Review

Chronic Obstructive Pulmonary Disease: Evidence for an Autoimmune Component

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Chronic obstructive pulmonary disease (COPD) is characterized by an irreversible limitation on pulmonary airflow associated with chronic inflammation and mucous hypersecretion (chronic bronchitis) and/or the pathological destruction of alveolar airspaces leading to emphysema. COPD, predominantly as a result of tobacco smoke exposure, represents the fourth leading cause of mortality worldwide and its prevalence is increasing. Despite this, much of the basic mechanisms which contribute to disease progression remain to be elucidated and current therapeutic approaches are, for the most part, based upon alleviating patient symptoms (bronchodilators) as opposed to treating the underlying pathological mechanisms triggered in response to cigarette smoke exposure. The classic disease paradigm suggests that an imbalance of pulmonary matrix proteases versus anti-proteases underlies the tissue destruction and inflammation associated with COPD. However, there is a growing appreciation of the complex and multifaceted nature of the pathological mechanisms associated with disease progression. Recently, there has been mounting evidence indicating that COPD patients exhibit many of the characteristics of a classical autoimmune response. We will discuss current evidence in support of this paradigm and outline how future therapeutic approaches may be tailored to address this. *Cellular & Molecular Immunology*. 2009;6(2):81-86.

Key Words: COPD, autoimmunity, emphysema, Th1, Th17

Introduction

Tobacco smoke exposure represents the single most prevalent predisposing factor towards chronic obstructive pulmonary disease (COPD), a progressive and irreversible chronic inflammatory condition, which is one of the highest causes of mortality globally (1). It is generally accepted that the inflammatory response observed in the lungs of COPD patients is intrinsically linked to the tissue destruction and alveolar airspace enlargement leading to disease progression. However, the precise nature of this complex immune response remains to be fully elucidated.

Cellular infiltration of the lungs in response to tobacco smoke exposure is composed of cells of both the innate and adaptive immune response including macrophages, neutrophils, dendritic cells, and T and B lymphocytes (2-4). The relatively large numbers of macrophages and neutrophils present in the airways of COPD patients has contributed to the hypothesis that both cell types are critical mediators of disease pathogenesis (5-7). Neutrophils, through the release of elastases and reactive oxygen species are thought to play a significant role in tissue destruction while macrophages have also been implicated in promoting alveolar airspace enlargement, primarily through the release of matrix metalloproteinases (MMPs). Although the presence of infiltrating lymphocytes and dendritic cells has also been well documented, their precise roles in promoting inflammation in the lungs of COPD patients are less well defined.

The observation that only 20-30% of habitual smokers go on to develop COPD suggests a degree of genetic susceptibility among certain individuals (8). Added to this, the fact that progressive pulmonary inflammation remains, even after smoking cessation, raises the possibility that there has been a breakdown in self tolerance stemming from the tissue injury caused by the initial noxious stimuli (9). Indeed, recent advances in our understanding of disease pathogenesis indicate that COPD patients exhibit many of the same features as patients suffering from classical autoimmune diseases.

We will examine the existing evidence for an autoimmune component in contributing to COPD progression and discuss these observations in the context of more extensively characterized mechanisms of disease. The use of immune based strategies as potential therapeutics in COPD will also be discussed.

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The innate immune system in COPD

Respiratory epithelium

Epithelial cells lining the large and small airways represent the first line of defence in pulmonary innate immune responses. As well as providing a physical barrier against both microbial pathogens and inhaled toxins such as those present in tobacco smoke, respiratory epithelial cells are now recognized to play a central role in initiating and mediating inflammatory responses in the lung (10, 11).

Upon exposure to cigarette smoke, respiratory epithelial cells undergo a range of structural alterations resulting in loss of barrier function, decreased mucocilliary clearance and squamous metaplasia (12, 13). It has been proposed that loss of structural integrity of the epithelial monolayer can lead to disruption of the naturally immunosuppressive micro-environment in the lung parenchyma. Under normal homeostatic conditions, respiratory epithelial cells keep alveolar macrophages in check through constitutive integrin mediated activation of the immunosuppressive cytokine TGF-β (14). As a result of the morphological changes and cytotoxicity induced by tobacco smoke exposure, TGF-β dependent signalling is disrupted leading to the release of proinflammatory cytokines by alveolar macrophages and the initiation of a proinflammatory cascade of cellular infiltration (14).

