Biochemistry & Analytical Biochemistry

Kanno, Biochem Anal Biochem 2015, 4:3
http://dx.doi.org/10.4172/2161-1009.1000194

Commentary Open Access

Alpha2-antiplasmin: A New Target for Fibrotic Diseases

Yosuke Kanno*

Department of Clinical Pathological Biochemistry, Faculty of Pharmaceutical Science, Doshisha Women's College of Liberal Arts, 97-1 Kodo Kyo-tanabe, Kyoto 610-0395, Japan

***Corresponding author:** Yosuke Kanno, Department of Clinical Pathological Biochemistry, Faculty of Pharmaceutical Science, Doshisha Women's College of Liberal Arts, 97-1 Kodo, Kyo-tanabe 610-0395 Kyoto, Japan, Tel: +81 0774-65-8629; E-mail: ykanno@dwc.doshisha.ac.jp

Rec date: June 16, 2015; **Acc Date:** June 26, 2015; **Pub date:** June 29, 2015

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 antifibrosis [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 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

This work was supported by Takeda Science Foundation and The Uehara Memorial Foundation.

References

1. Vernon MA, Mylonas KJ, Hughes J (2010) Macrophages and renal fibrosis. Semin Nephrol 30: 302-317.
2. Kaneto H, Morrissey J, Klahr S (1993) Increased expression of TGF-beta 1 mRNA in the obstructed kidney of rats with unilateral ureteral ligation. Kidney Int 44: 313-321.
3. Ueha S, Shand FH, Matsushima K (2012) Cellular and molecular mechanisms of chronic inflammation-associated organ fibrosis. Front Immunol 3: 71.
4. LeBleu VS, Taduri G, O'Connell J, Teng Y, Cooke VG, et al. (2013) Origin and function of myofibroblasts in kidney fibrosis. Nat Med 19: 1047-1053.
5. Collen D (1976) Identification and some properties of a new fast-reacting plasmin inhibitor in human plasma. Eur J Biochem 69: 209-216.
6. Lijnen HR, De Cock F, Van Hoef B, Schlott B, Collen D (1994) Characterization of the interaction between plasminogen and staphylokinase. Eur J Biochem 224: 143-149.
7. Kanno Y, Hirade K, Ishisaki A, Nakajima K, Suga H, et al. (2006) Lack of alpha2-antiplasmin improves cutaneous wound healing via over-released vascular endothelial growth factor-induced angiogenesis in wound lesions. J Thromb Haemost 4: 1602-1610.
8. Hou Y, Okada K, Okamoto C, Ueshima S, Matsuo O (2008) Alpha2-antiplasmin is a critical regulator of angiotensin II-mediated vascular remodeling. Arterioscler Thromb Vasc Biol 28: 1257-1262.
9. Kanno Y, Kuroki A, Okada K, Tomogane K, Ueshima S, et al. (2007) Alpha2-antiplasmin is involved in the production of transforming growth factor beta1 and fibrosis. J Thromb Haemost 5: 2266-2273.
10. Kanno Y, Kawashita E, Minamida M, Kaneiwa A, Okada K, et al. (2010) alpha2-antiplasmin is associated with the progression of fibrosis. Am J Pathol 176: 238-245.
11. Kanno Y, Kawashita E, Kokado A, Okada K, Ueshima S, et al. (2013) Alpha2-antiplasmin regulates the development of dermal fibrosis in mice by prostaglandin F(2a) synthesis through adipose triglyceride lipase/calcium-independent phospholipase A(2). Arthritis Rheum 65: 492-502.
12. Kanno Y, Kawashita E, Kokado A, Kuretake H, Ikeda K, et al. (2014) Î ±2AP mediated myofibroblast formation and the development of renal fibrosis in unilateral ureteral obstruction. Sci Rep 4: 5967.
13. Irving JA, Pike RN, Lesk AM, Whisstock JC (2000) Phylogeny of the serpin superfamily: implications of patterns of amino acid conservation for structure and function. Genome Res 10: 1845-1864.
14. Law RH, Sofian T, Kan WT, Horvath AJ, Hitchen CR, et al. (2008) X-ray crystal structure of the fibrinolysis inhibitor alpha2-antiplasmin. Blood 111: 2049-2052.
15. Tombran-Tink J, Aparicio S, Xu X, Tink AR, Lara N, et al. (2005) PEDF and the serpins: phylogeny, sequence conservation, and functional domains. J Struct Biol 151: 130-150.
