithelial cells.

Extracellular miRNAs as Biomarkers

Asthma is a complex disease that can be subcategorized to endotypes based on underlying cellular and molecular mechanisms [3, 4, 69]. The development of endotype-specific treatment modalities is important for better management of asthma and depends on identification of reliable biomarkers. The miRNA expression pattern is variable in different cell types and disease conditions. Moreover, miRNAs can be detected in different cell-free body fluids, such as blood serum, urine and saliva, suggesting that miRNAs are potential non-invasive biomarkers for numerous disease conditions [70–73]. Accordingly, a number of studies have confirmed that serum miRNAs are suitable biomarkers in the case of various cancers, tissue injury and inflammation [70, 73–75].

Very recent studies suggest that serum miRNAs can be used as biomarkers also in case of allergic diseases. In the serum from patients with chronic obstructive pulmonary disease (COPD), four miRNAs (miR-20a, miR-28-3p, miR-34c-5p and miR-100) are significantly downregulated, and one (miR-7) is upregulated [76]. Out of the ten most differentially expressed miRNAs in esophageal tissue from EoE biopsies, the differential expression of miR-146a, miR-146b and miR-223 has been detected in plasma from EoE patients [45•]. Significant differences in bronchoalveolar lavage fluid (BALF) exosomal miRNA profiles have been detected between patients with mild asymptomatic asthma and healthy subjects [77]. miRNAs have also been detected in exhaled breath condensate (EBC), whereas 11 miRNAs were somewhat differently expressed in asthmatic patients compared with healthy subjects [78]. Future studies will reveal whether serum and airway miRNAs can be used as biomarkers to distinguish different endotypes of asthma and other allergic diseases.

The Functions of Extracellular miRNAs

miRNAs can be secreted via cell-derived membrane vesicles, called exosomes, and by protein-miRNA complexes, such as high-density lipoprotein (HDL) and AGO2, which is a part of the RISC complex [79]. In

addition, a passive leakage from cells can occur because of apoptosis, necrosis, tissue injury and chronic inflammation. Extracellular miRNAs can be taken up by recipient cells; HDL-bound miRNAs enter into recipient cells via scavenger receptor class B type I in cultured hepatocytes [80]. However, most of the miRNAs in plasma exist in complexes with the AGO2 protein, not exosomes or microvesicles [81, 82]. AGO2 has been shown to protect miRNAs from degradation [83]. These findings came from initial studies, which proposed that miRNAs might also function in communication between cells and play a role in immune responses including allergic responses. Indeed, a very recent study demonstrated that CD8+ suppressive cells are capable of producing antigen-specific antibody-coated nanovesicles containing miR-150. These nanovesicles entered into effector T cells and thereby suppressed induced ACD and promoted antigen-specific tolerance in mice, whereas the nanovesicles from miR-150-deficient mice did not have a suppressive effect [84•].

The Impact of miRNAs in Allergic Tissue Inflammation

Allergic tissue inflammation in the skin, sinus or lungs is induced by the development of a strong allergen-induced Th2 type immune response, which is supported by the production of TSLP, IL-33 and IL-25 by epithelial cells [85]. The chronic phase of tissue inflammation is affected by a complex mixture of factors that includes not only Th2 type cytokines, but also IFN-γ [67, 86, 87], IL-17 and IL-22 [88, 89]. Secondary infections and innate immune response activation in epithelial cells also have a role during chronic inflammation in allergic responses [90]. In addition to Th2, Th1 and Th22 cells, other cell types contribute to the allergic tissue inflammation. These include Treg cells, CD8+ T cells and innate immune cells, such as natural killer cells, eosinophils, mast cells, neutrophils, macrophages, basophils and innate lymphoid cells [85, 91–95] (Fig. 1). Based on the current knowledge, we propose that there are three specific mechanisms by which miRNAs impact allergic inflammation in tissues. First, miRNAs impact the polarization of Th2 cells. Second, miRNAs influence the development and functions of CD8+ T cells and innate immune cells found in or recruited into the inflamed tissue. Third, miRNAs impact chronic inflammation through their effects in epithelial cells (Fig. 1).

miRNA-Based Therapeutics

The current therapies for asthma and allergic diseases are still inefficient in controlling severe forms of these diseases [12]. One direction in the development of novel therapeutics for allergic diseases is biological modification of immune responses for better and more individualized control [12, 96]. There is obvious potential for miRNAs as novel target

