The pathogenesis of allergic asthma - beyond immune response

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Abstract

Asthma is the most frequent chronic lung disease and affects over 250 million people worldwide with no curative therapy available. Moreover, the incidence of asthma is continually inclining and it is estimated to double every ten years by the WHO. Existing asthma drugs allow symptom control by only reducing inflammation and relaxing constricted airway smooth muscles, but they have no documented effect on airway wall remodeling. Thus, the hypothesis that airway wall remodeling results from chronic inflammation was questioned. Clinical studies indicated that airway wall remodeling occurs within days after airway provocation and is irreversible. Therefore, airway wall remodeling is today regarded as an independent pathology. Airway wall remodeling consists of at least four independent events: Derangement of epithelium; sub-epithelial fibroblasts hyperplasia and hypertrophy; extracellular matrix deposition by these fibroblasts and hyperplasia of airway smooth muscle cells. New studies provided evidence that the healthy epithelium actively suppresses activity and proliferation of sub-epithelial cells, and this function is significantly reduced in asthmatic airways. In turn, sub-epithelial cells become active, proliferate and secrete pro-inflammatory immune cell recruiting cytokines which increase the local inflammation. In addition, the sub-epithelial cells attempt to counteract inflammation by secreting more extracellular matrix, which leads to local tissue hypoxia and subsequently to vascularization of the thickened airway wall. Interestingly, most of these remodeling pathologies have recently been linked to the activation of epigenetic mechanisms including histone acetylation, protein methylation and mitochondria activity. Genetic studies failed to identify strong asthma susceptibility factors, but clearly indicated that the precondition to asthma is set early in life through epigenetic events, which can be handed down over three generations mainly through the maternal line. However, the nature of the mechanism(s) by which these epigenetic modifications become permanent in asthma have to be investigated and will present novel curative targets for therapy. Thus, understanding of the cause of airway wall remodeling in asthma is regarded today as the key to cure the diseases by many investigators.

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