16. Notari L, Baladron V, Aroca-Aguilar JD, Balko N, Heredia R, et al. (2006) Identification of a lipase-linked cell membrane receptor for pigment epithelium-derived factor. J Biol Chem 281: 38022-38037.
17. Yagame M, Eguchi K, Suzuki D, Machimura H, Takeda H, et al. (1990) Fibrinolysis in patients with diabetic nephropathy determined by plasmin-alpha 2 plasmin inhibitor complexes in plasma. J Diabet Complications 4: 175-178.
18. Ohmoto K, Yamamoto S, Ideguchi S, Yamamoto R, Takatori K, et al. (1990) Clinical significance of thrombin-antithrombin III complex and plasmin-alpha 2 plasmin inhibitor complex in chronic liver diseases. Nihon Shokakibyo Gakkai Zasshi 87: 1837-1845.
19. Kawakami M, Kawagoe M, Harigai M, Hara M, Hirose T, et al. (1989) Elevated plasma levels of alpha 2-plasmin inhibitor-plasmin complex in patients with rheumatic diseases. Possible role of fibrinolytic mechanism in vasculitis. Arthritis Rheum 32: 1427-1433.
20. Jinnin M, Ihn H, Yamane K, Asano Y, Yazawa N, et al. (2003) Plasma plasmin-alpha2-plasmin inhibitor complex levels are increased in systemic sclerosis patients with pulmonary hypertension. Rheumatology (Oxford) 42: 240-243.
21. Chen Y, Shi-Wen X, van Beek J, Kennedy L, McLeod M, et al. (2005) Matrix contraction by dermal fibroblasts requires transforming growth factor-beta/activin-linked kinase 5, heparan sulfate-containing proteoglycans, and MEK/ERK: insights into pathological scarring in chronic fibrotic disease. Am J Pathol 167: 1699-1711.
22. Rodríguez-Barbero A, Obreo J, Alvarez-Munoz P, Pandiella A, Bernabéu C, et al. (2006) Endoglin modulation of TGF-beta1-induced collagen synthesis is dependent on ERK1/2 MAPK activation. Cell Physiol Biochem 18: 135-142.
23. Sullivan DE, Ferris M, Pociask D, Brody AR (2005) Tumor necrosis factor-alpha induces transforming growth factor-beta1 expression in lung fibroblasts through the extracellular signal-regulated kinase pathway. Am J Respir Cell Mol Biol 32: 342-349.
24. Alcorn JF, van der Velden J, Brown AL, McElhinney B, Irvin CG, et al. (2009) c-Jun N-terminal kinase 1 is required for the development of pulmonary fibrosis. Am J Respir Cell Mol Biol 40: 422-432.
25. Shi-Wen X, Rodríguez-Pascual F, Lamas S, Holmes A, Howat S, et al. (2006) Constitutive ALK5-independent c-Jun N-terminal kinase activation contributes to endothelin-1 overexpression in pulmonary fibrosis: evidence of an autocrine endothelin loop operating through the endothelin A and B receptors. Mol Cell Biol 26: 5518-5527.
26. Utsugi M, Dobashi K, Ishizuka T, Masubuchi K, Shimizu Y, et al. (2003) C-Jun-NH2-terminal kinase mediates expression of connective tissue growth factor induced by transforming growth factor-beta1 in human lung fibroblasts. Am J Respir Cell Mol Biol 28: 754-761.
27. Wang XM, Zhang Y, Kim HP, Zhou Z, Feghali-Bostwick CA, et al. (2006) Caveolin-1: a critical regulator of lung fibrosis in idiopathic pulmonary fibrosis. J Exp Med 203: 2895-2906.
28. Parks WC, Mecham RP (1998) Matrix metalloproteinases. Academic Press. San Diego, California, USA 33: 1-362.
29. Bauman KA, Wettlaufer SH, Okunishi K, Vannella KM, Stoolman JS, et al. (2010) The antifibrotic effects of plasminogen activation occur via prostaglandin E2 synthesis in humans and mice. J Clin Invest 120: 1950-1960.
30. Hattori N, Mizuno S, Yoshida Y, Chin K, Mishima M, et al. (2004) The plasminogen activation system reduces fibrosis in the lung by a hepatocyte growth factor-dependent mechanism. Am J Pathol 164: 1091-1098.
31. Kochtebane N, Choqueux C, Passefort S, Nataf P, Messika-Zeitoun D, et al. (2010) Plasmin induces apoptosis of aortic valvular myofibroblasts. J Pathol 221: 37-48.