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Review

Update on molecular mechanisms of corticosteroid resistance in chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is an inflammatory and irreversible pulmonary disorder that is characterized by inflammation and airway destruction. In recent years, COPD has become a global epidemic due to increased air pollution and exposure to cigarette smoke. Current therapeutics using bronchiodialator and anti-inflammatory corticosteroids are most widely used for all patients with persistent COPD, but these approaches are disappointing due to limited improvement in symptom control and survival rate. More importantly, a certain number of COPD patients are resistant to the corticosteroid treatment and their symptoms worsen. Therefore, more effective anti-inflammatory drugs and combinational treatment are required. Understanding of the underlying molecular and immunological mechanisms is critical to developing new therapeutics. Lung inflammation and the released pro-inflammatory cytokines affect glucocorticoid receptor (GR), histone deacetylase 2 (HDAC2) and surfactant protein D (SP-D) activities in many cell types. Macrophages, neutrophils, airway epithelial cells and lymphocytes are involved in the induction of corticosteroid resistance. This review updated the recent advances in molecular and immunological mechanisms of steroid resistance among patients and animal models with COPD. Meanwhile we discussed novel therapeutic approaches in controlling lung inflammation and improving corticosteroid sensitivity among the steroid resistant patients with COPD.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease, characterized by progressive lung tissue destruction, shortness of breath, chronic coughing and mucus

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production. Recent clinical surveys revealed that COPD accounted for 1.6% of all hospital admission in China and ranked fourth as a leading cause of mortality in urban areas and third in rural areas of China [1]. Due to the increased prevalence and incidence, COPD places a burden on employers and individuals in terms of lost productivity and lost income related to absenteeism, activity limitation, and disability [2]. Cigarette smoke (CS) and biomass fuel use are major contributors to the high incidence of COPD in China [1]. Other factors include occupational hazards and pathogen infections [3]. Mice with experimental COPD are predisposed to influenza infection. Rhinovirus (RV)-infected mice have high risk of COPD exacerbation [4,5]. CS-exposed animals develop emphysema, characterized by irreversible alveolar destruction and airspace enlargement [6]. In CS-exposed A549 cells, a large amount of hydrogen peroxide (H2O2) is produced and responsible for cell apoptosis and autophagy [7,8]. In additional to the debilitating effect on lung epithelial cells, CS acts on alveolar macrophages via oxidative stress, under which macrophage phagocytosis activity is largely suppressed [9,10].

Under oxidative stress, multiple pro-inflammatory cytokines and chemokines such as tumor necrosis factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma), interleukin-1beta (IL-1beta), interleukin-6 (IL-6), CXCL8, monocyte chemoattractant protein-1 (MCP-1), matrix metalloproteinase-12 (MMP-12), macrophage inflammatory protein-2 (MIP-2), MIP-1alpha are increasingly produced from activated macrophages, airway epithelial cells, neutrophils, lymphocytes and other cells types. They contribute to the pathogenesis of COPD among patients and animal models [11,12]. Anti-inflammatory drugs are major therapeutic agents for relieving COPD symptoms. Dexamethasone (Dex) is a synthetic corticosteroid and has been widely used for the treatment of asthma and COPD. However, its effectiveness was recently challenged by developing corticosteroid resistance among 30% of the treated patients [13,14]. A high dose of inhaled or systemic corticosteroid is required for symptom control, but in rare cases, high inhaled doses of steroids fail to control symptoms. Recent research suggests that pro-inflammatory cytokines and other mediators contribute to the development of corticosteroid resistance. In association with increased lung inflammation, the expression and activity of corticosteroid receptor (GR), histone deacetylase-2 (HDAC2) and other important molecules are reduced. This review updated the recent advances in molecular and immunological mechanisms of COPD and discussed the novel therapeutic approaches in overcoming corticosteroid resistance during the COPD treatment.

2. The role of inflammation in COPD

CS exposure creates great damage to lung epithelial cells and activates alveolar macrophages. The CS-exposed lung epithelial cells produce a greater amount of H2O2 and superoxide radicals, contributing to cell apoptosis [7,15]. The CS-exposed lung develops emphysema and the lung parenchyma destruction is irreversible even after smoking cessation [7,14,16–18]. CS-exposed mice and human subjects have increased bronchoalveolar lavage (BAL) protein levels, hyperplasia of airway epithelial cells and alveolar-capillary barrier permeability [19,20]. Current smokers have more pro-inflammatory cytokines than ex-smokers [21]. Multiple lung resident cell types such as airway epithelial cells, alveolar macrophages, smooth muscle cells and fibroblasts, are activated and release greater amount of cytokines and chemokines [22–24]. Serum IL-27 and IL-33 levels are elevated in serum, sputum and BAL of COPD patients and their expression levels are correlated to disease exacerbation [23,25,26]. In addition, IL-33 can up-regulate IL-6 and IL-8 expression in alveolar macrophages in ex vivo [27].

