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Lymphotoxins: New Targets for Hepatocellular Carcinoma

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In this issue of *Cancer Cell*, Haybaeck et al. unravel the role of lymphotoxin pathway in the development of hepatocellular carcinoma (HCC). Aberrant activation of this cascade in mice livers recapitulates the stages of fibrosis and inflammation that precedes human liver cancer, providing a novel family of potential therapeutic targets.

Hepatocellular carcinoma (HCC) is, worldwide, the third cause of cancer-related death and one of the fastest growing malignancies in terms of incidence in Western populations (Llovet et al., 2003). Despite recent progress, HCC is still considered a disease with poor prognosis because less than 30% of cases are eligible for potential curative treatments (e.g., surgical resection, liver transplantation, or percutaneous ablation). Recent results of a phase III trial showed that sorafenib, a multikinase inhibitor of BRAF, PDGFR, and VEGFR, significantly improved survival in patients with advanced tumors (Llovet et al., 2008). This pivotal study established a new standard of care for these patients and cleared the path for the development of novel molecular therapies for this malignancy.

Molecular bases that link inflammation and cancer have been progressively uncovered. Robust epidemiological data support the role of inflammation induced by chronic hepatitis B or C viral infections and alcohol abuse as a key player in HCC development. However, the exact molecular mechanisms and gatekeepers accounting for cellular transformation remain elusive. In this issue of *Cancer Cell*, Haybaeck et al. describe the role of sustained lymphotoxin signaling in HCC development (Haybaeck et al., 2009). The authors found aberrant expression of lymphotoxins α and β and LTβ receptor in human samples, and by applying numerous animal models, they teased out some relevant molecular mechanisms of hepatitis-induced HCC. Transgenic mice overexpressing lymphotoxins α and β in hepatocytes developed chronic hepatitis at 9 months and HCC at 12 months, which ultimately disseminate. To investigate the mechanisms by which hepatitis and HCC were induced, the authors crossed these mice with 4 different knockout mice (TNF receptor 1, TNF receptor 2, hepatocyte IKK kinase β, and mature B and T lymphocytes depletion), showing that NF-κB pathway is important for liver inflammation and HCC development.

The identification of lymphotoxin activated signaling as key in HCC development was confirmed by the fact that the administration of lymphotoxin antagonists for 2 months in mice with chronic hepatitis reduced inflammatory activity and prevented the development of HCC compared to control animals. Overall, these data introduce lymphotoxins as a novel family of potential targets for HCC chemoprevention and suggest antifibrotic activity by blocking lymphotoxin signaling. In addition, it complements previous knowledge on NF-κB involvement in HCC (Karin, 2006), and supports efforts to evaluate pharmacologic modulation of this pathway in the clinical arena.

Despite several attempts, there is no efficacious drug for prevention of HCC development in cirrhotic patients. Chronic administration of interferon failed to show significant benefits in preventing cancer development in patients with advanced fibrosis or cirrhosis (Di Bisceglie et al., 2008). This disappointing scenario results from the elementary understanding of the key gatekeepers and early molecular events leading to human hepatocarcinogenesis and also reflects the lack of an accurate marker to identify patients at high risk for HCC development. The potential role of growth factors in this process has been highlighted by recent studies with human and experimental data. A case-control study found a 4-fold increased risk of HCC development in cirrhotic patients with a specific single nucleotide polymorphism located in the epidermal growth factor (EGF) gene (Tanabe et al., 2008). Subsequent experiments showed that this polymorphism favors EGF stability and, thus, enhances signaling through the EGF receptor in vitro. Furthermore, gefitinib, a selective EGF receptor tyrosine kinase inhibitor, was able to prevent tumor development in a chemical-induced model of HCC in rats (Schiffer et al., 2005). Another growth factor cascade, the platelet-derived growth factor (PDGF) pathway, has also been implicated in the transition from liver inflammation to HCC. Transgenic mice overexpressing PDGFR-C adequately recapitulate the sequence of histological events that precede HCC in humans (i.e., esteatosis, fibrosis, and dysplasia), ultimately developing HCC at 9 months of age (Campbell et al., 2005) (Figure 1).

