The Pathogenesis of Chronic Obstructive Pulmonary Disease
Advances in the Past 100 Years

Steven D. Shapiro and Edward P. Ingenito

Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts

In 1826, Laennec said of emphysema that “it consists simply in the dilatation of the air cells” (1). Osler’s 1892 Textbook of Medicine stated that hypertrophic emphysema, also known as substantive or idiopathic emphysema, “is a well marked clinical affection, characterized by enlargement of the lungs due to distention of the air cells and atrophy of their walls, and clinically by imperfect aeration of the blood and more or less marked dyspnea” (2). The pathologic description of chronic obstructive pulmonary disease (COPD) in this text was beautiful: “Grossly, the lungs are large, they have lost their elasticity, and to touch they have a peculiar downy, feathery feel, and pit readily against pressure. In the larger tubes (bronchi) the mucous membrane may be rough and thickened from chronic bronchitis. Microscopically, there is seen atrophy of the alveolar walls, by which is produced the coalescence of neighboring air-cells.”

Insights regarding etiology and pathogenesis were not as pre-scient. The prevailing hypothesis regarding pathogenesis was that air cells received heightened pressure during forced expiratory efforts. Support for this theory came from the contention that there was a high frequency of the condition in “players of wind instruments, in glass blowers, and in occupations necessitating heavy lifting or straining.” While our current understanding of COPD pathogenesis has progressed, this idea is not as dated as it seems. A recent accurate computer model of emphysema was generated by combining initial proteolytic damage of extracellular matrix in a centriacinar heterogeneous manner with subsequent respiratory forces that propagate this injury (Figure 1) (3).

CIGARETTE SMOKING AND GENETIC PREDISPOSITION TO COPD

In fairness to the unusual epidemiology proposed above, the prevalence of cigarette smoking in the United States at the turn of the century was very low—around 1% in 1900—but it skyrocketed during the first half of the twentieth century and peaked in the 1960s, with nearly 65% of men and 45% of women being active smokers. In the 1950s, air pollution and airway infections added. In 1962, the ATS weighed in to define emphysema as an “anatomic alteration of the lung characterized by an abnormal enlargement of the airspaces distal to the terminal, non-respiratory bronchiole, accompanied by destructive changes of the alveolar walls” (8).

While most textbooks from this era contain a dizzying array of pathologic classifications for various sub-types of emphysema, Reid stated that “the diagnosis of emphysema by itself is incomplete unless it has taken into account the presence or absence of chronic bronchitis—and vice versa” (9), where chronic bronchitis was defined by sputum production that correlated with enlarged mucus glands. This observation can be quantified by the Reid index, which measures the ratio of airway gland-to-wall thickness. Recognition that COPD has both airway and airspace characteristics led to the common definition of the disease, which required that one have either the pathologic description of emphysema or the symptoms of chronic sputum production that typified chronic bronchitis. This definition persisted until 2001, when COPD was redefined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a disease state characterized by exposure to a noxious agent resulting in airflow limitation that is not fully reversible (http://www.goldcopd.com/) (10). Current descriptions of COPD pathology include changes in...
large airways, small airways, and alveolar space. Large airway changes consist of mucous gland enlargement and goblet cell hyperplasia. These changes are proportional to the cough and mucus production that define chronic bronchitis, but these abnormalities are not related to airflow limitation. Neutrophil influx has been associated with the purulent sputum of upper respiratory tract infections that hampers patients with COPD. Independent of its elastolytic activity, neutrophil elastase is a potent secretagogue.

The major site of increased resistance in most individuals with COPD is in airways 2 mm or less. Characteristic cellular changes include goblet cell metaplasia and replacement of surfactant-secreting Clara cells with mucus-secreting and infiltrating mononuclear inflammatory cells. Smooth muscle hypertrophy may also be present. These abnormalities may cause luminal narrowing by excess mucus, edema, and cellular infiltration. Fibrosis in the wall may cause airway narrowing directly, and predispose to nonspecific hyperreactivity. Surrounding lung parenchymal elastin provides radial traction on bronchioles at points where alveolar septa attach. Hence, elastolysis may lead to loss of alveolar attachments with airway distortion and narrowing in COPD. Destruction of small airways may directly contribute to an increase in flow resistance through destruction of parallel conducting pathways.

