Cholangiocarcinomas are adenocarcinomas arising from cholangiocytes, the epithelial cells lining the bile duct apparatus. Because the biliary tree is both intra- and extrahepatic, cholangiocarcinomas likewise may arise within the liver parenchyma or from the extrahepatic bile ducts. Cholangiocarcinomas arising within the hepatic parenchyma often present as intrahepatic mass lesions whereas cancers developing along the extrahepatic ducts cause mechanical biliary obstruction with jaundice, pruritus, acholic stools, and weight loss. For reasons unexplained, the extrahepatic ductal cholangiocarcinomas frequently involve the hilum of the liver, the junction of the right and left hepatic ducts. These perihilar ductal cholangiocarcinomas, therefore, frequently present with biliary obstruction of one or both lobes of the liver.

Several epidemiologic studies have now demonstrated an increase in the incidence of cholangiocarcinoma in Western countries [1–4]. Because the incidence of cholangiocarcinoma is increasing, most hepatologists now frequently encounter this disease. Many patients with cholangiocarcinoma do not have identified risk factors for this disease. However, established risk factors include primary sclerosing cholangitis, biliary-enteric drainage procedures associated with cholangitis, Caroli’s disease, congenital choledochal cysts, chronic hepatic lithiasis, and liver fluke infestations (Clonorchis sinensis and Opisthorchis viverrini infections) [5]. In primary sclerosing cholangitis the risk of developing cholangiocarcinoma is approximately 0.5–1.5% per year [6]. The common link between these risk factors and cholangiocarcinoma is chronic inflammation. Like other organs in the gastrointestinal tract, chronic inflammation of the biliary tree predisposes to carcinogenesis. Chronic inflammation is associated with inflammatory cytokines which serve as cholangiocyte mitogens (interleukin-6), nitrosative and oxidative stress causing DNA damage, and the induction of tumor promoting proteins (i.e. cyclooxygenase-2) [7–10]. These concomitant processes likely promote initiation, promotion and progression of these neoplasms.

Therapy for cholangiocarcinoma is limited. Surgical extirpation is thought to be the treatment of choice, but resection for cure is often not feasible due to: (i) anatomic location of the cancer (spread to the secondary bifurcations of both the right and left hepatic ducts or involvement of the contralateral lobar vessels with ipsilateral extension into the secondary duct bifurcations of the primarily affected lobe); and/or (ii) the presence of extra- or intrahepatic metastases [11,12]. Furthermore, death due to recurrent disease occurs in the majority of patients thought to be resected for cure (i.e. disease-free margins). Liver transplantation leads to excellent long-term disease-free survival in highly selected patients receiving preoperative chemoradiation therapy [13–15]. However, most patients present with advanced disease and are not eligible for this therapeutic modality. For these patients, relief of biliary obstruction via mechanical or plastic biliary stents with or without photodynamic therapy constitute the only palliative options [5]. A recent consensus conference on this disease concluded that there are no data supporting a survival advantage for patients receiving radiation and/or cytotoxic chemotherapy [5]. Thus, therapeutic options are limited for many cholangiocarcinoma patients. Further, advances in the therapy of cholangiocarcinoma will most likely be predicated on a molecular understanding of this disease.

Advanced cancers are like military institutions manifesting growth, possessing strong defense mechanisms (e.g. avoidance of apoptosis), and having the ability to attack, e.g., processes authorizing tissue invasion and metastasis. To accomplish these cellular alterations molecular events activating oncogenes, inactivating tumor suppressor genes, blocking DNA repair processes, and inducing limitless replication for survival must occur. Recent advances have demonstrated that cholangiocarcinomas frequently express COX-2 (an enzyme involved in prostanoid metabolism), and c-erbB-2 and c-met, receptor tyrosine kinases [16].
COX-2 may help these cells avoid apoptosis [17], while c-erbB-2 is a growth promoting receptor tyrosine kinase. These observations suggest that selective receptor tyrosine kinase inhibitors and COX-2 inhibitors may ultimately have a therapeutic role in the treatment of these cancers [16]. However, clearly other therapies and approaches will also be needed.

A major characteristic of cholangiocarcinomas is their highly infiltrative growth pattern, resulting in lymphatic and intrahepatic metastases. The identification of genes and gene products responsible for authorizing this invasive behavior may lead to additional therapeutic approaches for this neoplasm. In this issue of the Journal, Maeda et al. report on such a protein: aspartyl (asparaginyl) β-hydroxylase (AAH), an α-ketoglutarate-dependent dioxygenase that catalyzes post-translational hydroxylation of aspartate and asparagines residues in EGF-like domains of proteins [18]. This research group had previously demonstrated overexpression of AAH in cholangiocarcinomas, and minimal expression in normal, regenerating and benign cholangiocytes [19,20]. Given the fact that AAH hydroxylation consensus sequences are present in Notch proteins which are important in cell migration, the current authors assessed the role of AAH in regulating invasive cholangiocarcinoma growth [21]. Employing five human cholangiocarcinoma cell lines, and a directional motility assay using Boyden chambers, the importance of AAH in directional cell motility, a surrogate for invasion/metastases, was examined. The cellular number on each side of the chamber was quantitated as a surrogate for invasion/metastases, was examined. The cellular number on each side of the chamber was quantitated employing a clever assay measuring ATP to assess cell viability. Inhibiting AAH expression with well-controlled antisense approaches also attenuated cell migration in the Boyden chamber. Thus, AAH expression by cholangiocarcinomas may contribute to the infiltrating growth of this neoplasm, although such a conclusion will ultimately require in vivo studies.

What are the therapeutic implications of this research? The obvious question is whether inhibiting a cancer from invading tissues and developing metastasis is beneficial. From a conceptual perspective such a tumor would still obstruct bile ducts and expand from its growth potential but may not be able to infiltrate adjacent structures. Treating such a tumor with antisense or perhaps small inhibitory RNAs directed against AAH may render the tumor a chronic disease which could be treated with additional cytotoxic modalities such as radiation therapy. Alternatively, inhibiting tumor infiltration could be very useful as an adjuvant therapy following surgical resection as it may render the micrometastases responsible for many recurrent cancers clinically unapparent. Given the disappointing clinical experience with angiogenesis inhibitors, a unidimensional approach, however, is unlikely to be successful and will need to be coupled to additional oncologic therapies.

AAH is also unique in that it is a surface protein preferentially expressed by cholangiocarcinomas as compared to normal cholangiocytes [20]. This selective and preferential expression by these cancers suggests that AAH could be used to target therapies. For example, monoclonal or polyclonal antisera against AAH coupled to anti-cancer agents would allow specific targeting of therapies against cells expressing this surface antigen. Thus, the work with AAH has many potential therapeutic implications for which we eagerly await their development and application.

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References


