Role of T-lymphocytes and pro-inflammatory mediators in the pathogenesis of chronic obstructive pulmonary disease

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Abstract: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the US and a major worldwide healthcare problem. The pathophysiologic mechanisms that drive development and progression of this disease are complex and only poorly understood. While tobacco smoking is the primary risk factor, other disease processes also appear to play a role. Components of the innate immune system (eg, macrophages and neutrophils) have long been believed to be important in the development of COPD. More recent evidence also suggests involvement of the adaptive immune system in pathogenesis of this disease. Here we will review the literature supporting the participation of T-cells in the development of COPD, and comment on the potential antigenic stimuli that may account for these responses. We will further explore the prospective contributions of T-cell derived mediators that could contribute to the inflammation, alveolar wall destruction, and small airway fibrosis of advanced COPD. A better understanding of these complex immune processes will lead to new insights that could result in improved preventative and/or treatment strategies.

Keywords: COPD, T-lymphocytes, adaptive immunity, cytokines

Chronic obstructive pulmonary disease (COPD) is characterized by expiratory airflow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal intrapulmonary inflammatory response to noxious particles or gases (Rabe et al 2007). COPD is a leading cause of death worldwide, and one of the few diseases in which mortality rates continue to increase (Manino 2002; Rabe et al 2007). Management of patients afflicted with COPD is often frustrating, and it is uncertain that any of the currently available treatments actually modify the natural history of the disease. While direct injury to airway and alveolar epithelium from chronic exposure to smoke is undoubtedly the primary risk factor for the development of COPD, the potential contributions of other disease mechanisms appear to be important. Individuals with COPD typically have at least a 10 pack-year history of tobacco smoking. However, only a minority of heavy smokers develop severe airflow abnormalities, suggesting that the disease is not solely attributable to smoke exposure. Furthermore, COPD often progresses, and intrapulmonary inflammation typically persists, despite removal of the inciting agent(s) with the cessation of smoking (Retamales et al 2001).

The presence of intrapulmonary inflammation in COPD has been appreciated for many years, and accumulations and functions of activated macrophages and polymorphonuclear leukocytes (components of the innate immune system) have long been believed to be important in disease development (Brain 1980; Schleime 2005; Tetley 2005; Quint and Wedzicha 2007). More recent reports have suggested that the adaptive

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immune response also contributes to the pathophysiology of COPD. The cellular effectors of adaptive immunity are lymphocytes (both B- and T-cells), and the distinctive hallmarks of this system include antigen specificity, clonal expansions of antigen-activated lymphocytes, and the generation of immunologic memory (Monaco et al 2004). A greater understanding of adaptive immune processes in COPD could perhaps lead to more effective disease interdictions, including elimination or eradication of the antigen(s), induction of tolerance to the antigen(s), manipulations of immunoregulatory mechanisms, or perhaps targeted depletion of specific disease-associated lymphocyte subpopulations.

Here we will review some of the evidence supporting the hypothesis that T-cell responses are important in the pathogenesis of COPD, comment on the potential contributions of individual T-lymphocyte subsets, and outline selected mediators elaborated by these cells.

Associations of T-lymphocytes with COPD

The presumed role of T-cells in COPD was first suggested by histopathologic studies that found associations between disease severity and the extent of intrapulmonary lymphocyte infiltrates. Finkelstein et al noted that lymphocytes and macrophages are the predominant cellular elements of the inflammatory infiltrates within airway walls of patients with COPD (Finkelstein et al 1995). These observations were extended by finding that numbers of $CD8^+$ lymphocytes in COPD lungs were directly related to the degree of airflow limitation (Figure 1) (Saetta et al 1998). Among many other analogous studies, the numbers of T-lymphocytes in surgical lung resections of patients with emphysema were shown to be significantly increased, compared to findings in smokers without evidence of airflow obstruction or nonsmokers (Majo et al 2001). A recent comprehensive study of the morphometric changes seen in the small airways of COPD patients further noted the relatively unique presence of sub-epithelial lymphoid aggregates, described as bronchus associated lymphoid tissue (BALT), and the number of these BALT lesions was associated with the severity of airflow obstruction (Hogg et al 2004).

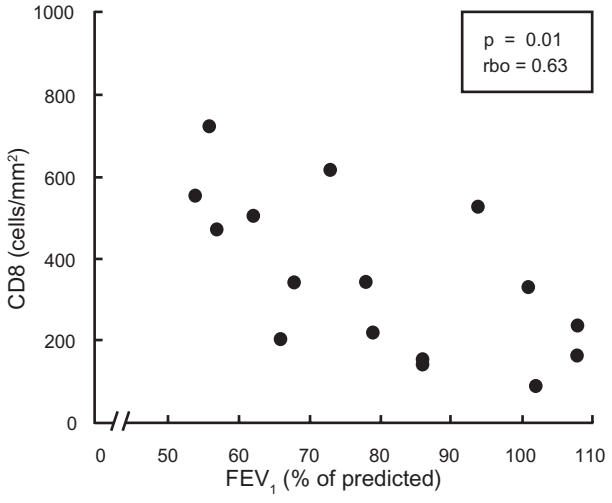

Figure 1 Inverse relationship between the presence of $CD8^+$ lymphocytes in the airway wall and forced expiratory volume in the first second (FEV_1) in smokers. Reprinted with permission from Saetta, et al 1998. *Am J Respir Crit Care Med*, 157:822–6. Copyright © 1998 American Thoracic Society.

