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Derleme / Review

Lung fibrosis molecular mechanisms

Akciğer Fibrozisinin Moleküler Mekanizmaları

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Abstract: Lung fibrosis is a highly heterogeneous and life-threatening disease in patients. Studies on the molecular pathogenesis of lung fibrosis have more often focused on the mechanisms regulating the increase of extracellular matrix and collagen. Although these studies have been conducted in this way, many different new studies are also being conducted. These studies have focused more on the mechanisms regulating fibroblast activation and differentiation, how fibrosis starts and how it progresses. In this review, especially the molecular mechanisms of lung fibrosis are emphasized and examined.
Keywords: Lung fibrosis, lung fibrosis pathology, molecular mechanism

Özet: Akciğer fibrozisi oldukça heterojen ve yaşamı tehdit eden bir hastalıktır. Akciğer fibrozisinin moleküler patogenezi üzerine yapılan çalışmalar daha çok hücre dışı matriks ve kollajen artışını düzenleyen mekanizmalara odaklanmıştır. Bu çalışmalar var olsa da, birçok farklı yeni çalışma da yapılmaktadır. Bu çalışmalar daha çok fibroblast aktivasyonunu ve farklılaşmasını düzenleyen mekanizmalara, fibrozisin nasıl başladığına ve nasıl ilerlediğine odaklanmaktadır. Bu derlemede özellikle akciğer fibrozisinin moleküler mekanizmaları üzerinde durulmuş ve mekanizmaları incelenmiştir.
Anahtar Kelimeler: Akciğer fibrozisi, akciğer fibrozisi patolojisi, moleküler mekanizma

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1. Introduction

Lung fibrosis, which occurs in patients with alveolar fibrosis, is quite resistant to treatment and has a high mortality. In patients, this process includes the progression of fibrosis in the lung, respiratory distress, and irreversible serious damage to the lung. Although the etiology of lung fibrosis is not yet known, idiopathic pulmonary fibrosis (IPF), a serious disease form, is predicted to live maximum 6 years after diagnosis (1).

Lung Fibrosis Pathology

Studies on lung fibrosis and responsible molecular mechanisms are ongoing. The fibrotic process can arise from many different etiologies. In particular, patients with acute respiratory distress syndrome (ARDS) (2) experience an increase in many factors leading to lung fibrosis. In other patients with pulmonary fibrosis, irradiation to the chest may occur from environmental factors such as exposure to asbestos or silica. Although very rare, lung fibrosis can develop very rapidly with unknown damage and this is mostly IPF. The pathology that causes lung fibrosis has become more complex over the years. Over the years, the number of cellular and molecular hypotheses of the disease has increased. In lung fibrosis, age-related loss of function occurs at the molecular, cellular and tissue levels (3, 4).

Lung Fibrosis and Molecular Mechanisms

Wound healing and fibrosis, effective in lung fibrosis, are characterized by complete inflammation, tissue injury, myofibroblast transformation, fibroblast migration, extracellular matrix deposition (ECM), and ECM remodeling. These pathological processes cannot be considered independent of each other and are mechanisms that trigger each other, thus exacerbating fibrosis. Fibrosis, characterized by these mechanisms, can occur in many vital organs such as the skin, lung, and liver, and plays an active role in many diseases. During fibrosis, fibroblasts, immune, epithelial, and endothelial cells are very actively involved (5, 6). Many environmental factors, such as exposure to organic and inorganic harmful compounds, infection, smoking, cause damage to the lung epithelium. It is here that tissue healing is activated in response to the damaged lung tissue. This process actually facilitates the repair of lung tissue and its transformation and adaptation to damage (7). In all fibrotic processes, the underlying mechanism of fibrosis is not fundamentally different, although the etiologies or causes of occurrence may differ. In summary, cellular fibrosis is mainly characterized by abnormal deposition of ECM components, especially collagen. There is an age-dependent irreversible breakdown of lung fibrosis as described above. In lung fibrosis, age-dependent inability to repair damaged tissue, resolve fibrosis, tissue scarring, disruption of tissue homeostasis and ultimately organ damage (8). In lung fibrosis, it can be said that the degree of damage and pathology increases with aging in the damaged lung. Under normal lung injury conditions, alveolar epithelial cell 2s (AEC2s) are replaced by proliferating and differentiating AEC2 cells and some stem cells, and new vessel formation, coagulation, migration and transformation of fibroblast cells, collagen synthesis in endothelial cells are stimulated. Chemokines such as transforming growth factor (TGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are involved in this entire fibrotic process. In the development of lung injury, inflammation is increased and levels of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), which are characterized by inflammation, are increased. The whole process creates an environment that favors alveolar regeneration and lung tissue remodeling (9).

