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Review Article

Redox-fibrosis: Impact of TGFβ1 on ROS generators, mediators and functional consequences

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ABSTRACT

Fibrosis is one of the most prevalent features of age-related diseases like obesity, diabetes, non-alcoholic fatty liver disease, chronic kidney disease, or cardiomyopathy and affects millions of people in all countries. Although the understanding about the pathophysiology of fibrosis has improved a lot during the recent years, a number of mechanisms still remain unknown. Although TGF-β1 signaling, loss of metabolic homeostasis and chronic low-grade inflammation appear to play important roles in the pathogenesis of fibrosis, recent evidence indicates that oxidative stress and the antioxidant system may also be crucial for fibrosis development and persistence. These findings point to a concept of a redox-fibrosis where the cellular oxidant and antioxidant system could be potential therapeutic targets. The current review aims to summarize the existing links between TGF-β1 signaling, generation and action of reactive oxygen species, expression of antioxidative enzymes, and functional consequences including epigenetic redox-mediated responses during fibrosis.

Contents

1. Introduction

Fibrosis is a major health problem and considered to be one of the most prevalent features of age-related diseases affecting millions of people in all countries. It can be considered to be a non-

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physiological scarring process in response to chronic diseases where an excessive extracellular matrix (ECM) deposition leads to irreversible tissue damage and failure or disturbance of proper organ function. Fibrosis has been found to affect all major organs and tissues including lungs, kidney, liver, heart, and skin. Moreover, the stroma of solid tumors can be considered to be partially fibrotic [1–4]. The pathophysiology of fibrosis has generally been studied in the context of the particular organ or tissue affected. However, recent research on the underlying molecular mechanisms provided evidence that common aspects for initiation and progression of fibrosis appear to exist in each of the affected organs/tissues. In particular, loss of metabolic homeostasis and chronic low-grade inflammation appear to play new emerging roles in the pathogenesis of fibrosis. Recent evidence indicated that oxidative stress, a condition where the balance between formation of reactive oxygen species (ROS) and their degradation by the antioxidant system is shifted in favor of a pro-oxidant state, appears to link metabolic homeostasis and inflammation thereby underpinning the concept of common fibrosis pathways that could be potential therapeutic targets. The current review aims to summarize the role of ROS and especially the anti-oxidative enzymes in fibrosis.

2. Fibrosis: common features and aspects

Fibrogenesis is a dynamic process and was proposed to occur in all organs in four common phases: i) initiation, due to injury of the organ/tissue; ii) inflammation and activation of effector cells, iii) enhanced synthesis of ECM; and iv) deposition of ECM with progression to end-organ failure [4]. The common aspects of a fibrotic pathogenesis can also be "visualized" because the same macroscopic and microscopic features are shared between the fibrotic organs. Macroscopically fibrotic organs usually display an uneven surface, are non-elastic, hard, and pale; signs resulting from accumulated ECM, contracted fibroblasts and reduced vasculature. Microscopically clear signs of an injured parenchyma, excess appearances of fibroblasts and fibrillar ECM, lack of capillaries (i.e. microvasculature), and a mononuclear infiltrate can be visualized [3]. Although there are obvious common elements in the fibrotic developments between organs, it appears that there are also some differences, which account for some organ specific aspects which become visible during the disease.