Although interactions between respiratory epithelium and other cell types present in the lung parenchyma play an important role in driving the proinflammatory response, it is also evident that epithelial cells themselves can directly express a number of chemokines and cytokines in response to noxious stimuli. Cigarette smoke exposure can directly lead to increased expression of chemokines such as IL-8 and CCL20 which promote the infiltration of neutrophils, dendritic cells and T cells respectively into the lung (15) (P. T. W.-unpublished observations). Respiratory epithelial cells have also been reported to express several members of the toll like receptor family (TLRs). TLRs are the prototypical innate sensing receptor family recognizing pathogen derived components and as such are likely to play an important role in proinflammatory responses to bacterial and viral infection often associated with COPD exacerbations (16).

Alveolar macrophages

Alveolar macrophages have long been considered as central orchestrators of the inflammatory response in COPD due to the observed increase in macrophage numbers present in the lungs of patients and a strong correlation between levels of infiltration and disease progression (6, 7). In addition, the infiltrating macrophages are found to be localised to areas of tissue damage and can express a wide array of proinflammatory mediators (17). Through enhanced secretion of matrix metalloproteinases, e.g., MMP-9/12, alveolar macrophages directly contribute to the tissue destruction observed in emphysema (18). Alveolar macrophages can also direct the recruitment of other immune cell subsets toward the site of inflammation through the release of chemokines. Macrophages from COPD patients have been reported to secrete elevated levels of IL-8 which promotes neutrophil infiltration while amplifying tissue destruction through enhanced protease secretion (19). Macrophages also have the capacity to promote T cell infiltration through the expression of Th1/Tc1 specific chemokines such as CXCL9, CXCL10 and CXCL11 (4, 20) (Figure 1). Increased levels of these chemokines have been reported in the sputum of COPD patients and directly correlate with increases observed in macrophage infiltration as well as decreased lung function. It has recently been demonstrated that alveolar macrophages isolated from COPD patients also express the chemokine receptor CXCR3 and upon stimulation with the specific ligands outlined above, expressed by Th1 type cells, exhibit enhanced MMP12 expression (21). Together, these observations raise the interesting possibility that macro-phages and infiltrating T cells may act in a coordinated and additive fashion to promote tissue destruction in COPD patients.

Dendritic cells

In line with the emerging concept that the generation of a specific adaptive immune response may be an important component in COPD pathogenesis, there has been a growing interest in the potential role of dendritic cells in disease progression. Dendritic cells are the 'sentinel' cell of the innate immune response and in their role as professional antigen presenting cells represent a critical interface between the innate and adaptive immune systems (22). Although dendritic cell subsets have been extensively characterized in inflammation associated with asthma, lung cancer or pulmonary infection, their role in COPD has received less attention. However, the clear correlation between lymphocyte infiltration and disease progression provides firm evidence that dendritic cells can play an important role in promoting progressive inflammation in response to cigarette smoke exposure.

Dendritic cells are present in lung parenchyma, residing in the intraepithelial spaces where they play immune surveillance role ready to respond to either infection or tissue damage. Upon exposure to such an environment the dendritic cell processes antigen and migrates towards the draining lymph nodes where after undergoing a process of maturation, it can activate a primary antigen specific immune response by naïve T cells (23).

