MECHANISM OF FIBROSIS AND THEIR ROLE IN TGF-β

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DOI: http://dx.doi.org/10.24327/ijrsr.2020.1105.5351

ABSTRACT

Fibrosis is an excessive accumulation of fibrous connective tissue. It is a pathological feature of most chronic inflammatory diseases. Every tissue in the body can be affected by fibrosis. If the fibrosis is highly progressive, it leads to organ failure and death. The alternate of regular structural elements of the tissue with extreme growth of scar tissue comprised of distorted collagens. Cellular and immunological changes occur along with age related tissue remodelling. In mechanical properties of ECM (Extra cellular matrix), the Mechanotransduction pathways impact such critical cellular functions as proliferation, differentiation, and migration. Those ECM properties were sensed by integrins. Preclinical studies with the mechanotransduction inhibitors in TGF Pathway have shown a variety of different tumor models. TGF- β pathways is upregulated and activated in fibrotic diseases and modulate the phenotype of fibroblast and its function. While promoting the matrix preservation induces myofibroblast trans differentiation. This review summarizes the role of TGF-β signaling pathways in the fibrosis.

INTRODUCTION

The excessive accumulation of connective fibrous tissue in and around inflamed or damaged tissue is called Fibrosis. The components of the extracellular matrix (ECM) such as collagen fibers, fibronectin etc., Fibrosis can leads to malfunction and permanent damaging of organ and leads to kidney and end-stage liver damage, heart failure and idiopathic pulmonary fibrosis (IPF) [1]. The major pathological feature of many chronic autoimmune diseases is Fibrosis, disease which includes rheumatoid arthritis, Crohn’s disease, ulcerative colitis, scleroderma, myelofibrosis and systemic lupus erythematosus. Tumor invasion, metastasis, chronic graft rejection and the pathogenesis are induced by the Fibrosis. In major chronic inflammatory diseases, fibrogenesis plays a major cause of mortality and illness. Few treatments are specifically target the pathogenesis of fibrosis (Wynn, T.A.2011).

Many parameters can involve to the development of fibrotic disease. Few parameters included irritants, toxins, smoke, autoimmune diseases, genetic diseases, infections, hypertension, diabetes, obesity, cholesterol, myocardial infarction and antigen mismatches in transplants [2]. Nevertheless of the introducing events, a main parameter common to all fibrotic diseases is the key intermediaries of fibrotic tissue remodeling, which is ECM-producing myofibroblasts activation. For example, the abnormal accumulation of ECM components and mainly collagen leads to chronic hypertension and left-ventricular hypertrophy [3].

Ageing

The loss of tissue or cellular function is considered as degenerative pathologies and leads to aging. The accumulation of extracellular matrix components leads to the overgrowth, hardening and scarring of various tissues is called Fibrosis. The common and most important factor for fibrotic heart and respiratory disease is aging. The interconnected biological processes and Age-related processes includes senescence, autophagy, inflammaging and mitochondrial dysfunction that reduce the regenerative capacity of the aged heart and lungs. Aging playsasessential role and acts as predisposing factor in cardiac fibrosis and idiopathic pulmonary fibrosis. Aging also leads to heart failure and fibrotic respiratory diseases such as idiopathic pulmonary fibrosis (IPF) [4]. The Structural remodeling of the ECM occurs followed by the aging of lung and cardiac tissue due to the alterations in the concentration and organization of ECM components includes collagen and elastin [5]. The main cause of biological aging occurred by the damage and stress that occurs during a lifetime [6]. The premature aging of the pulmonary system is exposed to

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challenges by airborne pollutants and pathogens [7]. The factors which reduce the regenerative capacity of the aged lungs and heart are involved in processes like inflammaging, autophagy, mitochondrial dysfunction and Senescence, and leads to cardiac fibrosis [8].

Role of ECM in fibrosis

Fibrosis acts as one of the most difficult problems in modern medicine [9]. Most network has been showed by implications from the advanced knowledge about fibrosis that follows a distinct injury [10]. The initiation of disease occurs by the activation of TGF-β pathway involves parenchymal cell injury [11]. This line of activation extends to give more information about the molecular mechanisms leading to parenchymal cell attrition and fibro proliferation [12]. Simultaneously, Fibrosis initiation and progression involves both cell autonomous and ECM driven mechanisms [13]. In studies, cell autonomous fibrogeniccy are studied using primary mesenchymal cells from fibrotic tissue and organs [14] and confirmed in zebrafish and mouse xenograft models [15], and also proved in mouse lineage tracing studies [16]. The complete proof in humans can be provided by the discovery of fibrogenic mesenchymal progenitor cells (MPCs) in the lungs of patients with IPF [17].

