Presentation Overview: Liver Growth Biology

Primary liver cancer (including hepatocellular carcinoma and tumors of the intrahepatic biliary tract) represents the fifth most common form of neoplastic disease world-wide (accounting for >5% of all human cancers) and the third most common cause of cancer-related death (1-4). The majority of primary liver tumors are hepatocellular carcinomas. The world regions of highest incidence of hepatocellular carcinoma include Eastern Asia and sub-Saharan Africa (3, 4). In contrast, North and South America, Northern Europe, and Australia have very low incidence of hepatocellular carcinoma (3, 4). The world-wide variation in incidence of hepatocellular carcinoma largely reflects variations in risk factors for the resident populations, particularly exposure to hepatitis viruses (5, 6). Other risk factors associated with the development of hepatocellular carcinoma include gender, dietary factors (including alcohol consumption and exposure to Aflatoxin B1), other environmental exposures, and various genetic (metabolic) diseases (6, 7). All of these risk factors contribute to chronic liver disease, which may be the most important determinant of liver cancer risk. Numerous recent studies have documented changes in the world-wide incidence of hepatocellular carcinoma, including increasing numbers of cases in historically low prevalence areas. These studies suggest that hepatocellular carcinoma will emerge as a major form of malignant cancer in the United States in the coming decades if current trends persist (8-11). The dramatic recent increase in hepatocellular carcinoma in the United States is attributed primarily to HCV infection, and less so to HBV infection (9). The continuing high incidence of hepatocellular carcinoma in Eastern Asia and sub-Saharan Africa, combined with the increasing incidence of this disease in other parts of the world, suggests that this disease will continue to represent a global health problem into the future. Thus, additional investigation of hepatocellular carcinoma is required to elucidate the molecular and cellular basis of the disease, and to uncover opportunities for development of new strategies for prevention, diagnosis, and treatment.

The adult mammalian liver is proliferatively quiescent under normal conditions, with minimal rates of cellular division and apoptosis (12). However, the regenerative capability of the mammalian liver is well known (13-15). The extensive proliferative capacity of the mature (fully differentiated) hepatocyte is clearly demonstrated following surgical partial hepatectomy (16, 17), and it has been suggested that the hepatocyte be unrestricted in its ability to give rise to new cells (18). Various forms of liver injury and certain disease states are characterized by reactivation of cellular proliferation. Important among these from the perspective of risk for development of hepatocellular carcinoma are chronic hepatitis and cirrhosis. In both chronic hepatitis (either viral or alcohol-related) and cirrhosis there are significant levels of hepatocyte cell death (necrotic injury) and cellular proliferation (regeneration). The majority of human hepatocellular carcinomas occur in the setting of the cirrhotic liver (19, 20). Since cirrhosis is a
consequence of persistent hepatitis, the association of cirrhotic liver with preneoplastic lesions (such as liver cell dysplasia) may reflect the culmination of long-term injury to the liver. Likewise, persistent proliferation of various cell types in chronic liver injury increases their susceptibility to carcinogenesis.

While the molecular mechanisms of hepatocarcinogenesis have been well studied (21, 22), the cells of origin of the various primary liver tumors (including hepatocellular carcinoma and cholangiocarcinoma) have not been definitively identified. Nonetheless, there are several obvious candidate cell types that might give rise to the major hepatocellular neoplasms. Hepatocellular carcinoma is a tumor composed of aberrant hepatocytes of varying degree of differentiation (from well differentiated to poorly differentiated). One possible cell of origin for this tumor is the mature parenchymal hepatocyte. Experimental studies show clearly that proliferative cells are much more susceptible to carcinogenic insult when they are proliferative (or contain a high S-phase fraction within the population) (23). Thus, the hepatocytes that constitute regenerative nodules in liver cirrhosis may be the targets of neoplastic transformation through endogenous mechanisms or exogenous exposures. In world regions that have a high prevalence of hepatocellular carcinoma, the at-risk population is HBV-positive and exposed to dietary Aflatoxin B1 (24-27). Thus, among these people, chronic liver injury related to HBV occurs in the presence of the potent and direct-acting hepatocarcinogen AFB1 (28, 29). This mechanism seems plausible for the origin and generation of well differentiated hepatocellular carcinoma. However, there is great debate over the origin of less well differentiated tumors. The concept of “de-differentiation” of hepatocytes has never been very popular, but remains a possibility. The alternative hypothesis invokes the possibility that undifferentiated (or less differentiated) stem cells might be the target cells for hepatocarcinogenesis (30-33). Clearly, a stem cell origin of liver tumors could account for all histological forms of these neoplasms, as well as the less differentiated and well differentiated tumor types. However, the existence of liver stem cells has been the subject of some controversy, particularly in humans (34, 35). Thus, the debate remains open to several possibilities. It is likely that with further investigation, we will discover that there are multiple cell types that can function as precursors for hepatocellular tumors, including differentiated cell types and liver progenitor cells.

In this presentation, the cell types and kinetics of cell proliferation in normal and pathological liver will be described with the objective of reviewing the evidence related to the possible cells of origin of the primary liver neoplasms. The literature cited in this overview represents a limited selection of major reviews and/or primary contributions to the field. Interested persons should consult these papers and the citations contained therein for a more complete treatment of the cell biology of normal and neoplastic liver.

**Literature Cited**