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Mesenchymal Cell Fate and Phenotypes in the Pathogenesis of Emphysema

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Abstract

Emphysema is characterized by the destruction of alveolar parenchymal tissue and the concordant loss of lung epithelial cells, endothelial cells, and interstitial mesenchymal cells. Key features in the pathobiology of emphysema include inflammation, alveolar epithelial cell injury/apoptosis, and excessive activation of extracellular matrix (ECM) proteases. Mesenchymal cells are versatile connective tissue cells that are critical effectors of wound-repair. The excessive loss of connective tissue and the destruction of alveolar septae in emphysema suggest that the mesenchymal cell reparative response to epithelial injury is impaired. Yet, the mechanisms regulating mesenchymal cell (dys)function in emphysema remain poorly understood. We propose that mesenchymal cell fate, modulated by transforming growth factor beta-1 (TGF- β 1) and the balance of ECM proteases and antiproteases, is a critical determinant of the emphysema phenotype. We examine emphysema in the context of wound-repair responses, with a focus on the regulation of mesenchymal cell fate and phenotype. We discuss the emerging evidence supporting that genetic factors, inflammation and environmental factors, including cigarette smoke itself, collectively impair mesenchymal cell survival and function, thus contributing to the pathogenesis of emphysema.

Keywords

Apoptosis; repair; fibroblast; myofibroblast; extracellular matrix; TGF- β 1; Chronic Obstructive Pulmonary Disease: A Global Health Crisis

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) refers to a heterogeneous group of clinical syndromes characterized physiologically by chronic airflow obstruction that is not completely reversible. The two main clinical phenotypes of COPD represent varying degrees of airway abnormality and emphysema (1), although overlapping features are seen in individual patients. Chronic bronchitis, defined clinically by the presence of productive cough for 3 months in 2 consecutive years, has been considered a common clinical phenotype. Emphysema, defined pathologically by airspace enlargement and destruction of alveolar septae in the absence of significant fibrosis, accounts for about 20–25% of COPD cases and is estimated to affect 4–5 million patients in the United States (2–5).

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Declaration of interest

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COPD is currently a leading cause of death worldwide and in the United States (6). Of the 6 leading causes of death in the United States, only COPD has been associated with increasing mortality since 1970 (7). While reports of prevalence vary based on country and methodology, studies have estimated that 9–10% of the worldwide population over 40 years of age has COPD and that COPD affects approximately 14% of the adult population in the United States (3, 8). The principal risk factor for COPD is exposure to tobacco smoke, which accounts for as much as 90% of cases (9). Environmental exposures such as pollution and biomass fuels are an increasingly appreciated cause of COPD worldwide (10).

There is remarkable heterogeneity in an individual's susceptibility to COPD. It is widely reported that only 15–20% of cigarette smokers develop COPD, but more recent literature estimates that up to 50% of long-term smokers actually have COPD (9, 11). The mechanisms underlying the variable susceptibility to tobacco smoke-induced COPD are unclear.

In this review, we will discuss emerging concepts of the pathobiology of the emphysema phenotype of COPD. Emphysema is unique in that it primarily involves the terminal alveolar units with relative sparing of the airways. It is characterized by the degradation of elastic fibers and loss of parenchymal “tethering,” which lead to increased lung compliance, hyperinflation, air trapping and airflow obstruction. These pathophysiologic changes result in dyspnea, the cardinal clinical manifestation of emphysema (12, 13).

Importantly, greater degrees of emphysema may be associated with impaired prognosis in COPD (14). Currently, management of emphysema relies on risk factor modification, prevention and treatment of acute exacerbations, and symptom relief with anti-inflammatory approaches, bronchodilators, and oxygen supplementation (13). In a subpopulation of patients with upper-lobe predominant emphysema, lung volume reduction surgery may improve pulmonary mechanics, quality of life, and survival (15). Novel therapeutic strategies for emphysema require improved understanding of the fundamental pathophysiologic mechanisms involved. Recent reviews have provided in-depth discussion of the roles of chronic inflammation, protease activation, oxidative stress and alveolar epithelial cell apoptosis in the pathogenesis of emphysema (4, 5, 10, 16).

