

MicroRNAs and Allergic Diseases

Wonsuck Yoon*

Institute of Allergy Immunology, Korea University, Republic of Korea

***Corresponding author:** Institute of Allergy Immunology, College of Medicine, Korea University, Seoul 136-705, Republic of Korea, Email: biokorea@korea.ac.kr

Published Date: August 16, 2017

ABSTRACT

microRNAs are a class of small, non-coding RNAs that regulate the expression of a diverse array of genes and pathways, with important roles in disease pathogenesis. Many of these microRNAs are currently under investigation as biomarkers or therapeutic options in a range of diseases. Here, we discuss the role of microRNAs in allergic diseases, allergic asthma, allergic rhinitis and atopic dermatitis as they have been strongly implicated in the pathogenesis of skin inflammation. We outline the history and application of microRNAs for the detection and treatment of allergic diseases in comparison with other diseases, such as cancer and other inflammatory diseases, which may assist the development of diagnostic and therapeutic strategies.

Keywords: MicroRNA, Allergic diseases, Biomarker, Therapeutic application

INTRODUCTION

microRNAs are a class of small, non-coding RNAs ~21-25 nucleotides in length. Over 1000 human microRNAs have been identified to date, primarily located in the intronic regions of other genes. These structures represent an important form of post-transcriptional gene regulation by directly inhibiting gene translation through their binding of the 3' untranslated regions of their target messenger RNA (**mRNA**), resulting in lower mRNA stability, or translation inhibition [1,2]. The effects of these microRNAs are far reaching, with more than 30% of the entire genome affected,

including critical processes, such as development, differentiation, cell growth, and apoptosis. This central role of microRNAs in overall cell function has drawn considerable interest from cancer researchers, as cancers ultimately arise as a result of aberrant gene expression. As microRNAs are readily detected in accessible body fluids, such as saliva, blood, urine, and even hair follicles, this suggests the possibility of microRNAs as potential biomarkers of human diseases. This review summarizes the molecular mechanisms of microRNA activity, highlights recent studies demonstrating their application as both biomarkers and therapy targets, and explores their therapeutic potential for the treatment of allergic diseases.

MICRORNAS AS BIOMARKERS AND THERAPEUTIC TARGETS IN DISEASE

microRNAs were first identified in the mid-1990s with the discovery of Let-7 and Lin-4 in the model organism *Caenorhabditis elegans* [3-4]. Homologs have since been identified in nearly all eukaryotic organisms, with significant conservation among species. Given the strong conservation of these structures, and their central role in processes such as development, differentiation, cell growth, and apoptosis, it was not surprising reports of aberrant microRNAs expressed in cancers and other diseases emerged soon thereafter.

Ongoing clinical trials are currently assessing the correlation between microRNA expression and disease prognosis in cancer. As *in vitro* expression profiles of many tumor-derived microRNAs have shown promise for the diagnosis of patients, microRNA expression profiles might be used to precisely classify various cancer types, and might be superior to gene expression profiles in classification of tumors. More widespread screening before the onset of disease is also possible; stable microRNAs detected in easily accessible fluids, such as serum, plasma, and urine, as well as hair, have shown distinctive patterns of microRNA expression among patients and controls highlighting their possible use as diagnostic markers [5,7].

Interestingly, a single microRNA can simultaneously regulate both tumor suppressive and oncogenic target genes within a single cancer. For example, miR-196b can target not only the *HOXA9/MEIS1* oncogenes, but also FAS tumor suppressor gene in mixed lineage leukemia-rearranged leukemia [8,9]. This implies that tumor initiation and development, as influenced by microRNAs, might be more complex than previously thought, which has important implications for using microRNAs as therapeutic agents. To date, several drugs have been shown to alter microRNA expression, including the bioactive agent docosahexaenoic acid, which inhibits the expression of miR-21, a protumorigenic microRNA [10]. Researchers are currently designing inhibitors for oncogenic microRNAs, along with mimics for tumor-suppressor microRNAs, which can act alone or synergistically with currently approved treatments [10-11].

