Chapter 41
Asthma and Autophagy

Xiaoxi Lv, Ke Li, and Zhuowei Hu

Abstract Asthma is one of the most common diseases of the respiratory system, with typical pathogenesis and pathological changes. The current research shows that autophagy is mainly involved in the pathogenesis of asthma by regulating the body's innate and adaptive immune responses. At the same time, a large number of epidemiological studies have shown that multiple autophagy genes affect the risk of asthma at the level of genetic polymorphism. This chapter will explore the relationship between autophagy and asthma.

Keywords Immune response · Viral infection · Gene polymorphism · Inflammation

41.1 Innate Immune Response and Adaptive Immune Response

Inflammation caused by asthma. The adaptive immune response is a series of biological effects mediated by antigen-dependent T helper cells (CD4+). Th1 cells secrete cytokines such as IFN-α and IFN-β, and Th2 cells mainly secrete cytokines such as IL-4, IL-5, IL-10, and IL-13, which together regulate the immune balance of the body. When the Th1/Th2 immune balance breaks, the body will have a corresponding inflammatory response. The immune response mediated by Th2 cells is a crucial starting factor for the pathogenesis of asthma. High levels of Th2-type immune responses can be detected in both animal models and clinical patient samples, and Th1/Th2 immune imbalance disorders can eventually lead to airway inflammation and exacerbate asthma attacks.

X. Lv · Z. Hu (✉)
Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
e-mail: huzhuowei@imm.ac.cn

K. Li
Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

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The innate immune response is a conserved immune response. It is the first barrier against pathogens. It can specifically recognize pathogen-associated molecular patterns (PAMPs) on the surface of pathogenic microorganisms and trigger immune responses. Unlike adaptive immune responses, innate immune responses are initiated more rapidly, with a large number of immune cells and nonimmune cells involved. TLR is a pattern recognition receptor that links innate immunity and adaptive immunity, and both TLR2 and TLR4 are included in the development of asthma.

So far, the role of autophagy in innate and adaptive immune responses has become clearer (Jyothula and Eissa 2013). Autophagy can deliver antigen to MHC II molecules via lysosomal catalysis, a feature of autophagy that has been used in animal models to enhance the immune effect of BCG. Autophagy is essential for the development and survival of lymphocytes. Both autophagy-deficient B-cell and T-cell differentiation and immunomodulatory capacity are affected.

The number of peripheral T cells in the mice with conditionally deficient ATG5 was significantly decreased, and the proliferation of T cells was reduced considerably after antigen stimulation. Autophagy activity in Th2 cells is relatively high, and these cells can tolerate more severe nutritional deficiencies. The tolerance to autoantigen also requires autophagy, and the autoimmune activity of mice with thymus knockout ATG5 is enhanced, and its autoantigen triggers a robust immune response due to the loss of autophagy monitoring. The regulation of autophagy by Th1 and Th2 cytokines is opposed. IFN-γ promotes autophagy activity, while IL-4 and IL-13 inhibit autophagy activity. Electron microscopic evidence shows an increase in the number of autophagosomes in bronchial tissue fibroblasts and epithelial cells in asthmatic patients (Haspel and Choi 2011). At the same time, researchers are gradually illustrating the relationship between the increase in autophagosomes and the autophagic flux.

41.2 Autophagy and Inhaled Viral Infection

Autophagy is an essential link between inhaled infection and asthma. Inhaled viral infection in adolescents is an important risk factor for asthma attacks. Epidemiological evidence suggests that viral infections in the lower respiratory tract in infants are closely related to the incidence of asthma. Inhaled viral infection is directly linked to acute exacerbations in most asthmatic populations (85% of adolescents, 80% of adult patients). Rhinovirus (HRV), syncytial virus (RSV), influenza virus, coronavirus, and adenovirus are often detected in the airway of patients with acute exacerbation of asthma. These viral infections can increase the inflammatory response in the lungs and increase the number of Th2 cells. The release of factors also increases the airway hyperresponsiveness of the patient. HRV2 can stimulate autophagy activation, and viral replication is increased when autophagy is activated, while viral replication is also inhibited after autophagy activity is blocked using autophagy inhibitors. RSV

infection of mouse dendritic cells induces autophagy activation and also promotes the release of IFN-β, TNF-α, and IL-6. The release of these cytokines is dependent on autophagy activity.

Autophagy also supports the interaction between antigen-presenting cells and T cells in the process of viral infection, thereby promoting the activation and maturation of dendritic cells. Asthmatic patients are also more susceptible to the influenza virus, and the number of autophagosomes in the lung tissue of asthma patients infected with H5N1 virus can be observed by electron microscopy. At the same time, in vitro experiments also proved that the H5N1 virus-infected lung epithelial cells autophagy activation and the emergence of autophagic cell death phenomenon. Inhibition of autophagy can attenuate H5N1-induced acute lung injury. After activating autophagy by coronavirus infection, increased nonstructural protein (ns6) in cells can produce a large number of autophagosomes through the endoplasmic reticulum effect.

The interaction of the adenoviral protein E1B19K with the beclin1/PI3KC3 complex results in increased PI3KC3 activity leading to autophagy. When the autophagy of the host cell is induced and activated, the pathogen can be encapsulated by the autophagosomes to promote its own reproduction in the cell. On the other hand, autophagy is also an important way for the body to protect from viruses. During pathogen infection, host cells can clear pathogens in cells by autophagy. This contradictory biological effect may be related to the specificity of the virus being infected, and also to the immune microenvironment in which the body itself is located. A variety of inhaled viral infections that induce asthma attacks can produce a Th2-type immune response, and the resulting Th2-type cytokines can mediate inhibition of autophagy activity. In fact, the inhibition of autophagy is partly blocked by the flow of autophagy, and this is one of the reasons why the virus escapes from the autophagy in the cell. In summary, autophagy mainly regulates the replication and proliferation of inhaled viruses in host cells during the pathogenesis of asthma. The immune suppression induced by the virus avoids its elimination by autophagy (Mabalirajan 2017).

41.3 Autophagy Gene Polymorphism and Asthma

A large number of studies including genome-based sequencing and genomics-based studies have identified susceptibility genes to increase the risk of asthma; many genes are involved in and regulate the pathogenesis of asthma, including some autophagy-related genes. A study which included 1338 patients with asthma explored the genetic role of autophagy-related genes such as ULK1, p62, LC3B, beclin1, and ATG5 in asthma attacks. Studies have shown that the mRNA expression of ATG5 in nasal epithelial cells is significantly increased in patients with acute asthma attacks. After genetic polymorphism studies, it was found that the rs12212740 gene locus of ATG5 is involved in the pathogenesis of asthma, which is located in intron 3 of the ATG5 gene. The allele *G* of rs12212740 was identified as a risk factor for asthma, and this allele was also positively correlated with the decline in FEV1.

Another study including about 600 clinical samples also demonstrated that the ATG5 gene polymorphism is closely related to childhood asthma attacks. The results showed that rs12201458 allele *A* in ATG5 could reduce the risk of asthma, while ATG5 rs510432 allele *G* can increase the risk of asthma. Unlike ATG5 rs12212740, rs510432 is located upstream of the first exon of the promoter. Through luciferase experiments, researchers found that STAT1 and C-FOS are essential transcription factors that activate the rs510432 *G* allele. Both transcription factors are increased in the pathogenesis of asthma and have been shown to promote the onset of asthma. The phagocytosis is likely an effector element during the asthma attack. However, how the autophagy reaction ultimately regulates the onset of asthma remains to be further studied.

References

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