It has been proposed that emphysema results from failed lung maintenance and repair following lung injury (4, 16, 17). The goal of this paper is to expand on this concept of failed lung repair and regeneration with a focus on mesenchymal cells, including fibroblasts and myofibroblasts, key effectors of wound-repair responsible for extracellular matrix (ECM) synthesis and remodeling (18, 19). We propose that mesenchymal cell fate, modulated by transforming growth factor- β 1 (TGF- β 1) and ECM proteases/antiproteases, may be a key determinant of the emphysema phenotype.

EMPHYSEMA PATHOGENESIS: A PARADIGM OF INEFFECTIVE WOUND REPAIR

The histopathology of emphysema is characterized by chronic inflammation and the destruction of lung alveolar-capillary units. This is typically associated with the loss of alveolar epithelial and endothelial cells in concordance with the loss of reparative interstitial mesenchymal cells. The loss of all three of these cell types suggests that the mechanisms underlying parenchymal cell injury may also lead to mesenchymal cell dysfunction and/or death, thereby impairing the reparative response and promoting emphysema.

The prevailing hypothesis of emphysema pathogenesis suggests that it begins with exposure to toxic substances in tobacco smoke (or other toxic inhalational substances) which induce a

chronic inflammatory response (10, 12). Neutrophils, macrophages and lymphocytes are recruited to the alveolar environment where they release elastases, cytokines and oxidants which may then perpetuate the cycle of epithelial injury and inflammation. Unless neutralized by antiproteases, elastases promote proteolysis of the ECM directly and through activation of collagenases. Elastin degradation products further amplify the inflammatory response (20, 21).

Interestingly, alveolar epithelial cell injury and apoptosis are observed in both emphysema and pulmonary fibrosis; yet, in emphysema there is an apparent loss of interstitial mesenchymal cells and matrix components while in fibrosis there is accumulation of activated myofibroblasts and ECM (5, 22). Thus, while pulmonary fibrosis may represent an exuberant mesenchymal cell response to alveolar epithelial injury and apoptosis, emphysema may be conceptualized as a deficiency in mesenchymal cell responses following epithelial cell injury. Despite the recognized role of mesenchymal cells in the reparative responses to tissue injury, little is known about the role of these cells in the pathobiology of emphysema.

Myofibroblasts in lung development and repair

There is better understanding of the role of interstitial mesenchymal cells in normal lung development. During fetal development, epithelial-mesenchymal communication is critical for branching morphogenesis and alveolar septal formation (23, 24). The completion of alveolarization requires lung fibroblast apoptosis (25). Mesenchymal cell responses following epithelial injury recapitulate, in many ways, their roles in lung development (26). General paradigms of wound-repair propose that recruited fibroblasts, derived from several different potential origins, infiltrate the wound microenvironment following injury (27, 28). Soluble factors and the extracellular matrix (ECM) induce differentiation into “activated” myofibroblasts which synthesize, secrete, and remodel new ECM.

The activated myofibroblast also serves as a source of cytokines, growth factors, and reactive oxygen species that function as autocrine and paracrine signaling mediators while the newly synthesized matrix serves as a functional scaffold for reepithelialization (18, 29–31). Establishing normal tissue architecture, however, requires the precise spatial and temporal regulation of myofibroblast function and appropriate myofibroblast apoptosis, which may herald the termination of the wound-repair response (26, 32, 33). On the one hand, prolonged or excessive myofibroblast activation is thought to contribute to pathologic scar formation, or fibrosis. On the other hand, a lack (or loss) of appropriate myofibroblast activity might result in ineffective or insufficient wound repair (28, 34). Thus, mesenchymal cell fate represents a critical determinant of physiologic and pathologic repair.

