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Short Communication

Yap Regulation of Hepatic Stellate Cells: Is there a Role for Metabolic Stress?

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Mannaerts et al. recently reported that the effect or protein, Yap of the Hippo pathway regulates liver fibrosis by controlling the activation of hepatic stellate cells. The authors elegantly demonstrate that Yap activation induces fibrotic phenotype using in vitro as well as in vivo models. Besides contributing to liver failure, cirrhosis an advanced stage of fibrosis is known to be a major underlying disease of primary liver cancer, Hepatocellular Carcinoma (HCC). Thus experimental characterization of Yap's role in fibrogenesis is clinically relevant due to the necessity for a viable antifibrotic therapy.

Emerging data show that Yap and hippo pathway in general are involved in liver enlargement and the associated clonal expansion of HCC. Yet, detailed mechanistic insights on the molecular regulation of fibrogenesis by Yap remain unclear. Recent reports document that energy producing pathways are altered in early/late cirrhotic stages and selective deregulation/ disruption of such metabolic alteration block fibrotic phenotype in vitro and in vivo [1-3].Thus, accumulating data indicate that metabolic alteration is indispensable for the progression of fibrosis/ cirrhosis. Corroborating this, Yap and Hippo signaling mechanism have also been found to be regulated by energy stress [4]. Importantly, glucose-mediated energy homeostasis has been shown to regulate Hippo pathway which in turn affects pro-glycolytic function of Yap [5]. Multiple lines of evidence have established that metabolism-related oxidative stress is a major facilitator of fibrosis. Intriguingly, evidences also show that Yap-Hippo pathway is affected by oxidative stress [6]. Taken together, it is thus far evident that cellular stress contributes for fibrogenesis and Yap-Hippo pathway is affected by such cellular stress during fibrogenesis. Future investigations focusing on molecular intricacies of Yap regulation by metabolic stress will be critical and relevant to identify potential therapeutic target (s) and development of any viable and translatable strategy to treat liver fibrosis/cirrhosis.

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