REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Robert F. Schwabe and John W. Wiley, Section Editors

Role of the Microenvironment in the Pathogenesis and Treatment of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the most common primary liver tumor and the third greatest cause of cancer-related death worldwide, and its incidence is increasing. Despite the significant improvement in management of HCC over the past 30 years, there are no effective chemoprevention strategies, and only one systemic therapy has been approved for patients with advanced tumors. This drug, sorafenib, acts on tumor cells and the stroma. HCC develops from chronically damaged tissue that contains large amounts of inflammation and fibrosis, which also promote tumor progression and resistance to therapy. Increasing our understanding of how stromal components interact with cancer cells and the signaling pathways involved could help identify new therapeutic and chemopreventive targets.

Keywords: Liver Cancer; Extracellular Matrix; Angiogenesis; Chemoprevention.

Hepatocellular carcinoma (HCC) is the most common primary form of liver cancer and the third most deadly type of cancer globally, following lung and stomach cancers.[1] With more than 750,000 new cases diagnosed every year worldwide, HCC is the sixth most common neoplasm.[2] Unlike other carcinomas, its incidence is steeply increasing, mainly due to the increasing prevalence of advanced hepatitis C virus (HCV) infection. HCC commonly arises in the setting of cirrhosis (>80% of cases), appearing 20 to 30 years after the initial insult to the liver. The use of antivirals and vaccination has successfully diminished the incidence of hepatitis B virus (HBV)-related HCC, although there are no effective chemopreventive strategies to attenuate the development of cancer once cirrhosis is established.[3] HCC is diagnosed in most patients at advanced/symptomatic stages, when limited therapeutic options are available. The results of the randomized phase 3 SHARP (Sorafenib HCC Assessment Randomized Protocol) trial showed that the multikinase inhibitor sorafenib improved overall survival of patients with advanced HCC,[4] representing a breakthrough in the clinical management of this cancer.

The liver tumor microenvironment is a complex mixture of tumoral cells within the extracellular matrix (ECM), combined with a complex mix of stromal cells and the proteins they secrete. Together, these elements contribute to the carcinogenic process. Cancer cells do not manifest the disease alone, and the stroma is inappropriately activated in cancer to contribute to malignant characteristics of tumor cells. The tumor microenvironment and the tumor cells create a complex cellular system with reciprocal signaling (Figure 1).

Stromal components of the microenvironment can be divided into 3 subclasses: angiogenic cells, immune cells, and cancer-associated fibroblastic cells. There is growing evidence of the contribution of stromal cells to the hallmarks of cancer: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming energy metabolism, and evading immune destruction.[5] Alterations within the microenvironment may favor tumor progression and play an important role in chemoresistance.[6,7] Targeting stromal cells to abrogate their tumor-supporting role represents an attractive therapeutic strategy.

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Abbreviations used in this paper: CSC, cancer stem cell; EC, endothelial cell; ECM, extracellular matrix; EGF, epidermal growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; HIF-1, hypoxia-inducible factor 1; IL, interleukin; MMP, metalloproteinase; NF-κB, nuclear factor κB; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; TAF, tumor-associated fibroblast; TAM, tumor-associated macrophage; TIMP, tissue inhibitor of metalloproteinase; Treg, regulatory T cell; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2013.01.002

