

Molecular mechanism responsible for collagenous matrix accumulation during chronic hepatic fibrogenesis

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Introduction

Fibrosis is characterized by extracellular matrix (ECM) remodeling and stiffening. However, functional contribution of tissue stiffening to non-cancer pathogenesis remains largely unknown. Fibronectin is an ECM glycoprotein substantially expressed during tissue repair. We have previously demonstrated using a mouse model lacking fibronectin that fibronectin-null livers do not interfere with reconstruction and resolution of collagen organization in initial stages of liver damage (*Gastroenterology*, 2011). However, it remains unknown whether the extent of the initial fibronectin deposition could contribute to the critical turning point from normal to abnormal healing during the development of chronic tissue fibrosis. Furthermore, how remodeling of ECM by myofibroblasts results in changes in mechanical tension that support the activation of pathogenic signaling pathways remain to be elucidated.

Materials and Methods

We utilized fibronectin-floxed mice and generated adult “liver fibronectin-null (mutant)” mice (fibronectin(fl/fl)/Mx-Cre+). Chronic liver injury was induced by well-established treatments with carbon tetrachloride.

Results

Unexpectedly, fibronectin-null livers lead to more extensive liver cirrhosis, which is accompanied by increased liver matrix stiffness and deteriorated hepatic functions. Furthermore, fibronectin-null livers exhibit more myofibroblast phenotypes, and accumulate highly disorganized/diffuse collagenous ECM composed of thinner and significantly increased number of collagen fibrils during advanced chronic liver damage. Mechanistically, mutant livers show elevated local TGF- β activity and lysyl oxidase expressions. A significant amount of active lysyl oxidase is released in fibronectin-null hepatic stellate cells in response to TGF- β 1 through canonical and non-canonical Smad such as PI3 kinase-mediated pathways. TGF- β 1-induced collagen fibril stiffness in fibronectin-null hepatic stellate cells is significantly higher compared to wild-type cells. Inhibition of lysyl oxidase significantly reduces collagen fibril stiffness, and treatment of fibronectin recovers collagen fibril stiffness to wild-type levels.

Discussion

Thus, our findings indicate an indispensable role for fibronectin in chronic liver fibrosis/cirrhosis in negatively regulating TGF- β bioavailability, which in turn modulates ECM remodeling and stiffening, and consequently preserves adult organ functions. This regulatory mechanism by fibronectin could be translated for a potential therapeutic target in broader variety of chronic fibrotic diseases.

Reference

Moriya K, Bae E, Honda K, Sakai K, Sakaguchi T, Tsujimoto I, Kamisoyama H, Keene DR, Sasaki T, Sakai T. (2011) A fibronectin-independent mechanism of collagen fibrillogenesis in adult liver remodeling. *Gastroenterology* 140:1653-1663.