T-lymphocytes can cause tissue injuries either by direct cytolytic activities or through the secretion of pro-inflammatory mediators that recruit and activate other immune cell types (eg, phagocytic cells and B-cells) (Monaco et al 2004). Pulmonary lymphocytes isolated from emphysematous lung tissue are frequently activated (Sullivan et al 2005) and capable of secreting mediators that have been implicated in the pathogenesis of COPD (Grumelli et al 2004). T-cells transit between inflammatory foci in organs and regional lymph nodes, and at least some proportion of these disease-specific lymphocytes also traffic within lymphatic and blood circulations (Lehmann et al 2001). Our studies of peripheral blood T-lymphocytes in patients with COPD have shown peripheral T-cells (particularly $CD8^+$) are more frequently activated and have increased productions of various mediators, and many of these T-cell abnormalities are highly correlated with disease severity (Gadgil et al 2006).

Animal models of emphysema further corroborate the importance of T-lymphocyte responses in the development of COPD. The potential for activated T-cells to cause lung injury in mice was evidenced after adoptive transfer of $CD8^+$ T-cells with specificities for neoantigens that were expressed on alveolar epithelial cells (Enelow et al 1998). $CD8^+$ T-lymphocytes were also recently shown to be critical for the induction of inflammation and tissue destruction in a murine model of smoke-induced emphysema (Maeno et al 2007). In addition, adoptive transfers of syngeneic $CD4^+$ lymphocytes that had been sensitized to endothelial cell antigens resulted in development of emphysema in naïve rats, thus highlighting the potential for $CD4^+$ T-cell associated autoimmune disease processes in COPD (Taraseviciene-Stewart et al 2005).

CD4/CD8 T-cell subsets in COPD

The majority of studies using patient-derived specimens seem to indicate that $CD8^+$ lymphocytes appear to play a particularly important role in the development and/or progression of

COPD (Finkelstein et al 1995; O'Shaughnessy et al 1997; Di Stefano et al 1998; Majo et al 2001; Hogg et al 2004; Saetta et al 1998). Most (but not all) investigators have reported that COPD $CD8^+$ lymphocytes secrete a T_h1 predominant cytokine pattern that includes increased production of IFN-γ, interferon-inducible protein-10 (IP-10), and monokine induced by interferon-gamma (MIG). In turn, these mediators can cause tissue destruction through the upregulation of matrix metalloproteinase (MMP) production by macrophages and other immune effectors (Grumelli et al 2004; Manneo 2007). $CD8^+$ T-lymphocytes can also mediate cell-death directly through the secretion of cytotoxic mediators (eg, granzyme and perforins), as well as expression or secretion of Fas (Henkart 1994; Kojima et al 1994).

While the function of $CD8^+$ lymphocytes are often highlighted in COPD studies, the potential contributions of $CD4^+$ T-cells in the disease process also appear to be substantial. Although typically less extensive than $CD8^+$ T-cell infiltrates, intraparenchymal $CD4^+$ lymphocytes are also present in abnormally increased numbers within emphysematous lungs (Majo et al 2001), particularly in proximity to BALT (Hogg et al 2004).

$CD4^+$ T-cells are largely responsible for orchestrating downstream immune processes by the release of activating cytokines, and are important if not critical in focusing and amplifying inflammatory responses by other immune effector cells. As an example, actions of $CD4^+$ T-cells are essential for the full development of adaptive immune cytotoxicity by priming (lowering thresholds of activation) and promoting the long-term survival of $CD8^+$ T-cells. The facultative help provided by $CD4^+$ lymphocytes is also important for the activation and differentiation of antibody-elaborating B-cells. This "help" is especially critical for induction of B-cells to undergo isotype switch from production of IgM to more potent and avidly-binding IgG antibodies, particularly against protein antigens.

We examined the possibility that CD4 T-cells could facilitate B-cell production of IgG autoantibodies in COPD patients. Somewhat to our surprise, we found that ~70% of these patients had circulating IgG autoantibodies against epithelial cells, as ascertained by indirect immunofluorescence assays, compared to 10% among non-smoking controls and 13% of cigarette smokers without evidence of lung abnormalities (Feghali-Bostwick et al 2008). An even more highly sensitive and specific immunoprecipitation assay showed that 34 out of 35 COPD patients (97%) had autoreactive antibodies against a variety of cellular self-antigens (Figure 2). Not only are circulating autoantibodies highly prevalent in COPD patients, but the immunoglobulins appeared likely to be pathogenic, as evidenced by findings of immune complex deposition and complement activation in surgically resected end-stage COPD lungs, and the evident

