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REVIEW

The role of regulatory RNAs (miRNAs) in asthma

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Abstract
Introduction: Recently, a great deal of attention has been paid to the investigation of regulatory functions of microRNA. Currently, many different mechanisms involved in the pathogenesis of asthma are known, but the whole picture of pathogenesis has not yet been studied.
Conclusions: MicroRNAs play an important role in the regulation of many cellular processes. Undoubtedly, these regulatory molecules are involved in the pathogenesis of asthma, and therefore can be potential targets for treatment.

Asthma is a chronic inflammatory airway disease that occurs as a reaction to inhaled antigens, such as respiratory viruses, allergens or air pollutants, which leads to airway inflammation, excessive airway hypersensitiveness and reversible airflow obstruction. The key link in bronchial asthma is bronchial obstruction.[2]

The pathogenesis of bronchial asthma is based on a non-specific increase in the bronchial hyper-reactivity. The higher the bronchial hyper-reactivity the more serious the disease is and the more difficult the treatment is.[9,21] It is still unknown why the bronchial hyper-reactivity increases in patients with bronchial asthma. An important role in the pathogenesis is played by mast cells, eosinophils, macrophages, neutrophils and lymphocytes. Mediators of inflammation that are released during degranulation of mast cells – histamine, bradykinin, leukotrienes C, D and E, etc. – cause a spasm of smooth muscles of the bronchi, vasodilation and mucosal edema. In addition, leukotrienes cause mucus secretion and mucociliary transport disorders, which creates conditions for the transition of acute inflammation to chronic inflammation.[7] Also, T-lymphocytes play an important role in the development of bronchial asthma.[1] There are many T-lymphocytes in bronchi in patients with bronchial asthma. They secrete cytokines and participate in the regulation of cellular and humoral immunity. Th1 produces IL-2 and IFNγ, which stimulate the proliferation and differentiation of T-lymphocytes and activating macrophages. Th2 produce IL-4, -5, -10, -13, which stimulate the proliferation of B-lymphocytes and synthesis of immunoglobulins. In addition, IL-5 stimulates the proliferation, differentiation and activation of eosinophils, and possibly the degranulation of basophils.[1,20] Currently, many different mechanisms

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Table 1 The role of miRNAs in the pathogenesis of asthma.

Name	Mechanism	Reference
MIR221	A high level of miR-221 expression was detected in the lungs of mice with ovalbumin-induced asthma. Inhibition of miR-221 reduced inflammation in the airways. The scientists suggested that miR-221 promotes the production of cytokines in vivo and the degranulation of mast cells.	8
MIR21	Large amount of miR-21 is produced by macrophages and dendritic cells. Scientists suggest that miR-21 is able to regulate Th1 and Th2 balance, changing the expression of IL-12p35, because IL-12p35 is a molecular target of miR-21. MiR-21-deficient CD4 T cells produce an increased level of IFN-γ and a decreased level of IL-4. The delayed-type hypersensitivity reaction is significantly enhanced after miR-21 inhibition. In experiments on the animal model of asthma, it was shown that miR-21 suppresses signaling pathways of Toll-like receptors. It has also been shown that miR-21 is activated in the epithelial cells of the human respiratory tract after treatment with IL-13.	17
	GM-CSF increases the expression of miR-21, which in turn promotes the action of the T-helper 2-cytokine IL-13 in the pathogenesis of asthma. Potentially, miR-21 plays an important role in allergic inflammation of the lungs	29
MIRLET7A1	Studies have shown that IL-13 is the direct target of let-7, and it was also found that Th1 had significantly higher expression of let-7a compared with Th2 cells	16,17
MIR145	In HDM (house dust mites) models of experimental asthma, an increased level of miR-145 in the airway wall was observed. Studies have shown that anti-miR-145 significantly reduces infiltration of eosinophils, mucus production, production of Th2 cytokines and airway hyperreactivity.	17
MIR155	Inhibition of miR-155 was shown to lead to an increase in transcription factors involved in the generation of a T-helper cell2 microenvironment, implicating this microRNA in the pathogenesis of asthma.	25
MIR155	Indeed, the miR-155 expression level was elevated in asthmatic samples than normal control.	13
MIR146A	In studies using mouse lymphocytes, it was shown that miR-146 participates in the determination of Th0 differentiation on the Th1 or Th2 pathway, because the level of miR-146 is increased in Th1 cells, and in the Th2, the level of miR-146 is lowered compared to the level of miR-146 in Th0.	28
MIR146A and B	Smooth muscle cells of the respiratory tract from healthy and asthma patients were obtained for the study. After treatment with a mixture of cytokines, the expression of miR146a and miR-146b increases in these cells. In asthmatic cells, miR146a expression was higher than in healthy cells. Perhaps miR-146a, to a small extent, negatively regulates the genes of COX-2 and IL-1.	5
MIR19A	Studies have shown that in the epithelial cells of the bronchi in patients with severe asthma, the level of miR-19a increased almost 2-fold compared to cells from control groups and mild asthmatics.	9
MIR21	The expression of miR-21 increases during allergic inflammation in patients with asthma	29
MIR126	Inhibition of miR-126 by antagonists reduces allergic inflammation, eosinophilia and airway hyperreactivity, the production of mucus, cytokines of Th2 and other features of asthma. It is suggested that miR-126 is a component of innate immunity in response to an allergen and stimulates Th2-mediated allergic inflammation.	19
MIR126 anti-miR-126	The study showed that anti-miR-126 reduces production of the Th2 cytokines (IL5 and IL-13).	3
MIRLET7A1	Inhibition of let-7a reduces the level of cytokines involved in allergic inflammation and alleviates the course of asthma.	22
	Inhaled lung introduction of the let-7a mimetic resulted in a decrease level of IL-13 and other features of asthma	12
MIR155	It was previously reported that miR-155 is involved in the regulation of Th2 cell differentiation in vitro. However, other studies have shown that targeting miR-155 stops the development of clinical manifestations of asthma.	20
MIR155 MIR181A1 MIR146B	The study showed that the expression level of miR-146a, -146b, -150 and -181a in OVA groups was higher than in the control groups. The highest levels of miR-146a, -146b, -150 and -181a were observed on day 37 than on day 32. There was also a correlation between the number of inflamed cells and miR-181a.	7

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