The role of alveolar interstitial mesenchymal cells in homeostasis and disease

In the adult lung, mesenchymal cells are present within the subepithelial and subendothelial matrix of the airways and alveoli. The subepithelial/subendothelial matrix and its cellular components become progressively attenuated at the level of the alveolus, and this space between the alveolar epithelium and the capillary endothelium is commonly referred to as the ‘interstitium’ of the lung. There is significant diversity and heterogeneity of mesenchymal cells that normally reside in the lung interstitium; these mesenchymal cells include fibroblasts, myofibroblast-like contractile cells, smooth muscle cells, pericytes, and some fibroblastic cells that appear less differentiated (35, 36). While the relationships between these cell types are not well understood, mesenchymal cells are likely to play major roles in maintaining homeostasis and in repair responses of the adult lung. Homeostatic roles are supported by the finding that mesenchymal cells form direct contacts with alveolar epithelial cells and capillary endothelial cells within the alveolar wall of the normal adult

lung (37–39). Loss of homeostatic relationships between these cell types during reparative responses to injury may give rise to specific disease phenotypes.

Sirriani and colleagues reported that the normal fibroblast-mediated linkage between type 2 pneumocytes and the capillary endothelium through basal lamina apertures was lost in emphysema (37). In fibrotic lung diseases, there is an expansion of the interstitium that may involve the activation and persistence of specific mesenchymal cell types such as myofibroblasts (37, 40). Our current understanding of the phenotype and function of interstitial mesenchymal cells, and how these phenotypes and functions are affected by cross-talk with other cell types, in different lung remodeling diseases is limited and requires further study.

Transforming growth factor- β 1 in lung injury and repair

The TGF- β gene family encodes for a number of signaling proteins that regulate developmental lung morphogenesis, adult tissue homeostasis and reparative responses to injury. TGF- β 1 is a 25 kDa dimeric polypeptide that regulates mesenchymal cell phenotype and fate (26, 41). Secreted as part of a latent complex by a number of cells, including myofibroblasts themselves, TGF- β 1 may be activated through the proteolytic activity of a number of mediators including plasmin, matrix metalloproteinases (MMPs), and thrombospondin (42). Recent studies have shown that integrin binding facilitates proteolytic activation of TGF- β 1 and that integrins can activate TGF- β 1 in a protease-independent manner (42). Activated TGF- β 1 binds to the TGF- β receptor complex, a heterotetramer composed of two type II receptors and two type I receptors. The type II receptor transphosphorylates the type-I receptor, inducing phosphorylation of receptor-associated SMADs (R-SMADs; SMAD2 and SMAD3). The R-SMADs dissociate from the receptor complex, partner with the common co-SMAD (SMAD4), and translocate to the nucleus where the SMAD-complex regulates gene transcription. Transcriptional regulation is cell-type and context-specific, and is modified by other transcription factors, co-activators, and co-repressors which cumulatively determine the outcome of TGF- β 1 signaling (43). Additional complexity is derived from studies demonstrating that TGF- β 1 also signals via non-SMAD pathways (44).

TGF- β 1 typically functions as a tumor-suppressor through growth inhibition and induction of apoptosis in epithelial cells (45). Additionally, TGF- β 1 has immunomodulatory actions (46). In mesenchymal cells, however, TGF- β 1 is a potent “activator” of myofibroblast differentiation, ECM synthesis, migration, oxidant production, and survival (18). In contrast to its typical pro-apoptotic and tumor-suppressive actions on epithelial cells, TGF- β 1 can also promote epithelial-mesenchymal transition, a process which may facilitate cancer metastasis and contribute to pulmonary fibrosis (47).

A POTENTIAL ROLE FOR TGF-B1 IN THE PATHOGENESIS OF EMPHYSEMA

Evidence from patients with emphysema and from animal models suggests that disruption of TGF- β 1 signaling, at the level of its synthesis/activation, receptor ligation or post-receptor signal transduction, may be critical to the pathobiology of emphysema. TGF- β 1 polymorphisms have been associated with COPD in a number of studies, although the specific effects of these polymorphisms on cellular functions have not been fully elucidated (48–52). One study examined the leucine-proline polymorphism in codon 10 of the TGF- β gene and found that the leucine allele is more common in COPD patients (50). Moreover, the proline allele, which results in increased levels of TGF- β 1 protein and mRNA, was shown to be associated with increased resistance to cigarette smoke-induced COPD (50, 53).

