

Review

Hepatocyte growth factor in lung repair and pulmonary fibrosis

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Pulmonary remodeling is characterized by the permanent and progressive loss of the normal alveolar architecture, especially the loss of alveolar epithelial and endothelial cells, persistent proliferation of activated fibroblasts, or myofibroblasts, and alteration of extracellular matrix. Hepatocyte growth factor (HGF) is a pleiotropic factor, which induces cellular motility, survival, proliferation, and morphogenesis, depending upon the cell type. In the adult, HGF has been demonstrated to play a critical role in tissue repair, including in the lung. Administration of HGF protein or ectopic expression of HGF has been demonstrated in animal models of pulmonary fibrosis to induce normal tissue repair and to prevent fibrotic remodeling. HGF-induced inhibition of fibrotic remodeling may occur via multiple direct and indirect mechanisms including the induction of cell survival and proliferation of pulmonary epithelial and endothelial cells, and the reduction of myofibroblast accumulation.

Keywords: hepatocyte growth factor; myofibroblast; alveolar epithelial cell; pulmonary fibrosis

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Pathophysiology of pulmonary fibrosis

Pulmonary fibrosis is a disease characterized by the replacement of the lung tissue with scar tissue, resulting in the permanent loss of the normal alveolar architecture. The disease is usually progressive, and death is often the direct result of either respiratory insufficiency or right heart failure due to pulmonary hypertension. Pulmonary fibrosis can be directly induced by a variety of insults to lung tissue including exposure to drugs, organic or inorganic particles, bacterial or viral infection, or clinical irradiation for the treatment of cancer^[1, 2]. The condition may also occur idiopathically^[1]. Treatments for pulmonary fibrosis consist of anti-inflammatory and immunomodulatory agents, cytotoxic agents (eg, methotrexate, cyclophosphamide), antioxidants (eg, *N*-acetylcysteine), antifibrotic agents (eg, pirfenidone, colchicine), interferon-gamma 1 β , and/or lung transplantation^[3, 4]. The pulmonary fibrosis patient's response to treatment often depends on the etiology of the disease. However, currently available treatments are largely ineffective in halting the progression of the disease.

The progression of pulmonary fibrosis is believed to involve a failed or dysregulated injury response, which may be accompanied by inflammation^[5]. An emerging view of lung remodeling suggests that the disease may develop as the result of

repeated stimuli, with early cycles of injury to alveolar epithelial and endothelial cells, followed by inflammation and attempted repair, ultimately leading to aberrant wound healing and fibrosis^[2, 6].

Cellular alterations in pulmonary fibrosis

In pulmonary remodeling, the loss of the normal pulmonary architecture is characterized by: 1) the loss of alveolar epithelial and endothelial cells; 2) the persistent proliferation of activated fibroblasts, or myofibroblasts; and 3) the extensive alteration of the extracellular matrix (Figure 1). Two primary animal models have been developed for the study of experimentally-induced pulmonary fibrosis: thoracic irradiation and the profibrotic chemotherapy drug bleomycin. Both of these agents induce pulmonary fibrosis in humans with similar pathophysiology.

Studies of lung fibrosis have demonstrated the presence of extensive and apparently progressive epithelial cell apoptosis, especially in regions adjacent to fibrotic foci^[7–10]. Endothelial cell apoptosis has been less studied but has also been identified as a prominent event in fibrotic human lung tissue^[9]. In rodent models of experimental lung fibrosis, extensive apoptosis occurs, similarly to that observed in human lung fibrosis patients^[11, 12]. Rodent models have also demonstrated lung microvascular and pulmonary artery endothelial cell injury and apoptosis^[11, 13, 14].

Pro-apoptotic factors are upregulated in fibrotic lung tissue.

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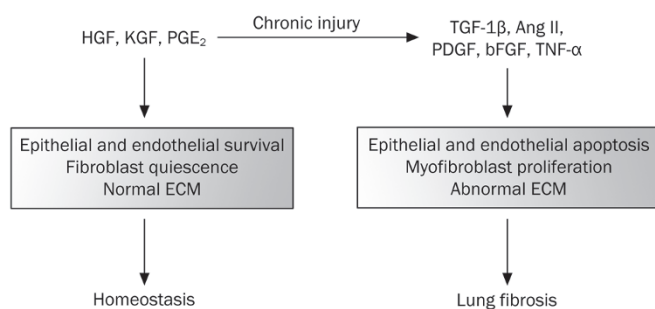


Figure 1. Schematic diagram depicting the development of lung fibrosis following irreparable damage to lung cells. A number of pro-survival factors including HGF, KGF and Cox-2 normally promote survival of epithelial and endothelial cells, fibroblasts quiescence and normal regulation of extracellular matrix (ECM) which altogether results in homeostasis in the lung. Injuries such as bleomycin, radiation, and pro-fibrotic factors may cause epithelial and endothelial apoptosis as well as fibroblast activation and myofibroblast proliferation – events observed in the development of lung fibrosis.