Changes in the alveolar space are characterized by chronic inflammation and destruction with coalescence into larger alveolar spaces. While the neutrophil has received most attention, macrophages are the predominant cell in the lower airspace in COPD. Examining autopsy specimens of young smokers dying in automobile accidents, Niewohner reported in 1974 that one of the earliest changes in smokers is accumulation of macrophages in the respiratory bronchioles, the site of centriacinar emphysema, the type most frequently associated with cigarette smoking (11). Moreover, in smokers’ lavage fluid, macrophages comprise over 95 percent of the total cell count, and neutrophils, nearly absent in nonsmokers’ lavage, account for 1–2 percent of the cells. T-lymphocytes are also increased in the alveolar space. A body of recent work by Saetta and others has demonstrated that T cells, particularly CD8+ T cells, are also associated with COPD (12).

PATHOPHYSIOLOGY OF COPD

Quantitative evidence of increased expiratory flow resistance in emphysema was first obtained in one patient by Neergard and Wirz in 1927 (13). In 1934, Christie described elastic properties or distensibility of the lung in emphysema (14). The introduction of the esophageal balloon in 1949 provided the ability to directly measure lung recoil in vivo, allowing investigators in the 1950s to confirm these findings in patients.

The “golden age” of pulmonary macrophysiology, extending from about the 1960s to the 1980s, provided new insights regarding the determinants of flow limitation at the levels of the airway and parenchyma. Corbin and coworkers showed that smoking was associated with the loss of lung recoil pressure and with increased static lung volumes (RV, FRC, and TLC), even among individuals who had relatively normal FEV1 (15). Up to a point, these changes appeared reversible with smoking cessation. In patients with symptomatic COPD and reductions in FEV1, more substantial irreversible changes in lung mechanics were observed.
Figure 3. Inflammatory cell interactions in COPD. Cigarette smoke leads to inflammatory cell recruitment and activation. T cells induce macrophage production of matrix metalloproteinases (MMP) via interferon-inducible chemokines (IP-10, ITAC, and Mig) and CD40. Cigarette smoke inactivation of histone deacetylase (HDAC2) allows NF-κB-mediated transcription of neutrophil chemokines/cytokines (TNF-α and IL-8) and MMPs. MMPs and NE degrade each other’s inhibitors, thus augmenting each other’s matrix-degrading capacity promoting emphysema.

Fry, Hyatt, and others demonstrated that while loss of recoil alone could account for airflow limitation in a minority of patients (16, 17), the vast majority of individuals with symptomatic COPD had abnormalities at the level of both the airway and the parenchyma. Loss of elastic recoil and a decrease in isopressure airway conductance were almost universally observed, and correlate with pathologic findings of tissue destruction and airway narrowing in patients with advanced disease (18, 19).

PATHOLOGY–PHYSIOLOGY (BIOCHEMICAL) CORRELATIONS

Hogg, Macklem, and others have, and continue to, correlate physiologic changes with pathology in COPD. Hogg has focused on the importance of small airway obstruction, most recently showing that airway remodeling and wall thickening, presence of inflammatory mucous exudates, and B and CD8 T cell inflammation are all associated with severity of COPD and progression of the disease (20). Christie, Thurlbeck, and others have championed emphysema as the dominant pathology accounting for abnormal physiology, and have shown, for example, that in a subgroup of patients, the relationship between flow and recoil pressure is indeed normal. While many important insights came from this line of investigation, to this day we still do not understand the relative contribution of small airway obstruction versus emphysema in an individual patient, nor the potential relationship between these two lesions. This line of investigation is still fruitful, particularly with the ongoing revolution in imaging.

THE ELASTASE:ANTIELASTASE HYPOTHESIS

Just over 40 yr ago, two lines of evidence, one experimental and one clinical, suggested that emphysema is caused by destruction of elastic fibers by elastases. The first was by Laurell and Eriksson who, in 1963, described five patients with deficiency of α1AT, the primary inhibitor of the neutral serine proteinase neutrophil elastase (NE). Three of these five patients had emphysema (21). The second came in 1965 when Gross and coworkers instilled papain into the lungs of rodents in an attempt to produce granulomas. Instead they found emphysema (22). Subsequently, investigators have instilled a variety of proteinases into animal lungs. Kuhn and colleagues (23), Senior and coworkers (24), Janoff and associates (25), and Snider and colleagues (26) were among the group of investigators who subsequently demonstrated that only elastolytic proteinases—including pancreatic elastase and the more relevant human neutrophil elastase (HNE)—caused emphysema. Hoidal’s group showed that proteinase 3 (27) also caused destructive lung disease.