Thus, a “high-producing” TGF- β 1 phenotype appears to confer protection against the development of COPD.

Animal models also support a role for TGF- β 1 signaling in resistance to emphysema. Morris and colleagues showed that mice lacking the β 6 subunit of integrin α v β 6 develop age-related emphysema due to an inability to activate latent TGF- β 1 and, consequently, increased expression of MMP-12, a matrix metalloproteinase that is a critical mediator of cigarette smoke-induced emphysema in mice (54, 55). Consistent with a role for TGF- β 1 signaling in the prevention of emphysema, two studies have found that mice deficient in SMAD3 develop emphysema (56, 57). Additionally, mice deficient in latent TGF- β -binding protein 4, which is involved in latent TGF- β 1 activation, have impaired nuclear localization of SMADs and defective alveolarization (58). It is currently unknown if emphysema in these studies results from defective alveolarization, impaired postnatal maintenance of alveolar septal structure, or a combination of these mechanisms. Finally, recent evidence supports the presence of impaired TGF- β 1 signaling in fibroblasts from humans with COPD (17). Collectively, these studies support a critical role for TGF- β 1 signaling in the maintenance of lung architecture and the prevention of emphysema.

ECM PROTEOLYSIS IN EMPHYSEMA AND MESENCHYMAL CELL PHENOTYPES

TGF- β 1 and the ECM are both critical to the maintenance of mesenchymal cell phenotypes. Recent studies demonstrate that plasmin-mediated proteolysis of ECM fibronectin induces fibroblast apoptosis, while TGF- β 1 upregulation of the antiprotease plasminogen activator-inhibitor 1 (PAI-1) inhibits fibronectin proteolysis and prevents apoptosis (59). Protease/antiprotease balance is important in the regulation of wound-repair, and excess antiprotease activity has been implicated in the pathogenesis of pulmonary fibrosis (60). The pro-tease/antiprotease hypothesis posits that emphysema results from protease (particularly elastase) activity in excess of anti-protease (α 1 antitrypsin) activity. Indeed, animal models show that the intratracheal administration of elastase induces emphysema and that elastase is increased following cigarette smoke exposure in humans and animals (61).

Cigarette smoke induces airway and alveolar inflammation. Recruited neutrophils and macrophages are the primary sources of elastase, which proteolytically cleaves elastin and other ECM components (10). The consequences of unopposed ECM proteolysis, however, extend beyond the loss of connective tissue. Cleaved elastin-fragments act as biologically active “matrikines” to further promote inflammation (20, 21). Thus, a vicious cycle of inflammation and ECM proteolysis contributes to the pathobiology of emphysema.

Mesenchymal cells are responsible for the maintenance and repair of ECM components, including elastin (18). Fibroblasts repair elastase-digested matrices through de novo elastin synthesis and by repair of degraded elastin fibers (62), suggesting that they may reduce inflammation by limiting matrikine generation. TGF- β 1 stimulates elastin production by myofibroblasts through transcriptional mechanisms (63, 64). In inflammatory states, however, neutrophil elastase inhibits elastin synthesis by suppressing expression of the elastin precursor, tropoelastin (65). Recent studies have elucidated the mechanism, demonstrating that elastin proteolysis liberates EGF and EGF-like peptides (66), which induce expression of the TGF- β co-repressor, TGIF, thereby reducing mesenchymal cell responsiveness to TGF- β 1 signals (67, 68).

A large body of evidence supports the role of MMPs in the pathobiology of emphysema (recently reviewed in ref (10)). Of the MMPs, there is compelling support for the pathogenic roles of elastolytic MMPs-9 and 12 (54, 55, 57, 69–73). In humans, polymorphisms in

MMP-9 are associated with the development of cigarette-smoke induced emphysema (71). Additionally, alveolar macrophages from patients with emphysema generate greater amounts of MMP-9 with higher levels of activity than those of normal subjects (72). Consistently, MMP-9 levels are increased in the BAL of smoke-exposed mice (73). A recent study has shown that transgenic overexpression of MMP-9 induces late onset emphysema (70).

