Review:

Regulation of macrophages in allergy by noncoding RNAs

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Abstract

Allergies are an immune reaction that is triggered by various substances known as allergens, which are represented by food and environmental substances such as plant pollen, fungal spores, and the feces and debris of mites and insects. Macrophages are immune cells with phagocytic abilities that process exogenous and endogenous antigens. The dysregulation of macrophage function leads to excessive inflammation, which includes allergic reactions. Thus, it is important to better understand how macrophages are regulated in the pathogenesis of allergies. Emerging evidence has highlighted the role of noncoding RNAs (ncRNAs) in macrophage polarization, which is involved in the pathogenesis of various immune-mediated diseases, including allergies. This review summarizes the current knowledge of ncRNA-regulated macrophage polarization that is related to allergies by focusing on three major ncRNA types: microRNAs, long ncRNAs, and circular RNAs. Furthermore, we discuss the potential therapeutic applications of targeting ncRNAs for allergy treatment.

Keywords: noncoding RNA; allergy; macrophage； macrophage polarization

1. Introduction

Allergies are a common immune disorder that affects millions of people worldwide and is characterized by an excessive type 2 immune response to normally harmless substances, generally known as antigens or allergens [1,2]. Consequently, this response leads to the development of various allergic symptoms, including asthma, allergic rhinitis, and atopic dermatitis. In the most severe cases, it results in anaphylaxis and possibly death. According to the World Health Organization, the prevalence of allergic diseases has been continuously increasing in industrialized countries for more than 50 years [3]. The process by which the immune system becomes sensitive to a particular allergen is called sensitization and is typically accompanied by the development of immunoglobulin E (IgE), a specific subclass of antibodies, against the allergen. Sensitization rates to one or more common allergens among schoolchildren are reported to be between 40%–50% [4]. Since antigen E was isolated from the pollen of common ragweed (*Ambrosia artemisiifolia*) as the first antigen in 1962 [5], a variety of environmental and food allergens have been identified, including 106 allergens that have recently (between 01/2019 and 03/2021) been accepted by the Allergen Nomenclature Sub-Committee (http://allergen.org/committee.php) [6]. For example, one of the authors (O.I.), together with colleagues, identified that *Liposcelis bostrychophila*, a booklouse species commonly found in house dust, is a potent environmental allergen source based on the data of IgE inhibition analysis, which demonstrated that approximately 20% of the studied patients with asthma were sensitized by the *L. bostrychophila*-specific antigen Lip b 1 [7,8]. It should be noted that sensitization to booklice antigens may lead to the misdiagnosis of food-induced allergies. Babaie *et al.* recently reported that a patient developed anaphylaxis after ingesting oatmeal, although the results of the skin prick test and serologic testing for oats were negative, and the cause was ultimately identified to be booklice contamination in the oatmeal [9]. As

insects may possibly become a popular food source in the future, it is important to consider their potential to harbor known and novel allergens [10].

Immune cells such as mast cells, basophils, and specific T cell subsets are well recognized as playing leading roles in allergic reactions. Conversely, macrophages have been less associated with allergies. However, macrophages critically regulate the proinflammatory immune responses in various tissues, and several lines of evidence have shown that macrophages are essential players in the pathogenesis of allergies [11-13]. Therefore, macrophage involvement in allergic diseases deserves further study.

It is generally accepted that macrophages can be divided into two major subclasses based on the inflammatory responses that they mediate, and macrophage polarization is determined depending on the circumstances (Figure 1). However, the mechanisms underlying *in vivo* macrophage polarization are complicated and remain largely unclarified, but various intracellular molecules, including receptors, signaling molecules, and enzymes, have been shown to regulate macrophage polarization [14-17]. Moreover, accumulating evidence has revealed that noncoding RNAs (ncRNAs), a class of functional RNAs that are not translated into proteins and are associated with various pathological events, are associated with both macrophage polarization and allergies. Herein, we summarize the current knowledge on ncRNA-regulated macrophage functions related to allergies and discuss the possibility of ncRNAs as potential targets for allergy treatment.

