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Epithelial–Mesenchymal Interactions in Pulmonary Fibrosis

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Abstract

Pulmonary fibrosis represents the sequelae of a variety of acute and chronic lung injuries of known and unknown etiologies. Tissue specimens obtained from patients with pulmonary fibrosis, regardless of the etiology, consistently show evidence of an ongoing wound-repair response. Epithelial–mesenchymal interactions have critical roles in normal lung development, tissue repair processes, and fibrosis. Current hypotheses propose that dysregulated function of, and impaired communication between, epithelial and mesenchymal cells prevent resolution of the wound-repair response and contribute to the pathobiology of pulmonary fibrosis. This hypothesis is supported by abundant evidence from patients, animal models, and cell-culture studies demonstrating abnormalities in epithelial cell and mesenchymal cell activities including proliferation, differentiation, and survival. This article reviews the aberrant epithelial and mesenchymal cellular phenotypes found in the context of pulmonary fibrosis and discusses the mechanisms that perpetuate these cellular phenotypes.

Keywords

Fibroblast; myofibroblast; apoptosis; wound repair; extracellular matrix

EPITHELIAL–MESENCHYMAL INTERACTIONS IN LUNG DEVELOPMENT, WOUND REPAIR, AND FIBROSIS

Epithelial and mesenchymal cell interactions have a critical role in lung development, and the precise temporal and spatial regulation of epithelial and mesenchymal cell functions is necessary for normal alveolarization.[1] The importance of these interactions is exemplified by studies demonstrating that normal alveolarization requires lung epithelial cell secretion of soluble growth factors such as platelet derived growth factor A (PDGF-A), which provide survival signals to myofibroblasts during alveolar septation.[2] Mice deficient in PDGF-A develop emphysema associated with excessive loss of myofibroblasts. During later stages of lung development, however, apoptosis of myofibroblasts is essential for alveolar wall thinning and remodeling to achieve the delicate alveolar structure seen in normal lung.[3,4] Thus aberrant "cross-talk" between epithelial and mesenchymal cells can lead to profound abnormalities in lung development.

The repair response to injury in adult lung recapitulates several aspects of embryonic lung development.[5,6] As in normal lung development, physiological wound-repair requires spatially and temporally regulated epithelial and mesenchymal cell responses to reestablish an intact epithelium. Epithelial cell proliferation, migration, and differentiation must be

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coordinated with mesenchymal cell recruitment, proliferation, differentiation with extracellular matrix (ECM) remodeling, and subsequent apoptosis of myofibroblasts.[7–9] Dysregulation of this orchestrated wound-repair response can result in pathological scar formation due to myofibroblast accumulation and ECM remodeling.[10]

Pulmonary fibrosis can result from a variety of acute and chronic causes of lung injury.[11] At the cellular level, pulmonary fibrosis—regardless of the etiology—represents an ongoing repair response to some form of persistent or recurrent injury, or perhaps a dysregulated or inappropriate repair response to a past stimulus of lung injury.[11,12] This article reviews the aberrant epithelial and mesenchymal cellular phenotypes found in the context of pulmonary fibrosis, with a focus on idiopathic pulmonary fibrosis (IPF), and discusses the mechanisms that perpetuate these cellular phenotypes and contribute to disease pathobiology.

EPITHELIAL–MESENCHYMAL INTERACTIONS IN PULMONARY FIBROSIS

Current hypotheses propose that progressive lung fibrosis results from dysregulated function of, and/or communication between, epithelial and mesenchymal cells leading to a “vicious cycle” of epithelial cell injury and mesenchymal cell responses.[11,13–15] Myofibroblasts, key effector cells in fibrogenesis, aggregate within fibroblastic foci of usual interstitial pneumonia (UIP), the histopathologic correlate of IPF.[16] These foci are thought to represent the organization of focal areas of acute lung injury, and the presence/extent of fibroblastic foci correlates with poor outcomes in IPF.[17–19] Overlying the fibroblastic foci are areas of damaged basement membrane and denuded epithelium.[20,21] Additionally, alveolar epithelial cells (AECs) that are in close association with myofibroblasts have phenotypic changes that suggest the activation of a stereotypic wound-repair response.[22] Supporting this concept, studies of IPF tissue have reported evidence of AEC proliferation and regenerative hyperplasia,[21,23] bronchiolar and squamous metaplasia,[24–26] and apoptosis.[27–29]