Lung fibrosis patient samples have increased levels of transforming growth factor $\beta 1$ (TGF- $\beta 1$) and angiotensin II (Ang II)^[15–17] that induce apoptosis and/or growth arrest in epithelial and endothelial cells^[18]. Tumor necrosis factor- α (TNF- α), a ligand for the death receptors, as well as death receptors themselves, are increased in the lung tissue of patients with IPF^[19–21]. Data indicate many of the same factors identified in human lung fibrosis are also increased in animal models of the disease^[22–29]. The imbalance of homeostatic factors created by increased production of pro-apoptotic factors is further exacerbated by a decrease in the production of factors that sustain epithelial and endothelial cell survival, including hepatocyte growth factor (HGF) and keratinocyte growth factor (KGF)^[30–34]. The inhibition of cellular apoptosis by a caspase inhibitor or by blocking Ang II signaling significantly mitigated fibrotic remodeling in mice treated with bleomycin^[35, 36]. Specific inhibition of endothelial cell death was also demonstrated to prevent TGF- $\beta 1$ -induced fibrosis in a rat model of lung fibrosis^[14].

Activated fibroblasts, or myofibroblasts, a central topic in pulmonary fibrosis research, are thought to be a primary causative cell type in the progression of the disease^[37–39]. Lung tissue from IPF patients contain increased levels in specific factors that support fibroblasts and/or mesenchymal cell growth including TGF- $\beta 1$, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), TNF α , interleukins-1 β and -8, and insulin-like growth factor^[15–17, 21, 25, 40–44]. At the same time, IPF lung tissue has reduced levels of factors that suppress fibroblast growth, such as cyclooxygenase-2 (COX-2) and its downstream product prostaglandin E₂ (PGE₂)^[45, 46]. Myofibroblasts, either from patient sample, or from animal models of pulmonary fibrosis, have pathophysiological characteristics consistent with their key role in affecting alterations associated with fibrotic remodeling^[47]. 1) They exhibit rapid proliferation and secrete autocrine factors including bFGF, PDGF, and TGF-

$\beta 1$ ^[48, 49]. 2) They display significant resistance to apoptosis, including that mediated by Fas^[50–52]. 3) They are contractile and express α -smooth muscle actin, and these cells are highly motile^[38]. And finally, 4) they significantly alter the extracellular milieu of the lung by secreting extracellular matrix proteins, including collagen types I and III, and by producing reactive oxygen species that contribute to the oxidative state of the lung in fibrosis and to the cross-linking of the extracellular matrix^[53–56]. Unlike normal fibroblasts that provide a supportive environment to the resident epithelial and endothelial tissues of the lung, myofibroblasts create a toxic environment for other lung cells. Myofibroblasts are a primary source of many pro-apoptotic factors that induce epithelial and endothelial cell death in lung fibrosis. Data from *in vitro* experiments using myofibroblasts cultured from fibrotic tissue indicate that these cells induce growth arrest and apoptosis in primary lung epithelial and endothelial cells^[35, 47].

Multiple cellular origins of myofibroblasts have been identified in pulmonary fibrosis. Originally, it was thought that resident lung fibroblasts provided the sole source for this pathological cell type. Myofibroblasts can be derived from fibroblasts through the process of transdifferentiation, believed to be driven by sustained over-expression of TGF- $\beta 1$ in fibrotic tissue^[4, 38, 57]. Myofibroblasts can also derive from alveolar type II pneumocytes through epithelial-mesenchymal transformation (EMT)^[58–60]; this process, like transdifferentiation, is also induced by TGF- $\beta 1$ ^[2]. A third potential source of myofibroblasts are the mesenchymal stem cells from adult bone marrow, which can be recruited to the injured lung^[61–63]. Circulating fibrocytes are increased in IPF patients compared to healthy control subjects^[64, 65], and studies tracking bone marrow-derived fibroblasts suggest that fibrocytes may migrate to the lung and contribute to remodeling^[61, 63, 66]. The inhibition of factors that induce myofibroblast transdifferentiation and EMT processes, such as TGF- $\beta 1$ and Ang II, significantly attenuates the development of pulmonary fibrosis in animal models^[17, 26, 36, 67–69]. Likewise, the inhibition of fibrocyte extravasation to the lungs, for instance by inhibiting CXCL12 signaling, was shown to reduce collagen deposition and fibrosis in mouse models^[2, 70].