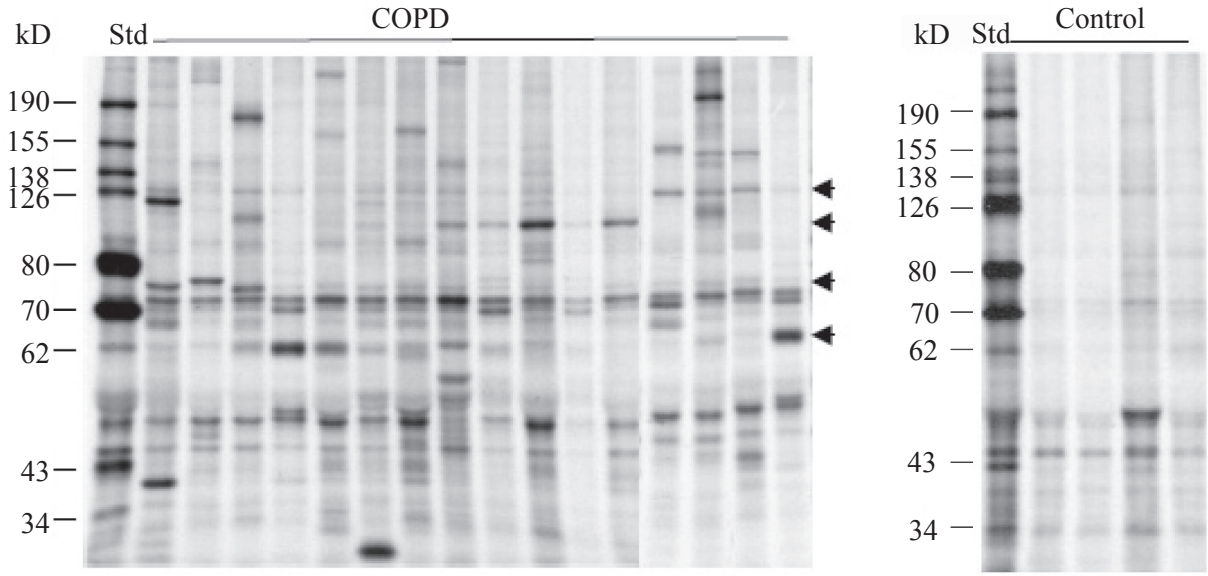

Figure 2 Immunoprecipitation of autoantibodies in plasma samples of COPD patients. Bands represent autoantigens precipitated by autoantibodies present in COPD plasma specimens (composite figure). Similarly treated plasma samples from non-smokers are shown here as controls. The most highly prevalent autoantigens are highlighted and were shown by other means to be distinct from antigens involved in other known autoimmune syndromes. Individual lanes correspond to a patient sample. Reprinted with permission from Feghali-Bostwick, et al 2008. *Am J Respir Crit Care Med*, 177:156–63. Copyright © 2008 American Thoracic Society.
Abbreviation: Std, molecular weight marker.

ability of these autoantibodies to induce antibody dependent cell-mediated cytotoxicity (ADCC).

In addition to the generally potent pro-inflammatory effects of $CD4^+$ lymphocytes, a subset of these cells may also (and perhaps more favorably) influence the progression of immunologic diseases, including COPD, by acting to dampen the intensity of inflammatory cascades. A small proportion of $CD4^+$ T-lymphocytes with distinctive phenotypic characteristics have been shown to exert suppressive effects on inflammatory processes common to many immunologic and autoimmune diseases (Rouse 2007). However, the role of these regulatory T cells (T_{reg}) in COPD has only recently become a topic of investigation. One contemporaneous study suggested that chronic cigarette exposure resulted in increased T_{reg} populations in the bronchoalveolar lavage (BAL) of COPD patients, but these cells were paradoxically believed to be functionally impaired (Smyth et al 2007). Conversely, another recent investigation found decreased numbers of functionally intact T_{regs} in emphysematous lung tissue compared to healthy lungs (Lee et al 2007). Further investigations into the potential impact of T_{reg} cells in the development of smoking related lung inflammation and injury are necessary, and could have considerable eventual importance for development of novel therapeutics.

Peptide antigens – triggers of adaptive immune activation

In the face of mounting evidence that T-lymphocytes likely participate in the pathogenesis of COPD, the circumstances that bring about initial activations of these cells remains a matter of speculation. A number of studies indicate that the lymphocyte proliferations seen in COPD patients are driven by specific peptide antigens. Identification of these antigen(s) would have far-reaching importance for furthering our understanding of COPD, and almost certainly enhance efforts at disease prevention or development of more effective treatments.

As previously mentioned, the specificity of antigen recognition and lymphocyte activation is a defining feature of the adaptive immune system (Murphy et al 2007). During maturation, developing B- and T-cells undergo random rearrangements of gene segments encoding their respective antigen receptors. These distinctive genomic sequences, in turn, result in highly individual antigen receptors expressed on the cell surface of the lymphocytes, ie, immunoglobulins (Ig) on B-cells, and T-cell antigen receptors (TCR). Since the avidity of these antigen receptors is determined by their structure, each individual lymphocyte can only engage a very limited number of distinct peptides. Thus, adaptive immune responses against any given antigen are characterized by initial activation of only the tiny proportion of lymphocytes whose surface Ig or TCR happen to have specificity for this antigen. However, the subsequent ability of these individual cells to undergo multiple divisions (clonal proliferations) results in large numbers of functional lymphocytes sharing identical antigen receptors (daughter progeny) that have specificity against the offending antigen (microbial or other exogenous peptides), and are capable of mounting an effective immune defense (usually). Because the antigen receptor sequences are definable by various cellular DNA and mRNA assays, it becomes possible to evaluate populations of lymphocytes to determine the proportion of these cells that have shared ancestors, as determined by commonality of antigen receptor sequences. Finding that a T- or B-cell infiltrate is comprised of daughter progeny derived from a small number of clonally expanded lymphocyte founders (ie, mono- or oligoclonality) demonstrates that a peptide antigen has driven these cellular proliferations (Feghali-Bostwick et al 2007). In distinction, lymphocytes that are induced to undergo promiscuous proliferations by mechanisms independent of antigen receptor specificity (eg, mitogens, growth factors), or nonspecifically recruited to an inflammatory foci and sequestered there, will comprise cells lacking shared ancesters (ie, polyclonal populations).

