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Research paper

Lung extracellular matrix and redox regulation

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ABSTRACT

Pulmonary fibrosis affects millions worldwide and, even though there has been a significant investment in understanding the processes involved in wound healing and maladaptive repair, a complete understanding of the mechanisms responsible for lung fibrogenesis eludes us, and interventions capable of reversing or halting disease progression are not available. Pulmonary fibrosis is characterized by the excessive expression and uncontrolled deposition of extracellular matrix (ECM) proteins resulting in erosion of the tissue structure. Initially considered an 'end-stage' process elicited after injury, these events are now considered pathogenic and are believed to contribute to the course of the disease. By interacting with integrins capable of signal transduction and by influencing tissue mechanics, ECM proteins modulate processes ranging from cell adhesion and migration to differentiation and growth factor expression. In doing so, ECM proteins help orchestrate complex developmental processes and maintain tissue homeostasis. However, poorly controlled deposition of ECM proteins promotes inflammation, fibroproliferation, and aberrant differentiation of cells, and has been implicated in the pathogenesis of pulmonary fibrosis, atherosclerosis and cancer. Considering their vital functions, ECM proteins are the target of investigation, and oxidation–reduction (redox) reactions have emerged as important regulators of the ECM. Oxidative stress invariably accompanies lung disease and promotes ECM expression directly or through the overproduction of pro-fibrotic growth factors, while affecting integrin binding and activation. In vitro and in vivo investigations point to redox reactions as targets for intervention in pulmonary fibrosis and related disorders, but studies in humans have been disappointing probably due to the narrow impact of the interventions tested, and our poor understanding of the factors that regulate these complex reactions. This review is not meant to provide a comprehensive review of this field, but rather to highlight what has been learned and to raise interest in this area in need of much attention.

1. Introduction

Lung fibrosis is characterized by, among other things, the effacement of the original architecture of the lung due to excessive expression and deposition of the extracellular matrix (ECM) [1]. In normal lungs, this acellular substance is a complex admixture of glycoproteins, collagens, and polysaccharides neatly assembled so as to maintain tissue integrity and to separate epidermal and mesenchymal cell layers in tissues [2]. In injured lungs, however, inflammation, oxidative stress, and other events drive the expression and turnover of ECM proteins. In most cases, this process is regulated and is inhibited once the injuring agent is eliminated. Yet, on occasion, this process remains activated leading to thickening of the interstitium followed by permanent obliterations of the alveolar spaces and loss of lung function [3] (Fig. 1). These events underlie fibrosing lung disorders affecting millions worldwide.

Cells differ in their capacity for producing, secreting, and assembling ECM, and its composition differs amongst organs and between organ compartments. The ECM was initially considered to be an inert substance providing scaffold for the adhesion of cells and for their organization into complex organs. In the early 1980s, however, a better appreciation of the true role of the ECM began to emerge with the discovery of a family of cell surface adhesion receptors termed integrins [4]. Integrin activation by ligand binding to ECM proteins triggers diverse intracellular signals capable of influencing gene expression [5]. This early work laid the foundation for our current understanding that cell functions are greatly influenced by the composition of their surrounding ECM

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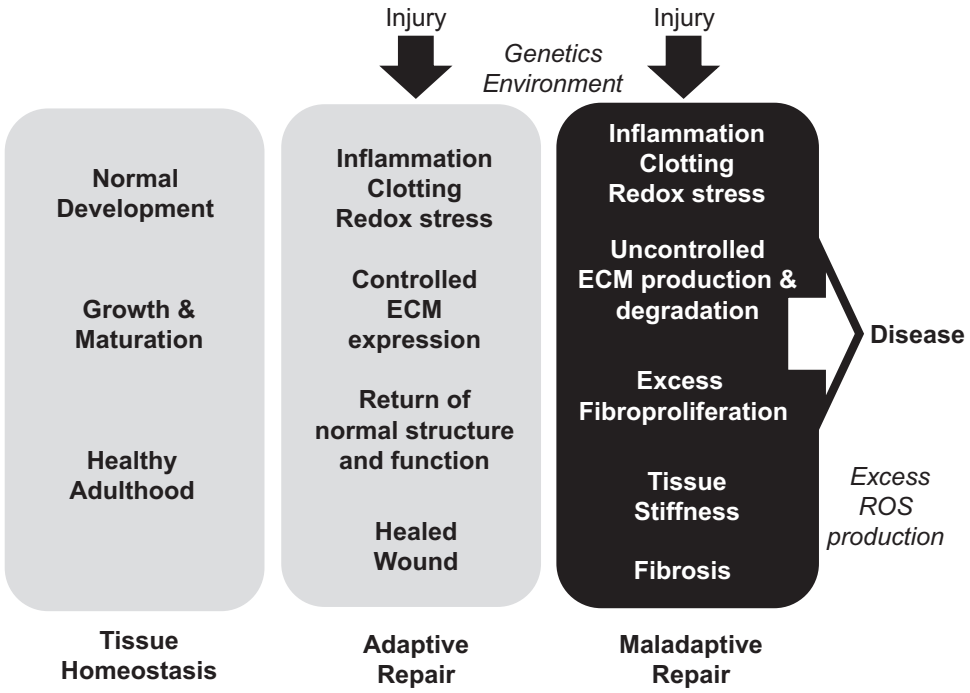