At present there is conflicting evidence from both human patient samples and preclinical animal models surrounding both the numbers and maturation state of dendritic cells present in the lungs after chronic smoke exposure. While some reports demonstrate an increase in mature dendritic cell numbers in the lungs associated with COPD, others show that DC numbers are decreased and have a diminished T cell stimulatory capacity (24-28). Such discrepencies likely reflect differences in terms of markers used to detect DC subsets as well as analysis of DC subsets from either whole lung tissue, bronchoalveolar lavage or immunohistochemistry on specific tissue sections such as the small airways. The observation that deficiency in the chemokine receptor CCR6

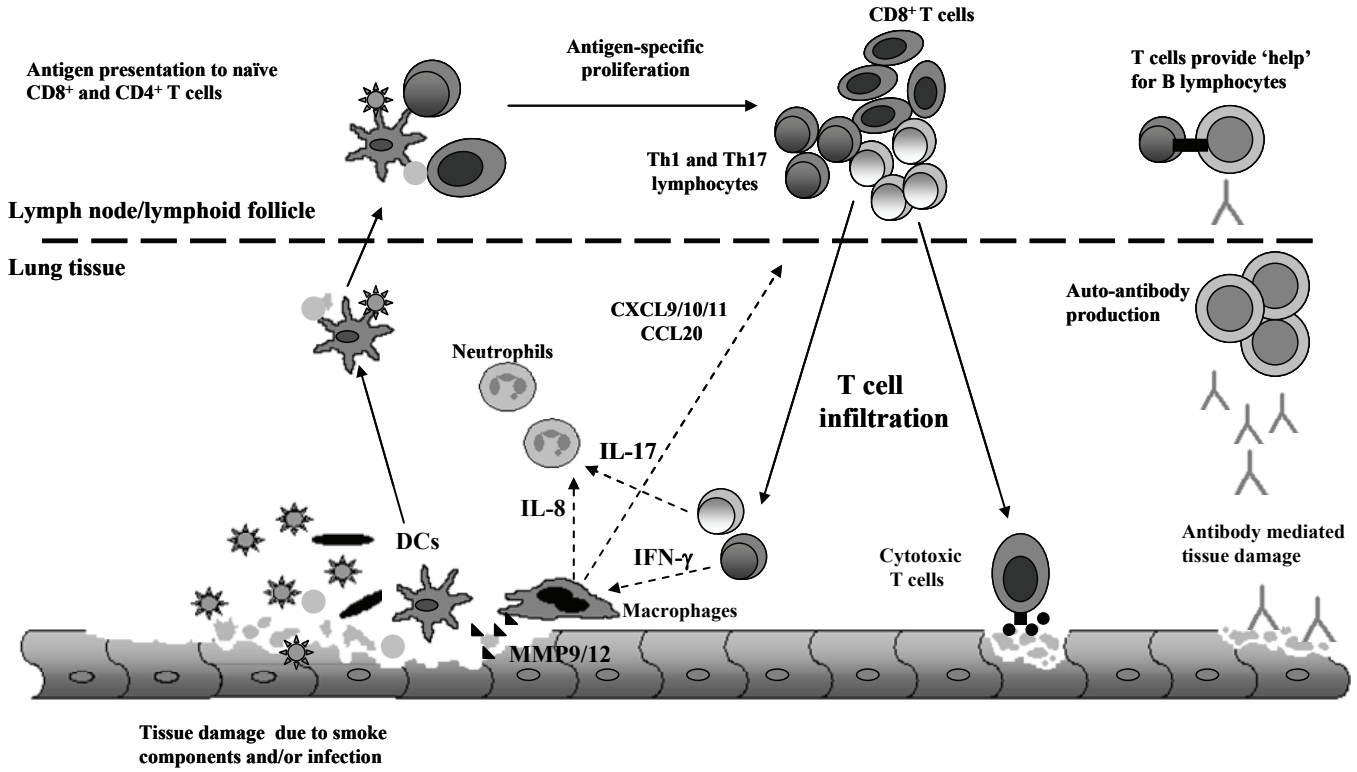

Figure 1. Generation of an adaptive immune response in COPD. Tobacco smoke induced tissue damage results in the recruitment and activation of innate immune cells such as macrophages and dendritic cells to the inflammation site. Both tobacco smoke constituents and endogenous molecules derived from damaged tissue may constitute a source of antigens which are processed and presented by dendritic cells to naïve T cells in draining lymph nodes. Antigen specific T cell activation results in oligoclonal proliferation of $CD4^+$ and $CD8^+$ T cell subsets which migrate to the site of inflammation in response to macrophage derived chemokines. Infiltrating T helper cells (Th1 and Th17) amplify the inflammatory response through the secretion of specific cytokines which promote neutrophil infiltration, macrophage activation, $CD8^+$ cytotoxic T cell responses and auto-antibody production by activated B cells.

