Abstract

Cholangiocarcinoma (CCA) is a rare, but highly malignant primary hepatobiliary cancer. CCA is usually diagnosed at the late stage of the disease. The current available conventional chemotherapy and radiation therapy are not effective in prolonging the long-term survival rate of patients. The development of new therapeutic interventions for CCA is especially urgent and is the **long-term objective** of this research project. The incidence and mortality of CCA have been increasing in the United States and worldwide for reasons which remain to be determined. CCA is commonly associated with chronic cholestasis and significantly elevated levels of primary and conjugated bile acids (CBAs), the metabolites of cholesterol. It has recently been shown that bile duct obstruction is a potent stimulus for CCA growth and progression, indicating a critical role of bile acids in the development of biliary tract carcinoma. Previous reports have indicated that bile acids can stimulate cholangiocyte growth and promote cancer progression by stimulating a variety of signaling pathways including activation of epidermal growth factor receptor (EGFR). In addition, bile acids also activate several nuclear receptors. Our recent studies demonstrated that CBAs, such as taurocholate (TCA), activate the ERK1/2 and AKT signaling pathways through the sphingosine 1-phosphate (S1P) receptor 2 (S1PR2) in hepatocytes. It is also well-known that S1P-mediated signaling pathways are closely linked to the development and progression of various types of human cancers including gastrointestinal cancers. Moreover, activation of ERK1/2 has been shown to promote cancer cell growth. However, the physiological and pathological links between bile acids, S1P receptors and intracellular signaling pathways, and their roles in regulating CCA growth and progression have yet to be elucidated and are the focus of this grant application. We recently identified S1PR2 as the predominant S1P receptor expressed both in human and rat CCA cells. CBAs activate S1PR2, which further activates the ERK1/2 and ATK signaling pathways in CCA cells. TCA-induced CCA cell growth, migration, and invasion were inhibited by a S1PR2 chemical inhibitor (JTE-013) and gene-specific shRNA. It also has been reported that the expression levels of FXR-α, a known tumor suppressor, were dramatically down-regulated in CCA cells and tissues. tissues; 2) Bile duct ligation (BDL) induced up-regulation of the S1PR2 expression in mouse primary cholangiocytes; 3) The expression of the ileal sodium-dependent bile acid transporter (IBAT or ASBT) and FXRα was dramatically down-regulated in CCA cells and tissues; 4) BDL significantly down-regulated the expression of IBAT and FXRα; 5) BDL-induced proliferation of cholangiocytes was markedly inhibited in S1PR2 knockout mice. Based on these studies and our new preliminary results, we **HYPOTHESIZE** that CBA-mediated activation of S1PR2 plays a critical role in promoting the proliferation of cholangiocytes and CCA progression. The overall hypothesis will be tested by the following two specific aims. Aim 1) To define the role of S1PR2 in CBA-mediated promotion of cholangiocyte proliferation and CCA progression using a mouse model of cholestasis-associated CCA. Aim 2) To identify the cellular mechanisms through which CBAs promote CCA progression. The pathogenesis and progression of CCA is still poorly understood. The available chemotherapies and radiotherapies are virtually ineffective. The development of other therapeutic interventions for this fatal disease is particularly urgent. This proposal addresses an important issue related to the cellular/molecular mechanisms by which bile acids and S1P receptors promote CCA cell growth. Completion of this project will provide important information for understanding the pathogenesis of CCA. It will also provide useful information for developing new therapeutic strategies for this deadly disease.