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Medicine in focus

Lung alveolar epithelium and interstitial lung disease

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ABSTRACT

Interstitial lung diseases (ILDs) comprise a group of lung disorders characterized by various levels of inflammation and fibrosis. The current understanding of the mechanisms underlying the development and progression of ILD strongly suggests a central role of the alveolar epithelium. Following injury, alveolar epithelial cells (AECs) may actively participate in the restoration of a normal alveolar architecture through a coordinated process of re-epithelialization, or in the development of fibrosis through a process known as epithelial–mesenchymal transition (EMT). Complex networks orchestrate EMT leading to changes in cell architecture and behaviour, loss of epithelial characteristics and gain of mesenchymal properties. In the lung, AECs themselves may serve as a source of fibroblasts and myofibroblasts by acquiring a mesenchymal phenotype. This review covers recent knowledge on the role of alveolar epithelium in the pathogenesis of ILD. The mechanisms underlying disease progression are discussed, with a main focus on the apoptotic pathway, the endoplasmic reticulum stress response and the developmental pathway.

1. Introduction

Interstitial lung diseases (ILD) comprise a group of lung disorders characterized by various levels of inflammation and fibrosis (ATS, 2000, 2002). The understanding of the mechanisms underlying the development and progression of ILD remains elusive. Indeed, for a long time, chronic ILD and pulmonary fibrosis were believed to result mainly from chronic inflammation following an initial injury to the alveolar epithelial lining (Bringardner et al., 2008; Wells and Hogaboam, 2008). In cases of limited injury, it was thought that the reparative attempt could reverse the trend toward fibrosis. By contrast, in situations of continuing injury, the repair process driven by inflammatory molecules produced by the local cells will result in scarring and structural changes. Therefore, by targeting the inflammatory response, the belief was that fibrosis could be prevented or limited. This theory explained the large use of anti-inflammatory therapy. However, despite extensive efforts, no available therapy aimed at reducing the inflammatory process has been shown to reverse the course of the disorder. This has progressively led to question the importance of the role of inflammatory mechanisms in the pathogenesis of the disease, and the hallmark of lung fibrosis being inflammation is no longer sustained.

Based on clinical and experimental observations, a new paradigm has progressively emerged with the alveolar epithelium being viewed as a key actor in the development of ILD (Ley and Zarbock, 2008; Studer and Kaminski, 2007; Thannickal et al., 2004). Following injury, alveolar epithelial cells (AEC) may actively participate in the restoration of a normal alveolar architecture through a coordinated process of re-epithelialization, or in the development of fibrosis through a process known as epithelial–mesenchymal transition (EMT; Thiery and Sleeman, 2006). Complex networks orchestrate EMT leading to complex changes in cell architecture and behaviour, loss of epithelial characteristics and gain of mesenchymal properties. EMT has an important role in the development of many tissues during embryogenesis, but similar cell changes are recapitulated during pathological processes such as fibrosis (Lee et al., 2006). In the lung, AEC themselves may serve as a source of fibroblasts and myofibroblasts by acquiring a mesenchymal phenotype (Henson, 2003; Horowitz and Thannickal, 2006a,b). This article reviews recent advances in the understanding of the mechanisms supporting a central role of the alveolar epithelium in the development of chronic ILD and fibrosis, with a main focus on the apoptotic pathway, the endoplasmic reticulum (ER) stress response, and the developmental pathway. In addition, possible links with conformational diseases are discussed.

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2. Central role of alveolar epithelium in the pathogenesis of ILD

2.1. Altered repair of the alveolar epithelium

Recently, much interest has been focused on the alveolar structure with the marked disruption in the integrity of the epithelium observed during the course of the disease (Selman and Pardo, 2006). The alveolar epithelium consists of type I and type II alveolar epithelial cells (AECIs and AECIIs) which occupy about 96% and 4% respectively of the surface, although they are present in similar numbers. AECIs are membranous cells usually found overlying the capillaries and are very sensitive to injury. The AECIIs are large cuboidal cells located in the alveolar corners. From numerous studies, the role of AECIIs in the process of repair of the disrupted surface appears critical. Indeed, in contrast to AECIs, AECIIs have the ability to re-enter the cell cycle and to divide (Uhal, 1997). AECIIs are now considered as multipotent cells with high plasticity and are believed to serve as the progenitors of the alveolar epithelium, being capable of both self-renewal and of giving rise to AECIs through a process of transdifferentiation (Adamson and Bowden, 1974a,b). The first step includes the transition of post-proliferative AECIIs to intermediate cells. These cells may lack lamellar bodies characteristic of AECIIs and often have a modified cuboidal shape with short, attenuated cellular extensions suggestive of AECIs. They continue changing their shape by further flattening, by dramatically increasing their total cell volume and surface area, and by relocating the cell nucleus to a central location some distance away from that of the parent AECIIs. These cells increasingly express all available AECI phenotypic markers. Experimental conditions have also been developed that induce cells that have acquired AECIIs characteristics to revert to an AECI phenotype, confirming the remarkable plasticity of the differentiated AEC. The endogenous triggers of type II cell division likely include keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF, scatter factor). The proliferative response quickly generates a large number of AECIIs, thus repairing the epithelial barrier, but also thickening the gas exchange surface. Reconstitution of the normal alveolar epithelium requires removal of the excess hyperplastic AECIIs by apoptosis. The non-excess post-proliferative AECIIs differentiate into AECIs allowing to restore a normal tissue architecture.