The antigen receptor repertoires of lymphocytes in COPD patients have been analyzed in a limited number of studies. Sullivan et al examined T-lymphocytes isolated from emphysematous lung tissue and demonstrated these populations were comprised of oligoclonal T-cells (Sullivan et al 2005). This finding was echoed by Korn et al who further showed that clonal expansions were most particularly pronounced among $CD8^+$ T-lymphocytes, in both the lung and in the blood of chronic smokers (Korn et al 2005). Additionally, circulating T-lymphocytes and those isolated from COPD lungs frequently exhibit down-regulation of CD28, a co-stimulatory molecule, which, in turn, is another, if less immediately evident consequence of chronic antigen exposure and repeated cell divisions (Sullivan et al 2005). CD28 down-regulation has been documented in a number of chronic inflammatory syndromes including autoimmune diseases (Schirmer et al 1998) and lung allograft rejection (Studer et al 2008).

The origin of the peptide antigen(s) responsible for initiating this inflammatory cascade remains speculative at this time. While there are numerous possibilities, a few of the seemingly more likely potential antigens will be discussed here:

Microbial peptide antigens

The hypothesis that chronic or recurrent microbial infections in patients could be the source of the COPD antigenic stimulus is particularly attractive (Figure 3). Bacterial colonization of the airways in COPD patients with even mild airflow obstruction is frequent (Soler et al 1999; Sethi et al 2006), and hence these particular microbes seem to be likely suspects as the source of disease-causing exogenous antigens. These bacterial colonizations are associated with recurrent COPD exacerbations, more rapid declines in lung function, and are correlated with a number of inflammatory markers in sputum and in BAL (Hill et al 2000; Patel et al 2002; Wilkinson et al 2003; Banerjee et al 2004).

Patients with COPD are also more susceptible to viral infections, and childhood viral infections have even been speculated to predispose individuals for development of COPD (Samet et al 1983). A small number of studies have found evidence that various viral infections may be associated with COPD, notably including a report that severe emphysema was associated with up to 40-fold greater prevalence of adenoviral E1A protein expression in alveolar epithelial cells (Retamales et al 2001).

Pneumocystis jiroveci is another organism that has been implicated in the pathogenesis of COPD. This organism has been reported to colonize 36% of lung tissues from patients with end-stage COPD versus 5% of specimens from healthy controls or those with less severe disease (Morris et al 2004). Smokers infected with Human Immuno-deficiency Virus (HIV) also appear to have accelerated development of emphysema, particularly in those that also have high $CD8^+$ lymphocyte counts in BAL fluid (Diaz et al 2000). *Pneumocystis* colonization in lungs of rhesus macaques infected with Simian Immunodeficiency Virus (SIV) generated CD8-lymphocyte and neutrophil predominant cellular inflammation in association with progressive airflow limitation and local increases in IL-8, IFN-γ, and TNF-α, reminiscent of the findings in emphysematous patients (Norris et al 2006). These clinical and experimental results interestingly raise the possibility that Pneumoncystis and/or HIV (or perhaps other relatively indolent organisms) may be