Mice deficient in the $\beta 6$ subunit of the integrin $\alpha v\beta 6$ are unable to activate TGF- $\beta 1$ from its latent form and develop spontaneous emphysema associated with increased macrophage expression of MMP-12. However, when these mice transgenically overexpress active TGF- $\beta 1$ (obviating the need for activation by $\alpha v\beta 6$), MMP-12 expression is normal and emphysema fails to develop (54). MMP-12 deficient mice, consistently, are protected from cigarette smoke-induced emphysema (54, 55). SMAD-3 knockout mice, which develop emphysema, have increased levels of MMP-9 and MMP-12 (57). In guinea pigs subjected to cigarette smoke inhalation for 6 months, a pharmacologic inhibitor of MMP-9 and MMP-12 attenuates the pulmonary physiologic effects of cigarette smoke while reducing emphysema and BAL evidence of elastolysis (69). This is consistent with another study demonstrating that a broad-spectrum MMP inhibitor attenuates tobacco smoke induced inflammation and emphysema in guinea pigs (74). In humans with COPD, several studies have shown increased expression of MMP-12 (75, 76). Some studies, however, have failed to identify increased MMP-12 in humans with emphysema, suggesting additional mechanisms independent of MMP-12 (77).

Myofibroblasts secrete MMP inhibitors (TIMPs), which would be expected to limit the proteolytic actions of MMPs and alter the protease-antiprotease balance. However, few studies have reported on the specific regulation of MMPs and TIMPs by mesenchymal cells in the context of emphysema. Elastase promotes cleavage/inactivation of TIMPs while inducing fibroblast production of MMP-2 (78, 79). Moreover, pro-MMP-1, MMP-2 and MT1-MMP are increased in fibroblasts exposed to cigarette smoke extract (CSE) and high concentrations of CSE are sufficient to activate MMP-1 (80, 81). Collectively, these studies suggest that CSE and elastase induce ECM proteolysis, in part, by regulating mesenchymal cell function.

A direct effect of elastase on mesenchymal cell survival has not been demonstrated; however, recent studies suggest that elastases may regulate fibroblast survival. While elastase does not directly function as a collagenase, it induces collagen degradation and augments collagen gel contraction when added to fibroblasts in culture (79, 82). Moreover, elastase-mediated collagen degradation is enhanced in the presence of inflammatory cytokines (79, 83, 84). Inflammatory cytokines induce fibroblast synthesis of MMPs which are activated by elastase, thereby promoting collagen degradation (79). An additive or synergistic role for inflammation in fibroblast-mediated collagen degradation is further supported by a recent study that showed conditioned media from stimulated CD4+ T-lymphocytes induces collagen degradation by fibroblasts (85). As both ECM proteolysis and collagen gel contraction have been shown to induce fibroblast apoptosis, these studies support a mechanism whereby elastases may promote fibroblast apoptosis (59, 86, 87).

While the deleterious effects of elastase in emphysema pathogenesis extend beyond elastin proteolysis, the “protective” actions of antiproteases extend beyond inhibition of proteolysis. $\alpha 1$ -AT has been shown to stimulate fibroblast proliferation and procollagen production (88). Additionally, serine protease inhibitors block cigarette smoke-induced fibroblast secretion of inflammatory cell chemoattractants (89). Finally, although the role of $\alpha 1$ -AT on mesenchymal cell survival/apoptosis has not been investigated, $\alpha 1$ -AT protects endothelial cells from apoptosis by inhibition of caspase-3 (90, 91). These findings suggest that anti-

proteases (α 1-AT, serpins and TIMPs) promote apoptosis-resistant cellular phenotypes and support the role of an alveolar microenvironment that promotes emphysema not only through ECM proteolysis, but also through inhibition of mesenchymal cell repair functions.

