Targeted Therapy for Cholangiocarcinoma

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Cholangiocarcinoma is a highly lethal neoplasm originating from the intra- and extra-hepatic biliary tree. It often arises in the context of chronic biliary tract inflammation and fibrosis. Given this context for biliary tract carcinogenesis, we have examined the role of inflammatory cytokines in biliary tract carcinogenesis and progression. The inflammatory cytokine IL6 is a potent survival factor for cholangiocarcinoma cells. IL6 via a STAT3 signaling cascade, induces expression of the anti-apoptotic Bcl-2 protein, Mcl-1. Mcl-1 is the most potent survival factor of the Bcl-2 family of protein against TRAIL-mediated cytotoxicity. Mechanisms to inhibit STAT3 signaling by Sorafenib down regulate Mcl-1 expression, and sensitize cholangiocarcinoma cells to TRAIL-mediated cytotoxicity. Indeed, Sorafenib sensitizes cholangiocarcinoma cells to TRAIL cytotoxicity both in vitro and in vivo in a syngenic/orthotopic rodent model. These data suggest that mechanisms to inhibit IL6 signaling, STAT3 signaling, in combination with TRAIL therapy is a viable therapeutic strategy for the treatment of human cholangiocarcinoma.

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