Hepatocyte growth factor in normal and fibrotic tissue repair

HGF is a paracrine factor produced by cells of mesenchymal origin (*eg*, fibroblasts and macrophages), while the HGF receptor, Met, is expressed by epithelial and endothelial cells^[71]. HGF is a heterodimeric protein comprised of a 55–60 kDa α chain and a 32–34 kDa β chain linked by a single disulfide bond^[71]. The Met receptor is a tyrosine kinase receptor with a single transmembrane spanning region and a conserved tyrosine kinase domain. Met is translated as a single polypeptide chain which is proteolytically cleaved to form a ~145 kDa β heavy chain and a ~35 kDa α light chain linked by a single disulfide bond^[71]. The exclusion of Met expression from fibroblasts provides specificity for HGF-induced survival and proliferative activities on epithelial and endothelial cell

types. Met contains a number of critical tyrosine residues that are phosphorylated in response to HGF binding (Figure 2)^[72]. A juxtamembrane tyrosine (Y1001) is involved in down-regulation of Met following activation^[72]. Two tyrosines in the kinase domain (Y1234 and Y1235) are required for kinase activity of the receptor^[73]. Two other critical tyrosines (Y1349 and Y1356) are found in the carboxy terminal domain of Met, in the “multifunctional docking region”^[74]. These latter phosphorylation sites are required for the association with multiple adaptor proteins and signaling molecules^[75].

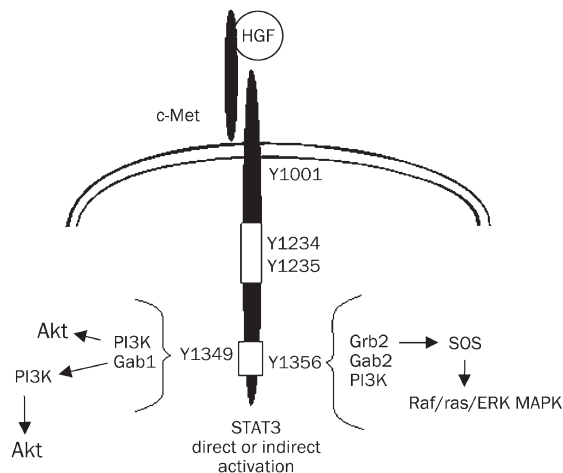


Figure 2. HGF/c-Met signal transduction. Two tyrosine phosphorylation sites (Y1349/Y1356) in the multi-functional docking domain interact with multiple adaptor proteins and signal transduction enzymes. STAT3 has been shown to bind directly to c-Met in some cell types, but the site has not been defined.

Signal transduction by HGF leads to a variety of biological responses including migration, proliferation and morphogenesis, especially branching tubulogenesis in specific cell types^[71]. HGF is required for normal embryogenesis and development^[76, 77], including for the lung^[78]. However, in the adult a primary function of HGF is tissue repair^[79]. HGF promotes normal tissue regeneration and prevents fibrotic remodeling in the lung, heart, kidney, and liver^[80–84]. HGF is expressed locally in response to injury in a number of tissues, including the lung, kidney, and liver^[82, 83, 85–88]. HGF is also produced in the lung in response to distal injuries, suggesting an endocrine function for tissue repair^[89].

The role of HGF in lung tissue repair has been well established^[82, 90]. Studies indicate that HGF is elevated in the lung following injury. HGF mRNA levels are elevated in damaged lung tissue^[82, 91], and HGF protein levels are increased in bronchoalveolar fluid extracted from injured lungs^[92]. The time course of HGF induction following lung injury correlates with proliferation of the alveolar epithelial cells^[82, 93] and lung vascular endothelial cells^[94]. Administration of HGF neutralizing antibodies resulted in reduced DNA synthesis in alveolar epithelial cells after ischemia-reperfusion lung injury in rats^[95].

Although HGF is increased in response to tissue injury, an inverse correlation has been identified for HGF expression during the development and/or progression of fibrosis in several tissues including the lung^[31, 96, 97]. Lung tissue from patients with pulmonary fibrosis has reduced expression of factors that sustain epithelial and endothelial cell growth and survival, including HGF^[31]. Lung fibroblasts isolated from IPF patients have decreased HGF expression and activation relative to fibroblasts from control patients^[30]. In cell culture and animal models, suppression of HGF synthesis occurs in response to treatment with the pro-fibrotic factors TGF- β and Ang II^[98–101].