Studies among human COPD samples and mouse models indicate that neutrophils are major cell infiltrates in the inflamed lung of COPD. Other infiltrates include peripheral monocytes, CD4+ and CD8+ T cell lymphocytes are recruited into the lung and contribute to lung inflammation, tissues destruction and remodeling [28]. The activated neutrophils and alveolar macrophages releases multiple pro-inflammatory cytokines, chemokines and other mediators such as myeloperoxidase (MPO), TNF-alpha, IL-1beta, IL-6, IL-17, MCP-1, CCL2, CXCL2, CXCL5, CXCL8 [29,30]. The increased production of MMP-9 can break down the extracellular matrix of lung tissues into small peptides that are subsequently recognized by T cells for T cell activation and infiltration [31,32]. Macrophages constitute a heterogeneous cell population, composed of classically activated macrophages (M1 cells) and alternatively activated macrophages (M2 cells). There are altered macrophage phenotypes in the inflamed lung of COPD. Most of them are presented as intermediate phenotypes [33]. A study by Kunz et al. indicated that the percentage of CD163 + M2 macrophages was increased, but the total number decreased among COPD ex-smokers compared to that of current smokers, indicating that smoking cessation affects macrophage phenotypes and related function [34]. In general, COPD smokers have dominant M2 type macrophages, characterized by high expression of MMP-2, MMP-7 and adenosine A3 receptor (ADORA3) [35]. However information about the dynamic changes and involvement of alveolar macrophage phenotypes is limited in the pathogenesis and inflammation of COPD. More investigation on patients and animal models will address these issues in the future.

Recent studies also indicated that CD4+ and CD8+ T cells play an important role in the pathogenesis of COPD via releasing IFN-gamma, TNF-alpha, serine protease and granzyme B. However, COPD exacerbation was inversely associated with the proportion of circulating CD4+ and CD8+ T lymphocytes, but positively associated with the lung T lymphocyte infiltrates. The differences are possibly caused by T cell extravasation from peripheral blood circulation into inflammatory sites and the circulating T cell apoptosis may result in decreases in circulating T cell numbers [36–38]. Hodge et al. reported that bronchial brushing-derived CD8+ T cells were increased among COPD patients and the expression of TNF-alpha was elevated [39]. In vitro stimulation of the lung derived CD8+ T cells with IL-18 and IL-12 leads to greater production of IFN-gamma and TNF-alpha from the stimulated CD8+ T cells [40]. The role of CD8+ T cells in the pathogenesis of COPD is also recently demonstrated in CD8 knock-out mice, in which long-term exposure to CS did not induce emphysema. Lung inflammation and cytokine expression, such as IFN-gamma-inducible protein-10 (IP-10) and MMP-12 were greatly reduced [41]. A low-dose of azithromycin can suppress CD8+ infiltration and airway inflammation in COPD patients [39]. Additional study in ex vivo showed that targeting CD8+ T cells, natural killer (NK) cells and, natural killer T (NKT)-like cells through anti-CD137 antibody can efficiently reduce IFN-gamma, TNF-alpha and granzyme B from the isolated peripheral mononuclear cells (PBMC) [42]. Thus T lymphocytes are critically involved in the pathogenesis of COPD. Suppressing T lymphocyte activation and cytokine expression via molecular intervention may have therapeutic potential in COPD control.

Additional study also indicated that there was increased expression of IL-17A in the infiltrating macrophages, neutrophils, NK cells, NKT cells and gamma delta T-cells after CS exposure [43]. As a major source of IL-17A, Th17 cells also play an important role in lung inflammation. A high number of Th17 cells was observed in the peripheral blood and BAL fluids of COPD patients. The Th17 cell number and IL-17 levels are related to disease severity [44–46]. In contrast, anti-inflammatory T lymphocytes, cytokines and mediators such as regulatory T cells, IL-10 and indoleamine 2,3-dioxygenase (IDO) are reduced among COPD patients [44,47,48].