Role of Th17 Cell and Autoimmunity in Chronic Obstructive Pulmonary Disease

Seok Chan Hong and Seung-Hyo Lee*
Graduate School of Medical Science and Engineering, Biomedical Research Center, KAIST Institute for the BioCentury, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea

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.

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...
Role of Th17 Cell and Autoimmunity in Chronic Obstructive Pulmonary Disease
Seek Chan Hong and Seung-Hyo Lee

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-γ-producing 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 components 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 chemottractant 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.

ACKNOWLEDGEMENTS

This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0015291).

CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

REFERENCES

1. Hogg JC, Timens W: The pathology of chronic obstructive pulmonary disease, Annu Rev Pathol 4:435-459, 2009
2. Mathers CD, Loncar D: Projections of global mortality and burden of disease from 2002 to 2030, PLoS Med 3:e412, 2006
3. Fletcher C, Peto R: The natural history of chronic airflow obstruction, Br Med J 1:1645-1648, 1977
4. Inad PW: COPD disease progression and airway inflammation: un-coupled by smoking cessation, Eur Respir J 26;764-766, 2005
5. Simmons MS, Connett JE, Nides MA, Lindgren PG, Kleerup EC, Murray RK, Bjornson WM, Tashkin DP: Smoking reduction and the rate of decline in FEV(1): results from the Lung Health Study, Eur Respir J 25:1011-1017, 2005
6. ChungKF, Adcock IM: Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction, Eur Respir J 31:1334-1356, 2008
7. Sharafkhaneh A, Hanania NA, Kim V: Pathogenesis of emphysema: from the bench to the bedside, Proc Am Thorac Soc 5:475-477, 2008
8. Taraseviciene-Stewart L, Voeckel NF: Molecular pathogenesis of emphysema, J Clin Invest 118:394-402, 2008
9. Tuder RM, Yoshida T, Arap W, Pasqualini R, Petracchi I: State of the art, Cellular and molecular mechanisms of alveolar destruction in emphysema: an evolutionary perspective, Proc Am Thorac Soc 3:503-510, 2006
10. Motz GT, Eppert BL, Sun G, Wessellkeram SC, Linke MJ, DeLa R, Borchers MT: Persistence of lung CD8 T cell oligoclonal expansions upon smoking cessation in a mouse model of cigarette smoke-induced emphysema, J Immunol 181:8036-8045, 2008
11. Motz GT, Eppert BL, Wessellkeram SC, Flury JL, Borchers MT: Chronic cigarette smoke exposure generates pathogenic T cells capable of driving COPD-like disease in Rag2/- mice, Am J Respir Crit Care Med 181:1223-1233, 2010
12. Sullivan AK, Simonian PL, Falta MT, Mitchell JD, Congrove GP, Brown KK, Kozin BL, Voeckel NF, Fontenot AP: Oligoclonal CD4+ T cells in the lungs of patients with severe emphysema, Am J Respir Crit Care Med 172:590-596, 2005
13. Lee SH, Goswami S, Grado A, Song LZ, Bandi V, Goodnight-White S, Green L, Hacker-Bitar J, Huh J, Baleezen F, Coxson HO, Cogswell S, Stormes-Bliss C, Corry DB, Kheradmand F: Antielastin autoimmunity in tobacco smoking-induced emphysema, Nat Med 15:507-569, 2007
14. Hogg JC, Chu F, Utkaparch S, Woods R, Elliot WM, Buzatu L, Chemiack RM, Rogers RM, Schifiru FC, Coxson HO, Paré PD: The nature of small-airway obstruction in chronic obstructive pulmonary disease, N Engl J Med 350:2645-2653, 2004
15. Baraldo S, Turato G, Badin C, Bazzan E, Beghè B, Zain R, Galabrese F, Casoni G, Maestrelli P, Papi A, Fabbrri LM, Saetta M: Neutrophil infiltration in the airway smooth muscle in patients with COPD, Thorax 59:308-312, 2004
16. Keatings VM, Collins PD, Scott DM, Barnes PJ: Differences in interleukin-8 and tumor necrosis factor-alpha in induced sputum from patients with chronic obstructive pulmonary disease or asthma, Am J Respir Crit Care Med 153:530-534, 1996
17. Traves SL, Gulpit SV, Russell RE, Barnes PJ, Donnelly LE: Increased levels of the chemokines GROalpha and MCP-1 in sputum samples from patients with COPD, Thorax 57:590-595, 2002
18. Shapiro SD, Goldstein NM, Houghton AM, Kobayashi DK, Kelley D, Beloaouaj A: Neutrophil elastase contributes to cigarette smoke-induced emphysema in mice, Am J Pathol 163:2329-2335, 2003
