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THE ROLE OF THE INNATE IMMUNE SYSTEM IN THE IMMUNOPATHOGENESIS OF CHRONIC OBSTRUCTIVE BRONCHIAL DISEASE (REVIEW ARTICLE)

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Abstract:
Chronic obstructive pulmonary disease (COPD) is a common, socially significant disease characterized by progressive restriction of airflow as a result of chronic bronchial inflammation. Although the causes of COPD are considered known, the pathogenesis of the disease continues to be an urgent topic for study. The mechanisms of the innate immune system are involved in various links in the pathogenesis of COPD, lead to the preservation of chronic inflammation in the bronchi, their bacterial colonization and disruption of the structure and function of the lungs. Bronchial epithelial cells, neutrophils, macrophages and other cells are involved in the development and progression of the disease through multiple compromised immune mechanisms.

Keywords: COPD, innate immune system, inflammation, bronchial epithelium.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, socially significant disease. This is one of the leading causes of hospitalization, disability and mortality [1]. The prevalence of the disease has a negative trend in many countries of the world, which is associated with a high prevalence of smoking and exposure to airborne pollutants [2]. At the same time, epidemiological data on the prevalence of COPD vary depending on the methods of diagnosis and classification of the disease used. COPD is associated with a significant economic burden for patients and their families, and may also have an impact on the health care system in some countries [2]. This effect is due to the negative impact on working capacity and prognosis, which are associated with both the disease itself and comorbid pathology, which is widespread in patients with COPD. Indeed, cardiovascular diseases, osteoporosis and cachexia are often associated with COPD and make a significant contribution to the overall clinical picture of the disease.

COPD is a chronic disease, the leading cause of which is associated with prolonged inhalation of tobacco smoke components [1]. Chronic inflammation persists for many years, and subsequent remodeling of the bronchi leads to the development of airway obstruction and increased tissue hypoxia. Hypoxia and systemic inflammation contribute significantly to the development of pulmonary and extrapulmonary clinical heterogeneity of COPD, which affects the natural course of the disease [3]. There is increasing evidence that dysregulation of the innate immune system is associated with the development and progression of COPD. Recent research has significantly expanded our understanding of the mechanisms available to the innate immune system to protect the body. Inflammation in the bronchi involves many cells that exhibit complex cross-links in the innate immune response.

The purpose of this review is to discuss the role of the innate immune system in the development of COPD and how impaired mechanisms of the innate immune system are associated with the immunopathogenesis of COPD.

2. The innate immune system in the pathogenesis of COPD

The innate immune system is an evolutionarily ancient defense system that allows the body to maintain the constancy of its macromolecular composition by detecting and removing foreign molecules and providing resistance to infectious agents [4]. Given that large volumes of inhaled air containing various airborne pollutants and microorganisms pass through the lungs every day, this organ needs serious immune protection. Respiratory epithelial cells are exposed to many different inhaled particles and gases on a daily basis. These cells form a barrier between the external and internal environment of the body and play a key role in the organization of inflammatory and immune reactions in the lungs [4].

The accumulated knowledge has expanded the understanding of the role of the respiratory epithelium in the innate immune system of the lungs. Thus, the function of the epithelium in protecting the host from infection involves several known mechanisms. The first line of defense is provided by the barrier function of epithelial cells through dense intercellular junctions and mechanical purification of the respiratory tract, which is considered a key protective mechanism of the epithelium [5]. Epithelial mucus production and mucociliary clearance are mechanisms that provide bronchial clearance of inhaled and aspirated particles and pathogens. This function is provided by the production of mucus, as well as by the presence of coordinated beats of the cilia of epithelial cells. Mucins, through their side chains, are able to bind to various particles that reach the epithelium and can remove them from the respiratory tract through the mechanism of mucociliary clearance [6]. In COPD, these mechanisms can be disrupted, which is accompanied by hypersecretion of mucus. Mucus hypersecretion is associated with mucins, of which MUC5AC is considered the most important. MUC5AC is produced mainly by goblet-shaped cells of the bronchial epithelium. Excessive MUC5AC production in COPD leads to increased obstruction of the

respiratory tract by mucus [7]. In addition to influencing the quantitative and qualitative parameters of mucus, exposure to cigarette smoke reduces the length of the cilia, which also reduces the effectiveness of mucociliary clearance [7].