2. M1/M2 macrophage classification

Macrophages are white blood cells that are crucial to the functioning of the immune system. They are characterized by high plasticity, which allows them to functionally adapt depending on their microenvironment. Two major macrophage polarization states exist: classically

activated macrophages (M1 macrophages) and alternatively activated macrophages (M2 macrophages) (Figure 1). The balance between the two macrophage polarization states is critical to maintaining healthy immune functionality (Figure 1) [18,19].

Polarization of M1 macrophages is typically activated by factors such as interferon (IFN)-γ and bacterial products like lipopolysaccharides (LPS) [20,21]. They initiate immune responses by phagocytosing and destroying foreign elements that enter the body, including microorganisms and viruses [22,23]. M1 macrophages occasionally show reactions against endogenous substances in the body. This reaction involves critical physiological functions such as removing cancer cells that are generated in the body [24]; however, it can also cause pathological states such as autoimmune diseases [25].

The effector functions of the M1 macrophages are characterized by the production of high-level proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, and the expression of inducible nitric oxide synthase (iNOS), which recruits other types of immune cells to the infection or injury site [16,18]. Besides these molecules, some cell-surface proteins, such as CD80 and CD68, also serve as M1 macrophage markers [26]. Furthermore, it has been reported that M1 macrophages are involved in the formation of granulomas, which are masses of immune cells that wall off infected tissue [27].

In contrast, M2 macrophages are activated by type 2 cytokines, such as IL-4 and IL-13. They typically produce anti-inflammatory cytokines, such as IL-10 and transforming growth factor (TGF)-β, which help suppress the immune response and promote wound healing, tissue repair, and remodeling [18,19]. Additionally, M2 macrophages are involved in clearing apoptotic cells and tissue debris as well as promoting angiogenesis [28,29]. Compared to M1 macrophages, M2 macrophages show more diverse characteristics and can be subdivided into several subclasses based on their functions and the signals that they receive [20]. The distinct

subclasses of M2 macrophages and their characteristics, including their selective markers, are summarized below. However, it should be noted that the validity of the classification and markers remains controversial.

1. M2a macrophages: This is a subclass of macrophages that are activated by IL-4 and IL-13, which are produced by T helper type 2 (Th2) cells and innate lymphoid cells type 2 (ILC2). These macrophages are involved in tissue repair and remodeling and are known to promote blood vessel growth. Several proteins have been accepted as representative markers of M2a macrophages, which include arginase-1, CD163, CD206, and C-C motif chemokine ligand (CCL) 22 [13,31,32].

2. M2b macrophages: This is a subclass of macrophages that are alternatively known as "regulatory macrophages" or Mregs. These macrophages are activated by immune complexes and Toll-like receptor (TLR) ligands, which are molecules that activate the innate immune system, and are characterized by high levels of IL-10 and low levels of IL-12 production [18]. They are involved in immune regulation and the resolution of inflammation; therefore, they are essential in preventing the development of autoimmune diseases [30]. CD86, MHC2, and CCL1 are accepted as typical markers that characterize M2b macrophages [13,33].

3. M2c macrophages: This is a subclass of macrophages that are activated by anti-inflammatory cytokines, such as IL-10 and TGF-β. M2c macrophages are involved in tissue repair and immune regulation, as well as helping to suppress the inflammatory response. They are typically characterized by the expression of CD206, CD163, TLR1, and TGF-β [13,34].

4. M2d macrophages: This is a subclass of macrophages that are alternatively known as tumor-associated macrophages. They are the major inflammatory component of the tumor microenvironment [13,35].

3. Association of allergy with macrophage polarization

Although several types of immune cells are involved in allergic reactions, recent research has revealed the crucial role of macrophages in the development and modulation of these allergic responses [11,36]. For example, macrophages are the most abundant immune cells present in the lungs (approximately 70% of the immune cells) and play a crucial role in asthma caused by environmental allergen-induced airway inflammation [37]. As antigen-presenting cells, macrophages phagocytose and process various substances, including allergens, and present these allergen-derived peptides to the T cells, which in turn activates the adaptive immune system and the subsequent production of allergen-specific IgE in B cells. The M1 and M2 polarization of macrophages is closely associated with the balance of the Th1-Th2 T cells, and the macrophage-T cell-B cell cascade forms the foundation of allergic sensitization [38]. Furthermore, macrophages are closely associated with the modulation of allergic reactions through their phenotypic plasticity. It has been demonstrated that M2 macrophages regulate allergic responses by suppressing the activity of lymphocytes that are involved in allergic reactions [11,12,39]. For example, M2 macrophages produce Resistin-Like Molecule α (RELMα), which correlates with the appearance of Foxp3-expressing regulatory T cells [40]. It is reasonable to assume that maintaining immune tolerance is crucial to suppressing allergic reactions.