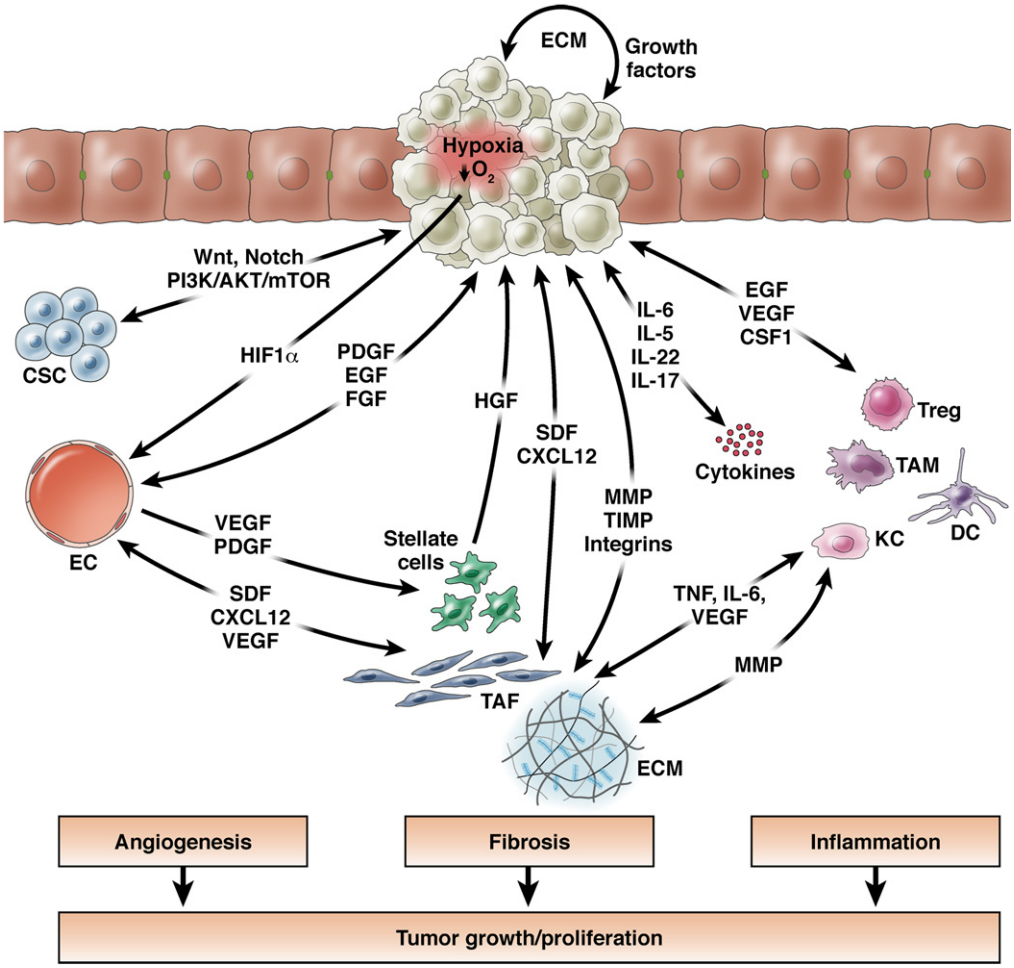

Figure 1. Cellular components of the microenvironment and molecular mechanisms influencing tumor growth and progression. Interactions among stromal, inflammatory, and cancer cells create a complex, permissive microenvironment that favors tumor progression. TAFs, tumor associated fibroblasts; CSF-1, colony stimulating factor 1; EC, endothelial cells; KC, Kupffer cells; VEGF, vascular endothelial growth factor; FGF, Fibroblast growth factor; PDGF, platelet-derived endothelial cell growth factor; Tregs, regulatory T cells; HGF, Hepatocyte Growth Factor; EGFR, Epidermal Growth Factor Receptor; MMPs, metaloproteinases; TIMP, Tissue Inhibitor of Metalloproteinases; HIF-1, HIF-1, hypoxia-inducible factor 1; TAM, Tumor associated macrophages; SDF-1, stromal cell-derived factor 1; CSC, Cancer stem cells; DC, Dendritic cells; TNF, Tumor Necrosis Factor.

The role of the microenvironment in tumor initiation and progression in HCC is critical. For instance, the status of nontumoral tissue has an important role in predicting tumor recurrence, which affects 70% of patients after resection or local ablation.[8] Typically, there are 2 patterns of HCC recurrence: true metastasis of the primary tumor (generally within 2 years following resection/transplantation, defined as "early recurrence") and de novo tumor (after 2 years from treatment or "late recurrence").[9,10] Among these features, late recurrence is generally dictated by the persistence of protumorigenic signals within the damaged milieu of the fibrotic and cirrhotic liver[11]; distinct molecular subgroups of HCC have been identified and linked to poor prognosis.[12–17] In another context, the information encoded within the surrounding adjacent nontumoral tissue is essential to predicting the outcome of patients at very early stages (ie, tumors less than 2 cm without vascular invasion or extrahepatic spread) and may be even more relevant than the genomic profile of the tumor itself.[10] These findings highlight the profound involvement of a dynamic network of nontumoral cells, molecules, and soluble factors in the generation of a supportive and permissive environment for initiation and progression of HCC.

In this review, we provide an overview of current knowledge on the role of the tumor microenvironment in HCC and highlight potential prognostic and therapeutic implications.

Importance of the Tumor Microenvironment

The development and progression of HCC is a multistage process. A chronic insult (eg, HCV, HBV, and alcohol) induces liver injury through reactive oxygen species (ROS) production, cellular DNA damage, endoplasmic reticulum stress, and necrosis of damaged hepatocytes. Most HCCs arise in the setting of chronic hepatitis induced by HCV or HBV infection. HCV is a single-stranded RNA virus that cannot integrate into the host genome but triggers an immune-mediated inflammatory response that promotes neoplastic transformation of damaged hepatocytes. Conversely, HBV can integrate into the genome of infected hepatocytes and promotes hepatocarcinogenesis through sustained inflammatory damage, hepatocyte regeneration, direct oncogenic transformation following integration of the viral genome into host genes, and the transactivating potential of several viral oncoproteins, especially HBx. The sustained dysregulation of the liver cell by HBV infection can ultimately affect DNA repair mechanisms and promote mutational events, which contribute to malignant transformation of hepatocytes.

The hepatic response involves the activation of hepatic stellate cells and macrophages, which produce