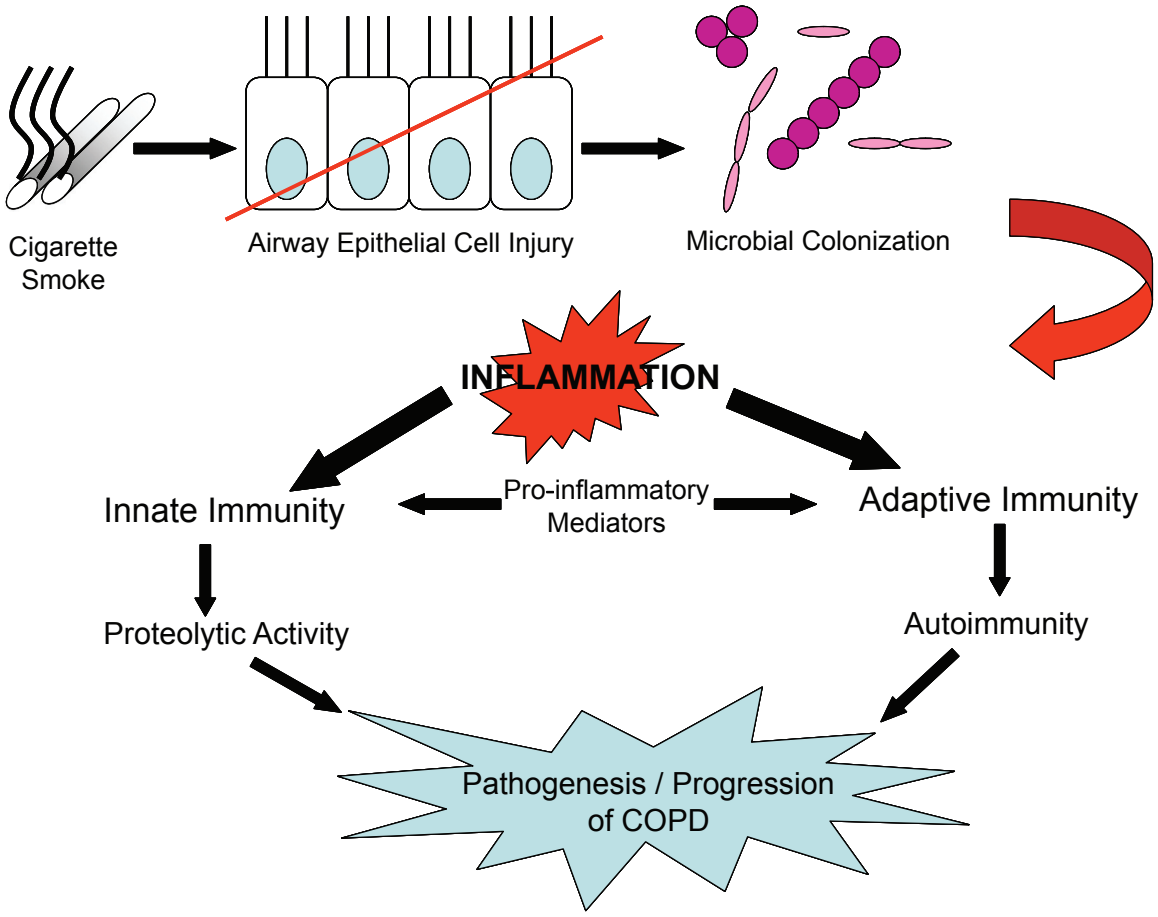

Figure 3 Schema depicting the proposed role of microbial organisms in propagating pathogenic mechanisms in COPD.

capable of contributing to the pathogenesis of lung disease, and obviously warrant further study.

Tobacco smoke related peptides

Exogenous antigens could plausibly be among the complex constituents of the tobacco smoke *per se*. Early reports noted tobacco glycoprotein (TGP), a polyphenol-rich glycoprotein isolated from cured tobacco leaves, could stimulate T-cell proliferation and activation in cell culture (Francus et al 1988). Nonetheless, to our knowledge there is no conclusive evidence directly linking TGP or other components of smoke to cellular immune activation in COPD. Furthermore, the persistence of intrapulmonary inflammation long after smoking cessation argues against the dependence of COPD on antigenic stimulation provided by a smoke constituent, unless an immune response initially triggered by such an antigen subsequently generalized to include self-antigens (see below).

Tobacco smoke, as well as some other air pollutants, also contains highly reactive substances that are capable of chemical modification of pulmonary proteins (eg, glycosolation, oxidation). Although not yet demonstrated, it is also plausible that some lung proteins altered by these processes could subsequently act as haptens, or even be so changed they are no longer recognized as "self" by immune cells and, thus provoke autoimmune responses.

Elastin peptides

A recent report has proposed that elastin peptides could be antigens that drive adaptive immune responses in COPD (Lee et al 2007). Elastin is an important extracellular matrix protein that helps maintain the structural integrity of the lung and other tissues. Under pathologic circumstances, elastin is degraded and digested by matrix MMP, which, as noted previously, have been shown to have increased activity in advanced emphysema. Elastin fragments stimulate monocyte chemotaxis and disease progression in a cigarette smoke model of murine emphysema (Houghton et al 2006). Circulating T-lymphocytes from COPD patients have recently been found to proliferate and secrete increased amounts of IFN-γ and IL-10 in co-incubations with elastin digestion fragments, and circulating antielastin antibodies were also present in these subjects (Lee et al 2007). The role of adaptive immune responses to elastin in development of COPD remains an intriguing area for further investigation. However, findings elsewhere of analogous anti-elastin reactions in varied immune syndromes and some normal individuals, as well as demonstrations of multiple intracellular autoantigens in COPD patients (Feghali-Bostwick et al 2008) may indicate that the anti-elastin responses are not necessarily all-encompassing elements of disease pathogenesis.

Other autoantigens

Autoreactivity can also arise in the course of immune responses that were initially and more appropriately directed against exogenous antigens (eg, inhaled proteins or microbes). In some cases it appears that the molecular characteristics of the inciting antigen resemble or "mimic" those of self-determinants, which then become targets of immune responses that were initially triggered and fueled by the exogenous antigen (Oldstone et al 2005). In addition, highly focused and appropriate responses against foreign antigens can spread to include targeting of otherwise quiescent self-antigens by functional errors of specificity or "epitope spreading" (Figure 4) (Vanderlugt and Miller 2002). As previously described, the lower airways of COPD patients are frequently colonized and/or infected with various microbes (Soler et al 1999; Sethi et al 2006) that are known to be capable of immune activation (Adlovitz et al 2006). Thus, adaptive immune responses that arose to eradicate these organisms could ultimately lead to self-reactivity by processes of microbial mimicry and/or epitope spreading, particularly in patients with chronic exposure to these organisms (Oldstone et al 2005; Vanderlugt and Miller 2002; Croxford et al 2002).