With respect to α1AT, we now know that patients with the deficiency have mutations in the α1AT gene. The most common mutation is the Z mutation that converts 342Glu to Lys. These mutations impair secretion of the protein from hepatocytes, resulting in markedly decreased circulating levels of this serine proteinase inhibitor. PiZ-α1AT is slightly less effective as an inhibitor, owing to its slower rate of association with NE than normal PiM-α1AT. These genetic changes allow NE to act relatively unopposed, thereby shifting the balance in favor of elastolysis (28). More recently, we have learned that PiZ-α1AT is prone to polymerization, which inhibits hepatic secretion, impairs NE inhibition, and promotes inflammation.

These seminal experiments formed the basis for the elastase:antielastase hypothesis, which states that the relative balance between elastases and their inhibitors determines the susceptibility of the lung to the destruction characteristic of emphysema. To this day, the elastase:antielastase hypothesis remains a prevailing
concept in emphysema. However, our concepts regarding the influence of cells and their proteinases involved in the pathogenesis of emphysema have become much more complex.

INFLAMMATION–EXTRACELLULAR MATRIX TURNOVER

During the 1970s and 1980s, almost all research in the field focused on the role of the neutrophil and HNE, leading to a sophisticated understanding of serine proteinase and matrix biology. However, the relationship of PMNs and NE in smoking-related emphysema has yielded conflicting results. For example, a classic study by Damiano and coworkers correlated the presence of HNE with COPD using immunogold staining (29). However, other studies actually showed a negative correlation between emphysema and HNE or neutrophil number (30, 31). As discussed above, macrophages are abundant in COPD, yet the capacity of the macrophage to degrade elastin and hence contribute to disease pathogenesis was unproven until Senior and colleagues demonstrated that macrophages produce elastolytic matrix metalloproteinases (32, 33), and Chapman and coworkers found elastolytic cysteine proteinases (34).

This set the stage for the “protease wars” of the mid-1980s to mid-1990s. A typical battle involved an investigator picking his/her favorite cell and proteinase (the dominant empire being the PMN and NE) and arguing that, given elastase X’s potency and level of expression relative to its inhibitors, elastase X must be the cause of COPD. Unfortunately, simple mathematics cannot be directly applied to complex biological systems. For example, Campbell described the concept of enzymatic microenvironments whereby cell–matrix contact can allow for release of a proteinase into a small area shielded from inhibitors (35). Later, he and Owen determined that serine and metalloproteinases can bind to the cell surface and remain active in the presence of excess inhibitors (36).

The controversy regarding inflammatory cells in COPD highlights the fact that studies in human tissue provide a snapshot in time of a dynamic process. It is possible that an inflammatory cell proteinase could have caused lung destruction yet no longer be present in a sample from “burnt out” end-stage disease. This, however, does not appear to be the case, as Retamales and colleagues (37) found that even in end-stage lung disease, long after smoking cessation, there remains an exuberant inflammatory response. This suggests that the mechanisms of cigarette smoke–induced inflammation that initiate the disease differ from mechanisms that sustain inflammation after smoking cessation. Moreover, this study suggests that multiple inflammatory (and likely structural) cells interact to cause COPD, and that focusing on single cells and proteinases in isolation will not provide a comprehensive understanding of the disease process.

The advent of genetic engineering in the 1990s allowed investigators to circumvent these limitations and directly determine causality and define pathogenetic pathways. Transgenic and gene-targeted mice provide powerful techniques with which to conduct highly controlled experiments in mammals in vivo. Gain-of-function models may be achieved by overexpression of proteins in transgenic mice, while loss-of-function models are created by targeted mutagenesis or gene targeting with a null mutation, often referred to as “knockout” models. It must be recognized that findings from these animal models may not translate directly to human (patho)biology. However, it is likely that general biological processes do translate from mice to humans, with perhaps significant differences in the particular proteins that perform these functions. While it is too early to know the impact of genetic engineering on clinical care, novel findings from these studies have invigorated COPD as a field worthy of investigation.