When macrophage functions are dysregulated, various allergic diseases can occur. For example, dysregulated macrophage functions in the lung and nasal tissues can cause allergic asthma and allergic rhinitis [11-14,41,42]. Recent studies have demonstrated the involvement of macrophages in the development of food allergies. For example, macrophages in the gut play an important role in maintaining tolerance to antigens present in ingested food. The

dysfunction of macrophages in the gut mucosa can disrupt this tolerance, which leads to an increased risk of developing food allergies [43].

Considering the knowledge presented above, targeting macrophage polarization to manipulate their phenotype switch from M1 to M2 macrophages may promote immune tolerance and suppress exaggerated immune reactions. Therefore, this could be a potential therapeutic strategy to reduce allergic responses.

4. ncRNAs in macrophage polarization

ncRNAs are RNA molecules that do not encode proteins. There are at least three classes of ncRNAs that regulate gene expression: microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs). Furthermore, ncRNAs that regulate protein activity have been described [44,45]. While miRNA-mediated regulation of gene expression occurs at the post-transcriptional level, lncRNAs and circRNAs may utilize diverse mechanisms of action. Emerging evidence has highlighted the critical role of ncRNAs in regulating macrophage polarization, which may lead to the development of allergies [46-48]. Although the mechanisms by which ncRNAs regulate macrophage polarization are diverse and complex, several studies have shown that ncRNAs potentially regulate M1 and M2 macrophage polarization by targeting the regulators of pro-inflammatory signaling pathways or regulating the expression of anti- or proinflammatory cytokines.

Although published studies have thus far highlighted the functional association between ncRNAs and macrophage polarization or that between ncRNAs and allergic diseases, few reports have described the ncRNA-macrophage polarization-allergy axis. Therefore, in the following sections, we summarize these previous studies on how the individual ncRNA classes are involved in macrophage polarization and related to allergic diseases.

4.1 miRNA-mediated regulation of macrophage polarization

miRNAs are small (typically 22 nt in length) ncRNAs that post-transcriptionally regulate gene and protein expression by binding to the 3′-untranslated region of the target mRNAs, which induces mRNA degradation and translational repression. Several miRNAs have been demonstrated to regulate macrophage polarization related to allergic diseases (Table 1). For example, Paoletti *et al*. demonstrated that elevated expression of *miR-155-5p* in monocytes isolated from patients with rheumatoid arthritis, which is categorized as a type-3 allergy, inhibits their polarization into anti-inflammatory M2-like macrophages by attenuating the downstream signaling of the macrophage-colony stimulating factor receptor [49]. Consistently, it was reported that *miR-155-5p* directly targeted the IL-13 receptor alpha1 and could be involved in the regulation of the M1/M2 macrophage balance by modulating signaling by IL-13, a typical pro-M2 cytokine signal associated with allergic diseases such as asthma [50]. Further, the enhanced proinflammatory response of RAW264.7 macrophage-like cells to IL-33, another proinflammatory cytokine associated with allergic diseases, in an allergic environment was shown to be paralleled with the increased *miR-155-5p* expression [51].

In addition, Jaiswal *et al*. reported the upregulation of *let-7c* and *miR-99a-5p* in macrophages in an ovalbumin-induced allergic airway inflammation mouse model, which promoted M2 macrophage polarization [52]. Although *let-7c* was previously demonstrated to target C/EBP-δ during M2 macrophage polarization [53], this study identified that TNF-α was the target of *miR-99a-5p* during M2 macrophage phenotype activation [52]. In contrast, angiotensin II was shown to enhance M1 macrophage polarization through the *lin28b*-mediated abrogation of *miR-99a-5p* activation [52]. Wang *et al.* demonstrated that M2 macrophage polarization in allergic rhinitis was promoted by the *miR-202-5p*-Matrilin-2 axis [54]. Further,

Lee *et al.* recently reported that the inhibition of *miR-21* suppresses the alveolar M2 macrophage polarization using an ovalbumin-induced allergic asthma mouse model [55].

