Pulmonary Emphysema: When More is Less
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Pulmonary Emphysema: When More is Less

Pulmonary emphysema results from the loss of intricate alveolar architecture and progressive simplification of small and highly effective gas-exchanging units into large, inefficient cyst-like spaces. Because of the loss of alveolar gas-exchanging units and the capillary bed within them, blood oxygen levels eventually fall and pressures within the pulmonary circulation rise. Recent insights from genetically manipulated mouse models have refined our understanding of the molecular events that prevent or promote the development of pulmonary emphysema. Capitalizing on an improved molecular understanding of emphysema with improved therapeutics has the potential to enhance both the survival and quality of life of patients with this common lung disease.

The Breath of Life

The lungs are the gas-exchanging organs of all land-dwelling vertebrates and sea mammals. They are a conduit for hemoglobin-mediated oxygen uptake and carbon dioxide elimination from circulating blood. This exchange maintains gradients of soluble gas between circulating blood and tissue cells. These gradients are vital to sustaining cellular metabolism and, therefore, life. The lungs are composed of conducting airways, which connect them to the outside environment, and the parenchyma, where virtually all gas exchange occurs. Lung ventilation is also the principal mechanism by which physiological pH is maintained through the buffering of hydrogen ions (H+) with bicarbonate ions (HCO₃⁻). These combine to form dissolved carbon dioxide in blood, which equilibrates through diffusion with alveolar gas in the lung and is then eliminated during exhalation.

Pulmonary emphysema is a pathological process that destroys the gas-exchanging function of the lung through irreversible alveolar enlargement and simplification. It often coexists with chronic small airway (bronchiolar) inflammation, fibrosis, and consequent narrowing with associated mucous hypersecretion. It is an exclusively human disease attributable mainly to chronic tobacco smoke exposure. Air pollution, early childhood respiratory infections, and occupational exposures (particularly chronic exposure to smoke from burning biomass fuels) are also important worldwide risk factors (41, 45, 53).

In emphysema, the gas-exchanging units of the lung (alveoli) are progressively lost over time. Patients must inhale and exhale ever larger volumes of gas to meet their metabolic needs of oxygen delivery, carbon dioxide removal, and maintenance of acid-base equilibrium. In addition, alveolar enlargement leads to progressively larger lungs that are fixed within an anatomically constrained chest cavity. This reduces the capacity of the chest wall to expand during inspiration and collapse during exhalation, thus limiting ventilation. Eventually, the loss of functional alveolar units leads to chronic respiratory failure, evidenced by low blood oxygen levels (hypoxemia), elevated levels of carbon dioxide (hypercapnia, hypercarbia, chronic respiratory acidosis), and eventually death (FIGURE 1).

Abnormalities of the pulmonary circulation are also important in the pathogenesis and clinical physiology of patients with emphysema. The loss of alveolar capillary units and the compensatory vasospasm that occurs in the lung in response to chronic hypoxia cause increased resistance to blood flow from the right ventricle through the lungs to the left atrium. Interestingly, autopsy studies suggest that vascular remodeling, which results in increased resistance to pulmonary blood flow, precedes the development of hypoxia and appears be an integral part of the early disease process (35, 36). The molecular mechanisms of this process remain elusive, although recent animal studies, outlined below, are beginning to offer some glimpses into possible etiologies. In any case, chronically elevated resistance to blood flow from the right ventricle causes pulmonary hypertension. Over time, if pulmonary arterial pressure rises beyond the capacity of the right ventricle to compensate, patients with emphysema may develop cor pulmonale or chronic right heart failure. Patients with cor pulmonale develop severe swelling, or edema, of the legs and an accumulation of fluid in the abdominal space, known as ascites. The pathophysiology of this syndrome is complex and likely includes not only pulmonary hypertension but excessively avid sodium retention by the kidneys in response to a chronically low cardiac output. The only known effective treatment for cor pulmonale is supplemental oxygen, which serves to dilate blood vessels in areas that are effectively ventilated and to improve systemic oxygen delivery of oxygen. Diuretics, which promote excretion of sodium and
water by the kidneys, can reduce edema but do little to resolve the underlying hemodynamic problem of increased resistance to blood flow in the pulmonary circuit and reduced left ventricular output. Refractory right heart failure is also a common cause of death in patients with advanced emphysema.