confers protection in a murine model of cigarette smoke induced pulmonary inflammation and emphysema points to a mechanistic role for DC in promoting disease progression (29). CCR6 is a chemokine receptor whose expression is largely associated with tissue infiltrating proinflammatory DC (as well as with specific T cell subsets) and it has subsequently been demonstrated that COPD patients have significantly elevated levels of the CCR6 ligand, CCL20, in the lung (28).

As well as their potential role in promoting adaptive immune responses evidence also exists indicating that DC, as well as macrophages, can contribute to proteolytic mechanisms associated with tissue destruction in COPD through the expression of MMP-12 (30).

Despite the growing interest in the role of DC in the immunopathology of COPD, many critical outstanding issues remain to be resolved. Although it is generally accepted that COPD is associated with the generation of an adaptive immune response in which a role for DC is strongly implied, the source of antigen responsible for initiating such a response remains to be elucidated. One possibility is that tissue destruction as a direct result of tobacco smoke exposure leads to activation of the innate immune system and the presentation of endogenous antigens leading to the development of a classical type autoimmune response. Alternatively, the generation of adaptive immunity in COPD may be reflective of the increased susceptibility of these patients to pulmonary infection with both viral and bacterial pathogens. In order to adequately address such issues a more detailed investigation into the role of DC subsets in COPD pathogenesis is required.

The adaptive immune system in COPD

T cells

The infiltration of activated T cells, and particularly $CD8^+$ cytotoxic T cells, has long been recognized as a feature of chronic pulmonary inflammation in COPD (31). Oligoclonal $CD8^+$ T cell infiltrates are present in both the lungs of COPD patients and also in mice chronically exposed to cigarette smoke, where they persist even after a sustained period of smoking cessation (32, 33). Furthermore, a number of groups have demonstrated that $CD8^+$ T cell infiltration is positively correlated with airflow limitation and disease progression (31, 34). Although such observations implicate T cell

responses in COPD pathogenesis, the precise role of particular T cell subsets in disease progression remains ill defined.

A major consequence of effector $CD8^+$ T cell function is the apoptosis of target cells through a FasL or perforin/granzyme dependent mechanism and a number of groups have demonstrated a correlation between the levels of T cell infiltration and apoptosis related tissue destruction in the emphysematous lung (35, 36). Although the nature of the $CD4^+$ T cell response in the lungs of COPD patients is less well characterized it is accepted that in order for most classes of $CD8^+$ T cell responses to be mounted effectively, $CD4^+$ T cell 'help' is required. This indicates that $CD4^+$ T cell activation also plays a critical role in driving the adaptive immune response in COPD.

Activated $CD4^+$ T cells can differentiate into a number of specific subsets defined by their cytokine expression profiles. Th1 cells predominantly express IFN-γ, while Th2 cells, critical in allergic asthma responses, express IL-4 and IL-5. A more recent addition to the T cell differentiation paradigm is the Th17 cell characterized by the expression of IL-17. Most studies in both human and animal models indicate that a Th1 type response predominates in COPD, although the presence of lung infiltrating Th2 cells has also been demonstrated indicating a degree of mechanistic heterogeneity (21, 37, 38). Transgenic overexpression of IFN-γ, the prototypical Th1 (Tc1) derived cytokine, in the lungs of adult mice, also leads to the development of emphysema (39). We have recently demonstrated the presence of a distinct Th17 type response in conjunction with a Th1 type response in the airways of chronically cigarette smoke exposed mice (40) (Figure 1). It is tempting to speculate that Th17 cells play a role in disease pathogenesis given the role of IL-17 in promoting neutrophil chemotaxis as well as its reported ability to stimulate mucin production from respiratory epithelium (41, 42). It is also noteworthy that Th17 cells in the airways of emphysematous mice express the chemokine receptor CCR6 (40). CCR6 deficient mice have previously been found to be protected from cigarette smoke induced pulmonary inflammation and airspace enlargement perhaps indicating an important role for Th17 cells (29).