The mannose receptor MRC1/CD206 is expressed in immune cells, and its expression level is pronouncedly elevated in M2 macrophages; therefore, it is generally accepted as an M2 macrophage marker. MRC1/CD206 recognizes an extensive range of surface glycoproteins and plays a crucial role in a variety of immunological events, both physiologically and pathologically [56]. Interestingly, *miR-511-3p* is a miRNA that is transcribed from an intron of the *MRC1* gene and the expression of *miR-511-3p* and MRC1/CD206 has been shown to be co-regulated in macrophages [57,58]. Zhou *et al*. demonstrated that *miR-511-3p* directly targeted prostaglandin D_2 synthase, and suppressed its production of prostaglandin D_2, and regulated macrophage polarization and allergen-induced lung inflammation through the analysis of MRC1 knockout mice [59]. It was also reported by Do *et al*. that *miR-511-3p* prompted M2 macrophage polarization and attenuated the cockroach allergen-induced lung inflammation by targeting CCL2 [60]. Alternatively, Heinsbroek *et al*. demonstrated that *miR-511-3p* regulated intestinal inflammation by controlling macrophage-mediated microbial responses through the upregulation of TLR-4 [61]. These findings suggest that *miR-511-3p* regulates macrophage functions and polarization by targeting multiple mRNAs.

Chung *et al*. reported that asthmatic inflammation was promoted in mice that lacked *miR-451a*, which had a negative effect on IL-4-induced M2 macrophage polarization by targeting and silencing the expression of Sirtuin 2 [62]. Veremeyko *et al.* demonstrated that *miR-124* expression was upregulated in the lung alveolar macrophages of an ovalbumin-induced allergic lung inflammation mouse model and contributed to the development of M2, but not M1, macrophage polarization [63]. Another study conducted by Shi *et al.* highlighted the involvement of *miR-142-5p* and *miR-130a-3p* in pulmonary macrophage polarization and

asthma airway remodeling in ovalbumin-sensitized mice [64]. They also reported that *miR-142-5p* and *miR-130a-3p* functioned by targeting suppressor of cytokine signaling 1 (SOCS1) and peroxisome proliferator-activated receptor γ, respectively. Notably, this study revealed that SOCS1 had a negative impact on the M2 macrophage polarization in mice [64], while the M2 polarization of human macrophages has been shown to be promoted by SOCS1 [49].

4.2 lncRNA-mediated regulation of macrophage polarization

lncRNAs are long (generally defined to be >200 nt in length) ncRNAs that regulate gene expression at various levels, which include chromatin remodeling, transcriptional regulation, and post-transcriptional regulation [46-48]. Several lncRNAs have been shown to regulate macrophage polarization related to allergies. For example, MALAT1 promotes M1 macrophage polarization by inducing the expression of pro-inflammatory cytokines, such as TNF-α and IL-6 [65], whereas lncRNA-Cox2 promotes M2 macrophage polarization through the enhanced expression of anti-inflammatory cytokines, such as IL-10 [66]. These lncRNAs have been investigated in numerous studies and have been demonstrated to play roles in not only macrophage polarization but also other physiological and pathological events. However, AK085865 has only been investigated in a few studies, but it should be noted that all of the studies highlighted its role in macrophage polarization [67-68]. In particular, the study conducted by Pei *et al.* showed that AK085865-deficient mice were protected from allergic airway inflammation induced by Der f 1, a major mite allergen component of *Dermatophagoides farinae* [67]. They also found that AK085865 deletion suppressed M2 macrophage polarization, which subsequently decreased their susceptibility to Der f 1-induced airway inflammation. Alternatively, Zhang *et al*. demonstrated that AK085865 specifically interacted with interleukin enhancer-binding factor (ILF)-2 and functioned as a negative

regulator of the ILF2-ILF3 complex-mediated biosynthesis of *miR-192*, which promotes M2 macrophage polarization through the direct targeting of interleukin-1 receptor-associated kinase (IRAK) 1 [68]. In addition, Wen *et al*. recently demonstrated that *MIR222HG* acts on the *miR146a-5p*/TRAF6/NF-κB axis, leading to the attenuation of macrophage M2 polarization and allergic inflammation in allergic rhinitis [69]. However, the MEG8 sponging of *miR-181a-5p* contributes to M1 macrophage polarization by regulating SHP2 expression in an IgA vasculitis rat model, which is a disease triggered by some allergens [70].

