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Stem Cells and Liver Regeneration

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One of the defining features of the liver is the capacity to maintain a constant size despite injury. Although the precise molecular signals involved in the maintenance of liver size are not completely known, it is clear that the liver delicately balances regeneration with overgrowth. Mammals, for example, can survive surgical removal of up to 75% of the total liver mass. Within 1 week after liver resection, the total number of liver cells is restored. Moreover, liver overgrowth can be induced by a variety of signals, including hepatocyte growth factor or peroxisome proliferators; the liver quickly returns to its normal size when the proliferative signal is removed. The extent to which liver stem cells mediate liver regeneration has been hotly debated. One of the primary reasons for this controversy is the use of multiple definitions for the hepatic stem cell. Definitions for the liver stem cell include the following: (1) cells responsible for normal tissue turnover, (2) cells that give rise to regeneration after partial hepatectomy, (3) cells responsible for progenitor-dependent regeneration, (4) cells that produce hepatocyte and bile duct epithelial phenotypes in vitro, and (5) transplantable liver-repopulating cells. This review will consider liver stem cells in the context of each definition.

The adult mammalian liver is composed of diverse cell types that arise from various embryologic origins. In this review, the discussion of the "liver stem cell" or "hepatic stem cell" focuses on precursors of 2 liver epithelial cell types: hepatocytes and bile duct epithelial cells.

Organization and Functions of Adult Mammalian Liver

An appreciation of liver architecture is essential to the understanding of hepatic stem cell biology. An extensive description of liver organization/function is found elsewhere.[1] Briefly, the primary functional unit of the liver is the hepatic lobule (Figure 1*A* and *B*).[2] Located along the lobule perimeter, the portal triad consists of a small portal vein, hepatic artery, and bile duct. Blood enters the liver from the portal vein and hepatic artery, and it flows through liver sinusoids toward the central vein. Rows of hepatocytes form a hepatic plate. The basolateral hepatocyte surface is lined with fenestrated endothelium, unique among capillary beds, forming sinusoidal vessels. These vessels facilitate interactions between blood and the hepatocyte cell surface.[3] The apical face of adjacent hepatocytes forms a bile canaliculus. Bile is secreted by hepatocytes into the bile canaliculus and then drains toward bile ducts, which are lined by duct epithelial cells. Bile canaliculi connect with bile ducts via the Canal of Hering, which is also believed to be a niche for liver progenitor cells (see following text).

The liver is responsible for the synthesis of serum proteins; intermediary metabolism of amino acids, lipids, and carbohydrates; and detoxification of xenobiotic compounds. These functions are performed primarily by hepatocytes. Hepatocyte function (eg, gene expression profile and biochemical activities), however, is not identical among all hepatocytes. Rather, hepatocytes perform different roles depending on their physical location within the hepatic lobule. "Metabolic zonation" refers to the differential properties of periportal (adjacent to the portal triad) and pericentral (adjacent to the central vein) hepatocytes.[4] Periportal hepatocytes, for example, express urea cycle enzymes and convert ammonia to urea.[5,6] In contrast, pericentral hepatocytes express glutamine synthase and utilize ammonia to generate glutamine.[5]

Abbreviations used in this paper: AFP, α-fetoprotein; DDC, 3,5-diethoxycarbonyl-1,4-dihydrocollidine; ECFC, epithelial colony-forming cell; ESC, embryonic stem cell; HSC, hematopoietic stem cell; iPS, induced pluripotent stem cell; MSC, mesenchymal stem cell; TWEAK, tumor necrosis factor–like weak inducer of apoptosis.

