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Upregulation of Stromal-derived Factor-1 by Hypoxia Requires Hypoxia-Inducible Factor-1α and Transforming Growth Factor-1

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Following both acute and chronic liver injury, expression of the chemokine stromal-derived factor-1 (SDF-1), or CxCl12, is upregulated and plays a vital role in the activation of down-stream signaling pathways implicated in either driving hepatic injury progression or leading to its repair. For example, while SDF-1 has been implicated in promoting tumor growth and metastasis in patients with hepatocellular carcinoma, in acute injuries it may play an important role in liver regeneration. This suggests SDF-1 may represent a novel target for therapeutic intervention in both acute and chronic liver diseases. However, the mechanism by which SDF-1 is upregulated following hepatic injury is not fully known. The present study determined whether the transcription factor, hypoxia-inducible factor-1α (HIF-1α), regulates SDF-1 in primary mouse hepatocytes. To activate HIF-1α *in vitro*, primary hepatocytes were incubated for 72 hrs in either room air or hypoxic (1% O_2) conditions. Under hypoxic conditions, SDF-1 mRNA levels were upregulated after 72 hr in WT mouse hepatocytes, an effect that was prevented in hepatocytes isolated from either HIF-1α or HIF-1β knockout mice. We demonstrated previously that upregulation of several genes in hepatocytes during hypoxia requires autocrine release and activation of transforming growth factor-1 (TGF-β1). To determine if TGF-β1 is required for the upregulation of SDF-1 during hypoxia, primary mouse hepatocytes were pretreated with a TGF-β1 receptor antagonist (SB-431542) and placed in hypoxic conditions for 72 hrs. Pretreatment with SB-431542 completely inhibited upregulation of SDF-1 by hypoxia, suggesting TGF-β is required for upregulation of SDF-1 in hypoxic hepatocytes. Additionally, while treatment of hepatocytes with TGF-β1 upregulated SDF-1, this effect did not require HIF-1α, suggesting that TGF-β1 is downstream of HIF-1α activation. We previously demonstrated that hypoxia upregulates thrombospondin-1 in hepatocytes, which could be responsible for activation of latent TGF-β1. Upregulation of SDF-1 by hypoxia, however was not different between hepatocytes isolated from wild-type or thrombospondin-1 knockout mice. The results indicate that hypoxia activates HIF-1α in hepatocytes, which leads to activation of latent-TGF-β1. TGF-β1 then acts in an autocrine fashion to upregulate SDF-1. However, the mediator responsible for converting latent TGF-β to its active form remains unknown.

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