Studies in animal models have provided strong evidence that HGF-induced lung repair prevents the induction of fibrotic remodeling. *In vivo* studies have shown that HGF potently mitigates the effects of acute and chronic lung injuries caused by oxidative stress and inflammation. Administration of HGF protein or adenoviral expression of HGF prevents fibrotic remodeling in several animal models of lung fibrosis^[91, 102–104]. Transient *in vivo* expression of HGF, using non-viral plasmids, also prevents fibrotic lung remodeling. Using albumin-derived particles to transfect lung endothelial cells, *in vivo* transient transfection of HGF increased repair and prevented collagen deposition and remodeling in mice^[105, 106]. Because HGF is secreted, it was reasoned that “nondiseased-organ-targeting gene transfer” could also be used to produce HGF protein, which would then reach the lung through the circulatory system^[107]. Electrotransfer of an HGF-encoding plasmid into muscle tissue was also demonstrated to suppress bleomycin-induced fibrotic remodeling in mice^[107]. Importantly, studies show that HGF has protective activity when given either simultaneously with or 7 d after administration of a pro-fibrotic treatment, suggesting that HGF is effective during both the initiation phase and the progressive phase of the disease^[102].

Because human patients are usually diagnosed only during the progressive phase of pulmonary fibrosis, the identification of factors effective during this phase of the disease is critical for development of treatments and cures.

HGF signaling to induce epithelial and endothelial survival and growth

Regeneration of normal epithelium and endothelium is critical to healthy repair following tissue injury. Thus, normal tissue repair requires factors, such as HGF, that specifically support growth in epithelial and endothelial cells, but not in myofibroblasts, may be required for antifibrotic tissue repair^[93, 108]. HGF is mitogenic, motogenic, and induces survival in pulmonary endothelial and alveolar type II epithelial cells^[71, 109–114]. HGF also releases lung epithelial and capillary endothelial cells from growth arrest induced by the profibrotic factor TGF- β ^[115].

HGF blocks apoptosis in lung epithelial and endothelial cells. The cell survival activities by HGF have been attributed to the activation of a number of anti-apoptotic signaling pathways^[112, 116–119] although the specific anti-apoptotic mecha-

nisms of HGF appear to differ among cell types^[118, 120]. Three predominant pathways implicated in survival by HGF are ERK/MAPK, PI3K/Akt, and signal transducer and activator of transcription 3 (STAT3) (Figure 2)^[121]. Although much of the research on HGF signaling for proliferation and survival has been performed on cancer cell types, some studies have investigated the mechanisms for HGF-induced survival and proliferation in primary lung cells.

In murine lung endothelial cells subjected to hypoxic stress followed by reoxygenation, a procedure that activates the extrinsic apoptotic pathway through the death inducing signaling complex (DISC) and caspase-8. HGF confers protection against extrinsic apoptosis through PI3K/Akt-dependent up-regulation of the caspase-8 inhibitor FLICE-like inhibiting protein (FLIP) and through down-regulation of DISC formation^[122]. This report additionally showed that HGF inhibited Bax translocation into the mitochondria, also in an Akt-dependent manner^[122]. An investigation of the effects of HGF on H₂O₂- and TNF- α -induced apoptosis in pulmonary epithelial cells demonstrated that survival of epithelial cells by HGF involved the activation of nuclear factor-kappa B (NF- κ B)^[118]. The mechanism by which HGF activates NF- κ B in these cells is unknown.

Both cell culture and *in vivo* studies provide evidence that HGF regulates gene expression of the anti-apoptotic members of the Bcl-2 protein family. Studies of hypoxia-reoxygenation injury to endothelial cells demonstrate that HGF exerts Akt-dependent anti-apoptotic activity by enhancement of the expression of anti-apoptotic protein Bcl-x_L^[118, 122]. Investigation of HGF treatment prevented cellular apoptosis and increased Bcl-x_L expression in mice following ischaemic reperfusion injury to the lung^[123].

HGF may also block fibrotic remodeling through indirect mechanisms, including the regulation of pro-fibrotic factors. As stated above, Ang II is a potent inducer of epithelial and endothelial cell apoptosis in lung fibrosis, and studies suggest that *de novo* generation of Ang II is required for FAS- and TNF- α induced apoptosis of alveolar epithelial cells in cell culture^[124, 125]. The enzyme angiotensin converting enzyme (ACE) is required for the proteolytic activation of Ang II from its inactive precursor angiotensin I (Ang I), and bleomycin-induced fibrosis can be blocked *in vivo* using an ACE inhibitor or an Ang II receptor antagonist^[35]. Our laboratory demonstrated that HGF reduces ACE expression in lung endothelial cell culture^[126]. The down-regulation of ACE might provide a potential indirect mechanism for HGF reduction of lung cell apoptosis through Ang II suppression.

