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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

IGFBP-3: So Much More Than an IGF1/2 Binding Protein

Portal hypertension is a major consequence of the progression of chronic liver disease, leading to high morbidity and mortality.[1] The prognosis of patients with portal hypertension has improved dramatically in the past decades mainly owing to a better understanding of its pathogenesis and the discovery of new therapeutic targets. An uncontrolled increase in intrahepatic vascular resistance, derived from the profound deregulation in the phenotype of all hepatic cell types, is the primary factor in the development of portal hypertension.[2] During continuous hepatic injury, hepatic stellate cells (HSCs) acquire proliferative, procontractile, and procollagen–synthetic properties, which together with the increased extracellular matrix deposition results in enhanced vascular tone and augmented liver stiffness. Therefore, fibrosis remains the principal cause of increased vascular resistance in liver disease. Because HSCs are involved in both fibrosis and portal hypertension, HSC targeting is considered in the prevention and treatment of complications of chronic liver disease.[3]

Insulin-like growth factor binding protein 3 (IGFBP-3), one of the 6 known insulin growth factor binding proteins (IGFBPs), is a major IGF-1/2 binding protein and the most abundant in the blood circulation. IGFBP-3 can either trigger the activation of IGF-dependent signaling, owing to its ability to transport IGF1/2, or can perform distinct biological cause effects independent of the IGF axis. The list of IGF-independent roles for IGFBP-3 is increasing with time. The IGF-independent effects of IGFBP-3 are mediated through binding to matrix, cell-surface, cytoplasmic, nuclear, and mitochondrial molecules.[4] Interestingly, a single-cell RNA sequencing analysis of human liver identified IGFBP-3 as secreted primarily by HSCs,[5] suggesting a novel link between IGFBP-3 activity and HSC activation.

Transforming growth factor (TGF-β)–induced activation of quiescent HSCs and their transformation to myofibroblasts is a key event in liver fibrosis and portal hypertension. GAIP interacting protein, COOH-terminus (GIPC) (also known as synectin) is a central adaptor molecule in different signaling pathways and an important mediator of receptor stability. GIPC acts as a downstream signal activation molecule of TGF-β receptors.

In the current issue *of Cellular and Molecular Gastroenterology and Hepatology*, Yaqoob et al[6] sought to identify novel genes targeted by TGF-β and GIPC and elucidate if and how they may contribute to liver fibrosis. By performing messenger RNA sequencing analysis on TGF-β–stimulated HSCs from wild-type and GIPC-knockdown cells, they found IGFBP-3 was its main target and corroborated the role of HSCs as principal producers of IGFBP-3.

To functionally address IGFBP-3 participation, Yaqoob et al[6] studied the effect of global deletion of IGFBP-3 in vivo. By using bile duct ligation and chronic CCl_4 administration animal models they showed that IGFBP-3 knockdown significantly reduced HSC activation, collagen deposition, and portal hypertension in vivo. Of note, they also found enhanced IGFBP-3 serum levels in a small but significant group of patients with alcoholic cirrhosis.

However, exogenously added recombinant IGFBP-3 did not affect tube angiogenesis in liver sinusoidal endothelial cells or collagen expression in HSCs in vitro. In contrast, IGFBP-3 knock down in HSCs showed a reduction in cell proliferation, and recombinant IGFBP-3 clearly potentiated cell migration in HSCs. This last finding is especially important because further mechanistic analysis showed the dependence of IGFBP-3 on iron, as a co-factor, in enhancing HSC migration through binding to integrin β1–mediating PI3K–AKT signaling (Figure 1).

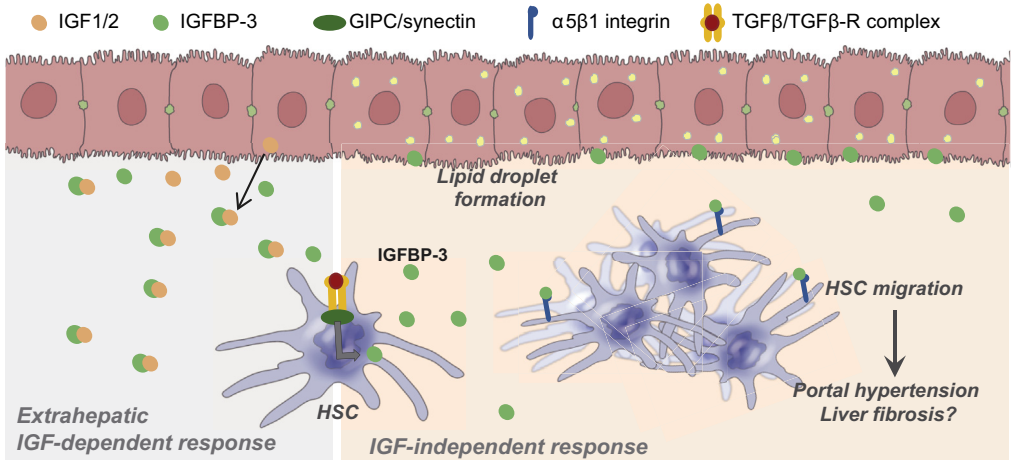

Figure 1. Scheme illustrating the roles of insulin-like growth factor binding protein 3 (IGFBP-3) in the liver. GIPC, GAIP interacting protein, COOH-terminus; HSC, hepatic stellate cell; TGF, transforming growth factor.

What does this article add to our understanding of portal hypertension in the context of chronic liver disease? Overall, this interesting study uncovers new aspects of IGFBP-3 biology and expands our knowledge about the mechanisms by which IGFBP-3 and HSCs contribute to portal hypertension. Yaqoob et al[6] provide evidence that the increased serum IGFBP-3 levels detected in cirrhotic patients may indeed be of functional relevance. Of importance, a study from the same laboratory[7] recently exposed that IGFBP-3 promotes lipid droplet formation, triglyceride content, and lipogenic gene expression in hepatocytes; thus suggesting that targeting IGFBP-3 in the liver can affect not only liver fibrosis/portal hypertension, but also lipid metabolism in the liver. Therefore, the intervention on IGFBP-3 signaling may be beneficial in clinical settings that currently are growing such as nonalcoholic steatohepatitis or metabolic syndrome. However, whether therapeutic blockade of IGFBP-3 is effective for the treatment of liver fibrosis and portal hypertension remains to be determined.

Clinical data regarding IGFBP-3 serum levels and its association with liver diseases still are inconclusive but suggest a major role of IGFBP-3 beyond IGF signaling. Thus, further studies are needed to better define IGFBP-3 cellular and molecular targets in the liver, and to establish associations of IGFBP-3 levels not only with liver fibrosis, cirrhosis, or portal hypertension, but also with metabolic diseases.

MONTSERRAT MARÍ, PhD
Department of Cell Death and Proliferation
IIBB-CSIC, IDIBAPS
Barcelona, Spain

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Correspondence
Address correspondence to: Montserrat Marí, PhD, Department of Cell Death and Proliferation, Institut d'Investigacions Biomèdiques de Barcelona (IIBB-CSIC), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Rossello 161, 6th floor, 08036-Barcelona, Spain. e-mail: monmari@clinic.cat.

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