Review

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The progenitor cell dilemma: Cellular and functional heterogeneity in assistance or escalation of liver injury

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Summary

Liver progenitor cells (LPCs) are quiescent cells that are activated during liver injury and thought to give rise to hepatocytes and cholangiocytes in order to support liver regeneration and tissue restitution. While hepatocytes are capable of self-renewal, during most chronic injuries the proliferative capacity of hepatocytes is inhibited, thus LPCs provide main source for regeneration. Despite extensive lineage tracing studies, their role and involvement in these processes are often controversial. Additionally, increasing evidence suggests that the LPC compartment consists of heterogeneous cell populations that are actively involved in cellular interactions with myeloid and lymphoid cells during regeneration. On the other hand, LPC expansion has been associated with an increased fibrogenic response, raising concerns about the therapeutic use of these cells. This review aims to summarize the current understanding of the identity, the cellular interactions and the key pathways affecting the biology of LPCs. Understanding the regulatory circuits and the specific role of LPCs is especially important as it could provide novel therapeutic platforms for the treatment of liver inflammation, fibrosis and regeneration.

Keywords: Progenitor cells; Regeneration; Immune crosstalk; Inflammation.

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Introduction

The liver represents a central organ in metabolism and homeostasis. It is also considered as a lymphoid organ that plays significant role in the induction of tolerance and involved in the regulation of systemic immunity [1,2]. Such diverse roles are carried out within a specialized microenvironment. The liver consists of parenchymal and non-parenchymal cells such as hepatocytes, liver sinusoidal endothelial cells, hepatic stellate cells (HSCs) and resident immune cells. Cholangiocytes are the epithelial cells of the biliary system that support and determine the secretion of bile. Importantly, the liver exhibits tremendous capacity for regeneration that might be connected with its unique exposure to metabolic and toxic challenge within the body. The regenerative process has been linked to the presence of liver progenitor cells (LPCs) and to the cellular plasticity observed during liver injuries [3].

Redefining LPC identity

In adult liver under steady state conditions, the cellular turnover is relatively low and homeostasis is maintained by mature parenchymal cells [4–7]. Previously, the general assumption was that during prolonged or extensive injury, LPCs become activated and regenerate the liver parenchyma [8]. LPCs were defined as cells that reside within the canals of Hering, exhibit bipotential differentiation capacity and carry markers for both hepatocytes and cholangiocytes [8,9]. LPC activation and expansion reflects cellular changes accompanied by proliferating ductules (derived from LPCs or existing cholangiocytes), and inflammatory cell infiltration collectively referred to as ductular reaction [10]. One of the critical questions was whether LPCs carrying bipotential markers could replace both hepatocellular and biliary compartments during regeneration. Various genetic tracing studies have been conducted, targeting biliary markers previously associated with LPCs such as Sox9, Foxl1 and Opn [5,6,11–14]. Some studies revealed no or minimal contribution of LPCs to hepatocyte regeneration [5,15] while others demonstrated their significant contribution [11–13,16]. Partially, this could be due to distinct genetic targeting strategies, e.g., Sox9-IRES-CreERT [11] supported this hypothesis; clonal labeling using a Sox9-Confetti reporter

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Key point

Liver progenitor cells (LPCs) are quiescent cells that are activated during liver injury in order to regenerate the liver parenchyma.

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mouse line [5] argued against LPC contribution. On the other hand, the studies differed in the induction of liver injury type that could have affected the observed responses. In particular, injuries affecting either portal or central areas of the liver lobule follow different kinetics of progenitor cell response [17], and/or induce the activation of different progenitor cell populations [18]. The interpretation of the data is further complicated by the fact that cells expressing hybrid makers of hepatocytes and cholangiocytes could be identified not only at the canals of Hering but also in portal bile duct and in periportal hepatocytes [15,19]. According to this, the Sox9$^+$ Hnf4a$^+$ CK19$^-$ diploid hepatocytes, called hybrid hepatocytes (HybHP), at the periportal region, undergo extensive proliferation and are capable of repopulating both hepatocyte and cholangiocyte compartments during various types of liver injuries [15]. It has been demonstrated by multiple studies that hepatocytes could transdifferentiate towards ductal cells, in a process controlled by Notch signaling [5,20–22]. Since mature hepatocytes were identified in these studies as either Hnf4a$^+$ CK19$^-$ cells, Sox9$^+$ cells or were indistinguishable from diploid hepatocytes [5,20,21], it is likely that these observations represent the injury related response of HybHPs. The ectopic overexpression of yes-associated protein 1 (YAP; a member of the Hippo pathway) in mature hepatocytes activated a progenitor program and transformed these cells to progenitor-like cells that were capable of differentiation [23]. Also, sorted polyploidy hepatocytes displayed engrafting potential upon transplantation [24]. While mature hepatocytes exhibit remarkable differentiation plasticity specifically upon manipulation [23], clear evidence that unequivocally confirm the *in situ* biliary transdifferentiation of adult mature polyploid hepatocytes without genetic manipulation is missing. Diploid hepatocytes have also recently been identified near the central vein, expressing the hepatoblast markers Tbx3 and Axin2 [7]. These cells exhibited self-renewal capacity and supported the homeostatic tissue replenishment of hepatocytes [7]. It remains to be elucidated whether they could also represent a cellular source for liver regeneration during hepatic injuries.