**Emphysema, chronic bronchitis, and chronic obstructive pulmonary disease: What’s the difference?**

Clinicians, researchers, and patients are often confused about the diagnoses of emphysema, chronic bronchitis, and the more general term of chronic obstructive pulmonary disease. This confusion arises largely because patients often have both symptoms of chronic bronchitis and the pathological and radiographic findings of pulmonary emphysema. Chronic bronchitis is defined principally on clinical grounds by chronic cough productive of sputum associated with minimally reversible airflow obstruction manifested during exhalation. In contrast, emphysema is a structural condition of enlarged alveolar airspaces and a reduction in the pulmonary capillary bed. The more general term of chronic obstructive pulmonary disease (COPD) encompasses not only chronic bronchitis and emphysema but also rare diseases of the small airways such as constrictive and obliterative bronchiolitis. The vast majority of patients with structural emphysema also have airflow obstruction. Airflow obstruction due to mucous hypersecretion, infection, inflammatory cell infiltration, and constriction of airway smooth muscle is often partially reversible with agents that reduce inflammation (corticosteroids), reduce bacterial infection or colonization (antibiotics), cause airway smooth muscle relaxation (inhaled β2-adrenergic agents), or reduce muscarinic stimulation (ipratropium, tiotropium). Airflow due to cicatricial airway fibrosis and loss of radial tethering of airways is not responsive to current medical therapy.

**Pathological Features of Pulmonary Emphysema**

Interestingly, although physiological decline is slowed following smoking cessation on a population basis, bronchoscopic studies in individual patients show that persistent airway inflammation is common. Clinical experience also indicates that patients’ symptoms and functional limitations often persist long after tobacco smoke exposure has ended. In other words, the pathological processes that underlie emphysema and COPD continue after the inciting exposure has resolved, at least in some.

The chronic inflammatory infiltration of the lungs in patients with emphysema is comprised of macrophages, polymorphonuclear leukocytes, and lymphocytes, of which most are CD8+ T cells and B lymphocytes (12, 19, 43). Although limited cytokine profiling has been done in humans, most studies suggest that these lymphocytes are more strikingly...
polarized toward the type 1 cytokine profile of increased expression of interferon-γ and CC chemokine receptor 5 (19). Mouse strains that are particularly susceptible to cigarette smoke-induced emphysema show a similar type 1 cytokine expression bias (20). Interestingly, overexpression of either IFN-γ, a type 1 cytokine, or interleukin (IL)-13, a type 2 cytokine, results in the development of pulmonary emphysema in experimental mouse models (34, 54, 58, 59). Neutrophilic inflammation is most clearly implicated in acute exacerbations of disease, but neutrophil numbers are often chronically elevated in sputum samples from patients with COPD. Increased expression IL-6, IL-8 (or CXCL8), and tumor necrosis factor (TNF) α, are also common (1, 48). Elevated levels of the macrophage chemoattractant, MCP1 (CCL2), and neutrophil chemoattractant growth-related oncogene (GRO) α also have been noted in sputum(52).

**Airway fibrosis with alveolar rarefaction**

Careful quantitative and semiquantitative microscopic studies of the lungs of patients that are removed for either lung volume reduction surgery or transplantation show that, despite rarefaction of the alveolar space, the airways of patients with emphysema are thickened. The thickening of these walls is due primarily to increased collagen deposition or fibrosis. The thickened walls result in a reduced caliber of the airway lumen leading to fixed increased resistance to airflow, particularly during exhalation when alveolar pressure exceeds airway luminal pressure. In addition to airway fibrosis, hyperplasia of mucous-secreting glands and mucous-containing airway epithelial cells is common. In its most extreme form, this mucous hypersecretory state, coupled with chronic lower airway bacterial colonization, causes chronic bronchitis that often coexists with emphysema.

**Alveolar and respiratory bronchiolar inflammation**

When lung biopsies are obtained in patients who are chronically exposed to tobacco smoke, accumulations of lightly pigmented macrophages fill scattered alveoli, and lymphocytes are found surrounding the smallest airways. This is termed respiratory bronchiolitis and may be a histological precursor to pulmonary emphysema (17, 23).

**Molecular Mechanisms of Pulmonary Emphysema**

Perhaps because of the stigma associated with emphysema as a self-inflicted disease caused by smoking cigarettes or because of the difficulties intrinsic to experimental systems used to study lung diseases in general, emphysema, although common, remains a poorly understood disease on a molecular level. Virtually all molecular insights into the pathogenesis of pulmonary emphysema come from the study of genetically manipulated mice. Other models have occasionally been used, particularly dogs, rats, and guinea pigs. However, the advantages offered by mice because of their size, exquisite genetic definition, and fecundity have obvious appeal. Unfortunately, the lungs of mice are notoriously resistant to the effects of chronic cigarette smoke inhalation. In the absence of specific genetic manipulation, the majority of strains of inbred mice require several months of twice daily tobacco smoke exposure to develop microscopically detectable alveolar enlargement, which is the experimental equivalent of pulmonary emphysema in humans (FIGURE 2).