In addition to cancer, many microRNAs have been identified as novel biomarkers and potential therapeutic targets for cardiac hypertrophy (miR-23a, miR-23b, miR-24, miR-195, miR-199a, miR-214), Down syndrome (miR-99a, let-7c, miR-125b-2, miR-155, miR-802), Alzheimer (miR-9,

miR-128a, miR-125b), Rheumatic arthritis (miR-155, miR-146), Systemic lupus erythematosus (miR-189, miR-61, miR-78, miR-21, miR-142-3p, miR 342, miR-299-3p, miR-198, miR-29, miR-196a, miR-17-5p, miR-409-3p, miR-141, miR-383, miR-112, miR-184) and Psoriasis (miR-203).

microRNAs play a crucial role in the biogenesis and function of the gene regulatory system, and have been implicated as dynamic regulators of many cell signaling and remodeling [12-14].

MICRORNAS AND ALLERGIC DISEASES

Recently, the role of microRNAs in disease pathogenesis has begun expanding outside of the realms of cancer to allergic diseases with significant attention paid to both genetic and environmental factors. In allergic disease, microRNAs have been reported that microRNA induced the pathogenic mechanisms of allergic inflammation [15].

microRNAs regulate Th1 versus Th2 polarization mechanism in multiple allergic inflammatory diseases by regulating cell types to the allergic inflammatory response, including basophils, eosinophils, T, B cells and mast cells.

Recent studies showed that many microRNA in patients with allergic diseases including allergic asthma, allergic rhinitis and atopic dermatitis are related pathological mechanism and these microRNAs are listed in Figure 1, which includes microRNAs that are up regulated or down regulated in allergic diseases. These allergy-related microRNAs were suggested as factors regulate the initiation and/or maintenance of allergic inflammatory responses.

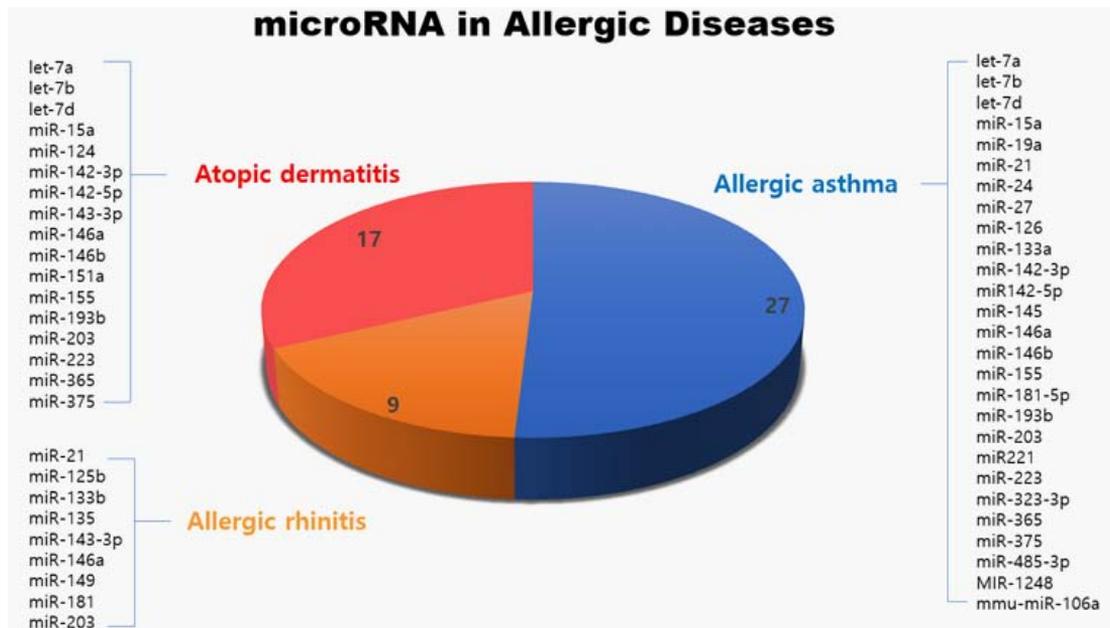


Figure 1: MicroRNAs related with allergic diseases in human and mouse.