Fig. 1. Development, tissue homeostasis, and response to injury are dependent on ECM expression and deposition. ECM expression and turnover are tightly controlled during organ development and during adulthood. Tissue injury triggers inflammation, clotting, redox stress, and regulated expression and degradation of the ECM. In general, elimination of the injurious agents is followed by 'turning off' this wound healing response resulting in inhibition of ECM expression and, ultimately, a return to the original tissue structure and function (Adaptive Repair). However, on occasion, injury triggers an exuberant response characterized by uncontrolled ECM expression and turnover leading to increased stiffness of the tissue and eradication of the original tissue architecture leading to loss of function (Maladaptive Repair). These events are greatly influenced by genetics and environmental exposures. Uncontrolled generation of reactive oxidant species (ROS) is thought to contribute to maladaptive repair, in part, by promoting aberrant ECM expression and fibroproliferation.

and by the repertoire of matrix-binding integrins expressed on their surface. Moreover, ECM proteins are the main contributors to tissue stiffness, which also influences cell behavior [6].

It is well documented that ECM proteins play roles in regulating important cell functions such as adhesion, migration, and differentiation as well as in complex processes like tissue morphogenesis and wound healing [7,8]. However, the exact roles ECM proteins play in cellular and tissue homeostasis in human health and disease remain incompletely elucidated mainly because in vitro models fail to reflect the complex nature of in vivo ECM, because genetically-engineered animals with knockout mutations of genes coding for ECM and matrix-binding integrin receptors are often embryonic lethal [9], and because of the complex, robust and insoluble nature of assembled ECM which makes their study arduous even in the most experienced hands [10]. However, these challenges are being partially overcome by the emergence of new experimental models (e.g., organ decellularization) and novel approaches to genetic targeting of proteins [11]. Together, these technologies have helped generate data about the lung 'matrisome', thereby adding to the overwhelming literature available in support of the role of ECM proteins in embryogenesis and tissue homeostasis after birth, as well as in the development of disorders ranging from atherosclerosis and kidney disease to rheumatoid arthritis and cancer [8,12,13].

In lung, ECM proteins have been implicated in lung branching morphogenesis, vasculogenesis, and alveolar maturation during development, as well as in tissue repair after injury [14,15]. However, ECM proteins have also implicated in pathologic processes leading to acute and chronic pulmonary disorders such as asthma, acute lung injury, and idiopathic pulmonary fibrosis (IPF) [16–18]. Considering the above, and the fact that essentially all pulmonary disorders are associated with alterations in the expression, deposition and turnover of ECM proteins, it is no surprise that understanding the factors that regulate ECM-dependent events in lung has remained a focus of attention for over two decades.

Oxidants and redox reactions have been found to influence ECM expression and turnover, and these appear to be important physiological processes relevant to health, but also to diseased states such as lung fibrogenesis [19]. Patients with fibrosing lung disorders manifest evidence of oxidative stress [20–23], which triggers intracellular signals that stimulate fibroproliferation and the expression of pro-fibrotic factors [24], while interventions targeting the oxidant-anti-oxidant balance ameliorate progression of fibrosis in animal models of lung injury [25,26]. Together, these observations strongly implicate oxidative stress in the pathogenesis of fibrosing lung disorders, and even though its role as a target for intervention in lung fibrosis remains controversial [27], the exploration of redox as an important modulator of ECM production, modification, function, and recognition by cells is justified. Excellent reviews have been published addressing aspects of this area of investigation [28–30]. Thus, we will focus on the impact of redox reactions on the lung ECM considering that this organ is exposed to higher levels of oxygen than other tissues. A description of the lung ECM and its functions in lung development and in injury and repair will be followed by a discussion of redox reactions considered to influence these events. Finally, information will be provided that provide strong evidence supporting the concept that ECM protein expression, turnover and recognition are redox-dependent events.

2. Role of lung ECM

The importance of ECM proteins in multicellular organisms is highlighted by their function as a multi-dimensional structural