The advent of high-throughput genomic technologies has allowed pinpointing potential gatekeepers and defining at-risk populations for tumor recurrence. Two recent translational studies have underscored the role of liver inflammation in the initiation and dissemination of HCC.

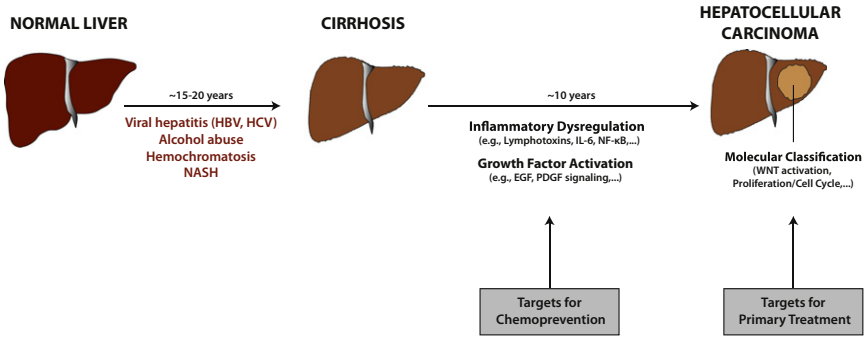

Figure 1. Potential Targets of Prevention and Treatment of Hepatocellular Carcinoma
Viral hepatitis and alcohol abuse are the main risk factors for developing chronic liver inflammation leading to advanced fibrosis and cirrhosis. Once advanced fibrosis has been established, evidence suggests the implication of inflammatory signals and growth factor cascades in the development of HCC. In this setting, chemoprevention strategies are expected to target key pro-oncogenic molecules. In established HCC, the molecular classification of the tumors would allow targeting specific pathways and oncogenic loops in a more personalized manner.

In the first study conducted in more than 300 HCC patients, downstream targets of interleukin-6 were strongly enriched in a gene signature able to identify patients with poor survival after surgical resection (Hoshida et al., 2008). Prognosis of these patients was mainly determined by the occurrence of de novo HCC, suggesting that the signature was capturing molecular features related to new primary tumors arising in an already damaged organ ("field effect"). The second study, conducted mainly on HBV cirrhotic patients, identified a gene signature correlated to the risk of developing intrahepatic metastasis (Budhu et al., 2006). This signature showed a marked increase in Th2 cytokines, implying that an anti-inflammatory status precedes patients with metastatic HCC (Figure 1). In the current study, lymphotoxin transgenic mice developed multifocal tumors with identical chromosomal aberrations, indicating clonal spread from the primary tumor. The implication of this pathway in intrahepatic dissemination also suggests that lymphotoxin antagonists could play a role in the treatment of overt HCC. Unfortunately, lymphotoxin pathway inhibitors, such as baminercept (Biogen Idec, Cambrigde, MA), have so far only been tested in inflammatory diseases (e.g., rheumatoid arthritis).

Different investigators have identified subgroups of HCC patients based on homologies in their tumor gene expression profiles. Among them, samples with activation of WNT canonical pathway and those enriched in genes related to cell cycling and proliferation are common among different studies. In addition, genomic data suggest that a subset of tumors (~15%–20%) may have a progenitor origin. Interestingly, Haybaeck et al. observed proliferation of A6+ oval cells in chronically inflamed lymphotoxin transgenic livers. Whether this pathway is relevant to cancer stem cell proliferation remains to be explored.

From the chemopreventive standpoint, it is plausible that modulation of the inflammatory response, (e.g., targeting IL-6, NF-κB, and lymphotoxin pathways) along with abrogation of different growth factor pathways (e.g., EGFR and PDGFR inhibitors) will be required to counteract some of the numerous oncogenic signals present in cirrhotic tissue. In this sense, an adequate monitoring of side effects related to new molecular therapies will be essential. Selection of the appropriate chemoprevention strategy will depend on the predominant molecular mechanism of tumor development in a given patient. Once the tumor has been developed, integration of the genomic information from the tumor and the adjacent cirrhotic tissue with other clinical variables will determine patient prognosis and guide the therapeutic decision making. In this sense, data presented by Haybaeck et al. provide scientists with a novel molecular bridge between hepatic inflammation and oncogenesis, opening new opportunities for selective therapies in the setting of prevention and treatment of primary liver cancers.

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