TGF-β cytokine is mainly involved in lung fibrosis. The TGF-β family are multifunctional cytokines that exist in three isoforms: TGF- β1, TGF- β2 and TGF- β3. The molecular and biological activities of the three isoforms differ from each other, but TGF- β1 plays a dominant role in pulmonary fibrosis (10). In the extracellular matrix, TGF-β plays very important roles and is the most

important promoter of the entire fibrotic process. It is also considered the most potent chemotactic factor for immune cells such as monocytes and macrophages. In monocytes and macrophages, TGF- β activates the release of cytokines such as PDGF, IL-1, basic FGF (bFGF) and TNF-α and automatically regulates its own cascade (10). TGF-β is increased in the lung tissue of patients with IPF (11) and increases in TGF-β generation are consistently observed in rodents with bleomycin-induced pulmonary fibrosis (12). TGF-β is increased in the lung tissue of patients with idiopathic pulmonary fibrosis (11) and increases in TGF- β generation is consistently observed in rodents with bleomycin-induced pulmonary fibrosis (12). The TGF-β Smad cascade is actively involved from the membrane to the nucleus (13). In this pathway, activated TGF-β receptors are translocated to the nucleus by regulating other Smad proteins, leading to the phosphorylation of Smad-2 and Smad-3.

One study shows that Smad-3 deficiency attenuates bleomycin-induced pulmonary fibrosis in mice (14) and that the inhibitor Smad-7 prevents phosphorylation of Smad-2 and Smad-3 through activated TGF-β's receptors (15, 16). In lung fibrosis, TGF-β1 is considered the most important chemokine. AEC2s produce TGF-β1 following actin-myosin-mediated cytoskeletal contractions induced by the unfolded protein response (UPR) following six integrins activation. αvβ6 integrin & TGF- β1 pathway, a pathway ready to recognize damaging stimuli, is actually a molecular sensing mechanism (17). In lung fibrosis, it is the most important profibrotic mediator that activates the profibrotic cascade, triggers myofibroblast transformation, promotes epithelial-mesenchymal transition (EMT), circulating fibrocyte recruitment, fibroblast activation, and proliferation and epithelial cell apoptosis, epithelial cell migration, and production of pro-angiogenic factors (17).

In lung fibrosis, another important factor is PDGF. It increases the proliferation of fibroblasts while inducing ECM synthesis. Alveolar macrophages with IPF produce higher amounts of PDGF-B mRNA and protein level (18, 19). Impaired PDGF levels have been observed in animal models, particularly in AEC2 and mesenchymal cells (20). PDGF-B transgenic mice have been observed to develop lung disease characterized by diffuse emphysematous lung lesions and inflammation/fibrosis in focal areas (21).

In another study, intratracheal instillation of recombinant human PDGF-B in rats produces fibrotic lesions in blood vessels and airways (22). In a bleomycin-induced experimental mouse model, gene transfer of the extracellular domain of the PDGF receptor ameliorated pulmonary fibrosis (23). Insulin-like growth factor (IGF)-1, which promotes fibroblast proliferation, has also been observed to work synergistically with PGDF (24).According to this study, alveolar macrophages from patients with IPF expressed higher levels of IGF-1 mRNA and protein than normal alveolar macrophages (24, 25).

In normal fibroblasts, after stimulation with TGF-β, increased phosphorylation of JAK-2 was observed to induce subsequent activation of STAT-3 and transcription of collagen. Selective inhibition of JAK-2 blocks TGF-β-induced collagen release in vitro and prevents experimental fibrosis *in vivo* (26). However, different studies may show that tumor cells and fibroblasts can become resistant to JAK-2 inhibitors in long-term treatment, which is essential for chronic fibrotic diseases (27, 28). This resistance is not due to somatic mutations but to transactivation of JAK-2 by JAK-1 and subsequent activation of downstream signaling through STAT proteins (27, 28). This escape mechanism may be blocked by simultaneous inhibition of JAK-1 and JAK-2 or by co-treatment with JAK-2 and heat shock protein-90 (HSP-90) inhibitors, which have promising antifibrotic effects in murine models of skin and lung fibrosis (28).

