Titel des Beitrags:
Angiotensin-II type 1 receptor-mediated Janus kinase 2 activation induces liver fibrosis.

Abstract:
Activation of the renin angiotensin system resulting in stimulation of angiotensin-II (AngII) type I receptor (AT1R) is an important factor in the development of liver fibrosis. Here, we investigated the role of Janus kinase 2 (JAK2) as a newly described intracellular effector of AT1R in mediating liver fibrosis. Fibrotic liver samples from rodents and humans were compared to respective controls. Transcription, protein expression, activation, and localization of JAK2 and downstream effectors were analyzed by real-time polymerase chain reaction, western blotting, immunohistochemistry, and confocal microscopy. Experimental fibrosis was induced by bile duct ligation (BDL), CCl4 intoxication, thioacetamide intoxication or continuous AngII infusion. JAK2 was inhibited by AG490. In vitro experiments were performed with primary rodent hepatic stellate cells (HSCs), Kupffer cells (KCs), and hepatocytes as well as primary human and human-derived LX2 cells. JAK2 expression and activity were increased in experimental rodent and human liver
fibrosis, specifically in myofibroblastic HSCs. AT1R stimulation in wild-type animals led to activation of HSCs and fibrosis in vivo through phosphorylation of JAK2 and subsequent RhoA/Rho-kinase activation. These effects were prevented in AT1R(-/-) mice. Pharmacological inhibition of JAK2 attenuated liver fibrosis in rodent fibrosis models. In vitro, JAK2 and downstream effectors showed increased expression and activation in activated HSCs, when compared to quiescent HSCs, KCs, and hepatocytes isolated from rodents. In primary human and LX2 cells, AG490 blocked AngII-induced profibrotic gene expression. Overexpression of JAK2 led to increased profibrotic gene expression in LX2 cells, which was blocked by AG490. Our study substantiates the important cell-intrinsic role of JAK2 in HSCs for development of liver fibrosis. Inhibition of JAK2 might therefore offer a promising therapy for liver fibrosis.

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