

Role of secretin in the growth of the biliary epithelium in normal and cholestatic mice

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Background: Secretin stimulates bicarbonate secretion in large ducts by interaction with receptors by a cAMP-dependent pathway [1]. In BDL rats, the growth of large (but not small) cholangiocytes is activated by the cAMP/ERK1/2/Elk-1 pathway; and is associated with increased secretin receptor (SR) expression [2]. The aim of our study was to define the role of secretin in experimental models of cholestatic mice.

Methods: We used (SEC+/+) (wild-type, WT) and SEC-/- male mice that underwent sham surgery or BDL for 7 days treated with saline or secretin. Then, we used: (i) liver sections to evaluate secretin protein expression, cholangiocyte growth, apoptosis, the presence of VEGF-A/C and NGF; (ii) purified and immortalized small and large BDL cholangiocytes to measure PCNA protein expression and the same previous growth factors.

Results: *In vivo*, we demonstrated that: (i) secretin is expressed in normal liver by large bile ducts; and (ii) secretin expression increases in large bile ducts following BDL. Isolated large cholangiocytes from BDL WT mice express higher levels of the mRNA for secretin and secrete greater amounts of this hormone compared to normal large cholangiocytes. Knockout of the secretin gene reduced BDL-induced increase in large IBDM compared to WT BDL mice, an event that was associated with enhanced apoptosis of large cholangiocytes and decreased expression of VEGF-A/C and NGF. Concomitant with reduced large IBDM there was increased small IBDM in SEC-/- KO BDL mice compared to WT BDL mice. After prolonged treatment, secretin increased the biliary expression of PCNA, VEGF-A/C and NGF.

Conclusions: The study introduces the novel concept that cholangiocytes express and secrete secretin and that manipulation of this gene may be an important target for the management of biliary disorders.

References

- [1] Onori et al. (2010) Secretin inhibits cholangiocarcinoma growth via dysregulation of the cAMP-dependent signaling mechanisms of secretin receptor. *Int J Cancer*. 127(1): 43-54.
- [2] Glaser et al. (2010) Knockout of secretin receptor reduces large cholangiocyte hyperplasia in mice with extrahepatic cholestasis induced by bile duct ligation. *Hepatology* 52(1): 204-214.

Key words

Secretin, biliary epithelium, cholestasis.