Our understanding of the direct interactions between epithelial and mesenchymal cells in the context of pulmonary fibrosis is quite limited. An ultrastructural examination of specimens from patients with pulmonary fibrosis identified epithelial cell extensions through “apertures” in the underlying basement membrane.[20] Further studies suggested that, during lung repair responses, dynamic interactions between epithelial and mesenchymal cells allow for reciprocal regulation of proliferation and differentiation.[30,31] A recent report demonstrated that the fibroblast “link” between the alveolar epithelium and endothelium is disrupted in emphysema specimens, providing further support for the important role of epithelial–mesenchymal interactions in a broader context of lung disease.[32] The mechanism(s) underlying dysregulated epithelial and mesenchymal cell phenotypes in pulmonary fibrosis remain poorly understood. Evidence suggests that these complex cellular interactions are mediated by soluble factors acting through autocrine and paracrine mechanisms. Additionally, the ECM itself likely contributes both directly and indirectly to the aberrant cellular phenotypes seen in pulmonary fibrosis (Figure 1).

EPITHELIAL CELL PHENOTYPES IN PULMONARY FIBROSIS

Regeneration of a damaged epithelium following injury is required for the reestablishment of normal tissue architecture and function. Failure to establish an intact epithelium may induce a persistent wound-repair response. In the context of pulmonary fibrosis, evidence from human disease, animal models, and cell-culture studies has identified abnormalities in epithelial cell survival/apoptosis, proliferation, and migration, which likely contribute to disease pathobiology.

Increased Epithelial Cell Apoptosis

Excessive AEC apoptosis is likely to play a key role in the pathobiology of IPF. Studies of IPF tissue have shown type II AEC apoptosis at the ultrastructural level and demonstrated that AEC apoptosis is increased in cells adjacent to fibroblastic foci.[28,33] Moreover, Kuwano et al reported increased expression of the proapoptotic p53 and p21 tumor suppressor proteins associated with alveolar and bronchial epithelial cell apoptosis in a majority of IPF specimens but found no such apoptosis in emphysema specimens or normal lung tissue.[27] In another study, p53 nuclear accumulation was identified in epithelial cells from IPF, but not other idiopathic interstitial pneumonia specimens.[26] A recent study reported similar findings of excessive AEC apoptosis associated with increased expression of proapoptotic proteins (caspase-3 and Bax) and decreased expression of the anti-apoptotic Bcl-2 protein in IPF specimens.[34]

Further supporting the role of AEC apoptosis in the pathogenesis of pulmonary fibrosis are animal models showing that inhibition of AEC apoptosis attenuates pulmonary fibrosis, whereas the induction of AEC apoptosis promotes fibrotic responses. Studies have reported that inhibiting caspases, which are key components of intracellular apoptotic signaling cascades, lead to decreased fibrotic responses to intratracheal bleomycin.[35,36] Moreover, several studies suggest that induction of AEC apoptosis may be sufficient for the development of pulmonary fibrosis. In one study, pulmonary fibrosis followed epithelial cell apoptosis induced by transient overexpression of the profibrotic mediator, transforming growth factor-β1 (TGF-β1).[37]

The Fas-Fas ligand pathway, a proapoptotic signaling cascade that is upregulated in patients with IPF, has also been investigated in the pathogenesis of pulmonary fibrosis.[29,38] Inhaled Fas-activating antibodies induce pulmonary fibrosis and AEC apoptosis in mice.[39,40] Additionally, Fas-mediated epithelial cell apoptosis is potentiated by TGF-β1.[40] Studies in the bleomycin model of pulmonary fibrosis, however, have reported conflicting results. One study reported decreased fibrosis in transgenic mice deficient in Fas or Fas-ligand, whereas another study, using similar transgenic mice on a different background strain, found that deficiencies in the Fas-Fas ligand system did not reduce bleomycin-induced pulmonary fibrosis.[41,42] A third study recently reported that bleomycin-induced pulmonary fibrosis was dependent on reactive oxygen species (ROS)-mediated epithelial cell apoptosis that is independent of the Fas pathway.[43] Collectively, these animal models support a role for AEC apoptosis in the pathogenesis of pulmonary fibrosis but fail to define a specific mechanism for AEC apoptosis. Strain-dependent differences in the effects of bleomycin on lung epithelial cells and susceptibility to pulmonary fibrosis are well described in murine models.[44,45] Thus it is likely that variable and overlapping mechanisms of AEC apoptosis may be induced in different contexts, depending on the stimulus for lung injury and genetic factors of the host.

