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REVIEW ARTICLE

Role of Th17 Cell and Autoimmunity in Chronic Obstructive Pulmonary Disease

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The molecular mechanisms involved in the pathogenesis of chronic obstructive pulmonary disease (COPD) are poorly defined. Accumulating evidences indicate that chronic inflammatory responses and adaptive immunity play important roles in the development and progression of the disease. Recently, it has been shown that IL-17 producing CD4 T cells, named Th17 cells, which have been implicated in the pathogenesis of several inflammatory and autoimmune diseases, are involved in airway inflammation and COPD. In addition, we and others suggest that autoimmunity may play a critical role in the pathogenesis of COPD. Here, we will review the current understanding of roles of Th17 cells and autoimmune responses in COPD.

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INTRODUCTION

COPD is a comprehensive disease including chronic bronchitis and emphysema, and is characterized by the pathological limitation of airflow in the airway associated with chronic inflammation and alveolar destruction (1). It is one of major causes of morbidity and mortality throughout the world and projected to become the third cause of death world-wide by 2030 (2). Although tobacco smoke is a well-known cause of the disease, the precise mechanisms of chronic progressive alveolar destruction are not well defined. Further, not all smokers develop the clinical overt COPD and pathological process persists despite smoking cessation (3-5). Recently, it has been proposed that other mechanisms such as chronic inflammation, cellular senescence, and apoptosis are implicated in the development and progression of the disease (6-9). A potential role for adaptive immune responses in COPD has been suggested in recent studies that show expansion of lung T cells and B cells with oligoclonality in patients with COPD and/or murine emphysema model (10-12). In addition, it has recently been proposed that COPD could be associated with autoimmune responses (13). In this review, we will briefly summarize and discuss the roles of inflammatory responses including Th17 cell-mediated response and autoimmunity in the pathogenesis of COPD.

INFLAMMATION IN COPD

In patients with COPD, there are accumulation of inflammatory mucous exudates in the airway lumen and increased numbers of inflammatory cells including neutrophils, macrophages, and T cells in the lung parenchyma. Progression of the disease is associated with an infiltration of innate and adaptive inflammatory immune cells that form lymphoid follicles (14). There have been a number of studies investigating the key inflammatory cells, cytokines, and chemokines in the pathogenesis of COPD (14-17).

Inhaled cigarette smoke activates lung epithelial cells and alveolar macrophages to release several chemotactic factors which attract inflammatory cells to the lung. Neutrophils are accumulated in the sputum, bronchoalveolar lavage (BAL) and airway smooth muscle of patients with COPD, and this correlates with disease severity (15,16). The infiltration of neutrophils is proportional to the production of chemokines

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such as CXCL1 (GRO-α) and CXCL8 (also known as IL-8), which act on CXCR2 to attract neutrophils and monocytes. The levels of CXCL1 and CXCL8 are markedly increased in induced sputum of patients with COPD (17). Neutrophils can contribute to the pathogenesis of COPD through secretion of proteolytic enzymes such as neutrophil elastase (NE) (18). NE has a potent catalytic activity against extracellular matrix including elastin that is one of major components of the lung. Further, NE can cause mucus hyper-secretion (19). In addition to neutrophils, macrophage is another chief candidate for causing lung pathology in COPD. There is evidence that alveolar macrophages play a critical role in the pathophysiology of COPD through release of chemokines that attract neutrophils, monocytes and T cells, and secretion of proteases, particularly, matrix metalloproteinase-9 (MMP-9) and MMP-12 (20). MMPs process a large array of extracellular and cell surface proteins, and it has been suggested that dysregulation of MMPs contribute to the destruction of lung tissue in COPD (21). In those studies, BAL fluid or alveolar macrophages of subjects with COPD show a higher concentration and activity of MMP-9 compared with normal controls (22,23). The importance of MMP-12 in COPD is also supported by an animal model that mice lacking MMP-12 were completely protected from cigarette smoking induced emphysema (24). In addition, lung tissues from COPD patients show larger number of macrophages expressing MMP-12 than those of control subjects (25).

Pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 have roles in the pathogenesis of other inflammatory diseases such as rheumatoid arthritis and inflammatory bowel diseases. The clinical benefit of blockade of those cytokines in chronic inflammatory diseases leads to interest in whether this approach might also have effect on treatment of COPD. In murine model, over-expression of TNF-α in lung tissue causes alveolar destruction, increases in lung volumes, and decreases in elastic recoil, which are characteristics of COPD and emphysema (26). The level of TNF-α is increased in sputum of COPD patients relative to that of normal control subjects, and the increase is more prominent during acute exacerbation of COPD (16,27). However, clinical application of TNF blocking antibody in COPD patients is not promising, and there is a risk of respiratory tract infections with this therapy, raising needs of additional work to elucidate the functional role of TNF-α in COPD (28,29). IL-1β and IL-6 are mediators of inflammatory responses, and the concentration of these cytokines is elevated in patients with COPD (30,31). IL-32 is a newly described pro-inflammatory cytokine produced by T cells, natural killer cells, monocytes and epithelial cells, and its expression is increased in lung tissue of COPD patients. This study demonstrated that IL-32 expression was positively correlated with TNF-α production and the degree of airflow limitation (32). However, the functional role of these pro-inflammatory cytokines that are increased in patients with COPD has not yet been fully elucidated.

TH17 CELL-MEDIATED IMMUNITY IN COPD

T lymphocytes are one of the key components of inflammation in COPD. Th17 cells are recently described effector T cell subsets characterized by the production of IL-17A, IL-17F and IL-22, which have been implicated in the pathogenesis of several inflammatory and autoimmune diseases (33,34). IL-17 is a pro-inflammatory cytokine that regulates recruitment of inflammatory cells including neutrophils and lymphocytes into the inflamed tissues by secretion of chemokines-CXCL8 and CCL20 (35,36). Additionally, IL-17 has an effect on most parenchymal cells including macrophages and dendritic cells (DCs) that express IL-17 receptors, and IL-17-mediated signaling induces target cells to produce various inflammatory mediators such as TNF-α and IL-6. Recently, it has been reported the role of Th17 response in lung physiology and pathology. IL-17 can induce airway epithelial cells to produce mucus and MMP-9 (37). Further, over-expression of IL-17 in murine lung epithelium causes accumulation of mononuclear cells and mucus production. This study has demonstrated that IL-17 transgenic mice have induced expression of many chemokines and MMP-9 (38). In animal model of cigarette smoke-induced emphysema, chronic smoke exposed mice have significantly higher number of IL-17 and IFN-γproducing cells in BAL (39). In contrast, the level of IL-17 in sputum is not different between patients with COPD and control subjects (40).

Th17 cells also produce IL-22, which has been linked to chronic inflammatory disease such as rheumatoid arthritis and psoriasis (41,42), and has an important role in host defense against extracellular bacterial infection in the lung (43). Recent study has shown that number of IL-22 positive cells is increased in bronchial epithelial cells of patients with COPD (44). Another study has demonstrated that IL-22 can promote airway inflammation by acting in synergy with IL-17A (45). In this study, bleomycin-induced lung disease is

ameliorated in IL-22 deficient mice or IL-22 blocking antibody treated mice, and pathological role of IL-22 is seen only in the presence of IL-17A. Interestingly, IL-23 that appears to be essential to expand and maintain Th17 cells plays a pivotal role in the establishment and maintenance of inflammatory autoimmune diseases. In particular, mice genetically deficient in IL-23 are highly resistant to the development of autoimmune disease such as multiple sclerosis and rheumatoid arthritis, whereas loss of IL-12 is not (46,47). These studies suggest that IL-23 rather than IL-12 is essential for induction of autoimmunity (48). The role of IL-23 in COPD has not been well investigated although there is a report in which describes increased expression of IL-23 in the lung tissues of patients with COPD (44). The exact role of Th17 immune responses in the development of COPD is still not well studied. As it may provide a potentially important therapeutic target for COPD, the additional careful studies are needed to investigate the precise role of Th17 responses in COPD.

