

The Role of miRNAs in Asthma

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Abstract – Asthma is a heterogeneous respiratory disease that causes cough and respiratory distress and is known to greatly affect the quality of life in the later stages. In asthma, as in all other inflammatory diseases, miRNAs control the cell's ability to grow, reproduce, and survive by regulating the interactions of cells that shape the bronchi, airway structure, and cells responsible for defense mechanisms in the lungs. In addition, miRNAs play an active role in synthesizing and secreting immune mediators and chemokines. More importantly, they are molecules with chemical and biological properties that allow patients to be classified for optimal drug selection, can be used as appropriate biomarkers for diseases, and simplify clinical management. At the same time, these molecules ease the burden of intensive care associated with diseases, while reducing the economic burden of the disease. In this review, we discussed the interrelationships between miRNAs and asthma pathologies as well as the effect of miRNAs on the disease trajectory in asthma.

Keywords – Asthma, miRNA, Biomarkers, Treatment

I. INTRODUCTION

Asthma is a chronic inflammatory childhood disease that occurs as a result of the interaction of genes and the environment. Shortness of breath may indicate symptoms such as chest tightness and coughing. There is no known definitive treatment for severe asthma disease. Asthma disease can be suppressed with medications and measures to be taken against allergens [1], [2].

miRNAs, which are non-coding RNA molecules, act as partial complements of mRNA. MiRNAs are involved in the development of immune cells, regulating the inflammatory response in tissues and signaling pathways in cells [3], [4].

Many studies have shown that miRNAs have a pathophysiological role in asthma disease. With the information obtained from these studies, miRNAs have been used as biomarkers and miRNA-based therapeutics have been developed in order to find a definitive treatment for asthma disease. The results obtained have been shown to be of a promising nature for definitive treatment [3], [4].

A. What is Asthma?

Asthma can be characterized by increased bronchial airway sensitivity and reversible airway obstruction in combination with various stimuli. It is a chronic inflammatory disease that can improve spontaneously or with treatment [3], [5].

Asthma is a childhood disease whose prevalence, morbidity and mortality increase over the years [6].

Inflammation and thickening of the airway wall are seen in asthmatic individuals. This is caused by excessive accumulation of mucus or inflammation. During an attack, smooth muscles contract and air becomes clogged in asthmatic individuals. Cough, wheezing, chest tightness and shortness of breath are the most common indications during acute attacks of asthma [7]- [9].

There is no known definitive treatment for asthma disease. Asthma symptoms can be prevented by taking precautions against allergens and substances that will irritate the respiratory tract [4], [6].

B. What is Allergic Rhinitis?

Allergic rhinitis is a disorder that is colloquially referred to as hay fever and shows symptoms similar to the classic cold [7], [10]. Allergic rhinitis can occur as a result of the body's immune system's response to various factors such as pollen, mites, feathers [11]. It is also known as seasonal allergy. This is because pollen is released from trees and flowers into the air at certain times of the year, such as autumn and spring [12]. Symptoms such as runny nose, tears, redness of the palate and itching may occur [11].

C. Factors Affecting Asthma

It is known that asthma is hereditary and therefore the risk of asthma in children of asthmatic parents increases. As asthma is not caused by a single gene mutation, it does not follow Mendelian inheritance, on the contrary, it is a multifactorial, polygenic disease [13], [14]. These factors that cause the development of the disease can be environmental or genetic [7], [15],[16].

C1. Environmental Factors

Respiratory allergens and occupational sensitizers are the main environmental risk factors for asthma. Allergens such as dust mites (cutaneous mites), pets, cockroaches, fungal spores, and pollen, which is especially common indoors and in infancy, are important risk factors for asthma [15]-[17].

In addition, nutrition, tobacco smoke exposure, socio-economic status, the number of family members and the living environment are also among the environmental risk factors that cause asthma [18]-[20].