Fibrosis progression gives a platform for established the role of individual ECM components and fragments for several years. Fragments of fibronectin, fibrin, and hyaluronan are all theoretically fibrogenic [18]. Using decellu
eralized lung ECM from patients with IPF, more recent research have delivered new understandings into ECM-mediated positive-feedbac

Wound healing versus fibrosis

The inflammatory mediators are released by the damaged epithelial or endothelial cells and leads to the initiation of anti-fibroin
lyotic coagulation cascade [23]. It also triggers the formation of blood-clot and ECM. ECM components, triggering, aggregation, haemostosis and clot formation are exposed by platelets. Vasodilation and improved blood vessel permeability can be promoted by platelet degranulation, while MMPs can be produced by epithelial or endothelial cells and myofibroblasts includes activated collagen secreting, α-SMA+ fibroblasts etc., which disrupt the basement membrane and leads the inflammatory cells to be easily enlisted to the injury site. The proliferation of leukocytes across the provisional ECM can be stimulated by the cytokines, chemokines and growth factors production. Tissue debris and dead cells can be eliminated by the macrophages and neutrophils [24]. Cytokines and chemokines are also produced. They are mitogenic and chemotactic for endothelial cells, which originate to surrou

mechanism of TGF in fibrosis

Transforming growth factor (TGF-β) has a wide range of pathological and physiological effects [26]. Further, it provides differentiation, cell proliferation, migration and tissues- and organ-specific immune responses [27]. The progression of fibrotic and inflammatory diseases can be associated by the TGF-β levels. The inflammatory disease includes diabetic nephropathy, cancers, cardiovascular diseases, autoimmune diseases, and neurodegenerative diseases [28]. Therefore, the important therapeutic target is TGF-β. In association with the dysregulated TGF-β signaling, many approaches have used to inhibit TGF-β signalling. The extracellular complex and space can be secreted by TGF-β are called the large latent complex (LLC) [29]. It mainly comprises of TGF-β-binding protein and latency associated peptide (LAP) [30]. TGF-β is inhibited by LLC and binding to its cognate receptors includes TGF-β receptor type-1 and 2 (TGF-βR1 and TGF-βR2). TGF-β is active, when it is dissociated by the LLC. Proteases, integrins, or physical stresses such as high temperature, low pH, and oxidation are activated by TGF-β [31]. Between many TGF-β activators, integrins are definite to the surrounding environment. All nucleated cells in tissues can be expressed by Integrins. By the binding of ligands on cell surface and ECM or binding to soluble glycoproteins mediates integrins [32]. All pathogenic processes can be involved by the expression or activation of integrins, leads to creation of this phenomenon a therapeutic target. Exactly, integrin is abundant in tumor cells and expressed in endothelial cells and epithelial cells. Under pathologic conditions such as cancer and fibrosis, its expression is high in tumor angiogenic blood vessels and injured epithelial cells [33] while the expression levels of different integrins differ in organ and tissue-specific manners [34].

The cell types as an inactive latent complex consists of C-terminal mature and an N-terminal latency-associated peptide (LAP) produces TGF-β and this complex is unable to combine with its receptors. LAP is secreted by the cell of a plasma membrane-bound furinconvertase, which cleaves TGF-β [35]. The Small Latent Complex (SLC) can be formed by the attachment of TGF-β to LAP after cleavage. The complex of Latent TGF-β Binding Protein (LTBP) can be bound by disulfide bonds, leads to the formation of a larger complex called Large Latent Complex (LLC). The extracellular matrix (ECM) components such as elastin fibrils and per cellular fibers can be bound and secreted by LLC in connective tissue [36]. The mature TGF-β is attached to the binding proteins and protects its active epitopes, leads to the prevention of interactions with the TGF-β receptors. The specific amounts of latent TGF-β are stored in the matrix for most of the tissues. The conversion of latent TGF-β to active TGF-β regulates the activation of TGF-β signaling. Maximal cellular response can be generated by the activation of small fraction of TGF-β and due to high between TGF-β and its receptors [37]. The LLC are
liberated from the matrix to activate and function the TGF-β at neighboring cells. Several proteases release LLC from ECM, which includes mast-cell chymase, plasmin and thrombin [38]. The disruption of the noncovalent bonds attaching it to the LAP can require the release of TGF-β.

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How to cite this article:


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