One of the earliest applications of transgenic mice to lung biology was performed in 1992 by D’Armiento, who generated mice that overexpressed interstitial collagenase (human MMP-1) in the lung (38). These mice developed airspace enlargement, suggesting that collagenases may also contribute to emphysema. The role of collagen turnover in COPD is complex. Clearly, upon loss of alveolar units, all matrix components disappear. Yet, as predicted earlier by Pierce (39), there is net collagen accumulation in COPD, with increases around the enlarged airspaces as well as small airway fibrosis. Of note, transgenic experiments that result in emphysema demonstrate that the particular protein overexpressed is “sufficient” to cause the phenotype, but not necessarily “necessary” in the disease pathway.

Alternatively, one can apply loss-of-function null mutant mice to specific disease models. Assuming there is no expression of the gene of interest during lung development, comparing wild-type and null mutant mice allows one to determine the contribution of the protein to the disease processes and tease out the biological pathway. For example, to directly determine the contribution of macrophage elastase (MMP-12) to pulmonary emphysema, macrophage elastase–deficient mice (MMP-12/−/−) were generated, as was a murine model of cigarette smoke–induced emphysema based upon previous experience in other species. Smoke exposure in wild-type littermate (MMP-12+/−) mice led to inflammatory cell recruitment followed by alveolar space enlargement similar to the pathologic defect in humans. However, MMP-12/−/− mice were protected from the development of emphysema despite long-term smoke exposure (40). MMP-12/−/− mice also failed to recruit monocytes into their lungs in response to cigarette smoke. This subsequently led to the finding that cigarette smoke causes constitutive macrophages to produce MMP-12, which, in turn, cleaves elastin into fragments chemotactic for monocytes. This positive feedback loop perpetuates macrophage accumulation and lung destruction. The concept that proteolytically generated elastin fragments mediate monocyte chemotaxis was not original. Independent studies by Senior and coworkers (41) and Hunninghake and colleagues (42) in the early 1980s demonstrated that elastase-generated elastin fragments were chemotactic for monocytes and fibroblasts. Gene targeting merely reinforced this as a major in vivo mechanism of macrophage accumulation in a chronic inflammatory condition. That human emphysema is dependent on this single MMP is unlikely. At the very least, this study demonstrates a critical role for macrophages in the development of emphysema and unmask a proteinase-dependent mechanism of inflammatory cell recruitment. Of note, last year Grumelli and coworkers found that human CD8+ T cells derived from patients with COPD generate interferon (IFN)-γ–inducible chemokines that also function to upregulate expression of human macrophage MMP-12 (43).

Studies involving several other genetically engineered mice have led to significant insight into the roles of and interplay between inflammatory and structural cells, chemokines and cytokines, oxidants and proteinases, and matrix turnover involved in COPD. For example, Elias and coworkers have developed several interesting COPD models using lung-specific transgenic mice expressing either the Th2 cytokine interleukin (IL)-13 (“Dutch mice”) (44) or the Th1 cytokine IFN-γ (“British mice”) (45). IL-13 overexpression induces inflammation with MMP-12– and MMP-9–dependent airspace enlargement, while IFN-γ overexpressors develop a cysteine proteinase/apoptosis–mediated form of emphysema. IL-13–transgenic mice also develop small airway remodeling with MMP-9–dependent activation of transforming growth factor (TGF)-β and fibrosis (46). The role of TGF-β in emphysema is not limited to fibrosis. Morris and colleagues found that α1β1/−/− mice, which are unable to activate TGF-β in the airspace, develop macrophage in-
flammation and MMP-12-dependent emphysema (47). Hence, TGF-β regulation is critical: total absence of TGF-β releases the brake on inflammation and destruction in the airspace, while too much TGF-β leads to fibrosis in the airways.

Other gene-targeted mice that develop emphysema include surfactant protein D−/− (SP-D−/−) mice, which exhibit macrophage activation, MMP production, and consequent emphysema (48). TIMP-3 deficiency leads to a combination of developmental airspace enlargement combined with progressive destructive emphysema in adults (49), supporting the role of MMPs in COPD. Yet serine proteinases, particularly NE, are also involved in experimental emphysema. NE−/− mice develop only 40% as much airspace enlargement as wild-type mice (50). These studies have uncovered several interactions between NE and MMPs. MMPs degrade α1-AT and NE degrades TIMPs, each potentiating the other’s proteinase activity. Moreover, NE mediates monocye migration. Studies by Churg and coworkers demonstrate that acute neutrophil inflammation secondary to smoking is related to MMP-12-dependent tumor necrosis factor (TNF) shedding (51).

