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Review Article

The advancements of heparanase in fibrosis

Qianying Lv[1], Ji Zeng[2], Long He[2]

[1]*Department of Nephrology, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430016, People's Republic of China;* [2]*Department of Clinical Laboratory, Puai Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430033, People's Republic of China*

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Abstract: Fibrosis is the endpoint in many chronic inflammatory diseases and is defined as an abnormal accumulation of extracellular matrix components. Fibrosis can affect almost any tissue, especially heart, lung, liver, and kidney, and numerous studies have been conducted to find satisfactory treatments. Since heparanase is a kind of endo-β-D-glucuronidase that is capable of cleaving heparan sulfate side chains of heparan sulfate proteoglycans on cell surfaces and the extracellular matrix, which further regulate the bioavailability of growth factors (FGF-2, TGF-β). Meanwhile, FGF-2 and TGF-β play a major role in the fibrosis process. Recent studies including ours have consistently demonstrated that heparanase could promote fibrosis process in different organs. Thus in this mini-review, we updated the advancement of heparanase in the regulation of fibrosis generation, and discussed its impact on several critical signaling pathways relevant to fibrosis.

Keywords: Heparanase, hepatic fibrosis, lung fibrosis, renal fibrosis

Introduction

Fibrosis is a pathologic feature of disease in virtually all organs. It has protean and often lethal consequences and accounts for substantial morbidity and mortality. There are four major phases of the fibrogenic response. First is initiation of the response, driven by primary injury to the organ. The second phase is the activation of effector cells, and the third phase is the elaboration of extracellular matrix, both of which overlap with the fourth phase, during which the dynamic deposition (and insufficient resorption) of extracellular matrix promotes progression to fibrosis and ultimately to end-organ failure [1]. Fibroblasts and myofibroblasts responsible for the synthesis of extracellular matrix proteins have been identified as key fibrosis effectors in many organs [2]. Beyond the multiple cells essential in the wounding response, the transforming growth factor beta (TGF-β) pathway is also important in virtually all types of fibrosis [3].

Heparanase is an endo-β-D-glucuronidase that cleaves the beta-(1,4)-glycosidic bond between glucuronic acid and glucosamine residues in heparan sulfate proteogylans (HSPG); it is expressed by several cell types and tissues where it participates in extracellular matrix remodeling and degradation, and the regulation of the release of HS-bonded molecules from extracellular matrix storages, such as growth factors, chemokines, cytokines, and enzymes involved in inflammation, wound healing and tumor invasion [4-6].

We and other previous literature support that heparanase is needed for pathological TGF-β over-expression in response to pro-fibrotic factors and heparanase is a key player in fibrosis by regulating epithelial-mesenchymal transition (EMT) and fibroblast-myofibroblast transition [7, 8]. Therefore, in this mini-review we intend to summarize the advancement for the impact of heparanase on fibrosis process and related signaling pathways in fibrosis process.

Heparanase in hepatic fibrosis

Hepatic fibrosis typically results from an inflammatory process that affects hepatocytes or bili-

ary cells. Inflammation leads to the activation of effector cells (mainly hepatic stellate cells), which results in the deposition of extracellular matrix. The end result of hepatic fibrogenesis is cirrhosis, an ominous parenchymal lesion that underlies a wide range of devastating complications that have adverse effects on survival. Heparan sulphate proteoglycans are major components of the liver extracellular matrix. Their cleavage by heparanase may be involved in liver-specific normal and pathological processes. M. Ikeguchi and colleagues reported that heparanase mRNA expression levels were reduced with increasing incidence of liver fibrosis in the noncancerous liver tissues of patients [9]. Orit Goldshmidt and colleagues demonstrated that both heparanase mRNA and protein are expressed during liver development, but not in the mature liver. They also found that elevated heparanase levels were noted in the early stages of thioacetamide-induced liver fibrosis, with no further increase in rats exhibiting higher fibrotic grades [10]. They further demonstrated that heparanase mRNA expression correlates with the level of VEGF during the induction and recovery stages of liver fibrosis. Then, they treated rat fibrotic livers with halofuginone, a multipotent antifibrogenic drug, and found halofuginone could enhance heparanase and VEGF expression and promote liver regeneration [11]. Radiation treatment of normal tissue results in fibrosis, which is perhaps the most universal late effect of radiation. Sook In Chung and colleagues had showed that the expression of heparanase precursor increased in both liver tissue and serum following radiation in thioacetamide-induced liver cirrhosis. Heparanase might be useful in detecting and monitoring radiation induced hepatic fibrosis [12]. In addition, suramin, a polysulfonated naphthylurea, restored hepatic HSPGs and reduced the activity of hepatic heparanase leading to ameliorated fibrosis and massive hepatic tissue breakdown in thioacetamide-induced liver injury model [13].