Thus, it seems that the hepatocyte compartment contains two complementing progenitor niches that could regenerate hepatocytes and biliary cells and restore tissue integrity under steady state and during inflammation (Fig. 1). It is an intriguing question whether there is a similar organization within the biliary compartment as well. Especially, since during ductular reaction, reactive cell proliferation of ductal cells accompanied by bipotential LPCs has long been reported [8,10,25]. Indeed, murine ductal cells showed a differentiation capacity towards hepatocytes and cholangiocytes [9,11,13,26,27] and human biliary ducts could form 3D organoids containing bipotential LPCs [28]. The regenerative potential of the biliary compartment was suggested when Foxl1$^+$ progenitors were depleted during liver injury using the DTR-based transgenic system [13]. Accordingly, Foxl1$^+$ cells were required for complete tissue recovery caused by choline-deficient, ethionine-supplemented (CDE) diet [13]. Additionally, a recent Mdm2 (E3 ubiquitin-protein ligase) deficient mouse model, where cellular senescence terminated hepatocyte contribution to liver regeneration, demonstrated that biliary cells expressing cluster of differentiation (CD)133$^+$ epithelial cell adhesion

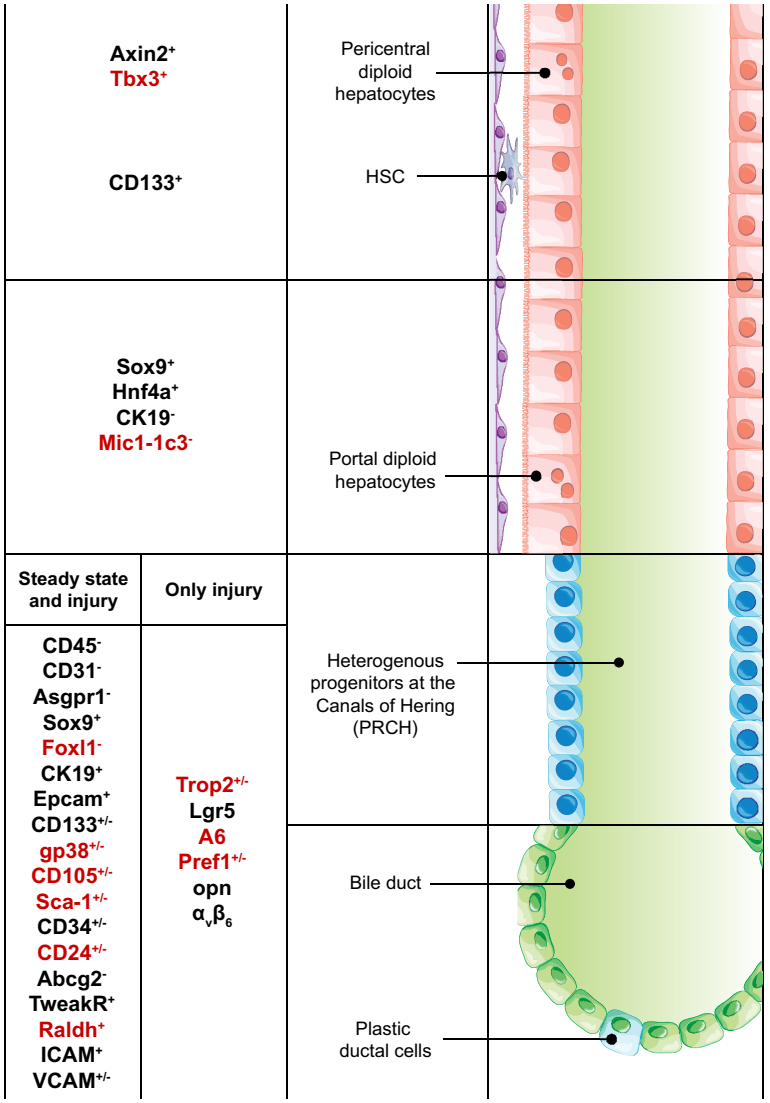

Fig. 1. Progenitor cell niche within the liver. Diploid hepatocytes, plastic biliary cells and progenitors residing in the canals of Hering (PRCH) could provide cellular recourses for regeneration. The markers associated with progenitors are depicted. Ductal cells and PRCH have not been distinguished by specific surface markers therefore markers indicated in progenitors other than hepatocytes are listed together. +: expressed; −: lack expression; ± indicates the expression only on a subset of progenitors; where this is not indicated, expression on specific subsets has not been investigated. Markers that are associated with only murine LPCs are marked with red color. All other markers have been described for both murine and for human LPCs.