As previously mentioned, a major unanswered question surrounding the T cell response in COPD and emphysema is the source of the antigenic stimulus driving the response. Antigenic determinants may be associated with viral or bacterial infection, which are often enhanced in COPD patients. Alternatively, antigens may be derived from constituents of tobacco smoke itself or may be 'self' antigens altered by tobacco constituents or associated with persistent tissue destruction. In this regard the recent demonstration of autoreactive $CD4^+$ T cells in the periphery of COPD patients is revealing (43). This observation points toward a break down in 'self' tolerance associated with tissue destruction and identifies elastin breakdown products as a potential antigen. Interestingly, Lee et al. also demonstrate an apparent deficit of $CD4^+CD25^+Foxp3^+$ regulatory T cells present in the lungs of emphysema patients raising the possibility that a breakdown in T cell mediated immune regulation may also contribute to disease progression (43).

B cells

In line with the growing appreciation of the role of $CD4^+$ T cell responses in COPD/emphysema, recent reports have also highlighted the potential importance of B cell responses and auto-antibody production. $CD4^+$ T cells are inherently associated with the humoral immune response by providing specific help for antibody-secreting B-cells. In particular, T cell help is required for appropriate antibody isotype switching and also plays a role in promoting B cell proliferation.

In emphysematous lungs from COPD patients, CD4 T cells were found to co-localize with B cells forming lymphoid follicles which contain germinal centers. The numbers of B cell follicles present in the lung were shown to increase with disease severity (44-46). In addition, the presence of auto-antibodies against pulmonary epithelial and endothelial cells has been described in the serum of COPD patients. Deposition of IgG as well as C3, indicative of antibody mediated complement activation and cell injury, has been demonstrated in the small airways of COPD patients but is noticeably absent in the airways of healthy controls (47).

As well the identification of peripheral elastin reactive T cells in emphysema patients, Lee et al. also reported increased levels of elastin specific auto-antibodies in the serum and increased numbers of B cells secreting anti-elastin antibodies in the lungs of emphysema patients (43). Interestingly, anti-elastin autoimmune responses may provide a mechanistic link between pulmonary tissue damage and pathology of other elastin-rich organs and tissues, given that habitual tobacco smokers are more susceptible to elastolytic skin disorders and coronary artery disease (43).

Summary

A greater understanding of the complex and multi-faceted nature of COPD has led to a growing awareness that disease progression results from the interaction of a number of cell types contributing to specific disease related mechanisms. It is now obvious that the protease imbalance model of disease pathogenesis, while of obvious significance, is an over simplification. It is also widely accepted that the generation of an adaptive immune response is an important characteristic of emphysematous tissue damage in COPD patients. While there remain many important questions about the precise nature of this response to be addressed, the hypothesis that an autoimmune component exists in COPD raises a number a novel therapeutic possibilities.

It remains to be determined whether immunotherapeutics used in the treatment of conventional autoimmune diseases such as rheumatoid arthritis or lupus exhibit any efficacy in treating COPD. However, current conventional treatment for COPD consisting of a combination therapy of long acting bronchodilators with immunosuppressive corticosteroids does appear to slow the rate of lung function decline although its effects on mortality are inconclusive (48). The issue of

whether steroids are beneficial to COPD patients remains controversial but the reported benefits from the aforementioned trials suggest that inhibition of the adaptive immune response may be effective, at least when other disease relevant mechanisms are also targeted.

As more specific information concerning the relative contribution of immune cell subsets towards COPD pathogenesis are elucidated, future therapeutic targets and strategies will be revealed. The likely scenario, given the complex nature of COPD, is that combination therapies designed to address distinct cellular pathological mechanisms will prove most beneficial. Whether such approaches include novel strategies aimed at suppressing or modulating the adaptive immune response remains to be seen.

