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Review

# Phenotypic Plasticity of Hepatocytes and Cholangiocytes in Chronic Liver Disease

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**Abstract**

The hepatic epithelial system, composed of hepatocytes and bile duct cells, exhibits remarkable phenotypic plasticity despite its highly differentiated state. During acute liver injury, hepatocytes rapidly regenerate through self-duplication; however, chronic or repetitive injury induces incomplete regeneration, fibrotic remodeling, and ductular reactions. Historically, a liver progenitor cell (LPC) population was proposed to mediate regeneration when hepatocyte proliferation is impaired, but recent lineage-tracing and single-cell analyses indicate that LPCs contribute minimally, and that most new hepatocytes arise from pre-existing hepatocytes. Ductular reactions, frequently observed in chronic liver diseases, primarily result from proliferation and remodeling of existing bile ducts, with a subset derived from hepatocyte transdifferentiation. Such hepatocyte-to-ductular transitions may help re-establish bile canalicular continuity in damaged tissue. Oncogenic activation in hepatocytes further reveals their plastic potential, producing diverse tumor phenotypes—ranging from hepatocellular carcinoma to cholangiocarcinoma and hepatoblastoma—through transdifferentiation or dedifferentiation programs reminiscent of liver development. These findings suggest that liver regeneration and carcinogenesis share common mechanisms of epithelial reprogramming. Future research should aim to identify subsets of hepatocytes capable of sustained replication and to elucidate how the injured microenvironment governs epithelial cell fate through processes such as paligenosis. Understanding and modulating hepatic epithelial plasticity may provide new strategies for treating chronic liver diseases and liver cancer.

**Keywords:** Cholangiocytes, dedifferentiation, ductular reaction, hepatocytes, liver progenitor cells, phenotypic plasticity, primary liver cancers, transdifferentiation

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The hepatic epithelial system, composed of hepatocytes and bile ducts, plays a central role in the liver's complex metabolic, synthetic, and secretory functions, supported by non-epithelial cells such as sinusoidal endothelial cells, hepatic stellate cells, myofibroblasts, and a variety of immune cells. Despite being highly differentiated and specialized, the liver is well known for its robust regenerative capacity following acute parenchymal injury, as demonstrated in rodent partial hepatectomy experiments and in the rapid recovery observed in several human acute liver diseases.[1] However, when parenchymal injury is prolonged or repetitive, regeneration becomes incomplete, leading to fibrotic remodeling and ultimately cirrhosis, which is characterized by regenerative nodules surrounded by fibrous septa.[2]

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Although hepatocyte phenotypes were long assumed to be fixed once maturation was complete, accumulating evidence indicates that the hepatic epithelial system retains substantial phenotypic plasticity, particularly under conditions of chronic injury, when the hepatic microenvironment is altered.[2] Hepatocytes can undergo transdifferentiation toward bile duct cells or dedifferentiation toward liver progenitor cells (LPCs), which are thought to represent bipotential intermediate hepatobiliary cells similar to hepatoblasts. Recent studies have also proposed that bile duct cells themselves may exhibit plasticity and transdifferentiate into hepatocytes. Nevertheless, the extent of this epithelial plasticity and its precise contribution to liver regeneration and hepatocarcinogenesis remain unclear, as experimental findings are often conflicting.

In this short review, I aim to synthesize recent data on hepatic epithelial plasticity and propose a more unified framework for understanding these processes.

## Development of the Hepatic Epithelial System

The epithelial cells of the liver are derived from hepatoblasts, which emerge from the hepatic diverticulum of the foregut at 3–4 weeks post-coitum in humans and at embryonic day 8.5–9.0 in mice.[3] During the early stages of hepatogenesis, immature hepatoblasts strongly express Myc and delta-like 1 (DLK1), but the expression of these markers declines rapidly before birth (Fig. 1).[4,5] Although hepatoblasts specifically express a variety of proteins and mRNAs—including α-fetoprotein (AFP), insulin-like growth factor 2, and H19 mRNA—that are absent in mature hepatocytes, their expression continues during the early postnatal period.[4,5]