MICRORNAS AND ALLERGIC ASTHMA

Differential expression of microRNAs has been more investigated in allergic asthma than other allergic diseases. microRNAs in biological fluids from asthmatic patients were considered as regulator of lung function. These microRNAs would be useful as potential biomarkers of disease. However, their use as inflammatory regulator in the allergic asthma remains unclear. The followings are summary of microRNA function in allergic asthma.

let-7a: In patients of asthma, expression of let-7a were shown to have important roles in asthma pathogenesis. Reduced let-7a levels in bronchial biopsies of patients would be a potential biomarker to discriminate asthma phenotypes [16].

let-7b: let-7b have been implicated in airway smooth muscle function, inflammation, and airways epithelial cell function. let-7b, inhibited eosinophilic inflammation, mucus hyper secretion, T(H)2 cytokine production, and airway hyper responsiveness [17].

let-7d: let-7d were observed in asthmatic patients compared to controls. Predictive algorithm analyses of these microRNAs revealed their specificity for different Th2 cytokines, including IL-5, which has not previously been shown to be post-transcriptionally regulated [18].

miR-15a: Lower levels of hsa-mir-15a, which decreases VEGFA, in the CD4+ T cells of pediatric patients with asthma [19].

miR-19a: MiR-19a was up regulated in epithelia of severe asthmatic subjects compared with cells from mild asthmatics and healthy controls. miR-19a enhances cell proliferation of BEC in severe asthma through targeting TGF- β receptor 2 mRNA. Moreover, repressed expression of miR-19a increased SMAD3 phosphorylation through TGF- β receptor 2 signaling and abrogated BEC proliferation [20].

miR-21: Over expression of microRNA-21 in the patients of bronchial asthma. Previous study showed that miR-21 that modulates IL-12, a molecule germane to Th cell polarization [21].

miR-24: miR-24 are considered as regulator of Th2 cellular immune reponses which each functioned independently to limit interleukin-4 (**IL-4**) production [22].

miR-27: miR-27 related with interleukin-4 (**IL-4**) production as regulators of Th2 cell biology [23].

miR-126: In animal model of chronic asthma, there was an increase in expression of a small number of miR-126 in the airway wall [24].

miR-133a: In a mouse model of allergic bronchial asthma, the level of miR-133a was significantly decreased with increased expression of IL-13 and RhoA and the bronchial smooth muscle hyper responsiveness [25].

miR-142: miR-142-3p and miR142-5p was up regulated in sputum of patients with asthma.

miR-142-3p expression in neutrophils, mono cytes, and macrophages was associated also with airway obstruction and related with neutrophilic airway inflammation [26].

miR-145: miR-145 was higher expression in asthma patients. miR-145 may regulate the imbalance of Th1/Th2 in asthma patients [27].

miR-146: miR-146a and miR-146b are negative regulators of inflammation in airway smooth muscle thereby contributing to pathogenesis of asthma. miR-146 mimics may be an therapeutic candidate for treatment of asthma [28].

miR-155: In patients with asthma, lower levels of miR-155 were detected in sputum from allergic asthmatics compared to healthy subjects. This miR-155 reduced by seasonal environment factor like as pollen in sputum [29].

miR-221: In airway smooth muscle cells cultured from bronchial biopsies of patients with asthma, miR-221 were increased from individuals with severe asthma. miR-221 may regulates the hyper proliferation of airway smooth muscle cells from patients with severe asthma [30].

miR-323: An expression of miR-323-3p were increased in PBMCs from patients with asthma. and miR-323-3p levels are re IL-22 production in PBMCs cultured in T-cell growth conditions was observed. miR-323-3p might be a negative regulator of the production of IL-22 in PBMCs cultured in T-cell growth [31].

miR-375: PM induced miR-375 in primary human bronchial epithelial cells. miR-375 maybe regulator of of thymic stromal lymphopoinetin by particulate matter like as diesel exhaust [32].

miR-1248: Altered expression of miR-1248 was observed in asthmatic patients. miR-1248 regulated with IL-5 expression and would be potential tool for the diagnosis and therapeutic tool of asthma [33].