The reasons for epithelial cell loss and inappropriate re-epithelialization are still debated, but ongoing apoptosis is believed to be a key component in the progression of the disorder (Fattman, 2008). A common feature of cells undergoing apoptosis is cell surface expression of phosphatidylserine, a molecule normally present on the inner part of the plasma membrane (Fadok and Henson, 2003). Recognition of phosphatidylserine by specific receptors on neighboring cells is associated with the production of several anti-inflammatory molecules including transforming growth factor (TGF)-β. TGF-β is thought to play an important role by allowing apoptotic cells to be cleared with minimal local reaction. In normal situations, the progressive diminution of apoptotic cells results in a decreasing supply of TGF-β. TGF-β has been shown to be overexpressed in fibrotic lung disorders. One explanation for this well-documented increased production of TGF-β involves up-regulation of the phosphatidylserine receptors through an altered balance of the release of proteases and anti-proteases. A consequence would be the perpetuation of a vicious cycle with TGF-β promoting epithelial cell apoptosis, which in turn increases the local production of TGF-β (Koli et al., 2008). Of importance is the fact that AEC apoptosis is detected adjacent to myofibroblast-containing fibroblastic foci, the presumed primary sites of epithelial injury in lung fibrosis.

2.2. Epithelial cell plasticity and epithelial–mesenchymal transition

A dysregulated communication between mesenchymal and epithelial pulmonary components after tissue injury is thought to play a key role in tissue remodeling. Prolonged denudation of the basement membrane may contribute to altered interactions and cross-talk between alveolar epithelial cells and mesenchymal cells, resulting in profound modifications of cell functions with imbalanced production of polypeptide mediators including cytokines, growth factors, oxidants, and proteases (Huber et al., 2005). The local population of fibroblasts and myofibroblasts progressively increases due to stimulation of proliferation by local mitogenic factors and reduction of apoptosis. This may lead to progressive aberrant tissue remodeling by disorganisation of extracellular matrix component deposition, including fibrillar collagen, elastic fibres, fibronectin and proteoglycans. In addition, the abnormal lung architecture appears to be associated with the formation of new blood vessels. This process requires the secretion of angiogenic molecules to promote endothelial cell migration and neovascularisation.

Histopathological analyses of fibrotic lungs have repeatedly documented the presence of fibroblastic/myofibroblastic foci. At the present time, the origin of the myofibroblast is not clearly established. Three potential sources are discussed (Kim et al., 2006). Until recently, conversion of resident fibroblasts and differentiation of circulating bone marrow–derived progenitors were the mechanisms mainly proposed. A new source is currently considered, which is the contribution of AEC (Strieter, 2008; Thiery and Sleeman, 2006). Indeed, due to their high plasticity, AEC can convert to mesenchymal cells by EMT. During this process, epithelial cells loose polarity and epithelial-specific markers, Molecular changes include dissolution of epithelial tight junctions, reorganisation of the actin cytoskeleton, loss of apical–basal polarity, induction of a mesenchymal gene-expression program and migration through basement membrane and tissues. The process of EMT is not restricted to the lung. It has been extensively investigated as a mechanism underlying fibrosis in a number of organs such as kidney. Early after injury during kidney fibrosis in transgenic mice, renal tubular epithelial cells migrate through damaged basement membrane into the interstitium, and transdifferentiate into fibroblasts and myofibroblasts. In this situation, it has been reported that almost one-third of the new fibroblasts come from EMT of the local epithelium (Selman et al., 2008).

Emergence of the myofibroblast phenotypes is regulated by a variety of factors. In response to injury, alveolar epithelial cells and inflammatory cells release and activate a number of cytokines and growth factors involved in fibroblast migration, proliferation and change to myofibroblasts, leading to accumulation and remodeling of the extracellular matrix. These factors include TGF-β, endothelin-1 (ET-1), KGF, HGF, connective tissue growth factor (CTGF, CCN2), insulin-like growth factor (IGF), and pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α and interleukin (IL)-1 (Huber et al., 2005; Kasai et al., 2005; Kim and Chapman, 2007; Shukla et al., 2008). Recently, the role of these molecules, in myofibroblast phenotype regulation has been reviewed (Ask et al., 2006; Scotton and Chambers, 2007).

TGF-β is thought to play a major role, in part by its capacity to promote myofibroblast survival and persistence (Willis and Borok, 2007). That pathologic fibrosis is mediated by TGF-β is supported by several findings including the following observations: Tissue damage increases TGF-β production before the production of extra-cellular matrix increases; TGF-β is a potent stimulator of the production and deposition of extra-cellular matrix; TGF-β induces fibrosis independently of tissue damage; inhibitors of TGF-β receptor binding reduce or abolish fibrosis (Aluwihare and