19. Vosnow JA, Young LR, Wang Y, Horger T, Rose MC, Fischer BW: Neutrophil elastase increases MUC5AC mRNA and protein expression in respiratory epithelial cells, Am J Physiol Lung Cell Mol Physiol 283:L867-873, 2002
20. Barnes PJ: Alveolar macrophages as orchestrators of COPD, COPD 1:59-70, 2004
21. Chung A, Wright JL: Proteases and emphysema, Curr Opin Pulm Med 11:153-159, 2005
22. Russell RE, Thorley A, Gulpit SV, Doddi S, Donnelly LE, Demattos C, Fitzgerald M, Barnes PJ: Alveolar macrophage-mediated elastolysis: roles of matrix metalloproteinases, cysteine, and serine proteases, Am J Physiol Lung Cell Mol Physiol 283:L867-875, 2002
23. Finlay GA, Russell KJ, McMahon KJ, D’arcy EM, Masterson JB, Fitzgerald MX, O’Connor CM: Elevated levels of matrix metalloproteinases in bronchoalveolar lavage fluid of emphysema-tous patients, Thorax 52:502-506, 1997
24. Haustamaki RD, Kobayashi DK, Senior RM, Shapiro SD: Requirement for macrophage elastase for cigarette smoke-induced emphysema in mice, Science 277:2002-2004, 1997
25. Grumelli S, Corry DB, Song LZ, Song L, Green L, Huh J, Hacken J, Espada R, Bug R, Lewis DE, Kheradmard F: An immune basis for lung parenchymal destruction in chronic obstructive pulmonary disease and emphysema, PLoS Med 1:e8, 2004
26. Fujita M, Shannon JM, Irvin CG, Fagan KA, Cool C, Augustin A, Mason RJ: Overexpression of tumor necrosis factor alpha produces an increase in lung volumes and pulmonary hypertension, Am J Physiol Lung Cell Mol Physiol 283:L39-49, 2001
27. Aaron SD, Angel JB, Lunau M, Wright K, Fex C, Le Saux N, Dales RE: Granulocyte inflammatory mediators and airway infection during acute exacerbation of chronic obstructive pulmonary disease, Am J Respir Crit Care Med 163:349-355, 2001
28. Dentener MA, Creutzberg EC, Pennings HJ, Rijkers GT, Aaron SD, Angel JB, Lunau M, Wright K, Fex C, Le Saux N, Dales RE: Granulocyte inflammatory mediators and airway infection during acute exacerbation of chronic obstructive pulmonary disease, Am J Respir Crit Care Med 163:349-355, 2001
29. Rennard SI, Fogarty C, Kelsen S, Long W, Ramsdell J, Allison J, Ikehuchi H, Kurisawa T, Hiramatsu N, Kaneko Y, Hirokura K, Ueki K, Nojima Y: Expression of interleukin-12 and tumour necrosis factor agonists and antagonists in stable COPD. J Clin Immunol 29:508-516, 2009
30. Bhowmik A, Seemungal TA, Sapsford RJ, Wedzicha JA: Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations, Thorax 55:114-120, 2000
31. Calabrese F, Baraldo S, Bazzan E, Lunardi F, Rea F, Maestrelli P, Turato G, Lokar-Oliani K, Papi A, Zuin R, Sfriso P, Balestro E, Dinarello CA, Saetta M: IL-32, a novel proinflammatory cytokine in chronic obstructive pulmonary disease, Am J Respir Crit Care Med 175;292-294, 2007
32. Saepys E, Ahmad A, Bayley D, Newbold P, Snell N, Rugman A, Stockley RA: Interleukin-1 and tumor necrosis factor agonists and antagonists in stable COPD. J Clin Immunol 29;508-516, 2009
33. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, McLaren A, MacKenzie W, Donaldson K, Artis D: Pathological versus protective functions of IL-12 in airway inflammation are regulated by IL-17A. J Exp Med 207:1293-1305, 2010
34. Chung KF, Barnes PJ, Papi A, Adcock I, Balbi B: T helper type 17-related cytokine expression is increased in the bronchial mucosa of stable chronic obstructive pulmonary disease patients, Clin Exp Immunol 157:316-324, 2009
35. Sonnenberg GF, Nair MG, Kim TJ, Zaph C, Fouser LA, Artis D: Interleukin-23 rather than interleukin-12 is the critical cytokine that drives a pathogenic T cell population that induces autoimmune inflammation of the brain. Nature 421:744-748, 2003
36. Capelli A, Magnani L, Neri M, Piccioli G, Giusini M, Cancedda T, Contoli M, Vicari C, Magno F, D'Antri S, Zanini A, Brun P, Gasolari P, Churg KF, Barnes PJ, Pap A, Adcock I, Balbi B: T helper type 17-related cytokine expression is increased in the bronchial mucosa of stable chronic obstructive pulmonary disease patients, Clin Exp Immunol 157:316-324, 2009
52. Cottin V, Fabien N, Khouatra C, Moreira A, Cordier JF: Anti-elastin autoantibodies are not present in combined pulmonary fibrosis and emphysema, Eur Respir J 33;219-221, 2009
53. Greene CM, Low TB, O’Neill SJ, McElvaney NG: Anti-proline-glycine-proline or antielastin autoantibodies are not evident in chronic inflammatory lung disease, Am J Respir Crit Care Med 181;31-35, 2010