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ABOUT COVER

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Yes-associated protein at the intersection of liver cell fate determination

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Abstract

A recent publication highlights the importance of high yes-associated protein (YAP) expressing cells in liver regeneration following partial hepatectomy. Although the names of the cell populations described in these articles [hybrid periportal hepatocytes (HybHP) or epithelial-mesenchymal transition (EMT)-reprogrammed hepatocytes] are not identical, they all express high levels of YAP. We hypothesize that the HybHP and EMT-reprogrammed hepatocytes might be a similar cell population. Hippo signaling is the primary pathway that regulates YAP activity. According to the contribution of these two types of cells to liver regeneration and the high YAP expression, Hippo-YAP signaling activation may be a common regulatory pathway experienced by cells undergoing dedifferentiation and reactivating proliferative activity during liver regeneration. Although no evidence has shown that HybHP cells contribute to hepatocellular carcinoma in mouse models, we can not rule out the possibility that these highly regenerative cells can further develop into tumor cells when they acquire mutations caused by viral infection or other risk factors like alcohol. The detailed mechanistic insight of the regulation of YAP expression and activity in HybHP (or other types of cells contributing to liver regeneration) is unknown. We hypothesize that liver regeneration under various conditions will eventually lead to divergent consequences, likely due to the duration of YAP activation regulated by Hippo-large tumor suppressor 1 and 2 pathway in a context- and cell type-dependent manner.

Key words: Hybrid periportal hepatocytes; Yes-associated protein; SOX9; Epithelial-mesenchymal transition; Hepatocellular carcinoma

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Core tip: Hybrid periportal hepatocytes (HybHP) and epithelial-mesenchymal transition-reprogrammed hepatocytes might be a similar cell population. The contribution of HybHPs to liver regeneration is associated with high expression of yes-associated protein (YAP). The detailed mechanistic insight of the regulation of YAP activity in HybHPs is undetermined. The context- and cell type-dependent regulation of Hippo-large tumor suppressor 1 and 2-YAP axes might lead to divergent consequences in liver regeneration.

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TO THE EDITOR

The recent publication in *Hepatology* by Jiang *et al* described that nuclear pregnane X receptor (PXR) activates hybrid periportal hepatocyte (HybHP) cell proliferation through YAP and played a key role in liver regeneration following partial hepatectomy^[1]. The authors found that HybHPs comprise a SOX9-positive, YAP-high cell population and that YAP is a key protein that regulates HybHP cell proliferation. Inhibition of YAP abolished PXR-induced liver enlargement in mice. HybHP was first characterized in 2015 as a pre-existing group of periportal hepatocytes in healthy livers^[2]. These cells have low Sox9 (a progenitor cell marker) expression and hepatic gene features. Another study published several months ago examined the role of epithelial-mesenchymal transition (EMT) in liver regeneration^[3]. They found that some hepatocytes overexpressed YAP during the repair process after liver damage and underwent an EMT-like process. YAP interacted with Smad2 in the TGF- β pathway to promote cell proliferation.

Although the names of the cell populations described in these articles (HybHP or EMT-reprogrammed hepatocytes) are different, they both express high levels of YAP. Even though whether such EMT-reprogrammed cells express SOX9 is unknown, EMT is an important pathway to generate progenitor cells. We hypothesize that the HybHP and EMT-reprogrammed hepatocytes described in these studies are a similar cell population. According to the contribution of these two cell types to liver regeneration and the high YAP expression, Hippo-YAP pathway activation may be a common regulatory pathway experienced by cells undergoing dedifferentiation and reactivating proliferative activity during liver regeneration, regardless of whether these highly proliferative cells are derived from hepatocytes or HybHP cells. YAP may be an effective target for promoting liver regeneration in liver failure patients.

Although no evidence showed that HybHP cells contribute to hepatocellular carcinoma (HCC) in three different mouse models^[2], we cannot rule out the possibility that these highly regenerative cells can further develop into tumor cells or cancer stem cells when they gain mutations caused by viral infection or other risk factors like alcohol. YAP is activated in 50% of human HCCs, and its activation level correlates with decreased survival after resection. Endogenous YAP activation perturbs hepatocyte differentiation and maintains this state in advanced tumors, and YAP silencing restores hepatocyte differentiation and leads to tumor regression^[4]. It is interesting to question whether YAP is activated during controlled liver regeneration and excessive cell proliferation is prevented by inactivating YAP. However, under pathological conditions, the control of YAP activity is disrupted, resulting in continuous YAP activation and the generation of HCC.

Hippo signaling is the primary signaling pathway that regulates YAP activity, and MST1/2 phosphorylation of large tumor suppressor 1 and 2 (LATS1/2) can inhibit YAP entry into the nucleus. However, LATS1/2 phosphorylation by MST1/2 is context- and cell type-dependent. Loss of MST1/2 in mouse embryonic fibroblasts does not significantly affect LATS1/2 phosphorylation or activation^[5]. Therefore, we hypothesize that liver regeneration under various conditions will eventually lead to divergent consequences, probably due to the duration of YAP activation regulated by Hippo-LATS1/2 pathway in a context- and cell type-dependent manner. A deeper understanding of this aspect may uncover the key to target YAP to promote liver regeneration in pathological conditions and to control its tumorigenicity at the same time.

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