Increasingly, variations across inbred mouse lines in susceptibility to emphysema following chronic tobacco smoke exposure are being recognized and
may provide some insights into key genetic susceptibility factors in humans (4-6, 15, 20).

**Protease-antiprotease balance**

The evidence that excessive proteases in the lung cause emphysema is strong and continues to accumulate as new animal models of emphysema are identified. From the initial observations that aerosolized papain caused emphysema to more recent models based on genetic manipulation, excessive protease activity or deficient antiprotease activity categorically causes emphysema. Genetically engineered mice that overexpress Mmp1 (collagenase) in the lungs develop rapidly progressive pulmonary emphysema (10, 18). Similarly, mice deficient in Timp3, a major inhibitor of Mmp1, 2, 3, and 9, also show abnormalities of lung development followed by an early onset, rapidly progressive spontaneous pulmonary emphysema (16, 31). Data in humans, although limited, also suggest increased expression of proteases and decreased antiprotease activity in the lungs of smokers with pulmonary emphysema (13, 19, 57). The most well-established example of increased genetic susceptibility to emphysema is alpha-1 antiprotease (antitrypsin) deficiency. Alpha-1 antiprotease is a serine protease inhibitor (SERPINA1) produced primarily by the liver, with some detectable production elsewhere, including the lung (50). Patients with alpha-1 antiprotease deficiency produce low levels of functional or nonfunctional protein variants. These either precipitate within synthesizing cells or are secreted but ineffective at binding to and inactivating the proteases neutrophil elastase and cathepsin G in the lung (33, 49). Augmentation therapy is commonly used in patients with genetic deficiency of alpha-1 antiprotease. Conclusive randomized controlled clinical trials have not been performed to date; however, smaller, nonrandomized studies have suggested a benefit (2).

In mouse models, and increasingly in human disease, a potent elastinolytic protease Mmp12 (macrophage metalloelastase) has been associated with the development of emphysema (57). Mmp12 overexpression is common to many otherwise divergent mouse models of pulmonary emphysema (9, 37, 54, 59). Genetic deletion of Mmp12 expression is sufficient to prevent or attenuate emphysema in these models, showing that it is also necessary, at least in part (21). Mmp12 has recently been shown to contribute to the development of an elastinolytic environment by degrading alpha-1 antiprotease, thereby enhancing the local activity of neutrophil elastase (46). In addition, Mmp12 plays a critical role in activating other latent matrix metalloproteinases and the proinflammatory cytokine TNF-α (9).

Beyond, neutrophil elastase, Mmp12, cathepsin S, and Mmp9 (gelatinase B), have also been implicated in a number of animal models of emphysema (56, 58). Cathepsin S is a member of the lysosomal cysteine endopeptidases that are principally involved in intracellular proteolysis. They are critical for antigenic processing before MHC presentation as part of the adaptive immune response. Unlike other cathepsins, cathepsin S functions as an elastase over a wide pH range, including the neutral pH of the extracellular space. The principal source of cathepsin S is activated macrophages. Although generally confined to the intracellular space, cathepsin S protein is detectable in the alveolar space under conditions of macrophage activation (59). Its genetic deletion also attenuates emphysema under some experimental conditions (59).

Mmp9 is a potent elastinolytic extracellular collagenase that preferentially degrades type IV and V collagen. Genetic polymorphisms in the Mmp9 promotor have been variably associated with an increased risk of pulmonary emphysema in humans (24, 25). Increased Mmp9 expression is found in several mouse models of emphysema, including IL-13 and IFN-γ-overexpressing mice, as well as in mice deficient in surfactant protein D (55, 58, 59).