References

1. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet. 2004;364:613-620.
2. Cosio MG, Guerassimov A. Chronic obstructive pulmonary disease. Inflammation of small airways and lung parenchyma. Am J Respir Crit Care Med. 1999;160:S21-25.
3. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol. 2008;8:183-192.
4. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J. 2003;22:672-688.
5. Quint JK, Wedzicha JA. The neutrophil in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2007;119:1065-1071.
6. Shapiro SD. The macrophage in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;160:S29-32.
7. Tetley TD. Macrophages and the pathogenesis of COPD. Chest. 2002;121:156S-159S.
8. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1:1645-1648.
9. Simmons MS, Connett JE, Nides MA, et al. Smoking reduction and the rate of decline in FEV(1): results from the Lung Health Study. Eur Respir J. 2005;25:1011-1017.
10. Bals R, Hiemstra PS. Innate immunity in the lung: how epithelial cells fight against respiratory pathogens. Eur Respir J. 2004;23:327-333.
11. Hiemstra PS, Bals R. Series introduction: Innate host defense of the respiratory epithelium. J Leukoc Biol. 2004;75:3-4.
12. Mehta H, Nazzal K, Sadikot RT. Cigarette smoking and innate immunity. Inflamm Res. 2008;57:497-503.
13. Araya J, Cambier S, Markovics JA, et al. Squamous metaplasia amplifies pathologic epithelial-mesenchymal interactions in COPD patients. J Clin Invest. 2007;117:3551-3562.
14. Morris DG, Huang X, Kaminski N, et al. Loss of integrin αvβ6-mediated TGF-β activation causes Mmp12-dependent emphysema. Nature. 2003;422:169-173.
15. Mio T, Romberger DJ, Thompson AB, Robbins RA, Heires A, Rennard SI. Cigarette smoke induces interleukin-8 release from human bronchial epithelial cells. Am J Respir Crit Care Med. 1997;155:1770-1776.
16. Iwamura C, Nakayama T. Toll-like receptors in the respiratory system: their roles in inflammation. Curr Allergy Asthma Rep. 2008;8:7-13.
17. Finkelstein R, Fraser RS, Ghezzo H, Cosio MG. Alveolar inflammation and its relation to emphysema in smokers. Am J Respir Crit Care Med. 1995;152:1666-1672.
18. Russell RE, Thorley A, Culpitt SV, et al. Alveolar macrophage-mediated elastolysis: roles of matrix metalloproteinases, cysteine, and serine proteases. Am J Physiol Lung Cell Mol Physiol. 2002;283:L867-873.
19. Culpitt SV, Rogers DF, Shah P, et al. Impaired inhibition by dexamethasone of cytokine release by alveolar macrophages from patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;167:24-31.
20. Saetta M, Mariani M, Panina-Bordignon P, et al. Increased expression of the chemokine receptor CXCR3 and its ligand CXCL10 in peripheral airways of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2002;165:1404-1409.
21. Grumelli S, Corry DB, Song LZ, et al. An immune basis for lung parenchymal destruction in chronic obstructive pulmonary disease and emphysema. PLoS Med. 2004;1:e8.
22. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature. 1998;392:245-252.
23. Tsoumakidou M, Demedts IK, Brusselle GG, Jeffery PK. Dendritic cells in chronic obstructive pulmonary disease: new players in an old game. Am J Respir Crit Care Med. 2008; 177:1180-1186.
24. Robbins CS, Dawe DE, Goncharova SI, et al. Cigarette smoke decreases pulmonary dendritic cells and impacts antiviral immune responsiveness. Am J Respir Cell Mol Biol. 2004;30: 202-211.
25. Robbins CS, Franco F, Mouded M, Cernadas M, Shapiro SD. Cigarette smoke exposure impairs dendritic cell maturation and T cell proliferation in thoracic lymph nodes of mice. J Immunol. 2008;180:6623-6628.
26. D'Hulst A I, Vermaelen KY, Brusselle GG, Joos GF, Pauwels RA. Time course of cigarette smoke-induced pulmonary inflammation in mice. Eur Respir J. 2005;26:204-213.
27. Tsoumakidou M, Elston W, Zhu J, et al. Cigarette smoking alters bronchial mucosal immunity in asthma. Am J Respir Crit Care Med. 2007;175:919-925.
28. Demedts IK, Bracke KR, Van Pottelberge G, et al. Accumulation of dendritic cells and increased CCL20 levels in the airways of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;175:998-1005.
29. Bracke KR, D'Hulst A I, Maes T, et al. Cigarette smoke-induced pulmonary inflammation and emphysema are attenuated in CCR6-deficient mice. J Immunol. 2006;177:4350-4359.
30. Bracke K, Cataldo D, Maes T, et al. Matrix metalloproteinase-12 and cathepsin D expression in pulmonary macrophages and dendritic cells of cigarette smoke-exposed mice. Int Arch Allergy Immunol. 2005;138:169-179.
31. Saetta M, Di Stefano A, Turato G, et al. CD8+ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157:822-826.
32. Motz GT, Eppert BL, Sun G, et al. Persistence of lung CD8 T cell oligoclonal expansions upon smoking cessation in a mouse model of cigarette smoke-induced emphysema. J Immunol. 2008;181:8036-8043.
33. Korn S, Wiewrodt R, Walz YC, et al. Characterization of the interstitial lung and peripheral blood T cell receptor repertoire in cigarette smokers. Am J Respir Cell Mol Biol. 2005;32:142-148.
34. O'Shaughnessy TC, Ansari TW, Barnes NC, Jeffery PK. Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+ T lymphocytes with FEV1. Am J Respir Crit Care Med. 1997;155:852-857.
35. Majo J, Ghezzo H, Cosio MG. Lymphocyte population and

