Insights about cholangiocarcinoma and its pathology as well as pathogenesis.

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Introduction

The second most frequent primary malignancy is Cholangiocarcinoma (CCA). Despite being more prevalent in Asia, it has become more widespread in Europe and North America in recent years. The outlook for CCA is bleak. The sole potentially curative option is surgery, but most patients have severe disease and recurrence after resection is frequent. Our knowledge of the molecular biology of this cancer has greatly expanded over the past 20 years and new diagnostic procedures and therapeutic strategies have been devised [1].

Description

The most frequent primary hepatic cancer and the most frequent biliary tract cancer are both Cholangiocarcinomas (CCA). It is divided by subtypes that are intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA). The most frequent primary hepatic cancer and the most frequent biliary tract cancer are both Cholangiocarcinomas (CCA). It is divided by subtypes that are intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA) [2].

Globally, hepatobiliary malignancies account for 13% of cancer related deaths, but they only account for 3% in the US. 15% to 20% of primary hepatobiliary cancers are CCAs. The incidence rates of CCA vary significantly between and between continents. The regions with the greatest CCA incidence rates are Southeast Asia and Australia, respectively. Its annual incidence in Southeast Asia ranges from 0.1/100,000 to 71.3/100,000. Incidence rates in the United States range from 0.6/100,000 to 1.0/100,000, whereas those in Europe range from 0.4/100,000 to 1.8/100,000.

Age Adjusted Incidence Rates (AAIR) of iCCA has risen in Western Europe during the past three decades, while extrahepatic CCA incidence has been constant to declining. It is interesting to note that over the past 40 years, the AAIR of extrahepatic CCA has dramatically grown in the United States whereas the total incidence of iCCA has remained steady [3]. There are no known reasons for the shifting incidence trends. Annual mortality rates of iCCA fell by 2.5% in the US during the past ten years while rising by 9% in Europe. CCA has a male to female ratio of 1:1.2-1.5.

Most patients don't have any known risk factors when they develop CCA. A lifetime risk of 5% to 20% exists for CCA in PSC patients. Only 10% of CCA, however, may be linked to PSC. Typically, CCA is identified 4 years, on average, after the PSC diagnosis. Bowel inflammation is not a standalone risk factor for CCA in PSC. One potential independent risk factor for iCCA has been identified: Cirrhosis. The prevalence based variability in the data on hepatitis B and C viruses as risk factors for CCA calls for additional validation [4].

CCA are categorised as mass forming, periductal infiltrates or intraductal papillary according on their macroscopic development pattern. iCCA tend to develop large masses, whereas pCCA frequently infiltrate periductal tissues. 90% to 95% of CCAs are histopathologically classified as moderately to poorly differentiated adenocarcinomas with typical mucin expression and strongly desmoplastic stroma. Although CK7 and CK19 expression are specific to CCA, both proteins can also be seen in metastatic adenocarcinomas and Hepatocellular Carcinoma (HCC) [5].

Preclinical studies indicate that hepatic progenitor cells are the cells of origin for CCA, an epithelial cancer that develops from converted cholangiocytes. Cholangiocarcinogenesis is largely influenced by inflammation and cholestasis. Interleukin-6 (IL-6) and other proinflammatory cytokines cause excess nitric oxide, which in turn causes oxidative DNA damage, inhibits DNA repair enzymes and induces the production of Cyclooxygenase-2. (COX-2). Cholestasis is a result of proinflammatory pathways' down regulation of hepatobiliary transporters. Oxysterols and bile acids stimulate COX-2 expression and EGFR activity, respectively. In addition to positively regulating pro-oncogenic signalling pathways such Hepatocyte Growth Factor (HGF), IL-6 and EGFR, COX-2 also dysregulates CCA growth and apoptosis resistance.

Conclusion

Key signalling pathways in cholangiocarcinogenesis include the IL-6 receptor, c-MET and the EGFR family members ERBB2 and ERBB1. In order to stimulate their respective receptors, CCA cells and cancer associated fibroblasts produce and secrete cytokines and other mitogenic growth factors (such as IL-6 and HGF). The inactivation of negative feedback mechanisms, receptor transactivation between c-MET/EGFR and COX-2/IL-6 and receptor overexpression (IL-6R, c-MET and EGFR) all contribute to constitutive system activation. Dysregulation of cell senescence, cell cycle regulation, proliferation and apoptosis result from abnormal activation of these receptor tyrosine kinases. These downstream signalling cascades include Janus Kinase (JAK)/Signal Transducer and

Activator of Transcription 3 (STAT3), PI3K/Akt, ERK1/2 and p38MAPK.

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