Impaired Epithelial Cell Regeneration and Migration

Impaired epithelial cell regeneration and migration following injury may contribute to the development of pulmonary fibrosis.[14] Several studies have reported abnormalities in epithelial cell proliferation in patients with IPF, although mechanisms remain unclear.[18,22,26,46] In animal models, epithelial cell mitogens and motogens, such as hepatocyte growth factor (HGF) and keratinocyte growth factor (KGF) have been shown to attenuate pulmonary fibrosis.[47,48] Similarly, granulocyte-monocyte colony stimulating factor (GM-CSF) induces epithelial cell migration, and mice deficient in GM-CSF develop increased fibrosis following lung injury.[49–51] Paracrine interactions between epithelial cells and fibroblasts may also contribute to impaired epithelial regeneration because TGF-β1 can block the mitogenic effects of KGF on AECs.[52]

The plasminogen activation system has been shown to have an important role in the pathogenesis of bleomycin-induced murine pulmonary fibrosis. Activation of plasminogen to plasmin is mediated by urokinase or tissue plasminogen activators (uPA or tPA), both of which are inhibited by PAI-1 (plasminogen activator-inhibitor 1). Plasmin, in turn, is a serine protease that participates in fibrinolysis, extracellular matrix regulation, angiogenesis, cell signaling, and cell migration.[53] Activation of the plasminogen system protects mice from bleomycin-induced pulmonary fibrosis, whereas inhibition of this system promotes fibrosis.[54–56] Additional studies have established that these antifibrotic effects are not a function of fibrinolysis, suggesting that alternative mechanisms mediate antifibrotic effects of plasminogen activation.[57,58]

The plasminogen-activation system has been shown to modulate epithelial cell migration and wound closure.[59–62] For example, plasminogen activator inhibitor (PAI)-1 deficient mice exhibit accelerated wound healing[60] and the presence of PAI-1 inhibits epithelial cell migration.[61] Consistent with these findings, uPA and plasmin promote epithelial cell migration.[59] Thus it is plausible that the antifibrotic effects of the plasminogen activation system are related, at least in part, to facilitation of epithelial cell migration.

MESENCHYMAL CELL PHENOTYPES

Fibroblasts are the most versatile of the mesenchymal cells and participate in the stereotypic repair and regenerative processes in virtually every human organ and tissue.[7,8,10] Myofibroblasts are differentiated, contractile fibroblasts with characteristics intermediate between fibroblasts and smooth muscle cells.[10,63–65] In response to injury, fibroblasts infiltrate the wound, differentiate into myofibroblasts, and secrete ECM proteins that form a provisional matrix, which serves as a “scaffold” for tissue repair.[64] Myofibroblast contraction of the provisional matrix facilitates repair by bringing healthy epithelial cells at the wound margin into close approximation. Collagen secretion stabilizes the contracted matrix surrounding myofibroblasts and provides tensile strength to granulation tissue.[10] Recent studies have shown that the mesenchymal cells in the lung following injury may be derived from different sources, including the interstitial fibroblasts,[63] circulating fibrocytes,[66–69] bone marrow–derived mesenchymal stem cells,[70] and epithelial cells.[71–73] It is not known if specific mesenchymal cell phenotypes are determined by the site of origin, the tissue microenvironment, or both. Interestingly, mesenchymal cells derived from different sites may contribute to different aspects of wound repair.[70] Moreover, mesenchymal cells isolated from different tissue microenvironments manifest phenotypic heterogeneity and “positional memory,” which may be maintained for extended periods in ex vivo cell culture.[74,75]