**OXIDANT–ANTIOXIDANT BALANCE**

Cigarette smoke and inflammatory cells have the capacity to produce reactive oxygen species, and they have been postulated to play a variety of roles in the pathogenesis of emphysema. One intriguing finding was that cigarette smoke can oxidize a methionine residue in the reactive center of A1PI, inactivating A1PI and thus altering the elastase/antielastase balance. Oxidants cannot degrade extracellular matrix but might modify elastin, making it more susceptible to proteolytic cleavage. MacNee (52) and others have found that intracellular oxidation of IKKβ promotes its ubiquitination and the release of free nuclear factor (NF)-κB, which translocates to the nucleus, resulting in transcription of proinflammatory genes such as IL-8 and TNF-α. Recently, Barnes and colleagues have found that cigarette smoke oxidizes and inactivates histone deacetylase 2 (HDAC2), which acts to counter histone acetylation (HAT) (53). Acetylation of histone unwinds chromatin, allowing transcriptional complexes to bind to DNA. Thus, in the absence of HDAC2, RNA polymerase II and NF-κB form a proinflammatory transcription complex. This might explain steroid resistance in COPD, because the activated glucocorticoid receptor acts to translocate HDAC2 to the nucleus, which keeps the chromatin wound inactive. Finally, reactive oxygen species may also promote apoptosis of structural cells, a recent concept for initiation of emphysema. Integration of knowledge regarding inflammatory cell interactions and the role of proteinases and oxidants is shown in Figure 2.

**APOTOPSIS**

Liebow proposed in the 1950s that COPD was due to vascular atrophy. This theory was given credence recently when Kasahara and colleagues found that exposure to agents that initiate endothelial cell death (via VEGFRII inhibition) leads to noninflammatory airspace enlargement (54). Nagai and coworkers then found that epithelial cell death (via caspase 3 delivery) also causes emphysema (55). As mentioned above, the loss of an acinar unit result from the destruction of both the extracellular matrix (ECM) and the structural cells. Traditionally, we have believed that inflammatory cell proteinases destroy ECM, and that cells unable to attach to the ECM float away and die. These models suggest that death of structural cells may be an initiating event, with subsequent release of matrix-degrading proteinases. Whether this occurs in human COPD as a primary event is uncertain, but it does raise interesting testable possibilities.

**INEFFECTIVE REPAIR**

The ability of the adult lung to repair damaged alveoli appears limited. In fact, as we define genetic predisposition to COPD, we speculate that smoking routinely leads to inflammation and lung damage, and those at risk lack the capacity to repair this damage. In emphysema, aberrant alveolar and extracellular matrix repair results in coalesced and enlarged airspaces with depleted and disordered parenchymal elastic fibers, and excess and abnormally arranged collagen. Whether one can temporally and spatially bring together the multiple components of an elastic fiber—let alone coordinate matrix repair with endothelial and epithelial migration and differentiation upon an injured matrix—is unknown. A study by Massaro and Massaro in 1997 has led to hope that we might be able to influence lung repair (56). After PPE-mediated injury, treatment with all-trans retinoic acid resulted in limited but significant repair. These findings do not appear to have been replicated in human trials, but at least we have “our foot in the door” regarding potential mechanisms that can influence repair. With the emergence of regenerative medicine and stem cell biology, there is hope that we can one day create new functional lung tissue. However, given the complex three-dimensional nature of the lung, its regeneration presents a special challenge relative to other organs.

**PAST, PRESENT, AND FUTURE**

With the rise in cigarette smoking over the past 100 yr, COPD has emerged as a critical health problem and unmet medical need worldwide. Small numbers of outstanding investigators have provided early accurate pathologic and physiologic descriptions of the disease. The general concept of the elastase:antielastase hypothesis remains intact 40 yr later. Over the past few years, as scientific techniques have allowed more research opportunities, there has been a palpable surge of interest in COPD from investigators, funding agencies, and the pharmaceutical industry. However, to date, we have little to show for this effort in terms of badly needed disease-modifying therapy. Yet, there is much hope that recent progress that has resulted in a more detailed understanding of the cell and molecular events in COPD (Figure 3) will result in new therapy. In the future, a multidisciplinary approach, bringing together scientists studying classic cell and molecular biology, animal models/genetic engineering, genetics, bioinformatics, regenerative medicine, and neurobiology of addiction will come together with clinical researchers to understand the disease process and translate this knowledge to new therapy, and ultimately, a cure.

References

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