Another potential mechanism that could conceivably account for auto-reactive adaptive immune activation in COPD stems from alterations of phagocytic functions and antigen processing. Abnormal or ineffective clearance of apoptotic cells and cellular debris (ie, "efferocytosis") (Vandivier et al 2006), resulting in defective phagocytosis of apoptotic bodies and/or other particulates, have been linked to the development of autoimmunity (Cline and Radic 2004). Hodge et al have shown that alveolar macrophages harvested from the BAL fluid of patients with COPD had an impaired ability to phagocytose apoptotic epithelial cells in vitro (Hodge et al 2003).

Certain, otherwise perplexing clinical features of COPD could be explicable by an autoreactive pathogenesis. The development of typical autoimmune syndromes in human patients (as well as experimental animal models) seems to involve complex interactions between environmental factors (eg, cigarette smoke and/or possibly microbes) and genetic backgrounds. If also true in COPD, previously reported familial predilections, as well as the considerable inter-individual variability for disease susceptibility with equivalent smoking exposures, could be explained.

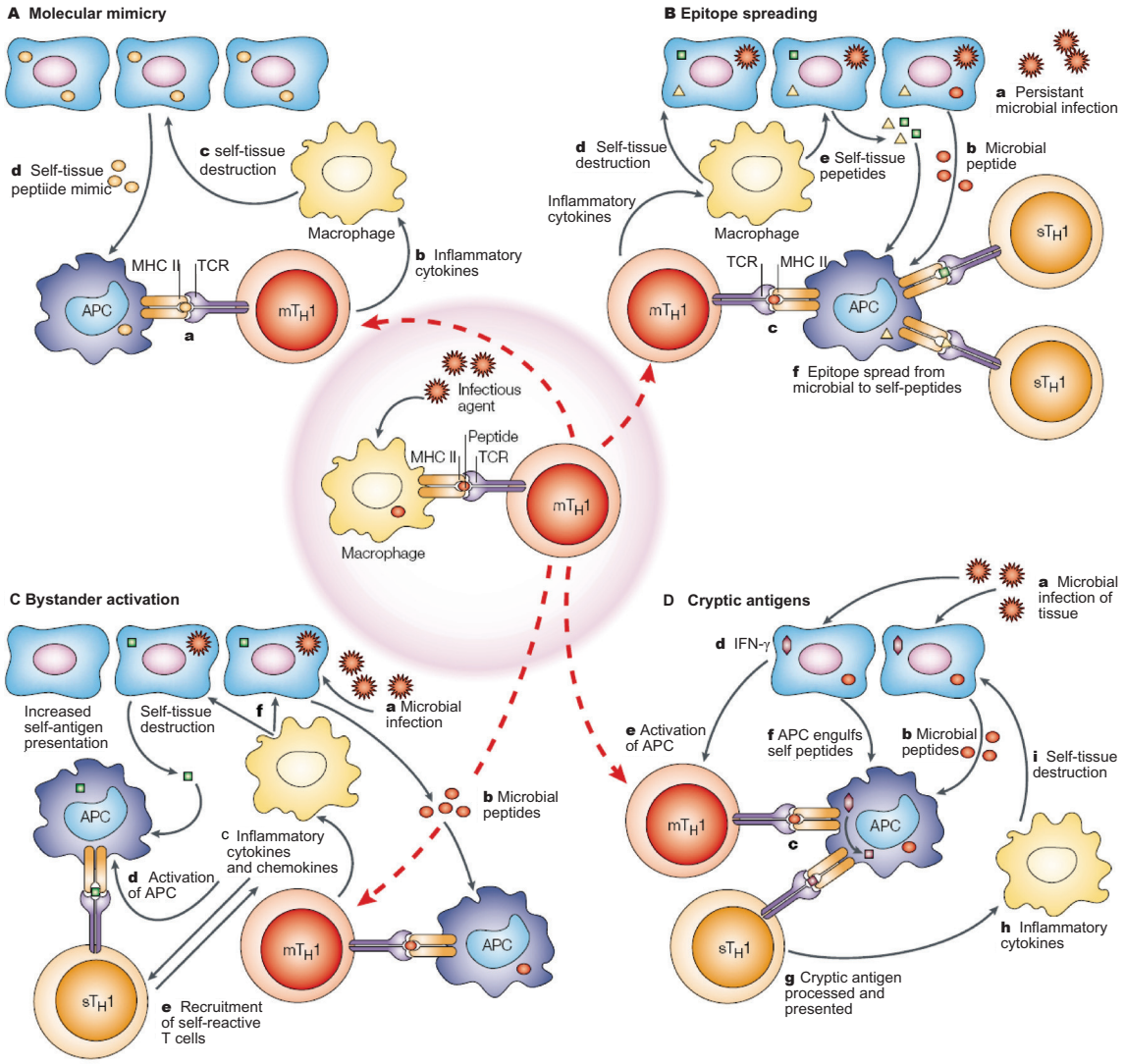

Figure 4 Mechanisms of infection-induced autoimmunity. After a microbial infection, activated microbe-specific TH1 (mTH1) cells migrate to the infected organ. **A** Molecular mimicry describes the activation of crossreactive T_H1 cells that recognize both the microbial epitope (mT_H1) and the self epitope (sT_H1) (**a**). Activation of the crossreactive T cells results in the release of cytokines and chemokines (**b**) that recruit and activate monocytes and macrophages, which mediate self-tissue damage (**c**). The subsequent release of self-tissue antigens and their uptake by APCs perpetuates the autoimmune disease (**d**). **B** Epitope spreading involves a persistent microbial infection (**a**) that causes the activation of microorganism-specific T_H1 cells (**b**,**c**), which mediate self-tissue damage (**d**). This results in the release of self peptides (**e**), which are engulfed by APCs and presented to self-reactive T_H1 cells (**f**). Continual damage and release of self peptides results in the spread of the self-reactive immune response to multiple self-epitopes (**f**). **C** Bystander activation is the nonspecific activation of self-reactive T_H1 cells. Activation of microorganism-specific T_H1 cells (**a**,**b**) leads to inflammation (**c**,**d**) and results in the increased infiltration of T cells at the site of infection and the activation of self-reactive T_H1 cells by TCR-dependent and –independent mechanisms (**e**) Self-reactive T cells activated in this manner mediate self-tissue damage and perpetuate the autoimmune response (**f**). **D** Cryptic antigen model describing the initiation of autoimmunity by differential processing of self peptides. Following microbial infection (**a**) IFN-γ is secreted by both activated microbe-specific T_H1 cells (**b**,**c**) and microbe-infected tissue cells (**d**). This activates APCs (**e**) and can lead to APC engulfing self-antigens (**f**). Cytokine activation of APCs can induce increased protease production and different processing of captured self-antigens, resulting in presentation of cryptic epitopes. The presentation of these cryptic epitopes can activate self-reactive T_H1 cells (**g**), leading to self-tissue destruction (**h**,**i**). APC, antigen-presenting cell; MHC II, major histocompatibility complex class II; TCR, T-cell receptor.

Moreover, fully developed autoimmune responses tend to be self-perpetuating, a possible mechanism for persistence (and progression) of COPD despite smoking cessation.

T-cell mediators and COPD