C2. Genetic Factors

More than 100 genes have been found to be associated with asthma, and miRNAs involved in asthma continue to be investigated. Genes associated with asthma were examined in three categories: genes that cause asthma by affecting the functioning of the immune system, genes that cause asthma by disrupting the basic function of the lung, and genes that cause asthma by disrupting mucosal function [13]. In addition, gender and race are among the genetic factors that cause asthma [13], [17].

D. Micro RNA

miRNAs, which have become increasingly important in recent years, are single-stranded RNA

molecules with a length of 18-25 nucleotides [8]. They act as a partial complement of messenger RNA (mRNA). These molecules are involved in the regulation of gene expression. It has been shown that disorders and mutations that may occur in mirnas disrupt the normal function of messenger RNA and therefore cause diseases by disrupting the number and shape of proteins and gene products produced [8], [9], [21].

miRNAs play a role in regulating the inflammatory response in tissues, developing immune cells, and controlling signaling pathways. Because of these properties, miRNAs are accepted as important biomolecules in the pathogenesis of asthma. In addition, miRNAs, which are known to be in an extremely stable state, can be used as biomarkers in asthma as well as in other diseases [4].

E. miRNA and Asthma

Various studies have shown that miRNAs differ in their expression in various asthma models [7]. Differential expression of miR-3620-3p, miR-4707-3p, miR-1229-3p, miR-145-5p, miR-338-3p, miR-4485, and miR-636 in serum from patients with asthma by Wang et al. has been observed [4], [22], [23].

Sinha and colleagues mentioned with their study that there are 11 miRNAs differentially expressed in EBC (Exhaled Breath Condensates) in asthmatic patients compared to healthy patients [4], [24].

MiR-570-3p levels are inversely correlated with lung function, and miR-570-3p levels were found to be lower in EBC and serum from asthma patients [4], [25].

It has been observed that the expression of miR-21 and miR-126 is upregulated in airway epithelial cells taken from asthma patients, and the expression of miR-21 and miR-126 is decreased in patients receiving inhaled corticosteroids (IC). In addition, it has been noticed that IL-13 increases the expression of miR-21 and miR-126 [4], [26].

Tiwari and colleagues conducted a study in which children with asthma studied the circulating miRNAs. In this study, they investigated the relationship of miRNAs with allergic inflammation and seasonal change in asthma symptoms. As a result of the research, they mentioned that the expression of miR-328-3p and let-7d-3p changes seasonally, that miRNAs are associated with

seasonal asthma symptoms and seasonal allergies [22], [27].

It has been proven that circulating miR-21 in plasma in patients with moderate asthma has an estimated diagnostic probability of 76% and miR-223 of 83% and can be used for biomarkers or targeted immunotherapies in asthma [22], [28].

With all these studies, it is shown that miRNAs may be associated with the occurrence of asthma. In addition, these studies strengthen the idea that miRNAs can be used as biomarkers in the treatment of asthma disease [4], [8], [22].

F. MiRNA Regulation of Asthma Pathogenesis

F1. MiRNA Control of Asthma Mechanisms and Regulation of Immune Responses

An effective immune system must have the ability to recognize and eliminate harmful pathogens [29]. When the immune system is not functioning effectively, chronic exposure to damaged cells, pathogens, antigens, allergens, toxins or irritants results in autoimmunity, impaired inflammatory response, tissue damage and allergic diseases. [4], [29].

miR-155, miR-21 and miR-146a are the most commonly studied miRNAs in both natural and adaptive immune responses [30]-[32].

Recently, a study has been conducted to determine the differences between individuals with asthma and normal individuals. In this study, miRNA samples taken from EBC were examined. As a result of the study, it is suggested that both miR-21 and miR-146a can be used as biomarkers in determining asthma severity [4], [33], [34].

An experimental asthma model has been created using dermatophagoides. It has been observed that this created model has higher than normal levels of miR-145 on the airway wall [8], [35]. With these studies, allergic inflammation of anti-miR-126 and anti-mir-145, mucus production, eosinophil infiltration, Th2 cytokine production (eg., IL-5 and IL-13) and has been documented to significantly reduce airway hyperreactivity [8], [35], [36]. MiR-126 is known to promote Th2-mediated allergic inflammation [8], [37].