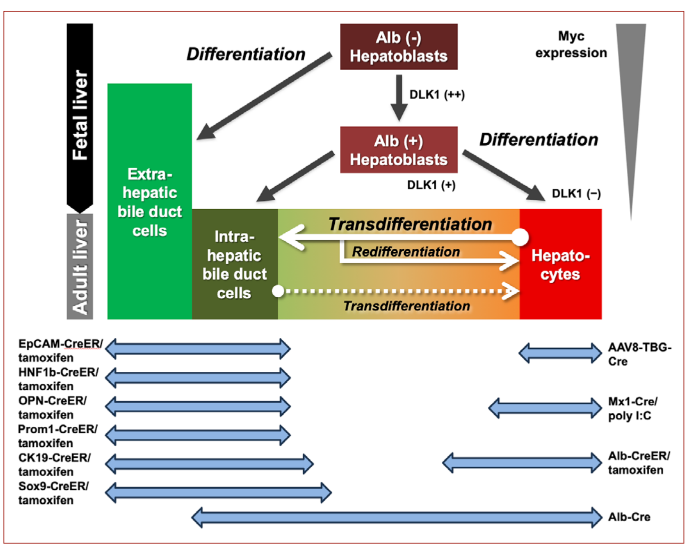


**Figure 1.** The lineage of hepatic epithelial cells.

Hepatocytes and bile duct cells (cholangiocytes) are derived from hepatoblasts. Although hepatocytes and intrahepatic bile duct cells can mutually transdifferentiate, hepatocytes are generally more malleable. The potential cellular spectrum labeled by various lineage-tracing systems is illustrated below.

While immature hepatoblasts proliferate and form the liver bud, they also give rise to the extrahepatic bile ducts, which connect the liver to the intestinal lumen (Fig. 1).[6] As hepatoblasts differentiate into hepatocytes and begin to express albumin, they simultaneously generate nascent intrahepatic bile ducts, appearing as ductal plates along the developing portal veins (Fig. 1).[6] Differentiation of the intrahepatic bile ducts is initiated by collagen deposition along the developing portal vein and activation of the Notch signaling pathway.[7] Development of the intrahepatic bile ducts continues during the postnatal period, ultimately giving rise to bile ductules—the terminal branches of the biliary tree, which abut periportal hepatocytes—and to interlobular bile ducts embedded within the portal connective tissue.

## Liver Progenitor Cell Hypothesis

It has been proposed that a small population of hepatoblast-like cells resides in the adult liver, serving as liver progenitor cells (LPCs) that are bipotential and contribute to regeneration when hepatocyte proliferation is impaired during chronic liver injury.[8] The most likely LPC candidates are intermediate hepatobiliary cells located in the canal of Hering, the junction between the hepatocyte canalicular system and bile ductules. Research on LPCs has long been hampered by the absence of specific markers. Nevertheless, Sox9 and osteopontin—both also expressed in bile duct cells—have been utilized for lineage-tracing experiments in mice.

Periportal Sox9-positive cells were once reported to contribute to liver homeostasis and regeneration,[9] but subsequent studies failed to reproduce these findings.[10] Lineage tracing of osteopontin-positive cells has yielded variable results; however, the generation of new hepatocytes from osteopontin-positive cells appears limited (at most a few percent).[11-13] Similarly, Axin2-positive cells, which were once proposed as unique centrilobular LPC candidates, were later shown not to significantly contribute to liver regeneration.[14]

Cholangiocytes have also been suggested to act as LPC-like cells in mice, particularly when hepatocyte proliferation is suppressed by chronic injury induced by Mdm2 deletion.[15] Subsequent studies demonstrated that reactive cholangiocytes may serve as important sources of hepatocytes following chronic injury induced by a methionine- and choline-deficient diet, 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC), or $CCl_4$.[13,16,17] Notably, these conclusions were largely based on the observation that clusters of unlabeled hepatocytes appeared in regenerating livers in experiments using the AAV8-Tbg-Cre system. Although this is currently the most efficient hepatocyte-lineage tracing method, unlabeled hepatocytes can sporadically arise anywhere in the hepatic lobule, gradually forming clusters and even regenerative nodules during chronic injury.[2]

Taken together, it is now evident that the small pool of intermediate hepatobiliary cells in the adult liver does not possess robust proliferative activity in chronic injury. Instead, new hepatocytes are generated primarily through self-duplication.[18,19] Thus, the liver may not require a dedicated stem cell system for its regeneration.

## Ductular Reaction: Cells of Origin and Significance

In various chronic liver diseases, abnormal proliferation of bile ductules occurs in association with progressive fibrosis. This phenomenon, termed the ductular reaction, has long been the subject of debate regarding its cellular origin, underlying mechanisms, and biological significance.[20] The presence of intermediate hepatobiliary cells around ductular reactions suggests that hepatocyte transdifferentiation into ductular cells may contribute to this process. Indeed, we have demonstrated ductular transdifferentiation of mature hepatocytes in three-dimensional cultures and transplantation experiments.[21-23] This transdifferentiation is not accompanied by reactivation of hepatoblastic proteins such as DLK1, is markedly enhanced by tumor necrosis factor-α, and is at least partially reversible.[22] Furthermore, ductular transdifferentiation of chronically injured hepatocytes has been reported to play a significant role in liver regeneration.[24,25]