CIGARETTE SMOKE INHIBITS FIBROBLAST FUNCTION

Cigarette smoke is the leading cause of emphysema and is known to induce inflammation and alveolar epithelial cell injury/apoptosis (10). Additionally, a number of studies have shown that cigarette smoke adversely affects the ability of mesenchymal cells to respond appropriately to epithelial injury. In a series of studies by Rennard and colleagues, volatile compounds in cigarette smoke extract (CSE) were found to inhibit fibroblast proliferation and fibronectin synthesis (92, 93). Functionally, CSE impairs the ability of fibroblasts to contract 3-D collagen gels (93, 94). The anti-oxidant, glutathione, restores contractile capabilities to the CSE-exposed fibroblasts, suggesting a role for oxidative stress as a mechanism of CSE actions on fibroblast function (95). Moreover, cigarette smoke stimulates collagen degradation by fibroblasts and inhibits fibroblast-mediated collagen cross-linking. In human fetal lung fibroblasts, CSE induces expression and activation of MMP-1, MMP-2, and MT1-MMP (80, 81). Finally, cigarette smoke condensate impairs the transcription, stability, and promoter activity of lysyl oxidase, a collagen cross-linking enzyme (96).

Epithelial cell death has been implicated in the pathogenesis of COPD. Although the precise mechanisms of cell death have not been clearly defined, a number of studies have shown activation of apoptosis pathways (97). More recently, CSE has been found to activate autophagy, a pro-survival mechanism that can ultimately lead to apoptosis, in epithelial cells (98, 99). In some cases, however, components in cigarette smoke have been shown to inhibit cellular apoptosis. In one example, acrolein was found to inhibit neutrophil apoptosis through inhibition of caspase-3, providing another potential mechanism for an ongoing inflammatory response in COPD. Moreover, nicotine and NNK (a carcinogen contained within tobacco) were shown to rapidly activate pro-survival signaling in human bronchial epithelial cells, a mechanism which would favor carcinogenesis (100).

Few studies have examined the effects of cigarette smoke on mesenchymal cell survival. Ishii et al. found that low concentrations of CSE induce fibroblast apoptosis while higher concentrations of CSE induce necrosis (101). CSE-stimulated fibroblast apoptosis is attributable, at least in part, to oxidative stress as overexpression of glutathione-S-transferase protected fibroblasts from apoptosis (101). Similarly, the glutathione precursor, N-acetyl cysteine, attenuates CSE-induced fibroblast apoptosis while glutathione depletion promotes fibroblast apoptosis (102).

Interestingly, Baglioni and colleagues used four different commercially available normal adult lung fibroblast cell lines to demonstrate significant heterogeneity in apoptotic susceptibility to CSE (103). This marked variation, with fibroblast viability ranging from 33% to 90%, highlights the potential role for genetic and epigenetic contributions to the apoptosis-susceptibility of fibroblasts. Collectively, these studies support the concept that cigarette smoke activates inflammatory pathways, promotes epithelial cell death and directly impairs the mesenchymal cell reparative response through inhibition of fibroblast activity and induction of apoptosis.

FIBROBLAST PHENOTYPES IN HUMANS WITH EMPHYSEMA

Several studies comparing normal mesenchymal cells with those isolated from the lungs of humans with emphysema support the hypothesis that an impaired mesenchymal cell reparative capacity contributes to the pathobiology of emphysema. Although there are differences between studies, several investigators report that emphysema fibroblasts have

reduced proliferative capacity compared with normal lung fibroblasts (104–106). Moreover, the reduction in fibroblast proliferation due to CSE is more pronounced in emphysema fibroblasts than in normal lung fibroblasts (105). Emphysema fibroblasts have decreased proliferation on exposure to the pro-inflammatory cytokine, interleukin-1 β (IL-1 β) (106). Similarly, Plantier and colleagues found that emphysema fibroblasts have decreased basal- and IL-1 β -mediated production of hepatocyte growth factor and decreased IL-1 β -stimulated production of keratinocyte growth factor (KGF) compared with normal lung fibroblasts (107, 108).

