Liver Research xxx (2017) 1–7

Contents lists available at ScienceDirect

Liver Research

journal homepage: http://www.keaipublishing.com/en/journals/liver-research

Review Article

Hepatic progenitor cell activation in liver repair☆

Adam Bria, Jorgensen Marda, Junmei Zhou, Xiaowei Sun, Qi Cao, Bryon E. Petersen, Liya Pi*

Pediatric Stem Cell Research and Hepatic Disorders, Child Health Research Institute, Department of Pediatrics, University of Florida, Gainesville, FL, USA

ARTICLE INFO

Article history:
Received 16 December 2016
Received in revised form
23 June 2017
Accepted 26 June 2017

Keywords:
Liver regeneration
Hepatic progenitor cells (HPCs)
Oval cells (OCs)
Liver injury
Hepatic fibrosis

ABSTRACT

The liver possesses an extraordinary ability to regenerate after injury. Hepatocyte-driven liver regeneration is the default pathway in response to mild-to-moderate acute liver damage. When replication of mature hepatocytes is blocked, facultative hepatic progenitor cells (HPCs), also referred to as oval cells (OCs) in rodents, are activated. HPC/OCs have the ability to proliferate clonogenically and differentiate into several lineages including hepatocytes and bile ductal epithelia. This is a conserved liver injury response that has been studied in many species ranging from mammals (rat, mouse, and human) to fish. In addition, improper HPC/OC activation is closely associated with fibrotic responses, characterized by myofibroblast activation and extracellular matrix production, in many chronic liver diseases. Matrix remodeling and metalloprotease activities play an important role in the regulation of HPC/OC proliferation and fibrosis progression. Thus, understanding molecular mechanisms underlying HPC/OC activation has therapeutic implications for rational design of anti-fibrotic therapies.

1. Introduction

The liver is a vital organ within the body. A broad range of hepatic insults such as hepatitis virus, alcohol, fat accumulation, and drug toxicity can damage the liver to result in steatohepatitis, fibrosis, cirrhosis, and even development of hepatocellular carcinoma. Liver diseases have been a major health concern worldwide because of their high prevalence and poor long-term clinical outcome. This is particularly true in China, where approximately 300 million people suffer from liver diseases.[1] Liver transplantation is the only curative option for end-stage liver disease, but sources of donors are limited. Thus, there is an urgent need to develop alternative therapeutic strategies. Hepatic stem/progenitor cells (HPCs), also known as oval cells (OCs) in rodents, are one potential suitable source for liver cell replacement. These cells can be activated through orchestrated signaling networks mediated by a plethora of growth factors, cytokines, and enzymes in response to severe liver injury and/or compromised hepatocyte function. Abnormal amplification of HPC/OCs is also associated with pathological scarring processes and may contribute to the development of liver cancer. Crosstalk among damaged epithelial components, pro-fibrotic mesenchymal elements, and pro-inflammatory immune cells, as well as specialized extracellular matrix (ECM) in the HPC niche, is of fundamental importance in sustaining HPC activation and liver fibrosis in disease conditions. This review covers experimental and clinical studies of HPC activation and associated liver fibrosis, with emphasis on mediators of ECM regulation in the HPC niche.

2. HPC/OC characteristics and origins

Liver stem/progenitor cells include unique populations that are able to differentiate into hepatic parenchymal cells, hepatocytes, and/or bile ductular epithelial cells. During development, hepatoblasts appear in the foregut endoderm, where they give rise to both hepatocytes and cholangiocytes.[2] Similarly, adult livers contain so-called HPC/OCs, a heterogeneous population of transit-amplifying cells that expand during severe liver damage upon inhibition of hepatocyte proliferation.[3] HPC activation in the form of ductular reactions has been observed in many pathophysiological processes of human liver diseases.[4] In rodents, HPC/OCs represent small hepatobiliary reactive cells approximately 10 μm in diameter with a large nuclear-to-cytoplasm ratio and oval-shaped nucleus (hence their name).[5] HPC/OCs represent dynamic cell populations that constantly change their phenotype depending on the injured cell type and consequent state of differentiation.[6] Despite lacking specific markers for HPC/OCs, a broad panel of surface antigens and intracellular proteins have been reported in these cells and their

☆ Edited by Peiling Zhu and Genshu Wang.

* Corresponding author.
E-mail address: lpi@peds.ufl.edu (L. Pi).

http://dx.doi.org/10.1016/j.livres.2017.08.002

Please cite this article in press as: Bria A, et al., Hepatic progenitor cell activation in liver repair, Liver Research (2017), http://dx.doi.org/10.1016/j.livres.2017.08.002

Table 1
Summary of markers immune-reactive for HPC/OC.