Mesenchymal Cell Survival and Apoptosis

Myofibroblast apoptosis is a normal event during the resolution of wound-repair responses.[76] Failure of apoptosis leads to myofibroblast accumulation, persistent ECM contraction, secretion, and remodeling that results in pathological scar formation.[10,77] Consistently, several studies have reported that both normal and fibrotic lung fibroblasts are resistant to apoptotic stimuli through several mechanisms.[78–84] Unlike epithelial cells, Fas activation is not sufficient to induce fibroblast apoptosis, although susceptibility to Fas-mediated apoptosis is increased in the presence of inflammatory cytokines.[78,79,81,82,85,86] Additionally, the profibrotic mediator, TGF-β1, confers fibroblast resistance apoptosis induced by serum-deprivation and interleukin-1β.[87,88] Contextual signals transmitted from the ECM may be important in the regulation of myofibroblast survival/apoptosis. A recent study, for example, showed that IPF-derived fibroblasts, compared with normal lung fibroblasts, had increased resistance to apoptosis imparted by expression the collagen binding receptor tyrosine kinase, discoidin domain receptor 1 (DDR1).[84] In contractile collagen gels, however, myofibroblasts undergo apoptosis associated with biomechanical unloading.[89,90] This stimulus for apoptosis

is overcome by activation of antiapoptotic signaling pathways involving focal adhesion kinase (FAK) and protein kinase B (PKB/Akt), both of which are activated by TGF-β1 in fibroblasts.[83,87,91,92] Paradoxically, a recent study reported that TGF-β1 may increase fibroblast apoptosis in a contractile collagen gel model.[93] Thus apoptotic susceptibility of myofibroblasts may be dependent on integrated soluble *and* matrix-associated signals within the cellular microenvironment.

Few studies have assessed the role of myofibroblast survival in the pathogenesis of pulmonary fibrosis in vivo. Pharmacological inhibition of prosurvival signaling proteins, focal adhesion kinase (FAK), and protein kinase B (PKB/Akt), activated in lung myofibroblasts, attenuates the fibrogenic response to bleomycin-induced lung injury.[94] Inhibition of p38 mitogen activated protein kinase (MAPK), which mediates TGF-β1-induced Akt activation and proliferative responses in myofibroblasts, similarly reduces bleomycin-induced pulmonary fibrosis.[87,95,96] Studies in humans support deficient mesenchymal cell apoptosis in fibrotic disease states. One study showed decreased apoptosis of myofibroblasts in UIP/IPF tissue in comparison with cryptogenic organizing pneumonia, an idiopathic interstitial pneumonia (IIP) that is more responsive to therapy and has better outcomes than UIP/IPF.[97] Furthermore, alveolar mesenchymal cells isolated from patients with nonresolving, or "fibroproliferative" acute respiratory distress syndrome (ARDS) are more resistant to apoptosis when compared with cells derived from patients with "resolving" ARDS.[83] Together, these studies suggest that mesenchymal cell resistance to apoptosis may be associated with persistent and progressive fibrotic diseases that respond poorly to current interventions, and that promoting myofibroblast apoptosis may be an effective strategy to halt the progressive nature of these forms of fibrotic lung disease.

Myofibroblast Proliferation

The accumulation of fibroblasts and myofibroblasts may be due to decreased apoptosis, increased proliferation, or both. Investigations of fibroblast proliferation in IPF have produced conflicting results. An early study showed increased proliferation in fibroblasts from pulmonary fibrosis compared with normal controls.[98] Among the fibrosis-derived clones, however, there was significant heterogeneity in proliferative rates, suggesting that a subpopulation of highly proliferative cells may account for the fibroblast accumulation.[98] In another study, fibroblasts from specimens with "early fibrosis" had increased rates of proliferation, whereas fibroblasts from specimens with "dense" fibrosis had decreased proliferation compared with normal fibroblasts.[99] Two other studies failed to find increased proliferation in IPF fibroblasts.[100,101] Fibroblast and myofibroblast proliferation is likely influenced by soluble fibroblast mitogens within the alveolar microenvironment.[95,102] IPF fibroblasts may possess enhanced, and sometimes divergent, mitogenic responses to certain soluble mediators[103] while being resistant to other antiproliferative signals.[100] Thus the variability in reported proliferative phenotypes of IPF fibroblasts/myofibroblasts may be explained, in part, by their derivation from heterogeneous fibrotic lesions of varying "maturity" and the presence of specific soluble factors within the cellular microenvironment.