As KGF attenuates elastase-induced emphysema in mice, these findings are consistent with impaired reparative capacity of emphysema fibroblasts (107). In further support of this concept, a recent study by Rennard and colleagues found that fibroblasts from COPD patients have decreased contractility and migration compared to normal fibroblasts (17). In this study, the COPD fibroblasts demonstrated increased generation of PGE₂, which has been shown to suppress myofibroblast differentiation, proliferation, and collagen expression. Additionally, these COPD fibroblasts have increased expression of the PGE₂ receptors, EP2 and EP4 and decreased responsiveness to exogenous TGF- β 1 (17, 109, 110). Importantly, this study also showed that impaired fibroblast contraction and migration correlate with declines in pulmonary function (17).

Decreased TGF- β 1 responsiveness in emphysema fibroblasts was also observed in another study in which fibroblasts from patients with severe emphysema showed a decline in TGF- β 1-induced decorin synthesis (111). Together, these studies demonstrate that mesenchymal cells from emphysema patients manifest decreased proliferative capacity, decreased ability to elaborate epithelial cell-protective growth factors, and decreased ECM production in response to TGF- β 1. These phenotypic alterations favor epithelial dysrepair and loss of connective tissue, key features of emphysema.

Age-associated alterations in the phenotype of epithelial cells, endothelial cells and fibroblasts may also contribute to the emphysema phenotype. A higher percentage of alveolar epithelial and endothelial cells in patients with emphysema express p16^{INK4a}, a marker of cellular senescence, compared to asymptomatic smokers and nonsmokers (112). This may be attributable, at least in part, to environmental stressors linked to emphysema as exemplified by the observation that cigarette smoke extract can directly induce cellular senescence (113). Genetic and epigenetic factors are also likely to play important roles in lung senescence phenotypes. Genetic deletion of the Klotho gene, which functions to limit oxidative stress and cellular senescence, leads to emphysema in addition to a number of other age-related manifestations in mice (114).

Mice deficient in senescence marker protein-30 (SMP30 knockout mice) demonstrate increased susceptibility to emphysema in association with increased oxidative stress and apoptosis of lung cells in response to cigarette smoke exposure (115). While these studies support the importance of host stress-repair responses to combat environmental toxins such as cigarette smoke, mechanisms for the deficiency of such responses in sporadic emphysema remain unclear. Additionally, the varying responses to cellular stress and senescent phenotypes of different cell types (e.g., mesenchymal vs. epithelial/endothelial cells) in the lung are not well understood. Future studies in these areas will provide novel insights into the divergent tissue remodeling responses (e.g., fibrosis vs. emphysema) that can result from exposure even to same environmental insult.

CONCLUSION

Emphysema, a sub-type of COPD characterized by loss of alveolar parenchyma, results from epithelial cell death in combination with failed reparative responses by mesenchymal cells. Specifically, the failure of mesenchymal cell accumulation, activation, contraction, synthetic function, and survival have all been shown. Evidence suggests that the same factors that drive inflammation and epithelial cell death, namely ECM proteases and cigarette-smoke, directly contribute to these dysregulated mesenchymal cell phenotypes (Figure 1).

The loss of interstitial mesenchymal cells in emphysema stands in contrast with the accumulation of mesenchymal cells associated with bronchocentric fibrotic processes such as asthma, chronic bronchitis, and obliterative bronchiolitis (116–118). Further studies are required to characterize the phenotype of mesenchymal cells within the airway vs. alveolar compartments and to determine if these differences may account for varying clinical phenotypes in COPD. Emphysema is a complex disease, and the substantial heterogeneity in disease susceptibility and severity support a role for genetic and/or epigenetic regulation of cellular responses. Future studies of mesenchymal cell fates and phenotypes in emphysema will shed light on the role of these cells in maintaining cellular homeostasis of the alveolar wall.

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Figure 1.

Loss of cellular homeostasis in emphysema pathogenesis. Exposure to inhaled toxins (such as cigarette smoke) leads to epithelial cell death, inflammation, and extracellular matrix proteolysis. In susceptible individuals, mesenchymal cell survival and reparative functions are impaired by direct effects of inhaled toxic substances, inflammatory mediators, and by the loss of the peri- and extracellular matrix. The result is the loss of structural cells of the alveolar wall and the associated matrix components.