apoptosis in the lungs of smokers and their relation to emphysema. Eur Respir J. 2001;17:946-953.
36. Kasahara Y, Tuder RM, Cool CD, Lynch DA, Flores SC, Voelkel NF. Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. Am J Respir Crit Care Med. 2001;163:737-744.
37. Hodge G, Nairn J, Holmes M, Reynolds PN, Hodge S. Increased intracellular T helper 1 proinflammatory cytokine production in peripheral blood, bronchoalveolar lavage and intraepithelial T cells of COPD subjects. Clin Exp Immunol. 2007;150:22-29.
38. Miotto D, Ruggieri MP, Boschetto P, et al. Interleukin-13 and -4 expression in the central airways of smokers with chronic bronchitis. Eur Respir J. 2003;22:602-608.
39. Wang Z, Zheng T, Zhu Z, et al. Interferon γ induction of pulmonary emphysema in the adult murine lung. J Exp Med. 2000;192:1587-1600.
40. Harrison OJ, Foley J, Bolognese BJ, Long E, 3rd, Podolin PL, Walsh PT. Airway infiltration of $CD4^{+}CCR6^{+}$ Th17 type cells associated with chronic cigarette smoke induced airspace enlargement. Immunol Lett. 2008;121:13-21.
41. Prause O, Bozinovski S, Anderson GP, Linden A. Increased matrix metalloproteinase-9 concentration and activity after stimulation with interleukin-17 in mouse airways. Thorax. 2004; 59:313-317.
42. Chen Y, Thai P, Zhao YH, Ho YS, DeSouza MM, Wu R. Stimulation of airway mucin gene expression by interleukin (IL)-17 through IL-6 paracrine/autocrine loop. J Biol Chem. 2003;278:17036-17043.
43. Lee SH, Goswami S, Grudo A, et al. Antielastin autoimmunity in tobacco smoking-induced emphysema. Nat Med. 2007;13: 567-569.
44. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:2645-2653.
45. Gosman MM, Willemse BW, Jansen DF, et al. Increased number of B-cells in bronchial biopsies in COPD. Eur Respir J. 2006; 27:60-64.
46. van der Strate BW, Postma DS, Brandsma CA, et al. Cigarette smoke-induced emphysema: A role for the B cell? Am J Respir Crit Care Med. 2006;173:751-758.
47. Feghali-Bostwick CA, Gadgil AS, Otterbein LE, et al. Autoantibodies in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177:156-163.
48. Keating GM, McCormack PL. Salmeterol/fluticasone propionate: a review of its use in the treatment of chronic obstructive pulmonary disease. Drugs. 2007;67:2383-2405.