4.3 circRNA-mediated regulation of macrophage polarization

circRNAs are a recently discovered class of ncRNAs that form covalently closed circular structures, which make them resistant to degradation by RNA exonucleases [71]. Although the function of circRNAs remains poorly understood, several circRNAs have been demonstrated to regulate macrophage polarization [72]. For example, circANKRD36 promotes M1 macrophage polarization by targeting *miR-197*, a negative regulator of JNK signaling, while circHIPK3 promotes M2 macrophage polarization by targeting *miR-124*, a negative regulator of M2 polarization [73]. Recently, luteolin, a flavone, has been revealed to activate M2 and suppress M1 macrophage polarization through the upregulation of hsa_circ_0001326 in the human macrophage cell line THP-1 [74]. They also elucidated the underlying mechanism of how hsa_circ_0001326 regulates downstream gene expression, including *hsa-miR-136-5p* and USP4.

5. Therapeutic implications of the ncRNA-allergy axis

The dysregulation of macrophage polarization is a primary feature of many allergic diseases, and targeting the ncRNAs that regulate macrophage polarization represents a promising

therapeutic approach for the treatment of these diseases. Several studies have shown that modulating the expression of specific ncRNAs can alter macrophage polarization and ameliorate allergic symptoms. For example, targeting *miR-155* with antisense oligonucleotides or small-molecule inhibitors reduced M1 polarization and alleviated allergic inflammation in asthma and atopic dermatitis animal models. Similarly, targeting lncRNA-MALAT1 with siRNAs or small-molecule inhibitors reduced M1 polarization and improved lung function in an asthma mouse model.

6. Concluding Remarks

As reviewed herein, significant progress has been made regarding the pathological involvement of macrophages in allergies, which includes the functional elucidation of ncRNAs in macrophage polarization. However, there were also limitations in the studies conducted. Since M1 and M2 macrophages have been mainly defined and characterized based on the results of simplified *in vitro* studies, their *in vivo* roles, where the environment is more heterogeneous and complicated, have not been fully elucidated. Nonetheless, it is widely accepted that macrophages are an attractive therapeutic target for immune diseases such as allergies. Moreover, ncRNAs have also been considered promising therapeutic targets in addition to biomarkers. Regulatory networks involving cytokines, chemokines, signaling molecules, and transcription factors, as well as epigenetic events such as DNA methylation and histone modification through methylation and acetylation, are essential for macrophage polarization [11]. Therefore, an improved understanding of how these ncRNAs are associated with these networks is required.

Author Contributions

O.I. wrote the first draft; Z.I. and S.A.M. edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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Table 1 MicroRNAs that regulate macrophage polarization related to allergy.

miRNA[*1]	Materials used	Affecting polarization[*2]	Target	Related pathophysiology	Reference
miR-155-5p	Blood monocytes from rheumatoid arthritis patients	M2 (-)	*SOCS1*	Rheumatoid arthritis	49
miR-155-5p	Blood monocytes from healthy donors and the human monocytic cell line THP1	M2 (-)	*IL13R*	Immune diseases such as asthma	50
miR-99a-5p	Mouse bone marrow-derived macrophages	M1 (-) M2 (+)	*TNF*	Allergic airway inflammation	52
miR-202-5p	Mucus-derived macrophages from allergic rhinitis patients	M2 (+)	*MATN2*	Allergic rhinitis	54
miR-21-5p	Ovalbumin-induced allergic asthma mouse model	M2 (+)	Possibly *IRF5*	Allergic asthma	55
miR-511-3p	Lung macrophages and an allergen-induced lung inflammation mouse model	M1 (-) M2 (+)	*HPGDS*	Allergic lung inflammation	59
miR-511-3p	Lung macrophages and an allergen-induced lung inflammation mouse model	M1 (-) M2 (+)	*CCL2*	Allergic lung inflammation	60
miR-451a	Allergen-induced mouse asthma model	M2 (+)	*SIRT2*	Allergic asthma	62
miR-124-3p	Ovalbumin-induced allergic asthma mouse model	M2 (+)	*CEBPA*	Allergic asthma	63
miR-130a-3p	Ovalbumin-induced allergic asthma mouse model	M2 (-)	*PPARG*	Allergic asthma	64
miR-142-5p	Ovalbumin-induced allergic asthma mouse model	M2 (+)	*SOCS1*	Allergic asthma	64

