# Hepatic Progenitor Cells
## An Update

Matthias Van Haele, MD, Tania Roskams, MD, PhD*

**KEYWORDS**

• Hepatic progenitor cell • Liver stem cell • Liver progenitor cell • Liver regeneration • Liver niche

**KEY POINTS**

- During normal liver homeostasis, the HPC and its niche are in a quiescent state. A significant activation and contribution to liver regeneration are seen after severe liver damage.
- The interaction among HPCs, the HPC niche, cytokines, chemokines, and growth factors is critical for the activation of the HPC compartment.
- Senescence of the parenchymal compartment after chronic liver injury is clearly an essential requirement for the proliferation of the HPCs.
- Recent evidence suggests the existence of other niches with potent stemness. However, further research of these subjects is required for better insights.

### INTRODUCTION

The liver is an intriguing organ because of its impressive regenerative capacity after considerable damage. This damage can be toxic, genetic, metabolic, viral, or immunologic. When this occurs in an unchallenged healthy liver, the loss of hepatocytes is replenished by the remaining mature and functional hepatocytes.[1] One of the exemplary illustrations, and also a classic animal model, is the recovery after a partial hepatectomy (HPx) in rats and mice. Over the years, many research groups have created various animal models to induce liver damage and regeneration. They studied both the self-renewal capacity of hepatocytes and cholangiocytes after liver injury, and possible differentation towards stem/progenitor cells in the liver. These stem/progenitor cells, called oval cells in rodent models, has the ability to differentiate into cholangiocytes or hepatocytes when regular liver homeostasis becomes compromised, such as by toxic inhibition of the proliferative capacity of hepatocytes or senescence in the setting of chronic liver diseases. The complicated process of regeneration is driven by many different cytokines and growth factors. In clinical practice, the regenerative

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Liver Research Unit, Department of Imaging and Pathology, KU Leuven and University Hospitals Leuven, Minderbroederstraat 12, 3000 Leuven, Belgium
* Corresponding author.
*E-mail address:* tania.roskams@uzleuven.be

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capacity of the liver is well known in living donor liver transplantation, which was first performed from adult to child and nowadays also from adult to adult.[2,3] Despite this success, there is still a significant shortage of liver transplants. A study in the United Kingdom showed that 19% of adult nonurgent registrants died within 1 year awaiting a graft.[4] For this reason, researchers are investigating the possibility of cell-based therapy. Next to isolated hepatocytes, stem/progenitor cells are potential candidates. Thanks to the increasing knowledge of stem cells, various potential targets are suggested.[5,6] Stem cells that have been investigated in the light of liver regeneration are hepatic progenitor cells (HPC), mesenchymal stem cells, and bone marrow cells. This article focuses on the HPC and its niche.

## HEPATIC PROGENITOR CELLS

The hepatocyte is a parenchymal cell with a long life cycle, which is responsible for liver regeneration under normal conditions.[7] When the regenerative capacity of the hepatocyte is compromised, because of senescence, which is indicated by p16 and p21 immunohistochemical positivity, it is accepted that a population of HPCs is activated.[8–10] This activation aids in the regeneration process.[11,12] The extent and the specific contribution of these cells in liver regeneration are not entirely clear. HPCs are located in the smallest part of the biliary tree, the canals of Hering, which are also known as the transition zone between the terminal segment of the bile duct epithelium and the hepatocytes.[13,14] This is a strategic location because of its regenerative possibilities toward hepatocytes or cholangiocytes. A difficulty for existing research in this domain is the widespread use of a diffuse nomenclature for these HPCs and its related reaction. Intermediate hepatobiliary cell, liver progenitor cell, liver stem cell, or atypical ductular cell are some examples of regularly used terms.[15–17] The term “oval cells” is used in many articles, and is the equivalent of HPCs in rodents.[18,19] Another phenomenon is the so-called ductular reaction. This ductular reaction is histologically recognized as the proliferation of ductular structures in the portal triad.[20] It is seen in a variety of liver diseases, ranging from acute to chronic injuries (**Fig. 1**). The ductular reaction is thought to harbor the HPC compartment.[20–23] The study by Yoon

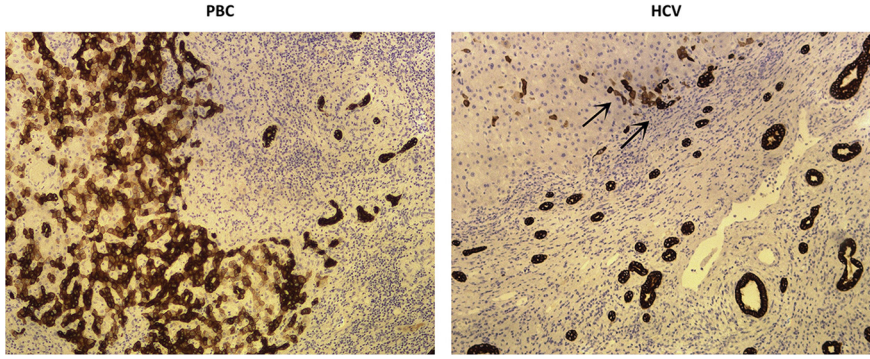


**Fig. 1.** (*Left*) Histologic example of an extensive ductular reaction, lymphocytic infiltration, and cholestasis in primary biliary cholangitis (PBC). In this chronic and progressive cholestatic disease, we stained the diffuse bile ductular reaction and cholate stasis with cytokeratin 7 (original magnification ×100). (*Right*) A case of hepatitis C virus (HCV) at a later stage with accompanying ductular proliferation. Note the differentiation process from strong- to weak-stained cytokeratin-7-positive cells toward the damaged hepatic compartment (*arrows*) (original magnification ×200).