Role of secretin in large cholangiocyte proliferation during extrahepatic cholestasisinduced by bile duct ligation in mice

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Background Cholangiocytes, morphologically distinct in small and large, are functionally heterogeneous [1]. Small cholangiocytes are mitotically dormant and normally do not express some specific markers of large cells such as secretin receptor (SR), CFTR and Cl^-/HCO_3^- exchanger. Secretin plays a key role in the biliary secretion and proliferation, it increases cAMP levels and induces the opening of the Cl^- channel (CFTR) leading to the activation of the Cl^-/HCO_3^- anion exchanger 2 (AE2) and secretion of bicarbonate in bile [2]. But direct evidence for secretin-dependent proliferation is lacking. We hypothesize that cholangiocytes express and secrete secretin regulating biliary growth by an autocrine mechanism.

Methods *In vivo*, SR wild-type (WT) or SR knockout (KO) mice underwent sham surgery or BDL for 7 days. We evaluated SR expression, cholangiocyte proliferation and apoptosis in liver sections and proliferating cell nuclear antigen (PCNA) protein expression and ERK1/2 phosphorylation in purified large cholangiocytes from WT and KO BDL mice. *In vitro,* small and large cholangiocytes were used to evaluate the effect of secretin (100 nM) on proliferation and protein kinase A (PKA) activity.

Results SR was expressed by large cholangiocytes. Knockout of SR significantly decreased large cholangiocyte growth induced by BDL, which was associated with enhanced apoptosis. PCNA expression and ERK1/2 phosphorylation were decreased in large cholangiocytes from KO BDL compared with WT BDL mice. *In vitro*, secretin increased proliferation and PKA activity of large cholangiocytes that was blocked by PKA inhibitors.

Conclusion SR is an important trophic regulator sustaining biliary growth. The current study provides strong support that modulation of biliary secretin expression may be important for the management of liver diseases.

References

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Key words
Liver, Cholangiocytes, Secretin