MICRORNAS AND ALLERGIC RHINITIS

Recent investigations suggested that the regulation by microRNAs is critical in allergic rhinitis pathogenesis. Relatively little research has been done in allergic rhinitis and microRNA. The followings are summary of microRNA researches in allergic rhinitis.

miR-21: miR-21 and miR-126, were lower in mono cytes from children with allergic rhinitis. miR-21 with expression of TGFBR2 expression would be regulator of IgE production and development of allergic rhinitis [34].

miR-143: The interleukin-13 (**IL-13**) related with allergic rhinitis were stimulated in nasal epithelial cells and miR-143 was decreased. When miR-143 suppressed IL-13 receptor $\alpha 1$ chain (IL13R $\alpha 1$) gene, inflammatory cytokines were increased in nasal epithelial cells from patient with allergic rhinitis [35].

miR-149: miR-149 were increased in patients with allergic rhinitis, compared with the

healthy subjects. When PBMCs obtained from the healthy controls were stimulated by house dust mite extracts, the levels of miR-149 were decreased [36].

miR-203: In analysis of extracellular vesicles from nasal mucus from patients with allergic rhinitis,

miR-203 was significantly increased, while microRNA-875-5p was decreased in patients with allergic rhinitis [37].

MICRORNAS AND ATOPIC DERMATITIS

There are many studies describing an expression of microRNAs in the skin or serum. Relatively little is known about the function of these microRNA in atopic dermatitis. The followings are summary of microRNA in atopic dermatitis.

miR-155: miR-155 was more increased expression in patients with atopic dermatitis than healthy subjects and co-related with severity of atopic dermatitis. miR-155 may be involved in pathogenesis of atopic dermatitis by modulating the function of Th17 cells [38].

miR-203: miR-203 and miR-483-5p were up-regulated from serum in patients with atopic dermatitis. The miR-483-5p was also associated with rhinitis or asthma. But, miR-203 was significantly decreased in urine of children with abnormal level of serum IgE in AD patients [39].

miR-223: In humans skin biopsies were collected from subjects with allergic responses to diphenylcyclopropenone, miR-21, miR-142-3p, miR-142-5p and miR-223 were over-expressed. Moreover, in animal model like human skin model, the same microRNAs were over-expressed in a mouse model of contact allergy [40].

In addition to these results, recent studies have shown that many of the allergy-related microRNAs regulate the initiation and/or maintenance of allergic inflammatory.

Especially, atopic dermatitis is an inflammatory skin disease that results from a combination of genetic predisposition, imbalanced immune responses, epidermal barrier abnormalities, and severe pruritus. A Th1/Th2 imbalance is a key factor in the pathogenesis of allergic diseases such as atopic dermatitis, with some reports implicating microRNA regulation of innate and adaptive immune responses in Th2 polarization [41-45]. Immune cells, including monocytes/macrophages, and dendritic cells, as well as T and B lymphocytes, play a key role in atopic dermatitis [46]. microRNAs have been shown to regulate an array of immune cell functions, including macrophage-derived cytokines (**MDC**) and the expression of inflammatory mediators in the context of atopic dermatitis [47,48]. microRNA expression profiling of human skin with psoriasis and atopic eczema revealed differential microRNA expression compared to healthy subjects, with multiple microRNAs differentially expressed in lesions skin relative to that of healthy controls [49]. Depending on the microRNA involved, these structures can function as suppressors or activators of various skin diseases.