HGF inhibition of myofibroblast accumulation

Rodent models for lung fibrosis indicate that HGF treatment restricts myofibroblast recruitment. Three potential mechanisms for this effect of HGF are: 1) the induction of quiescence in lung fibroblasts and inhibition of transdifferentiation; 2) the inhibition of EMT of lung epithelial cells; and 3) induction of apoptosis in myofibroblasts. Direct inhibition of fibroblast transdifferentiation by HGF has not been demonstrated, but

regulation of myofibroblast development may occur through indirect mechanism(s).

HGF reduces fibroblast activation to the myofibroblast phenotype. HGF may affect fibroblast activation indirectly through the regulation of lung endothelial cell expression of cyclooxygenase 2 (COX-2), a potent activator of prostaglandin E₂ (PGE₂) synthesis^[127, 128]. PGE₂ is secreted by pulmonary endothelial cells, induces fibroblast quiescence and is a potent inhibitor TGF- β 1-induced fibroblast transdifferentiation^[57, 129]. Our laboratory has shown that HGF regulates COX-2 expression in primary lung epithelial cells through Akt- and beta catenin-dependent up-regulation of COX-2 mRNA^[127]. This suggests a possible mechanism for HGF-mediated COX-2 inhibition of fibroblast transdifferentiation.

EMT is an important process during development and organogenesis, and HGF has been demonstrated to induce EMT under specific cellular conditions^[130, 131]. However, EMT associated with fibrotic remodeling is negatively modulated by HGF^[96]. Rat alveolar epithelial cells that were treated with TGF- β to induce EMT, HGF inhibits the expression of myofibroblast markers such as α -SMA, collagen type I, and fibronectin^[132]. The inhibitory activity of HGF on EMT requires upregulation of Smad7 expression and its export from the nucleus to the cytoplasm. The export of Smad-7 to cytoplasmic compartment results in the inhibition of signal transduction by the TGF- β receptor^[132]. HGF may also indirectly affect EMT processes. Endothelial nitric oxide attenuates EMT^[133]. Increased nitric oxide results in the retention of epithelial morphology while inhibition of NOS leads to increased α -SMA expression and fibroblast-like morphology in TGF- β 1-treated alveolar epithelial cells^[133]. HGF stimulates activity of endothelial nitric oxide synthase (eNOS) via a PI3K/Akt-dependent pathway in endothelial cells^[134, 135].

Finally, it has been shown recently that HGF affects the viability of myofibroblasts through direct mechanisms. Although normal fibroblasts lack the HGF receptor Met, myofibroblasts taken from the fibrotic lungs of experimental animals have been shown to express Met^[136]. In the Met-expressing myofibroblasts, HGF was shown to induce apoptosis in a caspase-dependent manner^[136]. This apoptotic activity of HGF is associated with increased degradation of the extracellular matrix. Treatment of myofibroblasts with HGF increases in the activities of predominant enzymes involved in fibronectin degradation and a decrease in a fibronectin central cell binding domain which is involved in FAK phosphorylation; both of these activities lead to decreased survival of myofibroblasts^[136].

Conclusion

Findings from animal models of pulmonary fibrosis show that HGF can inhibit both the initiation and progression of lung fibrosis (Figure 3). However, the critical mechanism(s) for HGF protection of the lung from fibrotic remodeling and promotion of normal tissue regeneration remains poorly understood. HGF directly induces epithelial and endothelial proliferation and survival, and may indirectly modulate myofibroblast accumulation in the lung after injury. Despite the

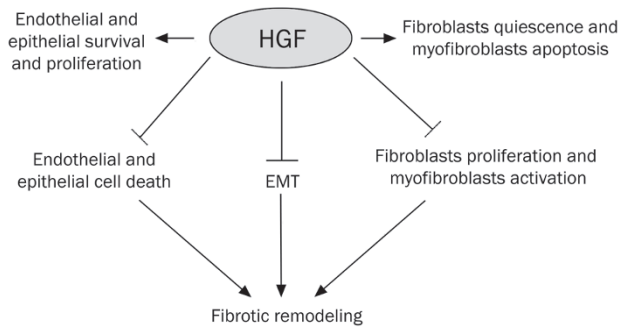


Figure 3. HGF actions for the inhibition of fibrotic remodeling.

potential clinical applications for HGF for wound repair and prevention of fibrotic remodeling, its complex structure has precluded its development for clinical use. The future development and study of HGF mimetics and/or Met agonists may aid in the understanding of HGF mechanisms of tissue repair as well as provide potential therapies for treatment of lung fibrosis.

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