**Homeostatic regulation of lung structure**

The intricate balance of proteases and antiproteases is intimately related to the regulation of inflammation and the homeostatic regulation of lung structure. Although obviously critical to tissue maintenance and function,
these master regulatory pathways are only beginning to be understood. One of those key pathways regulating both tissue inflammation and structure is integrin-mediated activation of the pleiotropic cytokine, transforming growth factor-β1 (TGF-β1) (26, 37). TGF-β1 was initially identified as part of a family of proteins with an ability to induce proliferation and eliminate contact growth inhibition of fibroblasts in culture, thereby giving them a “transformed” phenotype. Very shortly after its initial cloning and molecular characterization, investigators identified the potent immunoregulatory function of TGF-β1 through its effects on T lymphocyte proliferation and function (29). Recently, TGF-β1 has emerged as a particularly important regulator of lung structure and inflammation. Interestingly, excessive TGF-β1 activity has been most convincingly associated with the development of lung scarring or pulmonary fibrosis (32, 47), whereas deficiencies in either activation of latent TGF-β1 or defects in downstream TGF-β1 signaling are associated with spontaneous lung inflammation and the development of pulmonary emphysema (8, 37).

In light of its exceptional potency and central role in the regulation of key cellular processes, tight control of TGF-β1 signaling in vivo is essential. Unlike many inflammatory cytokines, which are regulated at the mRNA level (transcriptional regulation) and secreted in active form, TGF-β1 and related family members are secreted in latent form. Once secreted, they exist tightly bound to extracellular matrix proteins through association with members of another family, the latent TGF-β binding proteins (LTBPs) (3, 39). LTBPs are covalently cross-linked by disulfide bonds to complexes of latent TGF-β and, through the actions of tissue transglutaminase, to components of the extracellular matrix. Although a number of in vitro mechanisms of latent TGF-β1 activation exist, the key in vivo regulatory mechanisms remain less clear. Two integrins, members of a class of heterodimeric transmembrane proteins originally identified on the basis of their ability to bind to and mediate cellular responses to extracellular matrix proteins, have been recently identified as critical mediators of latent TGF-β1 activation. These integrins are αvβ6 and αvβ8 (14, 38, 40). αvβ8, in particular, plays a central role in both pulmonary fibrosis and pulmonary emphysema through the regulation of latent TGF-β1 activation in the alveolar space (37, 40) (FIGURE 3).

**Chronic infection and the role of recurrent bacterial infections on loss of lung function, failure of mucosal immunity, and efficacy of antibacterial host response**

Chronic tobacco smoke exposure degrades the lung’s intrinsic epithelial barrier function and commonly leads, over time, to chronic bacterial infection of the normally sterile lower respiratory tract. Physicians have long accepted that so-called COPD exacerbations with worsened airflow obstruction, increased production of purulent sputum, and worsened gas exchange are secondary either to overgrowth of normally non-pathogenic bacteria or superinfection with more virulent species. Although frequent exacerbations have been anecdotally associated with a more rapid decline in lung function, this postulate, with elusive molecular underpinnings, has remained difficult to prove.

Recently, investigators have identified nontypeable *Hemophilus influenzae* (NTHI) as colonizing up to one-third of patients with symptomatic COPD and underlying exacerbations in a considerable proportion (44). Exacerbations appear to be associated with the acquisition of new serotypes of the antigenically highly variable NTHI. Furthermore, resolution of the exacerbation is associated with the development of neutralizing antibodies, indicating a successful adaptive immune response. Suggestive evidence has also emerged positing specific defects in in vitro alveolar macrophage responsiveness to the outer membrane proteins and lipooligosaccharide components of NTHI in patients with COPD (7). These defects presumably allow the persistent, low-level infection observed in many patients even after acquisition of outer membrane protein-specific antibodies. Apparently, only when bacterial counts reach sufficient levels, or perhaps when new, as yet unidentified, virulence factors are expressed, do the innate and adaptive immune responses intervene. Interestingly, circulating monocytes from the same patients reacted normally to these antigens, suggesting a tissue-specific, potentially epigenetic modification of alveolar macrophage function in susceptible individuals. The precise molecular “blind spot” and the nature of the immunological “wake-up call” remain to be determined. The role of chronic corticosteroid therapy in perpetuating this cycle also remains uncertain.