3. Fibroblasts: key players during fibrosis

The name fibrosis is based on the very well and long-term known observation that fibroblasts are the major source of the ECM; in fibrosis fibroblasts are called "activated fibroblasts" or "myofibroblasts" due to their increased synthetic capacity. Although the name "activated fibroblasts" may also imply a higher proliferative capacity, they are in fact less proliferative but more metabolically active in particular in ECM production [5]. Moreover, fibroblasts are not homogenous; they were found to be heterogenous within single organs and also between organs [6]. The heterogeneity may result, at least in part, from different cells and modes used for fibroblast recruitment/activation. While the most common view considers that activated fibroblasts derive via proliferation from tissue resident fibroblasts, various studies have shown that bone marrow-derived fibrocytes [7], endothelial cells that have undergone endothelial-to-mesenchymal transition [8], vascular smooth muscle cells and pericytes shed off from vessels [9,10], and epithelial cells after epithelial-to-mesenchymal transition [11] are also able to contribute to ECM deposition and fibrosis (Fig. 1). This makes the molecular analysis of fibroblasts particularly challenging, and though α-smooth muscle actin, vimentin, fibroblast-specific protein 1, or desmin are used to identify fibroblasts, it may explain why a specific common marker for all fibroblasts has not been found yet (for review see [3] and [12]). Moreover, processes like aging also affect the fibroblast protein expression profiles [13] which further complicates the molecular analyses of fibroblasts.

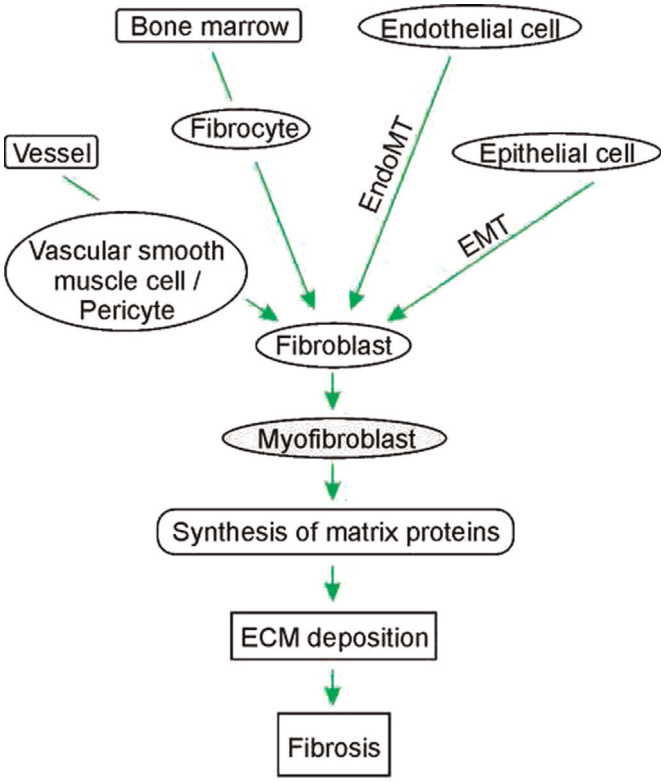

Fig. 1. *Fibroblasts as major extracellular matrix (ECM) producers*. Fibroblasts can be derived from different cells like vascular smooth muscle cells, pericytes, fibrocytes, endo-and epithelial cells or resident fibroblasts. Depending on their origin these cells undergo differentiation, poliferation, epithelial-to-mesenchymal transition (EMT) or endothlial-to-mesenchymal transition (EndoMT). The so emerged myofibroblasts show an increased synthesis of matrix proteins contributing to excessive ECM deposition and fibrosis.

4. Fibrosis, tissue injury and inflammation

Commonly the regenerative capacity of parenchymal cells is able to cope with the loss of parenchyma occurring during single tissue injury events. However, this regenerative ability is lost upon repeated injury with the consequence of deregulated wound healing and a chronic activation of the immune response with appearing inflammation. Although fibrosis and its associated inflammation can be caused by infectious agents (e.g. viral infection of the liver or bacterial infections of lungs and kidneys), in most cases no underlying infection could be determined. This indicates that the inflammation is due to other not yet fully understood mechanisms, likely involving cell death responses [14,15]. Interestingly, anti-inflammatory therapies are rather ineffective in the treatment of fibrosis suggesting a complex interplay between the fibroproliferative process and the inflammatory response where pro- and retrograde cellular crosstalk of parenchymal cells, fibroblasts, and immune cells needs to be differently considered (for review see [16–18]).