SOLUBLE FACTORS MEDIATE EPITHELIAL AND MESENCHYMAL CELL PHENOTYPES

Transforming Growth Factor-*β*1

TGF-β1 is a dimeric polypeptide that is implicated in the pathogenesis of fibrotic disease in multiple organs and tissues, including IPF.[104] Moreover, polymorphisms in the gene encoding TGF-β1 are associated with accelerated progression of IPF.[105] Bronchoalveolar lavage (BAL) fluid from IPF patients contain increased concentrations of TGF-β1 compared with normal controls or patients with hypersensitivity pneumonitis (HP).[40,106] Furthermore, BAL fluid

from IPF patients, but not normal controls or HP patients, induces epithelial cell apoptosis, an effect that is blocked by the presence of TGF-β1 blocking antibodies.[40] In animal models, lung-specific overexpression of TGF-β1 induces pulmonary fibrosis, whereas blockade of TGF-β1 or its downstream signaling pathways attenuates bleomycin-induced pulmonary fibrosis.[107–109] The cellular sources of TGF-β1 in the context of IPF have not been conclusively demonstrated, and there is evidence to suggesting that both myofibroblasts and damaged/aberrant epithelial cells may contribute.[110–117]

The biological activities of TGF-β1 vary depending on cell type and context. As a general paradigm, TGF-β1 mediates divergent effects on epithelial and mesenchymal cell phenotypes. As a tumor suppressor, TGF-β1 induces cell-cycle arrest and promotes apoptosis in epithelial cells.[40,118] TGF-β1 also antagonizes the mitogenic effects of KGF and enhances Fas-mediated apoptosis in lung epithelial cells.[40,52,119,120] In contrast, TGF-β1 activates fibroblasts by inducing myofibroblast differentiation,[92] survival,[87,88] and proliferation[95, 101,102]; moreover, TGF-β1 induces ECM production and remodeling[101,121,122] and generation of extracellular ROS.[123]

Hepatocyte Growth Factor

HGF is an epithelial cell mitogen and motogen[124,125] that is secreted by myofibroblasts and opposes certain TGF-β1 actions.[126] HGF has antifibrotic activity in animal models of renal, hepatic, pulmonary, and myocardial fibrosis.[48,127–129] IPF fibroblasts secrete decreased levels of HGF compared with normal lung fibroblasts,[130] and TGF-β1 decreases HGF expression by fibroblasts.[131] The mechanisms by which HGF exerts its antifibrotic effects are likely related to its divergent effects on epithelial and mesenchymal cell phenotypes. HGF promotes proliferation and migration of epithelial cells, facilitating reepithelialization.[61] In contrast, HGF induces apoptosis of myofibroblasts and mediates antifibrotic effects in vivo.[128]

Studies show that the antifibrotic effects of other mediators may be mediated through enhanced activation or responsiveness of cells to HGF. For example, the protective effects of plasminogen activation in animal models are mediated, at least in part, by HGF.[132] Additionally, prostaglandin E_2 (PGE_2), an arachidonic acid metabolite that inhibits several aspects of myofibroblast function, increases HGF secretion by IPF-derived myofibroblasts to normal levels.[130] Interferon gamma (IFN-γ), a cytokine with potential antifibrotic properties,[133] upregulates HGF receptor expression on AECs.[134]

Keratinocyte Growth Factor

KGF is another fibroblast-secreted epithelial cell mitogen/motogen that attenuates pulmonary fibrosis in animal models.[47,135–137] KGF confers resistance to Fas-mediated apoptosis in lung epithelial cells.[138] Furthermore, KGF induces the secretion of PGE_2 by fibroblasts in coculture with AECs.[139] The proliferative effects of KGF on AECs, however, are antagonized by TGF-β1.[52] Moreover, a recent study shows that IPF-fibroblasts secrete decreased amounts of KGF following stimulation with IL-1β than normal fibroblasts.[140] Collectively, these studies suggest that impaired regulation of KGF, through decreased fibroblast secretion, decreased epithelial cell responsiveness, or a disruption in homeostatic epithelial–mesenchymal interactions may contribute to the pathogenesis of pulmonary fibrosis.

