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Review Article

Role of redoximiRs in fibrogenesis

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ABSTRACT

Fibrosis can be defined as an excessive accumulation of extracellular matrix (ECM) components, ultimately leading to stiffness, scarring and devitalized tissue. MicroRNAs (miRNAs) are short, 19–25 nucleotides (nt), non-coding RNAs involved in the post-transcriptional regulation of gene expression. Recently, miRNAs have also emerged as powerful regulators of fibrotic processes and have been termed "fibromiRs". Oxidative stress represents a self-perpetuating mechanism in fibrogenesis. MiRNAs can also influence the expression of genes responsible for the generation of reactive oxygen species (ROS) and antioxidant defence and are termed "redoximiRs". Here, we review the current knowledge of mechanisms by which "redoximiRs" regulate fibrogenesis. This new set of miRNAs may be called "redoxifibromiRs".

Contents

1. Fibrosis

Fibrosis is the final common pathological feature of most chronic inflammatory diseases. In some diseases, such as idiopathic pulmonary fibrosis (IPF), liver cirrhosis, cardiovascular fibrosis, systemic sclerosis and nephrosclerosis, extensive tissue remodeling and fibrosis can ultimately lead to permanent scarring organ failure and death [1]. Fibrosis results when a normal wound-healing response persists or becomes dysregulated, usually in response to a severe or repetitive injury [2]. Regardless of their distinct etiology and clinical features, chronic fibrotic disorders share the portfolio of growth factors, proteolytic enzymes, angiogenic factors and fibrogenic cytokines that stimulate the excessive production, deposition and contraction of ECM components, such as hyaluronic acid, fibronectin (FN), proteoglycans and interstitial collagens that progressively remodel and damage the normal tissue architecture [3]. Transforming growth factor-β (TGF-β) is considered to be the most potent and ubiquitous pro-fibrogenic cytokine [4,5]. TGF-β and local mechanical forces, produced by infiltrated macrophages or resident cells,

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together with the ectodomain A (ED-A) sequence of FN stimulate the activation of alpha-smooth muscle actin (α-SMA)-expressing and ECM-producing myofibroblasts, which are the key mediators of fibrotic tissue remodeling and ECM assembly [6,7]. The persistent activation of myofibroblasts leads to an excessive accumulation of ECM components that progressively distorts normal tissue architecture [2]. The origin of myofibroblasts has been a controversial subject in recent years because they differentiate from various precursor cells that differ according to the nature of the insult and the affected organ [8]. Thus, although activation of local tissue fibroblasts is thought to be the primary instigator of ECM production following injury in many organs [8,9], epithelial and endothelial cells [10–13], hepatic stellate cells [14,15], pericytes [16], smooth muscle cells [17,18] and bone marrow-derived cells [19–21] have been shown to differentiate into pro-fibrotic myofibroblasts during fibrosis development. Whilst myofibroblasts are the primary drivers of fibrosis, it is becoming increasingly clear that various monocyte-derived cell populations can control the fibrotic process by exerting direct effects on matrix remodeling and regulating activated myofibroblasts [22].

Although it is well established that TGF-β and myofibroblasts play central roles in the development of fibrosis, no effective therapy is yet available to revert the evolution of this group of severe connective tissue disorders.

2. Oxidative stress and fibrosis

Oxidative stress as a concept in redox biology and medicine was formally defined in 1985 by Helmut Sies [23] and it is currently known as an unbalance between the generation of ROS or reactive nitrogen species (RNS) and the capacity of cells and tissues to detoxify or scavenge them [24]. Mitochondria electron-transport chain (ETC), membrane-bound NADPH oxidases (NOXs) and endoplasmic reticulum (ER) are the three major intracellular sources of ROS [25]. ROS-derived NOXs are particularly interesting in fibrogenesis, as described in the following sections. Glutathione (GSH) is considered the most abundant molecule among endogenous anti-oxidants [26]. GSH contributes to detoxify deleterious metabolites maintaining redox homeostasis by preserving redox potential and facilitating redox signaling [26]. The nuclear factor-erythroid 2 related factor 2 (Nrf2) pathway is the major regulator of cyto-protective responses to oxidative stress by regulating the expression of several enzymes involved in the anti-oxidant response such as NOX:quinoneoxidoreductase1 (NQO1), glutathione S-transferase (GSTs), cysteine–glutamate exchange transporter and multidrug resistance associated protein [27,28]. ROS, generally through the action of its quintessential signaling arm, hydrogen peroxide (H_2O_2), have a role in various signaling cascades, such as in the response to growth factor stimulation and control of inflammatory responses [29]. They participate in the regulation of many cellular processes, including differentiation, proliferation, growth, apoptosis, cytoskeletal regulation, migration, and contraction [30]. ROS have crucial roles in critical physiological processes [31], including the intracellular killing of bacteria by neutrophil granulocytes [29], detoxification by the liver [32], thyroid hormone production [33] and crosslinking of ECM [34]. Despite its important role in physiological signaling, excessive amounts of ROS cause direct cellular injury by inducing lipid and protein peroxidation and damaging nucleic acids [35–37]. ROS contribute to a wide range of pathologies including cancer, cardiovascular diseases, neurological disorders, chronic inflammation and autoimmune diseases [33]. Although many of the important pathogenetic mechanisms that promote fibrosis have been identified in the last decades, the precise molecular mechanisms involved are not fully understood. There is a substantial and growing body of evidences indicating the involvement of oxidative stress in the development of fibrosis in multiple organs.