Epithelial-mesenchymal transition (EMT) is the pathological phenomenon in lung fibrosis in which epithelial cells lose their normal phenotype and profibrogenic markers such as α-smooth muscle actin (α-SMA), fibroblast-specific protein 1 (FSP1), collagen type 1 and fibronectin are highly secreted (29). Some studies have demonstrated the capacity of

alveolar epithelial cells to trans-differentiate into fibrogenic myofibroblasts (30, 31).
In lung fibrosis, EMT stimulation is initiated by overexpression of TGF- β by damaged epithelial and endothelial cells as well as macrophages and fibroblasts, thus leading to a positive cycle of stimulation. With the induction of EMT, SMAD activation occurs in the "canonical" TGF- β signaling pathway (32). In addition, another pathway that promotes fibrosis is the "non-canonical" TGF-β signaling involving the extracellular signal-regulated kinase (ERK) pathway, which leads to EMT trans-differentiation (32).
Furthermore, EMT induction is mediated by the cross-interaction of TGF-β1 with the canonical WNT/β-catenin pathway (33), through the interplay of WNT and TGF-β signaling pathways, β-catenin accumulates in the nucleus and promotes EMT in alveolar epithelial cells (34) , resulting in the transformation of alveolar cells into myofibroblasts characterized by ECM deposition and fibrosis. It is also known that EMT pathogenesis is linked to autophagy of alveolar epithelial cells, leading to fibrosis and other lung pathologies (35). Hedgehog signaling, an important regulator of tissue repair and EMT, is involved during fibrosis (36, 37). In the lung, normally, Hedgehog signaling ensures fibroblast normalization and maintains homeostasis (36). However, in pathological states of the lung, Hedgehog signaling is too overactive, as shown in bleomycin-induced lung fibrosis, and blocking hedgehog epithelium-fibroblast trans-differentiation can attenuate experimental pulmonary fibrosis (38, 39, 40). Fibroblast growth factor receptors (FGFR-1, -2) have been found to be elevated in myofibroblast cells, which are fibrosis cells, and in patients with IPF. Also, basic fibroblast growth factor (bFGF) plays a role in lung fibrosis. In alveolar macrophages are a dominant source of bFGF in intra-alveolar fibrotic areas following acute lung injury (41). In a study of IPF, mast cells were found to be the predominant bFGF-producing cells and bFGF levels correlated with bronchoalveolar lavage cellularity and severity of gas exchange abnormalities (42).
In fibrosis, there is resistance to apoptosis and this process exacerbates fibrosis. Activation of the PI3K-AKT-mTOR signaling pathway reduces autophagy in fibrosis (43), and inhibition of EF2K and p38 MAPK signaling reduces autophagy, which in turn reduces lung fibroblast apoptosis (44). In the lung, this suppression of apoptosis and autophagy also exacerbates fibrosis and increases inflammation.
In our knowledge, all over these molecular regulation of lung fibrosis, inflammation is so active and activator of fibrosis. In lung fibrosis, fibroblast proliferation and myofibroblasts, lymphocytic cytokines are active and act profibrotic. The role of Th-1, Th-2 and Th-17 T-cells in pulmonary fibrosis is known. The Th1 T-cell subset produces IL-1, TNF- α, PDGF and TGF- β1 and has clear profibrotic effects. Th-2 and Th-17 responses appear to be more important in the pathogenesis of IPF. They lead to direct activation of certain interleukins (IL-4, IL-5, IL-13) and fibroblasts (45-47).

2. Conclusions

In conclusion, lung fibrosis is a serious life-threatening lung disease. Although many pathways involved in lung fibrosis are known, its etiology and pathology are not yet fully understood. Many molecular pathways in lung fibrosis exhibit heterogeneous behavior and there is a therapeutic need. The large number of therapeutic interventions suggests that in the near future there may be more specific therapeutic options for the disease.

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