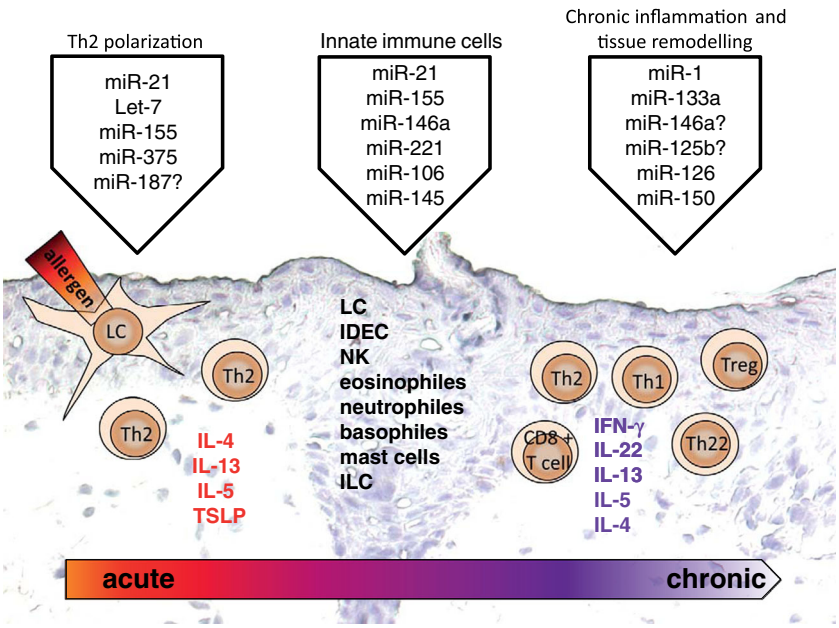

Fig. 1 miRNAs in allergic tissue inflammation. Allergic inflammation in the skin, sinus or lungs starts with an allergen-induced Th2 type immune response, which is supported by the production of TSLP in epithelial cells. The chronic phase of tissue inflammation involves Th2, Th1 and Th22 cells. In addition, Treg cells, CD8+ T cells and innate immune cells, such as Langerhans' cells (*LC*), inflammatory epidermal dendritic cells (*IDEC*), natural killer (*NK*) cells, eosinophils, mast cells, neutrophils, macrophages, basophils and innate lymphoid cells (*ILC*), contribute to allergic tissue inflammation. miRNAs impact the polarization of Th2 cells, influence the development and functions of CD8+ T cells and innate immune cells, and impact chronic inflammation and tissue remodeling through their functions in epithelial cells

molecules for the development of biological therapeutics as miRNAs can be either inhibited or overexpressed. As the biological functions of miRNAs are shaped by evolution, miRNA-based therapeutics have a low likelihood of inducing toxicity if inadvertently transduced into healthy cells, suggesting that miRNA-based therapeutics would have few side effects if used as a future approach to treat various inflammatory diseases [97].

Several studies endorse the potential of miRNA-based therapeutics. Silencing of miR-122 inhibits hepatitis C virus (HCV) replication in primates [98]. Miravirsen, the first miRNA-targeting drug, has entered into clinical trials for the treatment of HCV infection. Miravirsen is a very short LNA-based anti-miR-122 oligonucleotide, which is capable of independently entering cells. Similarly, the first miRNA replacement therapeutic, a mimic of tumor suppressor miR-34, has been successfully used in animal models [99]. Currently, an intravenously injected liposome-formulated miR-34 mimic, MRX34, is in clinical trials for patients with advanced or metastatic liver cancer [100]. As described above, intranasal inhalations of different formulas of miRNA inhibitors and mimics have been successfully used to reduce allergic airway inflammation in mice [33–35, 37]. Although miRNAs themselves are not toxic, the delivery vehicles still can cause unexpected cell differentiation, activation of immune responses or other side effects. In addition, several tissues and cell types are difficult to access by the currently available delivery methods [97]. Improved techniques for controlling miRNA overexpression and inhibition, combined with increased knowledge about the biological functions of miRNAs, could lead to the development of very specific gene expression modulators that could be applied as personalized therapeutics for allergic diseases in the future.

Conclusions

Asthma and other allergic diseases are multifactorial and heterogeneous conditions. More than 1 billion people in the world suffer from some form of allergic diseases. Accordingly, there is a need for more individualized treatment techniques, especially for the difficult-to-treat forms of these diseases. The roles of miRNAs in relation to allergic diseases are just beginning to be explored. Further characterization of miRNA functions is important because of the high potential impact on the treatment of allergic diseases as the modulation of miRNA expression could potentially be used for therapeutic purposes in the future. In addition, miRNAs are potential non-invasive biomarkers. Further studies are needed to reveal the full impact of miRNAs in relation to allergic diseases.

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Compliance with Ethics Guidelines

Conflict of Interest Ana Rebane and Cezmi A. Akdis declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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