Decoding fibrosis: Mechanisms and translational aspects

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Abstract

Fibrosis, a complex process of abnormal tissue healing which inevitably leads to loss of physiological organ structure and function, is a worldwide leading cause of death. Despite a large body of research over the last two decades, antifibrotic approaches are mainly limited to organ replacement therapy generating high costs of medical care. In this translational issue, a unique group of basic and clinical researchers provide meaningful answers to a desperate call of society for effective antifibrotic treatments. Fortunately, a plethora of novel fibrogenic factors and biomarkers has been identified. Noninvasive diagnostic methods and drug delivery systems have been recently developed for the management of fibrosis. Consequently, a large number of exciting clinical trials addressing comprehensive, organ and stage-specific mechanisms of fibrogenesis are ongoing. By critically addressing previously unsuccessful and novel promising therapeutic strategies, we aim to spread hope for future treatments of the various forms of organ fibrosis.

Definition of fibrosis

The medical term “fibrosis”, created in the late nineteenth-century, originates from Latin “fibra” meaning fibre and the Greek/Latin suffix “osis” denoting a process or a pathological state.

Fibrosis is defined as a degenerative process of connective tissues with excessive accumulation of a collagen-rich extracellular matrix (ECM) characterized by abnormal crosslinking [1,2]. Following the initial injury, various tissues and organs such as the kidney, lungs, liver, cardiac and skeletal muscle, central nervous system, and pancreas undergo a dynamic process of wound healing resulting either in controlled tissue repair and regeneration or uncontrolled organ damage, further influenced by mesenchymal stem and stromal cells [3]. Fibrosis is also involved in certain diseases of the eyes [4], skin [5,6], joints, bone marrow, intestine, peritoneum and retroperitoneum [7]. Thus, fibrosis is a common response to a broad spectrum of injuries in various organs.

Rapid ECM accumulation underlies all fibrotic scar formation, which is essential for tissue repair by protecting against microbial invasion and reestablishing organ integrity. However, for proper tissue regeneration a large number of well-orchestrated steps and some fine-tuned crosstalk between cellular and extracellular compartments are required. In contrast, pathological wound healing is a prolonged and unresolved process resulting in organ fibrosis that replaces physiological structures and in the end causes organ failure [8,9]. Thus, it is becoming increasingly accepted that there are two sides of the same coin in fibrogenesis: tissue protection and organ damage.

Comprehensive mechanisms of fibrosis

Despite of a multitude of initial injuries, an uncontrolled production and activation of profibrotic cytokines, such as transforming growth factor-β (TGF-β) [10] and connective tissue growth factor

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(CTGF/CCN2) [11,12], ECM overproduction and stiffening [9,13,14], heterogeneous populations of myofibroblasts [15,16], various differentiation states of macrophages (M1) [17,18] and T cells (e.g. Th-1, Th-2, Th-17) [19,20], galectin-3 expression within nucleus pulposis cells [21] and chronification of inflammation are crucial pathways, driving organ deterioration in fibrosis. Furthermore, platelet-derived growth factor (PDGF) [22,23], angiotensin II [24,25], endothelin-1 [26], proinflammatory cytokines and chemokines [27,28], Wnt- [29–31], Notch- [32,33], reactive oxygen species (ROS)- [34–37], sphingolipid- [38,39], ECM-signaling (e.g. biglycan) [40–44], and respective receptors (e.g. integrins, several tyrosine kinase receptors, Toll-like receptors) [45–50], are important profibrotic factors and pathways. In addition, endoplasmic reticulum (ER) stress [51,52], senescence [53], apoptotic- [54,55] and authophagic-pathways [56,57] contribute to organ fibrosis. Subsequently, the interaction of these potent mechanisms results in extensive ECM accumulation, which in the end replaces and damages the physiological organ architecture.