The Th1/Th2 imbalance plays a central role in the clinical expression of allergy and asthma, with Th2 cytokines acting as a driving factor in the pathophysiology of allergic diseases [41,44,45]. This balance of immune responses is heavily influenced by microRNAs, with serum levels providing insights into the pathology of allergic diseases [50]. The let-7 family of microRNAs has been shown to regulate IL-13 production by human T cells, resulting in reduced IL-13 production in the lungs, and alleviation of airway inflammation in a murine model of asthma [51]. Similarly, the miR-200 family of microRNAs regulates expression of E-cadherin, with suppression of E-cadherin is associated with increases in CCL17, a Th2 cell chemo attractant [52]. Other microRNAs, such as miR-1 and miR-155, also play a role in allergic inflammation, as suppression of these microRNAs by VEGFA contributes to Th2 inflammation in the endothelium and promotes recruitment of activated T cells and subsequent eosinophilic inflammation, together with Th2 cytokine production [53,54].

Recently, our group demonstrated that microRNA targeting CCL22 suppressed inflammatory responses in macrophages and in an animal model of atopic dermatitis [55,56]. This MDC/CCL22 axis was directly implicated in Th2-associated skin inflammatory reactions with significant increases in serum concentrations strongly correlated with disease severity in atopic dermatitis. In those studies, a recombinant strain of *Salmonella typhimurium* expressing CCL22 microRNA (**ST-miRCCL22**) was used for the *in vivo* knockdown of CCL22 as a treatment for AD. ST-miRCCL22 was shown to significantly down regulate CCL22 expression in activated lymphocytes *in vitro*. Subsequent *in vivo* analyses in a mouse model of atopic dermatitis revealed decreases in both IL-4 and IgE expression, alongside increases in IFN- γ ; Th17 cells were also suppressed in atopic like model mice treated with ST-miRCCL22. Together, these data suggest that targeted microRNA delivery may be an effective method for the treatment against atopic dermatitis (Figure 2).

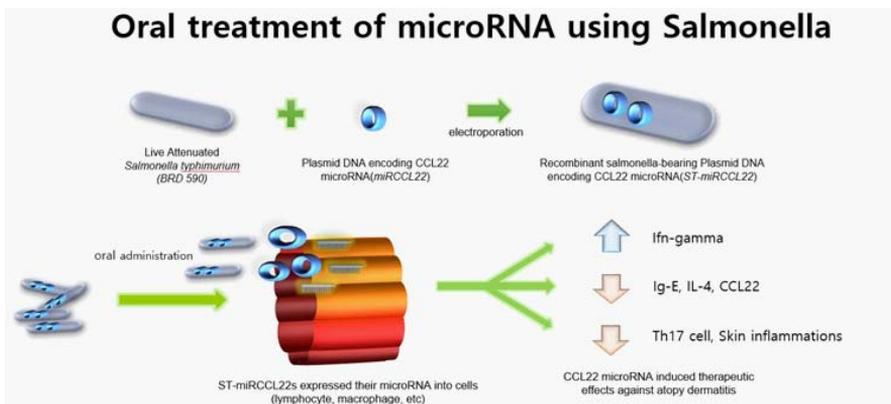


Figure 2: Oral treatment of microRNA using Salmonella. Recombinant *S. typhimurium* expressing CCL22 microRNA (**ST-miRCCL22**) were constructed by pcDNATM6.2-GW/EmGFP-miR expression vector using electroporation. In atopic like animal model, Changes in IL-4, IFN- γ and IgE levels in serum were tested by elisa, Th 17 cells were tested by FACS analysis (R&D system). Samples were collected seven days after oral inoculation.

CONCLUSIONS

microRNAs have been suggested as potential biomarkers and therapeutic agents for the treatment of human diseases, such as cancer; similar strategies may also be applicable for the treatment of allergic diseases, such as AD, with multiple products currently in development. Although the current state of knowledge regarding the expression, regulation, pharmacokinetics, and safety of microRNAs as a therapeutic strategy remain limited, these compounds hold tremendous promise for the treatment of all stages of allergic diseases. Collectively, these researches suggested that microRNAs are regulators of allergic inflammation and have potential importance as diagnostic and therapeutic options.

ACKNOWLEDGEMENT

The author thanks Nanim Ha for technical assistance. This study was also supported by NRF Fund grant number NRF-2015R1D1A4A01019910.

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