Cytokines and chemokines are extracellular signaling proteins that mediate the effector functions of a variety of inflammatory cells. A number of putative effector molecules have been implicated in the pathogenesis of COPD, and it is likely that an imbalance between the various pro- and anti-inflammatory mediators may play a part in the development of disease. This chronic pro-inflammatory cytokine/chemokine milieu could also contribute to the apparent susceptibility of patients suffering from COPD to bronchogenic

carcinoma and cardiovascular disease (Coussens et al 2002; Lu et al 2006; Sin et al 2008).

A T_h1 predominant cytokine secretion pattern (eg, IFN-γ) has been described in most studies using COPD clinical specimens (Majori et al 1999; Hodge G et al 2007), although T_h2 biased responses (eg, IL-4, IL-10) have conversely also been reported (Barcelo et al 2006; Barczyk et al 2006). The seeming disparities among these studies may be due to patient heterogeneity in terms of disease severity (or medications) and confounding introduced by typically small sample sizes (ie, *alpha* and *beta* errors). As in most complex disease processes, moreover, simple or rigid attempts to classify COPD as a particular T_h pattern is probably an oversimplification. The mediator environment responsible for the pathogenesis of this disease probably involves significant overlap between T_h1 and T_h2 cytokines.

While the potential contributions of specific mediators in COPD have been exhaustively described elsewhere (Chung, 2001; Reid and Sallenave, 2003), here we will comment on the roles of selected lymphocyte-associated mediators that have been particularly implicated in disease pathogenesis:

Interferon-gamma (IFN-γ)

Interferon-gamma is a pro-inflammatory cytokine produced primarily by T_h1/T_c1 lymphocytes and natural killer cells and, among other effects, this mediator is a potent stimulator of alveolar macrophages and epithelial cells. As previously noted, IFN-γ has been shown to be upregulated in lymphocytes isolated from emphysematous lung tissue samples (Grumelli et al 2004), bronchoalveolar lavage fluid (Hodge et al 2007), peripheral blood (Majori et al 1999; Hodge G et al 2007), and IFN-γ secreting $CD8^+$ T-cells are seen in increased frequency within sputum of patients with COPD (Tzanakis et al 2004). These and multiple other reports suggest that IFN-γ plays a major role in the development of COPD. In addition, clinical observations are also supported by findings that IFN-γ over-expression in the lungs of mice promotes development of emphysema (Wang et al 2000). Among a complex constellation of effects, tissue injuries of COPD may be particularly promoted by IFN-γ through the release of MMP from activated macrophages, or via injury by $CXC3R^+$ $CD8^-$lymphoyctes induced by IP-10 and MIG.

Tumor necrosis factor-alpha (TNF-α)

TNF-α is a pro-apoptotic cytokine which has been shown to be elevated in the serum of patients with stable COPD (Keating et al 1996), and further increased during acute exacerbations (Aaron et al 2001). A TNF-α gene polymorphism resulting in increased TNF-α levels has also been described in a population that is uniquely susceptible to the development of COPD (Huang et al 1997; Sakao et al 2002), although other studies have not been able to corroborate this finding (Higham et al 2000; Ferrarotti et al 2003). Interestingly, serum concentrations of TNF-α, as well as TNF-α secretion by monocytes, is particularly robust in the subset of COPD patients with weight loss or cachexia (Di Francia et al 1994; De Godoy et al 1996; Pitsiou et al 2002). It has therefore been hypothesized that TNF-α contributes to the systemic manifestations of emphysema, particularly muscle wasting and limitations in exercise tolerance.