2.1. Oxidative stress in pulmonary fibrosis

Pulmonary fibrosis is a lung disease that includes a heterogeneous group of lung disorders characterized by the progressive and irreversible destruction of lung architecture caused by scar formation that ultimately leads to death from respiratory failure [1]. Among the fibrotic lung diseases, IPF, with unknown etiology, is the more common and severe form. Lung fibrosis can also develop after viral infections and after exposure to radiotherapy, chemotherapeutic drugs and environmental toxins [38–41]. There are some evidences showing that ROS play an important role in the development of pulmonary fibrotic diseases. Oxidized proteins and lipid products have been identified in exhaled air, bronchoalveolar lavage fluid and lung tissues from patients with fibrotic lung diseases. Importantly, increased ROS and oxidative stress markers are detected in patients with IPF [42,43] and levels of ROS negatively correlate with pulmonary function in IPF and may predict disease severity [44]. An increase in oxidative DNA damage has been also detected in patients with silicosis and asbestosis [45]. The mouse model of bleomycin-induced pulmonary fibrosis, the most commonly used experimental model, is associated with a marked increase in ROS levels and in oxidized proteins, DNA and lipids [46]. In this experimental model the treatment with anti-oxidants attenuates fibrosis [47–49], suggesting a possible key role of oxidative stress in the development of this pathology. TGF-β isoforms are secreted in an inactive, latent form bound to a latency association protein (LAP). It has been proposed that ROS can increase the TGF-β-induced fibrosis by activating latent TGF-β in asbestos-induced fibrosis [50] and by increasing the gene expression and secretion of TGF-β in many cell types including alveolar epithelial cells (AECs) and macrophages [51]. ROS can also trigger the TGF-β1-induced ephitelial-to-mesenchymal transition (EMT), a process that results in a loss of epithelial markers and an acquisition of a mesenchymal phenotype in many fibrotic diseases, including IPF [52–54]. During EMT, epithelial cells lose their cell to cell junctions and the apical-basal polarity. EMT also enables cells to acquire invasive properties, thus degrading ECM and synthesizing new ECM components [55]. Several recent studies indicate that ROS production by NOXs plays a central role in the pathogenesis of pulmonary fibrosis and inflammation [47,56–59]. A recent study has found that TGF-β1 regulated the expression of NOX4, one of the major cellular ROS sources, thus generating oxidative stress [59]. Importantly, these NOX4-produced ROS are required for TGF-β1-induced myofibroblast differentiation, ECM production and contractility and genetic knock-down or pharmacologic inhibition of NOX4 prevented bleomycin-induced lung fibrosis in mice [59]. Moreover, NOX4 is up-regulated in lungs of mice treated with bleomycin and in patients with IPF [59], further highlighting the active role of ROS in the establishment and progression of pulmonary fibrosis. NOX4 is strongly expressed in the hyperplastic alveolar epithelium of patients with IPF, particularly in type 2 AECs. Death of AECs in pulmonary fibrosis is thought to be mediated, at least in part, by TGF-β1 and it constitutes a key initiating and perpetuating event in pulmonary fibrosis [60,61]. Studies in a NOX4 knock-down mouse support that NOX4-dependent ROS are critical for the induction of AECs death by apoptosis and the subsequent development of lung fibrosis, thus confirming an important role of NOX4 induction in the pathogenesis of tissue fibrosis [60].