Heparanase in renal fibrosis

The kidney has a unique cellular architecture that consists of the glomeruli, tubules, interstitium, and capillaries. Injury at any of these sites triggers the deposition of extracellular matrix [14]. Events that initiate renal fibrosis are diverse, ranging from primary renal injury to systemic diseases [15]. The kidneys are susceptible to hypertension and diabetes, the two leading causes of renal fibrosis. Tubulo-interstitial fibrosis is a structural marker of chronic, progressive kidney disease [16]. The epithelial-mesenchymal transition (EMT) of proximal tubular epithelial cells (PTECs) into myofibroblasts plays a central part in the establishment of tubulo-interstitial fibrosis that leads to the end stage of renal disease [17]. The heparanase up-regulation in tubular cells induced by albumin and advanced glycation end products leads to a down-regulation of both HS and syndecan-1 in the pathogenesis of diabetic nephropathy [18]. Valentina Masola and colleagues had reported that in vitro, heparanase is involved in the regulation of EMT of tubular cells induced by FGF-2. Heparanase is necessary for FGF-2 to activate the PI3K/AKT pathway leading to EMT, and for FGF-2 to produce an autocrine loop by down-regulating syndecan-1 (SDC1) and upregulating MMP9 and the same heparanase [7]. Following, they demonstrated that sulodexide (a highly purified glycosaminoglycan isolated from porcine intestinal mucosa) is an effective heparanase inhibitor capable of preventing FGF-2-induced EMT in renal tubular cells [19]. Apart from FGF-2, TGF-β is another main inducer of EMT of proximal tubule epithelial cells [20, 21]. Valentina Masola and colleagues following confirmed that heparanase modulates TGF-β induced EMT, in particular, the lack of heparanase which delays tubular cell transdifferentiation and impairs the TGF-β autocrine loop. Meanwhile, heparanase is needed for the pathological TGF-β overexpression in response to pro-fibrotic factors such as overload of albumin, AGE and FGF-2 [8].

Heparanase in lung fibrosis

Pulmonary fibrosis occurs in association with a wide range of diseases, including scleroderma, sarcoidosis, infection, bronchiolitis obliterans syndrome (BOS) after lung transplantation, and as a result of environmental exposures (e.g., silica dust or asbestos). The main pathogenesis of pulmonary fibrosis is that the injury to alveolar epithelial cells activates pulmonary fibroblasts, provoking their transformation to matrix-producing myofibroblasts [22]. As we know, BOS is a classic subtype of chronic lung allograft dysfunction (CLAD) characterized by the fibro-

proliferative tissue remodeling and increased airway extracellular matrix (ECM) deposition with resultant lung dysfunction [23]. In our recent study, we employed a mouse model of tracheal transplantation and demonstrated that blockade of HMGB1 alone or combined with heparanase attenuates the development of BOS. It was noted that HMGB1 was first passively released from necrotic/damaged cells as a result of early unavoidable allograft injuries, leading to macrophage infiltration along with HMGB1 active secretion. Mechanistic studies revealed that extracellular HMGB1 acted through its receptor, RAGE to activate NF-κB, which then bound to the heparanase promoter to transcribe its expression. The enhanced heparanase next released HS-bonded latent TGF-β from myofibroblast ECM by cleaving HS chains to promote the initiation and progression of BOS [2]. Given the complexity of BOS pathoetiology, this new insight may have great potential to develop novel therapies against fibrotic diseases, especially in the context of BOS after lung transplantation.

Perspectives

Fibrosis is a hallmark of pathologic remodeling in numerous tissues and a contributor to clinical disease. There is a great deal of interest in identifying means of slowing, arresting, or even reversing the progression of tissue fibrogenesis. Heparanase has been consistently recognized to function as an important regulator involved in different organs fibrosis processes. But it is worthy of note, the detailed mechanisms underlying the relationship between heparanase and pro-fibrosis pathways (mainly TGF-β signaling pathway) are yet to be fully addressed, perhaps involving the regulation of release of HS-bonded molecules from ECM storages, such as growth factors, chemokines, cytokines, and enzymes, and therefore, future investigations aimed to dissect these challenging questions will be necessary.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Long He, Department of Clinical Laboratory, Puai Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430033, People's Republic of China. Tel: 86-13871092003; E-mail: long5x19@126.com

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