Organ specific fibrosis

There is growing evidence that besides these general mechanisms of fibrogenesis, each organ responds differently to injury and develops unique features of fibrosis. Accordingly, the spontaneous repair of acute injury and fibrotic lesions, association of fibrosis with infection, and fibrosis-driven tumorigenesis differ in the kidney, lungs, liver and heart [58]. Furthermore, the list of organ specific genes including HAS2 in fibroblast senescence implicated in pulmonary fibrosis [59], proteins and their post-translational modifications, such as the extracellular citrullination of matrix associated TGF-β [60], involved in fibrogenesis is growing rapidly. This recent advance has been markedly accelerated by using multi-omics approaches (genomics, proteomics [61] or metabolomics) in the diagnosis and composition [62] of diseases associated with fibrosis. Recently, significant attention has been placed onto epigenetic gene regulation involving regulatory noncoding RNAs (e.g. microRNAs) and chromatin modifications such as DNA methylation and histone modifications [63–66].

The current special issue provides an extensive analysis of newly described comprehensive and organ-specific potential pharmacological targets (e.g. periostin, biglycan, porcupine, low density lipoprotein receptor-related protein (LRP1), lysyl oxidase-like-2 (LOX-like-2), miR-21, miR-208a, integrin α11β1, cartilage oligomeric matrix protein (COMP), a disintegrin and metalloproteinase (ADAM) 17, type I collagen synthesis, discoidin domain receptors (DDRs), which can stimulate collagen synthesis [67], fibroblast activation protein (FAP)) in fibrosis of the kidney, lung, liver, hart, skeletal muscles, central nervous system, and skin.

Concept of this special issue: translational aspects of fibrosis

Although the research on fibrosis, both basic and translational, has significantly enhanced our mechanistic understanding of both the triggers and reversibility of fibrogenesis, effective therapeutic strategies targeting fibrosis (e. g. pirfenidone and nintedanib in pulmonary fibrosis; tenofovir and entecavir in viral hepatitis B and C [68,69]) are still sparse. As fibrotic disorders are estimated to be the cause of at least 30% of deaths worldwide [7,70], there is still a huge unmet clinical need for antifibrotic therapeutic strategies.

Since the ECM plays a crucial role in the orchestration of fibrogenesis, the idea came up to publish a “Special Issue on Fibrosis” in *Matrix Biology*. Importantly, this is the first issue of the journal focusing on translational aspects. A consolidation of basic and clinical researchers undertook best efforts to present novel targets and biomarkers in fibrogenesis and to describe new noninvasive diagnostic methods [71] and drug delivery systems [72] useful in fibrotic conditions. Furthermore, new therapeutic antifibrotic strategies are introduced, e.g. to induce mitochondrial apoptosis with BH3 mimetics [73] or to enhance the intrinsic regenerative potential of tissues [74]. Possible explanations for poor outcomes of previous clinical trials in fibrosis are critically discussed. Finally, a fairly optimistic outlook for the future treatment of patients with fibrotic diseases is provided by referring to the numerous promising clinical trials undergoing at the moment.

In the chapter “Fibrosis: Comprehensive mechanisms and characterization methods” new strategies for neutralizing the profibrotic effects of TGF-β are proposed by blocking selected targets regarding the activation of TGF-β and its interaction pathways. By such approaches, the side effects of direct inhibition of TGF-β and its receptors might be avoided [75,76]. Molecular and biological characteristics of profibrotic CTGF and recent advances in its targeting in fibrosis are also addressed [77]. Wnt signaling is considered as a critical signaling cascade and therapeutic target in fibrosis [78]. This is followed by the description of “The Big Five” in fibrosis: Macrophages, myofibroblasts, matrix, mechanics and miscommunication together with the elegant concept of “The Good, the Bad and the Ugly” in fibrosis [79]. By manipulating apoptosis of myofibroblasts with BH3 mimetics, robust antifibrotic effects have been achieved across various organs [73]. Not only macrophages, but also pathways leading from tissue damage to inflammation and from inflammation to fibrosis are important determinants in long-term outcome [80]. The

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