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Cholangiocarcinoma: Estrogen-induced autocrine effects of VEGF on cell proliferation

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Cholangiocarcinoma arises from the neoplastic transformation of the epithelial cells that line the intra- and extra hepatic bile ducts ¹. Symptoms are usually evident after blockage of the bile duct by the tumor and, at this late stage; they are relatively resistant to chemotherapy and radiation therapy ¹. Therefore, the challenges posed by these often lethal biliary tract cancers are daunting, with conventional treatment options being limited and the only hope for long-term survival being that of complete surgical resection of the tumor ¹. Further understanding into the factors that are involved in tumor initiation, promotion and progression are required to design alternate therapies to combat this devastating disease.

Current theories of the pathogenesis of cholangiocarcinoma are centered on chronic inflammation and aberrant secretion of various growth factors, which lead to subsequent unchecked cell proliferation and neo-angiogenesis among other events. Indeed a number of risk factors for the development of cholangiocarcinoma have an inflammatory component including chronic hepatitis C infection, parasitic biliary infection, and such inflammatory diseases as primary sclerosing cholangitis and Caroli's syndrome ¹. Persistent inflammation is thought to promote carcinogenesis by causing DNA damage, activating tissue reparative proliferation and by creating a local environment that is enriched with cytokines and other growth factors such as epidermal growth factor, transforming growth factor- β and hepatocyte growth factor ². Furthermore, there is a considerable degree of angiogenesis in cholangiocarcinoma compared to that in other solid tumors ³ and that the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and angiopoietin 2 were found to be increased in the majority of cholangiocarcinoma samples studied ³.

Recently, Alvaro et al ⁴ showed that human biopsy samples from patients suffering from cholangiocarcinoma showed positive immunoreactivity for estrogen receptor (ER) α and β , insulin-like growth factor-1 (IGF-1) and IGF receptor (IGFR) that were absent in non-malignant biliary epithelia. Furthermore, addition of either estrogen or IGF-1 to cholangiocarcinoma cells increased cell proliferation, which could be blocked by the ER antagonist and IGFR blocking antibody, respectively ⁴. Addition of estrogen and IGF-1 together had an additive effect on cell proliferation and there was some evidence of crosstalk between the two receptor-systems with estrogen requiring an intact and functional IGFR for its proliferative effects ⁴. The crosstalk between estrogen and IGF in the modulation of cell proliferation has been noted in a number of other cell types ⁵

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In the current issue of *Digestive and Liver Diseases*, Mancino *et al* extend these findings to eloquently show that estrogen can enhance the expression and secretion of VEGF-A, VEGF-C, and the receptors VEGFR-1, -2 and -3 in a cholangiocarcinoma cell line, which could be inhibited by the specific ER antagonist or the IGFR blocking antibody. Furthermore, the growth promoting effects of estrogen could be partially inhibited by a receptor-based VEGF inhibitor, and that the addition of recombinant VEGF-A to cholangiocarcinoma cells also increased cell proliferation, although to a lesser extent as estrogen. Taken together these data clearly demonstrate that estrogen, via the activation of both ER and IGFR, increase the expression and release of VEGF which may then act in an autocrine fashion to regulate the enhanced cell proliferation observed after estrogen treatment. These data provide evidence to support the novel concept that, in addition to its role as an angiogenic factor, VEGF may also play a role in sustaining the unchecked proliferation that is a feature of neoplastic cells. The authors also confirm previous data ^{3, 6} showing the VEGF A and C immunoreactivity that is absent from non-neoplastic cholangiocytes is greatly enhanced in biopsy samples of cholangiocarcinoma, a finding that lends further support to the idea that VEGF is secreted by neoplastic cells, which can subsequently act in both an autocrine fashion (on cell growth) and paracrine fashion (on angiogenesis) to promote tumor growth and progression.

The idea of VEGF as an autocrine regulator of cell proliferation has also been demonstrated in cholangiocytes ⁷. There is also an increase in secretion of VEGF during hyperplastic cholangiocyte proliferation seen in an experimental rodent model of extrahepatic biliary obstruction and that treatment of these animals with neutralizing antibodies against VEGF effectively inhibited cell proliferation ⁷. In addition, treatment of mitotically quiescent normal cholangiocytes with VEGF induced cell proliferation ⁷, which provides further weight to the concept that VEGF can act as an autocrine regulator of cell proliferation. Interestingly, using this same animal model, ER antagonists effectively inhibited hyperplastic cholangiocyte proliferation whereas estrogen treatment of normal cholangiocytes induces a proliferative response ⁸, which completely parallels the effects observed in cholangiocarcinoma cells.

Although the results presented in the current article by Mancini *et al* provide insight into the proliferative effects of estrogens on cholangiocarcinoma, and highlight VEGF as a possible target for the design of therapeutic strategies, further studies are needed to confirm the role of ER and IGFR activation on tumor growth in an *in vivo* model of cholangiocarcinoma. These data also do not determine if estrogens can also stimulate neo-angiogenesis, through the expression and secretion of VEGF. Despite these limitations, the data presented provides solid evidence to support further research into the role of estrogens in the pathogenic process involved in the development of cholangiocarcinoma as well as the a rationale for the use of ER, IGFR and/or VEGF inhibitors either in combination or as adjunct therapies to existing treatment options to combat this devastating disease.

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