Finally, with recent studies, it has been reported that there is an inverse correlation between respiratory function parameters and miR-16 in asthma disease [5]. Silico analysis showed that the ADRB2 gene, a gene associated with bronchial smooth contraction and involved in the mechanism

of asthma, was predicted to be a target gene for miR-16. This prediction has been confirmed by luciferase analysis [8], [38].

F2. MiRNAs in Viral Exacerbations in Asthma

It is known that many viral acute respiratory infections (ARI) caused by viral exacerbations are the main cause of chronic respiratory diseases, especially. Asthma is also one of the chronic diseases that occur as a result of viral exacerbations [8], [39]. It is known that miRNAs act as regulators in the formation of an immune response to viruses that cause viral acute respiratory infection, such as the human rhinovirus (hRV), the flu virus [8], [40].

It is known that miR-128 and miR-155 in targeting hRV genetic material are potential regulators of the innate immune response to protect against hRV-1b [8], [41], [42]. In one study, gene silencing of miR-128 and miR-155 was performed. As a result of the study, it was stated that hRV replication increased by up to 50% [8], [41].

In another study, miR-27a, miR-18a, miR-155 and miR-128 were down-regulated in asthmatic HBECS (Human bronchial epithelial cells). It has been reported that the suppression of these four miRNAs causes a significant increase in the expression of IL-8 and IL-6, which are associated with asthma severity [8], [43].

It has been shown by many studies that many miRNAs are involved in viral exacerbations of asthma disease by different mechanisms. These studies try to explain how miRNAs control responses to specific viruses or how viruses interact with host cells [8],[22].

G. miRNA-Based Therapeutics

There is no known definitive treatment for asthma and allergic asthma. Asthma and allergic asthma can be suppressed by using certain medications or by taking precautions against allergens [4], [6]. Therefore, new approaches are needed to treat asthma. MiRNA-based therapeutics are used to develop new treatments for enhancing immunity against viruses that can cause asthma or reversing their allergic condition, preventing exacerbations in patients with severe asthma [4].

In a study conducted with patients who responded to asthma treatment; reslizumab or mepolizumab treatment was applied to patients. It has been stated that the amount of miR-338-3p in the serum of patients increased after this treatment was applied.

These results indicate that miR-338-3p can be used as a biomarker for reslizumab or mepolizumab response in patients with severe eosinophilic asthma [8], [44].

In addition, a study was conducted by administering the drug benralizumab to individuals with asthma for 8 weeks. As a result of this study, it was observed that the serum levels of miR-5100, miR-1246 and miR-338-3p changed in asthmatic individuals. However, it has been mentioned that the expression level of miR-1246 decays and there is a correlation between blood eosinophil counts. This study suggests that miRNAs can be used as biomarkers in the formation of early response to the drug benralizumab in asthma disease. [8], [45].

Finally, miRNA-based therapeutics are promising biomarkers in the treatment of severe asthma and allergic asthma. Also, miRNA mechanisms of action may not be as simple as thought [4], [8], [22]. Using miRNAs as a potential therapy can produce a large number of 'off-target effects' that we are not yet aware of [8].

II. CONCLUSION

As a result, numerous studies have shown that miRNAs can be used in the opinion and treatment of asthma. MiRNA- grounded curatives are promising biomarkers in the treatment of severe and allergic asthma. Also, miRNA mechanisms of action may not be as simple as study. Using miRNAs as implicit rectifiers can beget numerous off- target goods that we aren't yet apprehensive of. Still, bettered ways for targeting miRNAs and further information about the natural functions of miRNA in primary cells may lead to the development of specific gene controllers for asthma and allergic asthma in the future. Exploration on the remedial use of miRNAs in the treatment of asthma and allergic asthma is ongoing.

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