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Activin B promotes the initiation and progression of liver fibrosis

Background & Aims: Liver fibrosis is a pivotal pathology in multiple hepatic disease indications, profoundly characterizing disease severity and outcomes. The role of activin B, a TGFß superfamily cytokine, in liver health and disease is largely unknown. We aimed to investigate whether activin B modulates liver fibrogenesis.

Methods: Liver and serum activin B, along with its analog activin A, were analyzed in patients with liver fibrosis from different etiologies and in mouse acute and chronic liver injury models. Activin B, activin A, or both was immunologically neutralized in mice with progressive or established carbon tetrachloride (CCl4)-induced liver fibrosis. The direct effects of activin B and A on hepatocytes and hepatic stellate cells (HSCs) were evaluated *in vitro*.

Results: As a result, hepatic and circulating activin B was increased in human patients with liver fibrosis caused by several liver diseases. In mice, hepatic and circulating activin B exhibited persistent elevation following the onset of several types of liver injury, whereas activin A displayed transient increases. The results revealed a close correlation of activin B with liver injury regardless of etiology and species. We found that neutralizing activin B largely prevented, as well as remarkably regressed, CCl4-induced liver fibrosis, which was augmented by co-neutralizing activin A. Mechanistically, activin B directly promotes hepatocyte death, induces a profibrotic expression profile in HSCs, and stimulates HSCs to form a septa structure. In addition, activin B and A interdependently upregulated the transcription of profibrotic factors including connective tissue growth factor and TGFß1 in injured livers.

Conclusions: We demonstrate that activin B, cooperating with activin A, directly acts on multiple liver cell populations, and drives the initiation and progression of liver fibrosis. Our finding inspires the development of a novel therapy of chronic liver diseases.

Biography

Dr. Guoli Dai is an associate professor in the Department of Biology, School of Science, Center for Developmental and Regenerative Biology, in Indiana University-Purdue University Indianapolis (IUPUI). His research interest focuses on molecular and cellular mechanisms controlling liver growth and regeneration.

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