Pathogenesis and Prognosis of Hepatocellular Carcinoma at the Cellular and Molecular Levels

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KEYWORDS

• Hepatic progenitor cell features • Cell of origin • Phenotype switching
• Tumor behavior • Chemoresistant cancer stem cells • Prognosis
• Microenvironment

KEY POINTS

- Survival gene signature data sets that classify human hepatocellular carcinomas (HCCs) based on worse prognosis show a high expression of biliary-hepatic progenitor cell markers.
- Mechanisms of differentiation and/or dedifferentiation give rise to heterogeneity in human HCCs, reflecting the cell of origin.
- The plasticity of HCCs strongly depends on the interaction with the microenvironment.
- The expression of biliary-hepatic progenitor cell markers in HCCs linked with stemness features is a way to survive in a hostile environment.

INTRODUCTION

Liver cancer is the fifth most diagnosed cancer worldwide with an increasing incidence each year, making it the second leading cause of cancer-related death globally.[1] Hepatocellular carcinoma (HCC) represents the major histologic type of primary liver cancer, accounting for 70% to 85% of the total liver cancer burden worldwide, and has a phenotype resembling hepatocytes histologically, when examined microscopically on hematoxylin-eosin stain (H&E) specimens.[2,3] Although advances in imaging and surgery have improved the prognosis of HCC patients, HCC remains an ominous tumor because of high rates of metastases and recurrence.[4,5] About 80% of HCCs arise in a background of long-lasting chronic liver disease. To understand the pathogenesis of

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HCC, therefore, it is important to know what is happening in the chronically diseased liver. In normal, healthy circumstances the hepatocytes have a low turnover rate and a life expectancy of more than a year.[6] In response to parenchymal cell loss due to injuries such as partial hepatectomy or toxic injury, the liver can regenerate by proliferation of the main epithelial cell compartments (hepatocytes and cholangiocytes), followed by the proliferation of mesenchymal cell types (hepatic stellate cells) and endothelial cells. When the injury is too severe or when the hepatocytes become senescent (in part the result of ongoing proliferation during 20 to 30 years of chronic disease), activation and proliferation of a reserve compartment, the hepatic progenitor cells (HPCs), is observed.[7,8] This activation of HPCs is seen as a ductular reaction, which comprises an expansion of a transit amplifying cell compartment of small biliary cells located in the Hering canal, consisting of stem cell progeny that are destined to undergo terminal differentiation.[9,10] These small biliary cells can differentiate into biliary epithelial cells (cholangiocytes) or hepatocytes, depending on the underlying liver disease cause and which cell type is damaged the most. With differentiation toward hepatocytes, the HPCs gradually lose their biliary features. Keratin (K) 19, sex determining region Y-box 9 (SOX9), and tumor-associated calcium signal transducer 2 (TACSTD2 or TROP2) are some of the first markers they lose, followed by K7 and epithelial cell adhesion molecule (EPCAM), and an up-regulation of the HIPPO pathway and NUMB, an inhibitor of the Notch pathway (**Fig. 1**).[11–15] The regenerating liver is an ambient setting full of inflammation, stress, and signal-cell interactions pushing the HPCs toward a certain cell fate but also regulating apoptosis or senescence of the hepatocytes and forming scar tissue.[16] This background is a vivid and complex substrate in which HCCs arise. This article focuses on the pathogenesis of HCC at the cellular and molecular levels and, more specifically, on the mechanisms of differentiation and dedifferentiation in relation to their possible cells of origin and how the microenvironment plays an important role in tumor behavior and tumor heterogeneity.

PREDICTING TUMOR BEHAVIOR: A HIGH-THROUGHPUT APPROACH

In recent years, many research groups have linked molecular profiles with the prognosis of patients diagnosed with HCC. Although the molecular classification of HCCs is described in more detail in other publication, the authors would like to pause and highlight a few publications that are key to the understanding of human HCC behavior.[17–19] In 2004, Thorgeirsson and colleagues,[20] in collaboration with the authors' group, identified 2 different gene expression patterns, based on microarray analysis, in a set of 92 human HCC samples. The subclass, linked with a lower overall survival, showed a strong correlation with several survival genes involving hypoxia inducible factor 1a.[20] In extension of this research and using a larger data set of 139 HCC samples, models for predicting the risk of recurrence and the prognosis were constructed by integrating gene expression data from rat fetal hepatoblasts and from rat hepatocytes with human HCC profiles.[21] Patients whose tumors shared a similar gene expression pattern to that of fetal hepatoblasts and showed a higher expression for biliary-HPC markers (eg, *KRT19*, *KRT7*) had a poor overall outcome. During the succeeding years, many publications described the potential clinical use of gene signatures as prognostic markers for patients diagnosed with or treated for an HCC (**Table 1**).[22–28] Recently, a molecular scoring system based on the expression of only 5 genes (*HN1*, *RAN*, *RAMP3*, *KRT19*, and *TAF9*) was shown to predict the outcome of patients after resection of HCC.[29]

Stratifying human HCCs based on specific biliary-HPC markers and generating gene expression profiles of these subclasses, has been another approach to