In addition to the first line of defense of the epithelium, which is provided by mechanical cleaning of the respiratory tract, another important mechanism is considered to be chemical and immune protection through the production of certain molecules. These substances belong to different chemical groups and are involved in the regulation of the immune response. Antimicrobial peptides such as defensins and cathelicidins play an important role in the protective function provided by bronchial epithelial cells [4]. Defensins have antimicrobial activity, affecting membrane permeability in bacteria and fungi [8]. They also exhibit a number of antiviral effects, including direct effects on viral membranes, capsids, and glycoproteins. Elevated levels of the β-defensin-1 protein can be considered a marker of COPD. Sputum beta-defensin-1 has a negative correlation with OFV1 [9]. Moreover, the expression of human beta-defensin-2 (hBD-2) is elevated in the distal airways of patients with COPD [10]. Another representative of antimicrobial peptides in humans is LL-37, which belongs to the class of cathelicidins. LL-37 is induced by inflammatory or infectious stimuli and exhibits antimicrobial activity against Gram-positive and Gram-negative bacteria. Studies show that LL-37 may be involved in the pathogenesis of COPD [11]. An increased expression of LL-37 was found in the respiratory tract and alveoli of the lungs in COPD. Since LL-37 can promote the production of IL-8 and cause apoptosis in bronchial and alveolar epithelial cells, elevated levels of LL-37 in the sputum of patients with COPD have been associated with airway obstruction and worsening of the clinical course of COPD [12].

In addition to antimicrobial peptides, epithelial cells of the respiratory tract are involved in the production of bioactive lipid mediators of the development and resolution of inflammation. Eicosanoids are synthesized from some polyunsaturated fatty acids, mainly arachidonic acid, which can be released from membrane phospholipids by phospholipase A2. Secretory phospholipase A2 is secreted by ciliated cells and acts on goblet cells, causing the production of MUC5AC, leukotriene B4 and leukotriene C4 [13]. Goblet cells are considered effector proinflammatory cells in the respiratory tract [13]. In an experiment on a line of human bronchial epithelial cells (HBEC), the production of mainly prostaglandins (PGE2, PGD2) and epoxides was shown. PGE2 is an eicosanoid derived from arachidonic acid using COX-2. It causes many different effects by acting through four different receptors coupled to the G protein (EP1-4) [14]. PGE2 is known as a relaxant of the smooth muscles of the respiratory tract and may also have bronchoprotective properties, promoting cell growth in the bronchial epithelium [14]. PGE2 reduces the production of several pro-inflammatory cytokines, such as IL-8, IL-12, monocyte chemotactic protein (MCP)-1 and granulocyte-macrophage colony stimulating factor (GM-CSF) which are involved in leukocyte migration [14]. Some bacteria use PGE2 to counteract inflammation, which contributes

to their colonization of the respiratory tract of COPD patients and may play a role in the progression of the disease [15]. In particular, Streptococcus pneumoniae, M. catarrhalis and NTHi have been shown to induce COX-2 expression and prostaglandin E2 production in the respiratory epithelium [15]. It has also been shown that in addition to M. catarrhalis inducing COX-2 expression and increased PGE2 production in lung epithelial cells, EP2 and EP4 receptors are also activated in these cells [15]. Thus, an increased concentration of prostaglandin PGE2 in the lungs of patients may be associated with the pathogenesis of COPD.

Nitric oxide (NO) is another biologically active substance that is involved in many physiological and immune processes in the lungs [4].

In the epithelium of the respiratory tract, NO is involved in mucociliary function, where it increases the frequency of beating of the cilia. In addition, NO is considered a universal player in the immune system. NO modulates inflammation by regulating the production of epithelial inflammatory mediators, and also directly contributes to innate immune protection. Patients with COPD had a significant increase in iNOS mRNA and protein levels compared to non-smokers and smokers with normal lung function. In addition, a negative correlation was observed between the level of iNOS protein and lung function parameters such as OFV1 and OFV1/VEL [16].

Moreover, epithelial cells of the respiratory tract may be an important source of inflammatory mediators in smoking and COPD, such as IL-1β, IL-8, TNF-α and GM-CSF [17].IL-8 is an important mediator of respiratory tract inflammation and innate immunity. It is a chemoattractant for neutrophil cells. IL-8 levels are elevated in the induced sputum of patients with COPD [18]. It is known that cigarette smoke can increase the production of IL-8 by bronchial epithelial cells. The concentration of IL-8 was higher in the samples of the proximal respiratory tract than in the samples of the distal alveoli [19]. In addition, the combination of smoke exposure and bacterial infection has also been shown to increase the release of IL-8 from epithelial cells [20].

Conclusion

Thus, bronchial epithelial cells have various mechanisms for maintaining immunological homeostasis and providing microbial protection. These instruments can be disrupted by smoking, which leads to activation and maintenance of inflammation in the airways. Factors associated with impaired bronchial epithelial function are involved in the pathogenesis of COPD, lead to increased sputum formation and airway obstruction.

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