Plasticity of adult hepatocytes and readjustment of cell fate: a novel dogma in liver disease

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Acute liver failure (ALF) is a life-threatening syndrome characterised by rapid hepatocellular necrosis due to various types of insults including drugs, autoimmune disorders or viral infections, and thus represents a disease with high mortality and elevated societal costs. At present, most ALF treatment strategies are rather aimed at simply preventing complications and decelerating disease progression. Unfortunately, the only curative treatment for ALF at present is liver transplantation, an option which is limited due to financial constraints, shortage of donor livers and immunosuppression-related complications. 1 Therefore, novel therapeutic avenues for patients with ALF are urgently needed.

Normally, mature hepatocytes can orchestrate liver regeneration on loss of liver mass. When severe liver insult occurs, however, hepatocytes are unable to differentiate and hepatic progenitor cells (HPCs) are activated. HPCs, embryonic stem cells (ES) and induced pluripotent stem cells (iPS) have been considered a potential source for cell replacement in the injured liver since they possess hepatic differentiation capacity. 2 However, their clinical applicability remains still controversial. For long, it has been widely assumed that hepatocytes do not contribute directly to the progenitor or stem cell compartment. Recently, Chen and colleagues 2 reported...
the dedifferentiation of progenitor cells from isolated mature hepatocytes, refuting the current dogma.

Yet to be explored was the identification of molecular cascades that specifically dedifferentiate mature hepatocytes and activate a ‘fetal programme’. The Hippo/Yes-associated protein (YAP)-signalling pathway plays an essential role by determining cellular fates in the mammalian liver. Hippo signalling controls the phosphorylation of the transcriptional co-activator YAP whose constitutive activation in mature hepatocytes is sufficient to cause them to dedifferentiate into HPCs.14

In the work by Hyun and collaborators published in this issue of Gut,5 the group of Mae-Diehl expanded the previous studies by exploring the association between adult hepatocyte dedifferentiation and the activation of the Hippo/YAP pathway in acutely injured livers. In particular, they observed that in acutely injured livers that are regenerating, YAP1 and insulin-like growth factor-2 binding protein-3 (IGF2BP3), cooperate with each other to reprogramme subpopulations of hepatocytes to become more fetal-like. They hypothesised that ALF may result from dysregulation of fetal reprogramming mechanisms that are necessary for effective liver regeneration.

Human ALF livers are massively repopulated with cells expressing YAP, consistent with several studies supporting the involvement of YAP during liver regeneration in progenitor cells, which then undergo proliferation.6 In addition, these cells express IGF2BP3-, phospho-mothers against decantaplegic homologue (pSMAD2), SRY-Box9 (SOX9) and pan-cytokeratin (CK) positive—fetal markers—indicating that YAP activation may alter the fate of about 75% of adult hepatocytes which develop into progenitor cells. A further support of these data is found in a recent study7 where expansion of HPCs correlated with extensive liver damage and high patient mortality, indicating that HPCs proliferation might be detrimental to a correct liver function. Nevertheless, altogether these observations in patients with ALF warrant future studies using both a bigger cohort and a greater spectrum of liver disease.

Besides using elegant in vitro and knockdown studies, the authors employed mice with conditionally depleted Yap1 in mature hepatocytes but did not include animals with cell-specific depletion of IGF2BP3 which might be determinant to understand the cooperation between both transcription factors in liver repair. Moreover, the authors used 70% partial hepatectomy and the carbon tetrachloride (CCL4) models to induce ALF; however, both animal models fail to replicate many clinical signs observed in patients with ALF, and, specifically, CCL4 exerts extrahepatic toxicity. Therefore, the murine acetaminophen (APAP) model of acute liver injury and repair might have been a more suitable approach for this study since it closely resembles the phenotype of patients with ALF.8

Concomitantly with previous observations,7 Hyun et al5 observed that YAP activation dedifferentiates adult hepatocytes in both ALF models and the kinetics of IGF2BP3 induction parallels that of YAP1 activation suppressing the expression of lethal-7 (let-7) miRNA—a pivotal regulator of cellular differentiation—in regenerating hepatocytes. These data are important since YAP activation provides a mechanistic explanation for decreased let-7 expression in the injured liver by controlling let-7 biogenesis. Moreover, on liver insult, the liver may decrease let-7 expression, allowing an increase in LIN28 in an effort to repair the injury by induction of cellular transformation and more active proliferation, leading ultimately to hepatic carcinogenesis.

Furthermore, YAP1 activation in adult hepatocytes during liver regeneration induces epithelial-mesenchymal transition (EMT) in a transforming growth factor beta (TGFβ)-dependent manner, thus counteracting the hepatic commitment exerted by let-7 function.9 Evidently, EMT-driven dedifferentiation of adult hepatocytes might be playing a pivotal role in tumour formation.

According to the present study, the YAP1-IGF2BP3 axis is involved in turning ON the fetal programme, but what is the signal that switches off the fetal programme in adult hepatocytes? One possibility is to explore the TEA domain members, a family of transcription factors and primary binding partners of YAP. Another option could be epithelial splicing regulatory protein-2 (ESRP2), a hepatocyte specific factor that controls up to 20% of splicing occurring postnatally in the liver, might be the key to answer this important question. Evidence suggests that ESRP2 induces Hippo kinase splice variants that potentiate YAP1 inactivation thus switching OFF the fetal programme.10 Failure in turning off the fetal programme would cause the fetal programme to continue, thereby accounting for liver cancer development in experimental and human ALF.

In summary, the compelling work by Hyun and colleagues5 provides new evidence of prominent plasticity in hepatocytes that can readjust into progenitor cells which proliferate and finally re-differentiate for successful organ regeneration in the liver. Dysregulation in this process would trigger EMT-driven carcinogenesis (figure 1). Thus, the Hippo/YAP pathway, its targets and regulators as well as the microenvironment and the cellular crosstalk within the liver seem to be pivotal towards cell fate commitment, all of which merit further investigation. Altogether, this work lays the groundwork for the manipulation of mature hepatocytes taking advantage of their phenotypic plasticity not only for the treatment of ALF but also for other liver diseases that require liver transplantation.
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