Molecular basis of carcinogenesis of bile duct cancer

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Cholangiocarcinoma refers a tumor arising from epithelial cells lining intrahepatic or extrahepatic bile ducts. Intrahepatic cholangiocarcinoma occurrs in peripheral ducts of the liver and accounts for 10% of cholangiocarcinoma. Although extended resection has improved survival in patients with cholangiocarcinoma, large proportion of the tumors are discovered at advanced stage and are mandated for systemic chemotherapy. Chemotherapy brings poor response and only provides marginal survival benefit and improved quality of life, which is attributed to the inherent biochemical and cellular characteristics of tumor cells. Compared to more common colon or pancreatic cancer, the molecular pathogenesis of cholangiocarcinoma has not been well understood. This risk factors of cholangiocarcinoma include chronic parasite infestation such as Clonorchis sinensis and Opisthorchis viverrini, primary slcerosing cholangitis, choledochal cyst, and biliary stone disease, which accompany chronic inflammation. Thus, molecular changes involved in the formation of cholangiocarcinoma are associtated with chronic inflammation. Chronic biliary inflammation/infection and cholestasis induce cytokines expression from cholangiocytes and inflammatory cells, which in turn results in autonomous proliferation and dysregulation of apoptosis mechanism. This milieu caused by chronic inflammation is a fundamental step of cholangiocarcinogenesis constantly enhance cellular proliferation by ongoing expression of mitogenic factors. Among the cytokines, interleukin-6, TGFß, IL-8, TNFα, and PDGFB play crucial role in the development of cholangiocarcinoma. IL-6 production is commonly increased in the course of chronic inflammation and tumorigenesis, and exerts by both autocrine and paracrine mechanism. Downstream effects of cytokine signaling include activation of MAPK pathway, decrease of p21, upregulation of anti-apoptotic factors. Nitric oxide (NO) is also involved. Cytokines induce expression of iNOS, which has been observed in cholangiocytes under chronic inflammation and tumorigenesis. iNOS increases NO production resulting in inhbition of DNA repair proteins and pro-apoptotic enzymes. iNOS also activate notch signaling by up-regulation of Notch1 expression. Notch plays key role in cell differentiation and is frequently up-regulated in inflammed chongiocytes and tumor cells. COX2 overexpression is another finding bridging inflammation and cancer. COX2 overexpression enhances cellular proliferation. Among the growth factors and receptors, ErbB-2 and Met are well-known to be increased in early phase of cholangiocarcinogenesis. Dysregulation of apoptosis mechanism is also a crucial mechanism of tumorigenesis. Altered expression or mutation of Bcl-2, K-ras, and p53 gene has been documented in cholangiocarcinoma. At later stage of chol-

angicarcinomagenesis, overexpression of VEGF and MMPs play important role for angiogenesis and cell invasion/metastasis. Besides, altered expression of cell adhesion molecules is involved in cell invasion/metastasis. The dismal prognosis of cholangiocarcinoma is due to the facte that cholangiocarcinoma is usually diagnosed at advanced stage, when any therapeutic modalities are no longer curative but assume a role of palliation. Ongoing exploration of molecular pathogenesis for cholangiocarcinoma will offer the possibility of developing newer diagnostic tools for early diagnosis as well as potential therapeutic target for cholangiocarcinoma.