Angiotensin II

Angiotensin II (AII) is a fibroblast-derived soluble mediator implicated in the pathogenesis of pulmonary fibrosis. In animal models, pharmacologic inhibition of angiotensin converting enzyme (ACE) and inhibition of the type 1 angiotensin receptor (by pharmacological and genetic approaches) have been shown to abrogate bleomycin-induced pulmonary fibrosis.[35,

[141,142] IPF-derived fibroblasts secrete AII, and AII induces epithelial cell apoptosis.[33] Moreover, Fas-mediated epithelial cell apoptosis requires both AII and the angiotensin receptor.[143,144] Inhibition of ACE blocks Fas-mediated epithelial cell apoptosis.[145] In fibroblasts, however, AII promotes proliferation.[102,146] These autocrine effects may be indirect, however, because AII can induce the synthesis of TGF-β1 in several cell systems.[147,148]

Reactive Oxygen Species

Oxidant-mediated injury to epithelial cells has been implicated in the pathobiology of IPF.[149] Epithelial lining fluid from IPF patients contains increased levels of myeloperoxidase, and inflammatory cells from IPF patients generate increased levels of ROS.[149] Levels of the antioxidant, glutathione (GSH), are decreased in the epithelial lining fluid of IPF patients, and this increases following treatment with oral N-acetylcysteine (NAC).[150–152] Recent clinical trials have supported a role for antioxidant therapy as an adjunct to standard therapy in IPF; the effects of NAC monotherapy have yet to be determined.[153,154]

Although generally thought of in the context of leukocyte biology and inflammation, reactive oxygen species are also important mediators of intra- and intercellular signaling.[155] In IPF, extracellular oxidants are generated not only by inflammatory cells but by myofibroblasts as well.[123,149,156] Recent studies demonstrate that paracrine secretion of hydrogen peroxide (H_2O_2) by IPF myofibroblasts induces epithelial cell death in ex vivo coculture, demonstrating another potential mechanism of epithelial cell injury/apoptosis in IPF.[157]

Arachidonic Acid Metabolites

The balance between arachidonic acid metabolites, pros-taglandins and leukotrienes has been shown to have a role in the pathobiology of pulmonary fibrosis.[158] IPF patients have an imbalance in these mediators characterized by decreased PGE_2 in BAL fluid,[159] decreased epithelial expression of cyclooxygenase-1 and -2 (COX-1 and COX-2),[160] and increased levels of leukotrienes in lung tissue.[161] In animal models, COX-2 deficient mice develop increased fibrosis following intratracheal bleomycin, whereas leukotriene-deficient mice are protected from fibrosis.[162,163]

PGE_2 suppresses several fibroblast activities, including proliferation,[164–166] chemotaxis and migration,[167,168] differentiation,[169] and collagen production.[170] PGE_2 is secreted by lung epithelial cells and lung fibroblasts, suggesting that homeostatic suppression of myofibroblast function may be mediated through both autocrine and paracrine mechanisms.[165,168–171] Moreover, recent studies show that KGF can enhance alveolar epithelial cell secretion of PGE_2.[139] Thus the decreased expression of COX in IPF epithelial cells suggests that a decreased capacity for PGE_2 synthesis/secretion may contribute to pulmonary fibrosis through impaired suppression of myofibroblast activation.

Endothelin-1

Secreted by alveolar epithelial cells, vascular endothelial cells, and macrophages,[172] endothelin-1 promotes fibroblast proliferation, contraction, differentiation, and ECM production.[173–176] AECs from IPF specimens express high levels of endothelin-1.[177,178] In animal models, overexpression of endothelin-1 leads to progressive pulmonary fibrosis,[179] and an endothelin-1 receptor antagonist attenuates bleomycin-induced pulmonary fibrosis.[180]

THE EXTRACELLULAR MATRIX MEDIATES EPITHELIAL–MESENCHYMAL INTERACTIONS AND AFFECTS CELLULAR PHENOTYPES

The ECM provides a dynamic and biologically active substrate for epithelial–mesenchymal interactions; the composition of the ECM regulates cellular phenotypes in the context of lung injury and repair.[181,182] As an example, adhesion to an intact basement membrane (epithelial cells) or the ECM (mesenchymal cells) provides survival signals for these cells; the loss of adhesion-mediated signaling leads to a form of apoptosis termed anoikis.[183,184] Moreover, the ECM itself may promote or perpetuate aberrant cellular phenotypes. Adhesion-mediated signaling pathways activated by cell–matrix interactions are required for myofibroblast differentiation induced by TGF-β1 and promote myofibroblast survival.[91,92] Additionally, extra domain-A (ED-A) containing fibronectin has been shown to be necessary for myofibroblast differentiation, and myofibroblasts in fibroblastic foci of UIP/IPF colocalize with ED-A containing fibronectin.[16,185] Finally, the biomechanical properties of the ECM are also likely to regulate fibroblast/myofibroblast phenotypes.[10,186–188]

The composition and biomechanics of the ECM, in turn, are affected by mesenchymal and epithelial cells. Myofibroblast and epithelial cell–derived mediators interact with proteolytic pathways to regulate ECM remodeling.[189–192] Additionally, myofibroblast secretion of ROS induces posttranslational modifications in ECM proteins.[193] The dynamic composition and interactions between ECM components may lead to further changes in biomechanics and adhesion-mediated signaling, thereby promoting and perpetuating epithelial and mesenchymal cell phenotypes.

