Alpha2-antiplasmin: A New Target for Fibrotic Diseases

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Abstract

Fibrotic diseases are characterized by excessive scarring due to excessive production, deposition, and contraction of the extracellular matrix (ECM). However, the detailed mechanism underlying the development of fibrosis was unclear. Recently, it has been reported that alpha2-antiplasmin (α2AP), which is serine protease inhibitors (serpins), is associated with the development of fibrosis. This review considers the physiological and pathological roles of α2AP in the development of fibrosis, and proposes that α2AP may be a new target for fibrotic disease.

Introduction

Fibrotic diseases are characterized by excessive scarring due to excessive production, deposition, and contraction of the extracellular matrix (ECM). This process usually occurs over many months and years, and can lead to organ dysfunction or death. The development of fibrosis is generally considered to result from maladaptive repair processes induced by profibrotic factors such as transforming growth factor-beta (TGF-β) and connective tissue growth factor (CTGF). These profibrotic factors stimulate the formation of myofibroblasts via the differentiation from tissue-resident fibroblasts and bone marrow-derived mesenchymal stem cells (MSCs), and epithelial-to-mesenchymal transition (EMT). The accumulated myofibroblasts subsequently synthesize and deposit components of the extracellular matrix (ECM) [1-4]. However, the regulation and mechanism responsible for the development of fibrosis remain poorly understood. This review focuses on the role of alpha2-antiplasmin (α2AP) in the development of fibrosis.

The Role of α2AP in the Development of Fibrosis

It has been known that α2AP is serpins (serine protease inhibitors) with a molecular weight of 65 to 70 kDa [5], which rapidly inactivate plasmin, resulting in the formation of a stable inactive complex, plasmin-α2AP [6]. Recently, it has been reported that α2AP is associated with tissue repair, vascular remodeling and fibrosis, and α2AP may have multiple functions not by the action as a plasmin inhibitor [7-12]. α2AP is most closely related to the noninhibitory serpin pigment epithelium derived factor (PEDF) [13]. The structures of α2AP [14] and PEDF [15] are very similar, and they both have 3 β-sheets and 9 α-helices. α2AP can bind and activate adipose triglyceride lipase (ATGL), which is a receptor for PEDF [16], and then induces the production of TGF-β [11]. α2AP also can induce myofibroblast formation through EMT and the differentiation of tissue-resident fibroblasts and bone marrow-derived mesenchymal stem cells (MSCs) [12]. Conversely, the α2AP deficiency attenuates fibrotic changes, such as collagen production, and myofibroblast deposition induced by several fibrotic diseases model mice [9, 10, 12]. These studies suggest that α2AP may have a profibrotic effect, and play an important role in the development of fibrosis.

The Expression of α2AP in Fibrotic Disease

Many studies have reported that the levels of the plasmin-α2AP complex in the plasma are elevated in patients with fibrotic diseases, including diabetic nephropathy, systemic sclerosis, liver cirrhosis and rheumatoid arthritis [17-20]. Additionally, the expression of α2AP is elevated in fibrotic tissue of several fibrotic diseases model mice [10, 12]. It has reported that CTGF induces the expression of α2AP through both the extracellular signal-regulated kinase 1/2 (ERK1/2) and c-Jun N-terminal kinase (JNK) pathways in fibroblasts. Both the ERK1/2 [21-23] and JNK [24-27] pathways are associated with fibrotic changes such as collagen synthesis. Interestingly, α2AP induces TGF-β production through the same pathways, and the inhibition of ERK1/2 or JNK pathway attenuates the development of fibrosis [10]. Increased α2AP expression through the ERK1/2 and JNK pathways may be associated with the development of fibrosis.

The Role of α2AP as a Plasmin Inhibitor in the Development of Fibrosis

α2AP is known to inhibit plasmin activity. Plasmin can directly and indirectly (the activation of latent metalloproteinases (MMPs)) degrade some matrix proteins (collagen, fibronectin, laminin, entactin, tenascin, thrombospondin and perlecan), which is the proteinaceous component of fibrotic tissue [28]. Additionally, plasmin can activate HGF, which contributes to anti-fibrosis [29, 30], and promote the apoptosis of myofibroblasts [31]. The inhibition of plasmin by α2AP may attenuate ECM degradation and induce myofibroblast deposition, and promote the development of fibrosis.

Conclusion

α2AP induces the production of TGF-β through ATGL, and is associated with myofibroblast formation, ECM synthesis. Conversely, α2AP inhibits plasmin activity, and then attenuates ECM degradation. It is quite likely that α2AP plays a critical role in the development of fibrosis.
fibrosis such as myofibroblast accumulation and ECM deposition, and is a potential therapeutic target for fibrotic disease. The inhibition of α2AP-intitated pathways may provide a novel therapeutic approach to fibrotic diseases.

Acknowledgments

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References