AUTOIMMUNITY IN COPD

As discussed earlier, there are possible roles of chronic inflammation and Th17-mediated immune responses in the pathogenesis of COPD. However, not all chronic inflammation and/or Th17-mediated immune pathology are associated with autoimmune diseases. It has been recently proposed that COPD could be an autoimmune disease triggered by tobacco smoke (49,50). A potential role for adaptive immune response in COPD has been suggested that expansion of lung CD4 or CD8 T cells with oligoclonality in patients with COPD or murine emphysema model (10,12). These studies have demonstrated that chronic cigarette smoke exposure in mice cause oligoclonal expansions of CD8 T cells from lungs, and this response persist despite smoking cessation (10). The analysis of T cell receptor (TcR) repertoire revealed the oligoclonality of CD4 T cells from lungs of COPD patients. These studies suggested that there is a recruitment of antigen-specific T cells to the lung and cell-mediated immunity may play a critical role in the pathogenesis of COPD (12). In addition, it have been reported that T cells generated by cigarette smoke exposure are pathogenic in the development of emphysema phenotype in mice (11). Importantly, this report demonstrated that adoptive transfer of pathogenic T cells into the recombination activating gene-2 (Rag-2) deficient mice could induce the emphysema phenotype regardless of subsequent smoking exposure on recipient mice. It indicates that T cells by themselves generated by cigarette smoke exposure could be pathogenic and auto-reactive. However, auto-antigens responsible for the development of autoimmune response are not defined in this study.

Recently, we have shown that peripheral blood CD4 T cells from patients with COPD have higher level of IFN-γ but not IL-13 in response to elastin peptides, major constituents of the extracellular matrix in lung (13). In this study, it has also been reported that humoral response against elastin peptides which was assessed by the presence of anti-elastin antibody is markedly increased in subjects with emphysema. Further study showed that Th17 cells are present in lung parenchyma of patients with emphysema and elastin peptides stimulation could differentiate both Th1 and Th17 cells (51). In addition, this study demonstrated that lung myeloid DCs were sufficient to induce Th1 and Th17 responses of CD4 T cells in lungs from emphysema patients. IL-17A, enhances secretion of CCL20, a chemoattractant for DCs, and MMP-12 from lung macrophages. Therefore, these studies suggested that lung myeloid DCs are responsible for induction of adaptive immune response, and elastin protein could act as auto-antigen during the pathogenesis of COPD via induction of Th1 and Th17 immune responses. It proposes a new molecular mechanism focused on autoimmunity in the development of COPD and may provide a therapeutic target in this disease. However, other studies could not detect the evidence of anti-elastin humoral immune response in the COPD patients (52,53). In these reports, titers of auto-antibodies against elastin peptides from sera of patients with COPD were not increased compared with those of control subjects. At this point, reasons of the discrepancy between studies are unclear but there are some differences. For example, demographic profiles of the study population are different and functional significance of anti-elastin humoral responses is not confirmed. Identification of auto-antigen(s) that induce the adaptive immune response in autoimmune disease can provide an important clue in understanding the pathogenesis of the disease. Therefore, a great deal of additional work will be required to identify the auto-antigen(s) and elucidate the exact functional role of autoimmune response in the pathogenesis of COPD.

CONCLUSIONS

Whereas tobacco smoking is a well-known risk factor for the development of COPD, the molecular basis for individual sus-

ceptibility and disease progression remains largely unknown. Several mechanisms including chronic inflammation, cellular senescence, and apoptosis are proposed in the contribution of the disease development and progression. In addition, a number of different studies have suggested roles of Th17 cell-mediated immune response and autoimmunity in the pathogenesis of COPD. Further, recent studies have suggested that elastin, a major constituent of the extracellular matrix in the lungs, can act as auto-antigen in the disease. Although COPD is one of the major concerns in global public health, until now there is no effective treatment that can alleviate the disease progression or severity. Better immunological understanding is needed to determine the exact role of autoimmunity in COPD, as it might provide a new opportunity to control the disease.

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CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

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