**Table 1. Molecular mechanisms of pulmonary emphysema**

<table>
<thead>
<tr>
<th>Process</th>
<th>Implicated Mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease excess</td>
<td>Mmp1, 2, 3, 9, 12; cathepsin S, G; neutrophil elastase</td>
</tr>
<tr>
<td>Antiprotease deficit</td>
<td>Alpha-1 antiprotease, TIMP3</td>
</tr>
<tr>
<td>Impaired tissue maintenance</td>
<td>TGF-β1; integrin; αvβ6; LTBP; Smad3; VEGF; ceramide</td>
</tr>
<tr>
<td>Dysregulated inflammation</td>
<td>IFN, IL-13, CXCL8, IL-6</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>Nontypeable <em>H. influenzae</em></td>
</tr>
</tbody>
</table>

Mmp, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase; TGF-β1, transforming growth factor-β1; LTBP, latent TGFβ binding protein; IFN, interferon; IL, interleukin; CXCL8, CXC chemokine ligand 8 (IL-8)
**Dysregulated inflammation and repair**

Beyond the damage done by the virulence factors of invading bacteria and the proteolytic explosion of the host immune response, recent findings suggest that interactions between the alveolar epithelium and alveolar macrophages may be critical to the prevention of emphysema. Alveolar macrophages, when stimulated through toll-like receptors (TLRs), a set of ancient pattern-recognition receptors tuned to detect invading bacteria and viruses, were recently shown to rapidly downregulate expression of αβ integrin by lung epithelial cells. The αβ integrin is a heterodimeric cell surface protein that is critical for spatially restricted cell surface activation of latent TGF-β, in the lung. By downregulating integrin expression, the alveolar macrophage releases itself from tonic inhibition and shows accentuated bacteriocidal, proteolytic, and phagocytic capacity (51). After termination of stimulation by TLR agonists or the immune stimulant f-Met-Leu-Phe, IFN-γ-dependent induction of Mmp9, through activation of latent TGF-β, induces basal expression of the αβ integrin. Coculture studies suggest that a cellular synapse of sorts is created between the alveolar macrophage and alveolar epithelium whereby tonic TGF-β-induced macrophage inhibition is maintained. Stimuli that induced actin cytoskeletal rearrangement in alveolar macrophages, including ligation of TLRs, disrupt this synapse and allow full-scale macrophage activation to occur (51). Dysregulation of any of the steps in this homeostatic circuit, as might, for example, occur with smoldering low-grade bacterial infection, could thus allow unopposed macrophage activation and thereby contribute to the development of emphysema.

**Cellular apoptosis and defective regeneration**

As discussed earlier, emphysema is as much a vascular disease as it is a disease of alveolar structure. Using pharmacological blockers of vascular endothelial growth factor (VEGF) signaling, investigators have convincingly demonstrated that noninflammatory endothelial apoptosis causes pulmonary emphysema (27, 28). This apoptotic stimulus is mediated, at least in part, through increased release of the potent lipid mediator ceramide (42). Increased epithelial apoptosis has also been demonstrated in other animal models of emphysema, including IFN-γ overexpression (58).

**Genetic susceptibility factors identified in human populations**

A number of cohorts of patients have been assembled and are being analyzed. To date, statistically significant linkage disequilibrium has been found in a number of candidate loci, including associations with female gender, epoxide hydrolase, LTBP, TGF-β, surfactant protein B, and SERPINE2 (11, 22). Recently, a functional glycin to aspartate mutation in elastin (G773D) has also been identified in an extended pedigree of familial early onset emphysema (30). Polymorphisms in the IL-13, IFN-γ, TNF-α, and CXCR2 have also been associated with COPD in various cohort and population-based studies. The functional significance of many of these polymorphisms remains unknown.

“...recent findings suggest that interactions between the alveolar epithelium and alveolar macrophages may be critical to the prevention of emphysema.”

**Conclusions and Future Directions**

Emphysema, a disease in which more air in the lungs is associated with less-efficient gas exchange, less ventilatory capacity, and a reduced life expectancy, continues to vex clinicians and patients alike. Despite dramatic advances in our understanding of the molecular underpinning of emphysema over the last 10 years, medical management remains unchanged. Despite initial enthusiasm for surgical approaches, the long-term efficacy of these has been limited. The challenge to turn improved understanding into improved therapies remains great. Although experimental support for the idea that protease-antiprotease imbalance is central to disease pathogenesis continues to accumulate, alterations in other key regulatory processes, including cytokine dysregulation, the dysregulation of tissue repair, and increased apoptosis, indicate substantial complexity to the underlying pathobiology (Table 1). Increasingly, emphysema and chronic obstructive pulmonary disease are being recognized to have a significant systemic inflammatory component manifested by increased circulating cytokine levels, cachexia, and muscle dysfunction, and addressing the systemic component may well pose another major therapeutic challenge. In addition, translating biological insights obtained in mice to therapies addressing the human disease remains a considerable hurdle. Nevertheless, the convergence of genetic data from both species is suggestive that many of the observations in mice will hold true in humans and provide opportunities to improve disease outcomes.

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