Marker name	Sources	Species	Author and references
Cytokeratin (K)7	Adult biliary marker	Human	Xiao et al.[7]
Cytokeratin (K)19	Adult biliary marker	Human	Lee et al.[8]
Cytokeratin (K)14	Adult biliary marker	Human	Xiao et al.[7]
Epithelial cell adhesion molecule (EPCAM)	Fetal hepatoblast and adult biliary marker	Mouse	Tanaka et al.[9]
		Human	Okabe et al.[10]
		Rat	Dan et al.[11]
			Schmelzer et al.[12]
			Yovchev et al.[13,14]
Sry-like HMG box protein 9 (Sox9)	Fetal hepatoblast and adult biliary marker	Mouse	Furuyama et al.[15]
Cytokeratin (K) 8	Adult hepatocyte marker	Human	Xiao et al.[7]
Cytokeratin (K) 18	Adult hepatocyte marker	Human	Xiao et al.[7]
c-Met	Adult hepatocyte marker	Human	Xiao et al.[7]
α-fetoprotein protein	Fetal hepatoblast marker	Mouse	Nierhoff et al.[16]
		Rat	Kuhlmann et al.[17]
		Human	Rao et al.[18]
Albumin	Adult hepatocyte marker	Mouse	Fausto et al.[19]
		Rat	Kuijk et al.[20]
		Human	Xiao et al.[7]
c-Kit	Fetal hepatoblast and adult hematopoietic marker	Mouse	Petersen et al.[21]
Sca-1	Fetal hepatoblast and adult hematopoietic marker	Mouse	Nierhoff et al.[16]
			Petersen et al.[21]
Thy-1 (CD90)	Adult hematopoietic marker	Rat	Petersen et al.[22]
Prominin/CD133	Adult hematopoietic marker	Mouse	Suzuki et al.[23]
C-X-C chemokine receptor type 4 (CXCR4)	Adult hematopoietic marker	Mouse	Cardinale et al.[24]
Neural cell adhesion molecule (NCAM)	Adult neural cell marker	Human	Cardinale et al.[24]

progeny (see Table 1).[7–24] Moreover, the bi-potential ability of HPC/OCs is evidenced by detection of markers for both bile ductular epithelial cells and hepatocytes in numerous experimental models and human studies.[8,19] HPC/OCs are thought to differentiate into hepatocytes to restore lost liver mass and function in response to hepatocyte damage, such as that occurring with severe viral hepatitis or massive hepatocyte loss in human patients.[7,25,26] In contrast, HPC/OCs mediate biliary regeneration in circumstances where bile ductular epithelium is the most damaged cell type, including diseases such as primary biliary cirrhosis or primary sclerosing cholangitis.[27] Recent studies using genetic lineage-tracing techniques in transgenic mice have challenged the contribution of HPC/OCs to liver regeneration.[28,29] Nevertheless, HPC/OC activation is often associated with myofibroblast cell activation and liver fibrosis during chronic liver disease.[30–32] In human studies, HPC/OCs accumulate as injuries become more severe, indicating HPC proliferation increases with progressively worsening liver injury and fibrosis.[32] Correlation between degree of HPC activation and the severity of liver disease has been shown in both acute and chronic human liver diseases.[31]

The origin of HPC/OCs is also a topic of contention with many different theories. Traditionally, they are considered to be small bile ductular epithelial cells located in the Canal of Hering, a transitional zone between the bile canaliculi and interlobular ductal systems in mammals.[33] An extrahepatic origin of rat OCs, such as bone marrow, has also been suggested.[34] In addition, it has been proposed that HPC/OCs may be derived from hepatic stellate cells (HSCs), as HSCs contain many of the same signaling pathways and express similar genes as undifferentiated cells in rats.[35] Other recent studies have demonstrated that conversion from hepatocytes or bile ductular epithelial cells to HPCs is a reversible process after recovery from injury, suggesting HPC/OCs may originate from dedifferentiation of mature hepatocytes or bile ductular epithelial cells in response to liver damage.[36] At least four distinct niches have been demonstrated: canal of Hering, intralobular bile ducts, periductal cells, and peribiliary hepatocytes.[37] The liver is believed to regenerate through a multi-tiered, flexible system rather than a single HPC/OC location in response to severe damage. This multi-tiered, flexible system determines phenotypic expression, proliferative capability, and differentiation properties of HPC/OCs under specific pathologic or pathophysiologic circumstances. Taken together, "location is everything", as Petersen and Shupe stated.[38] This explains the diversity of HPC responses in different niches under distinct injury models.

3. Experimental models of HPC/OC activation

HPC/OCs can be activated in a number of animal models. In rats, surgical removal of two-thirds of the liver lobe by partial hepatectomy (PHx) has been combined with administration of hepatoxins such as 2-acetylaminofluorene (2-AAF) to trigger an HPC/OC response.[39] In addition, bio-reactivation of chemicals can cause zonation-dependent regeneration. Allyl alcohol (AA) is metabolized to highly reactive aldehyde acrolein by alcohol dehydrogenase, which is principally localized in the periportal area.[40] Cytochrome P450 enzymes can convert CCl_4 into highly reactive metabolites that trigger lipid peroxidation, leading to hepatocyte death at centrilobular areas.[41] As shown in Fig. 1, activation of α-smooth muscle actin $(SMA)^+$ myofibroblast cells and collagen deposition are common features of both types of liver damage. However, AA induces extensive periportal proliferation, whereas CCl_4 intoxication causes hepatocyte proliferation in central lobular parenchyma (Fig. 2). Combining 2-AAF implantation with either type of chronic liver injury triggers a robust HPC/OC response.[42]

There is remarkable heterogeneity of HPC/OCs in rat and mouse models. For instance, 2-AAF is unable to trigger an HPC/OC response in mice.[43] Instead, mouse HPC/OCs are activated using different dietary or toxin models, including the choline-deficient ethionine-supplemented diet, 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet, and phenobarbital/cocaine.[44,45] The methionine-choline deficient (MCD) diet is also well known to induce fatty liver with HPC proliferation in mice.[46] These toxins can interfere with cellular and molecular mechanisms of liver regeneration through membrane damage, inflammatory reactions, or even activation of non-parenchymal cells such as Kupffer cells.[47] Recently, genetic murine models of HPC activation have been developed. For example, a system using β-napthoflavone for inducible deletion of Mdm2, an E3 ubiquitin-protein ligase that

Please cite this article in press as: Bria A, et al., Hepatic progenitor cell activation in liver repair, Liver Research (2017), http://dx.doi.org/10.1016/j.livres.2017.08.002