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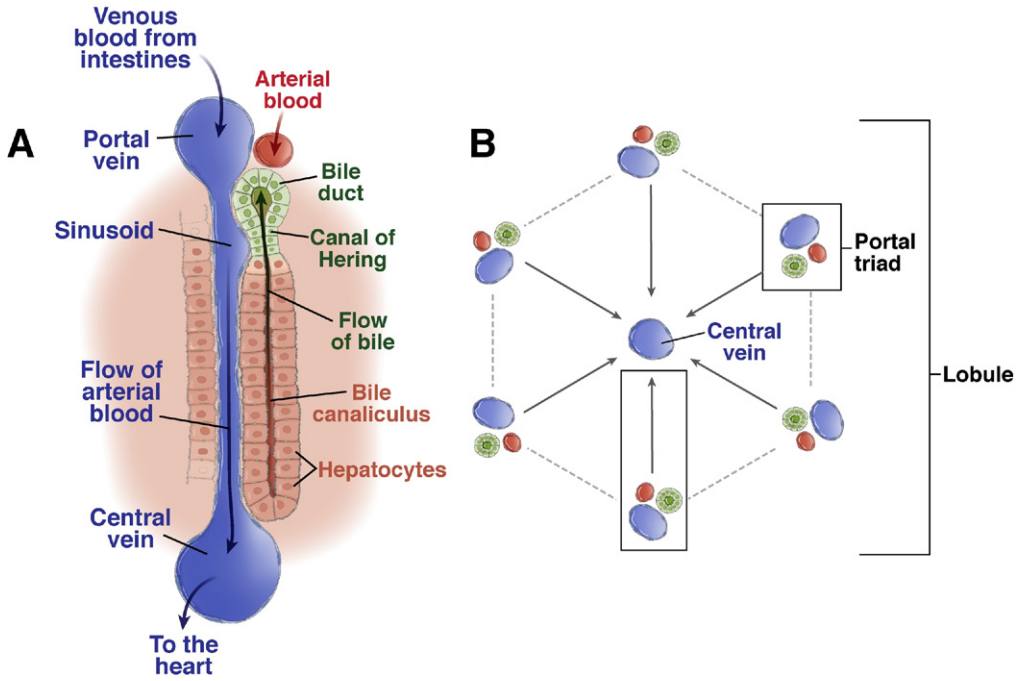

Figure 1. Structure of the hepatic lobule. (*A*) The portal triad consists of bile ducts, hepatic artery, and portal vein.[168] Mixed blood from the hepatic artery and portal vein flows past hepatocytes through the sinusoids, covered with fenestrated endothelial cells to the central vein. Bile produced by the hepatocytes is collected in the bile canaliculus and flows towards the bile duct. The Canal of Hering is the junction between the hepatic plate and the bile ducts. This is the region where oval cell precursors reside. (*B*) Each hepatic lobule consists of 1 central vein and 6 surrounding portal triads.

Cells Responsible for Normal Liver Tissue Turnover

Hepatocyte replacement occurs relatively slowly; the average life span of adult hepatocytes ranges from 200 to 300 days.[7] A number of different hypotheses have been proposed to explain hepatocyte turnover. In one of the earliest models, called "streaming liver," normal liver turnover was proposed to be similar to intestinal regeneration, with young hepatocytes originating in the portal zone and then migrating toward the central vein.[8] Differential gene expression by periportal and pericentral hepatocytes was believed to arise during the hepatocyte maturation process, which represented a typical lineage progression. Very recent data from Fellous et al support the streaming liver hypothesis in human tissue.[9] Clonal patches of hepatocytes harboring mitochondrial mutations were found to originate in periportal areas and extend into pericentral regions, suggesting a pattern of hepatocyte differentiation/movement.

However, strong evidence against the streaming liver hypothesis also exists. First, retroviral marking studies provide clear evidence against any hepatocyte migration during normal turnover.[10] Analysis of the X-inactivation pattern in livers from female mice also argues against hepatocyte migration within the lobule.[11] Secondly, the gene expression pattern in hepatocytes is dependent on the direction of blood flow.[12] If blood flow is reversed so that portal blood enters the lobule through the central vein and exits via the portal vein, the gene expression profile is inverted. Lobular zonation, therefore, could be explained by metabolite-induced gene regulation and not lineage progression. Although the contribution of stem cells to normal liver turnover in adult animals is debated, current evidence suggests that most liver maintenance is achieved directly by cell division of hepatocytes and bile duct epithelial cells.[13]

Cells That Give Rise to Regeneration After Partial Hepatectomy

Partial hepatectomy is a surgical procedure in which specific liver lobes are removed intact without damage to the lobes left behind. The process has been extensively studied and is the subject of several excellent reviews.[14–16] The excised liver lobes never grow back, but the remaining lobes grow to compensate for the mass of the resected tissue. Reconstitution of the entire liver mass, which is complete within 5–7 days in rodents, is mediated by mature cell types (ie, without stem cells). Classic thymidine labeling studies showed that virtually all rodent hepatocytes in the remaining liver divided once or twice to restore the original cell number within 3–4 days.[17,18] The earliest labeled hepatocytes are seen 24 hours after partial hepatectomy; the peak of thymidine incorporation occurs after 24–48 hours. Following hepatocyte division, the other hepatic cell types also undergo a wave of mitosis, thereby restoring the original number of all liver cells within 1 week.

The regenerative response after partial hepatectomy is mediated by a number of factors. The most important signals are hepatocyte growth factor,[19] interleukin-6, tumor necrosis factor α, transforming growth factor α, and epidermal growth factor. Nonpeptide hormones, including triiodothyronine[20] and norepinephrine,[21] can stimulate hepatocyte replication in vivo. Much less is known about how liver regeneration is terminated once the appropriate liver mass is restored. Although the exogenous