Epithelial–Mesenchymal Transition

Epithelial–mesenchymal transition (EMT) is a well-conserved cellular process by which epithelial cells acquire the morphological and molecular characteristics of mesenchymal cells; this process plays an important role in embryonic morphogenesis and cancer metastasis.[194,195] Recent studies report that alveolar epithelial cells are capable of TGF-β1-mediated EMT in vitro,[72,73,196] and one report found that epithelial and mesenchymal markers colocalize in UIP/IPF tissue.[71] Although there is evidence to suggest that EMT contributes to the development of renal fibrosis in murine models, the role of EMT in lung fibrosis remains undefined and requires further study.[194,197]

CONCLUSION

The regulation of epithelial–mesenchymal interactions is a key control point in normal and pathological wound-repair responses. In the context of tissue injury, coordinated and regulated interactions between epithelial cells, mesenchymal cells, and the ECM are required for the reestablishment of normal tissue architecture and function. In fibrotic disease, this delicate balance becomes dysregulated, as evidenced by inappropriate loss of epithelial architecture, persistent myofibroblast activation, and accumulation within fibroblastic foci. The causes of this dysregulation remain undefined but are likely due to a combination of genetic and environmental factors within the context of persistent or recurrent lung injury leading to aberrant autocrine and paracrine signaling between epithelial and mesenchymal cells.

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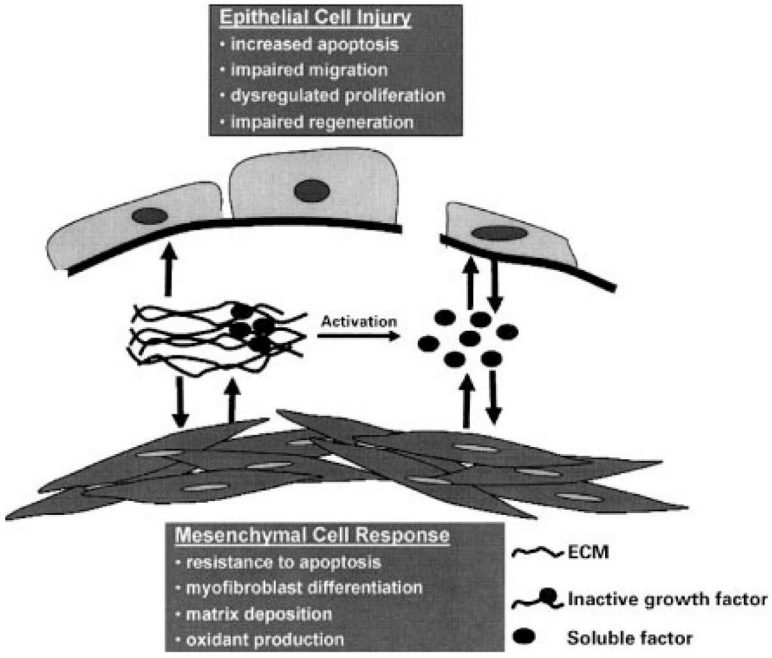

Figure 1.

Schematic representation of epithelial and mesenchymal cell phenotypes and their interactions in the context of pulmonary fibrosis. Epithelial cells overlying damaged basement membrane and fibroblastic foci demonstrate phenotypes suggestive of a dysregulated wound-repair response, including excessive apoptosis, dysregulated proliferation, and impaired migration and regeneration. In contrast, underlying mesenchymal cells demonstrate myofibroblast differentiation, resistance to apoptosis, proliferation and secretion of soluble factors, extracellular matrix (ECM) proteins, and oxidants. Both epithelial and mesenchymal cells secrete soluble mediators that function through paracrine and autocrine mechanisms to regulate cell phenotypes. Additionally, the ECM provides a substrate for epithelial–mesenchymal interactions and may also directly regulate epithelial and mesenchymal cell phenotypes.