In the context of COPD histopathology, the effects of TNF-α could explain the cellular apoptosis observed in the alveolar wall among emphysematous lung tissue sections. TNF-α also induces the production of interleukin-8 (IL-8) and MMP through the induction of nuclear factor-κB. Overexpression of TNF-α in the lungs of mice results in the development of classic pathologic features of emphysema (Fujita et al 2001). Studies performed in TNF-receptor knockout mice using a cigarette smoke-induced model of emphysema generated a lesser degree of lung disease compared to wild-type animals (Churg et al 2004). However, TNF blockade with Infliximab, an anti-TNF antibody, did not result in apparent benefit, with respect to lung function, in patients with moderate to severe COPD, although additional evaluation may be necessary to evaluate whether selected subpopulations (eg, those with cachexia) could specifically benefit (Rennard et al 2007).

Interleukin-1β (IL-1β)

IL-1β has functional similarity to TNF-α, and is a potent stimulator of alveolar macrophages. This mediator incites the production of a number of pro-inflammatory mediators implicated in COPD pathogenesis including IL-2,-6,-8, RANTES, GM-CSF, IFN-γ, and TNF-α (Chung et al 2001). IL-1β also appears to be important in the regulation of elastolytic proteases, including MMP-9, which could play a role in the development of emphysema. IL-1β/TNF-α double receptor knockout mice demonstrated progressive and more severe emphysema in response to intratracheal instillation of neutrophil elastase than cytokine single knockouts, or wild-type mice (Lucey et al 2002).

Interleukin-6 (IL-6)

Increased IL-6 levels have been found in induced sputum, exhaled breath condensates, and bronchoalveolar lavage fluid

from patients with COPD (Bhowmik et al 2000; Song et al 2001; Bucchioni et al 2003). IL-6 is another mediator with numerous, varied and generally proinflammatory effects. The precise role that IL-6 may play in the development of COPD is still unclear, but measures of this mediator may have utility as a biomarker of disease and inflammation.

Interleukin-8 (IL-8)

The C-X-C chemokine IL-8 is a potent neutrophil and lymphocyte chemoattractant that is elaborated by diverse parenchymal and immune effector cells, including monocytes and lymphocytes (Hitomi et al 2004). As neutrophils comprise the predominant inflammatory cell in COPD airspaces and, as noted earlier, lymphocytic infiltrates within lung tissue per se are highly correlated with disease severity, it follows that IL-8 could play a part in the development of emphysema. IL-8 levels are increased in sputum of patients with COPD (Keatings et al 1996; Yamamoto et al 1997), and are further augmented during disease exacerbations, presumably in association with neutrophilic inflammation triggered by bacteria (Crooks et al 2000; Aaron et al 2001; Gompertz et al 2001). Airway microbes induce IL-8 secretion by epithelial cells, and levels of this cytokine have been shown to correlate with airway bacterial load (Hill et al 2000; Patel et al 2002). Interestingly, blocking antibodies to IL-8 only led to a modest reduction in the neutrophilic inflammation (Beeh et al 2003). This suggests that other chemotactic agents are also involved, and blocking IL-8 alone would not be expected to bring about a significant clinical effect. On the other hand, blocking IL-8 receptors, (eg, CXCR2) that mediate the chemotactic responses of both IL-8 and other CXC chemokines may represent a more useful therapeutic target.

Interleukin-13 (IL-13)

IL-13 has been implicated in mucous hypersecretion and is thought to provoke the differentiation of goblet cells via EGFR (Shim et al 2001). Plasma levels of IL-13 have recently been shown to be inversely related to FEV_1 (% of predicted), and proportional to the severity of gas exchange abnormality as defined by diffusion capacity (% DLCO) in COPD patients (Lee et al 2007). The finding that overexpression of IL-13 in murine lungs results in emphysema (Zheng et al 2000), validates the notion that IL-13 could play a role in the pathogenesis of this disease, particularly among patients with a bronchitic-predominant phenotype.

Conclusions

COPD is a complex syndrome with poorly understood pathophysiologic determinants. The adaptive immune system appears to actively participate in disease development and progression by elaboration of cytokines and other mediators, and likely too by production of injurious autoantibodies. $CD8^+$ lymphocytes may be the predominant cellular element for direct mediation of tissue injuries, but the importance of $CD4^+$ lymphocytes in orchestrating the inflammatory response and facilitating autoimmune humoral responses also appears to be considerable. Identification of the antigen(s) responsible for the adaptive immune activation of COPD is an important goal of future research. Although many potential antigens have been hypothesized, microbes may be among the most likely source.

Better understanding of T-cell and other adaptive immune processes in COPD pathogenesis will eventually lead to the development of more selectively targeted and rational disease interventions. Given the awesome morbidity and mortality of COPD, and the generally limited effectiveness of currently available treatments, innovative approaches with greater therapeutic effectiveness are sorely needed, and would have profound clinical importance.

Disclosures

The authors report no conflicts of interest.

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