*1 MiRNAs are indicated as current miRBase identifiers.

*2 Plus and minus signs indicate positive and negative regulation, respectively.

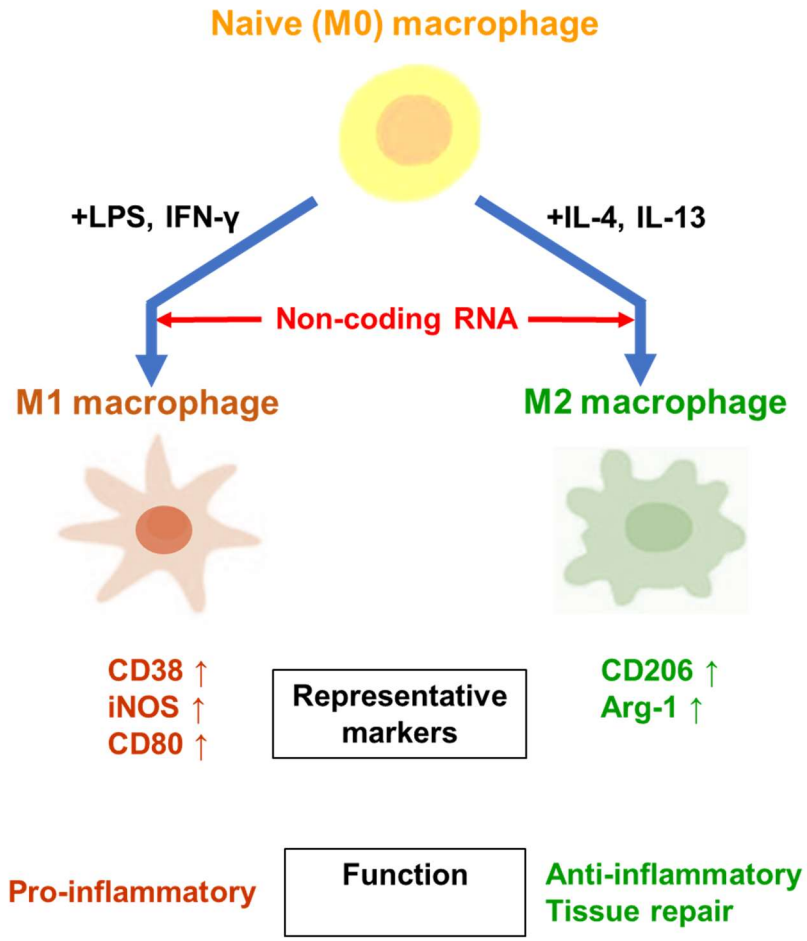

Figure 1. Macrophage polarization Naïve (M0) macrophages in their inactive state can be polarized into either of two types of active macrophages with distinct functions, M1 and M2 macrophages (also termed "classically activated" or "alternatively activated" macrophages, respectively), after exposure to certain stimuli. M1 and M2 macrophages are functionally associated with pro-inflammatory and anti-inflammatory reactions, respectively. Several mRNAs and proteins are used as markers to differentiate between these macrophages; however, macrophage polarization is complicated, and the validity of these markers remains controversial. M2 macrophages are heterogeneous and have been divided into subclasses termed M2a, M2b, M2c, and M2d macrophages based on their functions and marker expression. However, the criteria for the sub-classification still require further investigation.