Multiple groups have employed hepatocyte lineage-tracing systems in mice to assess the extent of ductular transdifferentiation in ductular reactions.[23,26-29] Using the Mx1-Cre/ROSA26R system, we estimated that hepatocyte transdifferentiation contributes to approximately 10% of ductular reactions during chronic injury.[23] Recent single-cell analyses have revealed substantial heterogeneity in the adult liver, including various hybrid hepatobiliary cell populations.[30-32] Depending on which subpopulation is labeled in a given lineage-tracing system, results may vary considerably (Fig. 1). When cholangiocyte lineage-tracing data are also considered,[26,33] it appears that most ductular reactions primarily reflect proliferation of pre-existing bile ducts and ductules.

Ductular reactions are also associated with extensive remodeling of the biliary system. In centrilobular ductular reactions induced by $CCl_4$, thioacetamide, or a 0.1% methionine/choline-deficient L-amino acid-defined high-fat diet, bile ductules emerge within the damaged centrilobular zones. Importantly, these remodeled ductular networks maintain communication with the common bile duct. The transdifferentiation of injured hepatocytes into ductular cells may therefore be critical for re-establishing junctions with the bile canalicular system.[23,34]

## The Histological Diversity of Hepatocytic Tumors: Transdifferentiation and Dedifferentiation Induced by Oncogenic Processes

Primary liver epithelial cancers are histologically diverse, including hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), combined hepatocellular-cholangiocarcinoma (cHCC-CCA), hepatoblastoma (HB), and other rare entities. The phenotypic plasticity of liver epithelial cells has important implications for understanding the diversity of these tumor types. Using somatic gene transfer via hydrodynamic tail vein injection of oncogene-harboring transposons into mouse hepatocytes, we have shown that a wide spectrum of liver tumors—including HCC, CCA, cHCC-CCA, and HB-like tumors—can be generated from transformed hepatocytes.[4,35–37] This hepatocarcinogenesis model is robust, enabling the induction of multiple liver tumors with defined oncogenic mechanisms, dependent on the introduced oncogene(s), within a few weeks.[38]

CCA was first generated by Fan et al.[39] from mouse hepatocytes through activation of the Notch pathway, which is critical for bile duct differentiation in the fetal liver, in combination with AKT pathway activation. Activation of AKT together with YAP also induces CCA,[37] consistent with the known reciprocal interaction between the Notch and YAP signaling pathways. cHCC-CCA can be induced by combinations of activated YAP (or Notch) with Myc, mutant HRAS with p53 knockout, or mutant HRAS, Myc, and p53 knockout.[36,37] Notably, some human intrahepatic CCAs may arise from hepatocytes via transdifferentiation, as recent evidence suggests.[40]

Although hepatocytes exhibit an intermediate hepatobiliary phenotype during chronic injury, they do not activate the hepatoblastic gene and protein expression program, including DLK1 and AFP. Interestingly, the combination of mutant HRAS and Myc generates HB-like tumors expressing DLK1, AFP, and stem cell markers.[4] Similar dedifferentiation occurs in tumors induced by YAP and Myc.[37] These findings suggest that Myc activation, which occurs during early liver development (Fig. 1), is essential for hepatocyte dedifferentiation.

## Conclusions and Future Directions

In chronic liver injury, hepatocytes and cholangiocytes exhibit considerable phenotypic plasticity, contributing to liver regeneration and the ductular reaction. The ductular reaction is primarily a consequence of biliary remodeling triggered by microenvironmental changes—including fibrotic matrix deposition and inflammatory cell infiltration—rather than activation of LPC. The ductular transdifferentiation of hepatocytes also plays an important role in maintaining the continuity of the biliary network.

Recent single-nucleus RNA sequencing studies have revealed significant epithelial plasticity in human chronic liver disease.[41] Interestingly, intermediate hepatobiliary cells identified in metabolic dysfunction-associated steatotic liver disease lack LPC-like properties and are largely nonproliferative.[41] These findings suggest that regeneration in chronic liver disease may depend on the selective proliferation of a subset of hepatocytes rather than on LPCs or intermediate hepatobiliary cells. Identifying hepatocytes capable of repeated replication will be an important goal for future research.

Tissue remodeling in chronic liver disease may be governed by paligenosis,[42] a process in which mature hepatocytes and cholangiocytes re-enter the cell cycle and regenerate damaged tissue without relying on professional stem cells. For hepatic epithelial cells to properly restore damaged tissue through their phenotypic plasticity, it is crucial to normalize the abnormal microenvironment in which they reside.

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