

Modulation of the biliary expression of arylalkylamine N-acetyltransferase alters the autocrine proliferative responses of cholangiocytes

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Cholangiocytes secrete several neuroendocrine factors regulating biliary functions by autocrine/paracrine mechanisms (Alpini et al., 1994). Melatonin inhibits biliary growth and secretin-stimulated choleresis in cholestatic rats by interaction with melatonin receptor 1 (MT1) (Renzi et al., 2011). We will try to localize the key enzyme involved in melatonin synthesis, arylalkylamine N-acetyltransferase (AANAT), in cholangiocytes and, possibly, we will try to determine the effect of modulation of AANAT on the autocrine proliferative/secretory responses of cholangiocytes. In liver sections we found that: (i) AANAT is expressed by cholangiocytes and hepatocytes; (ii) the cholangiocytes expression of AANAT decreased in morpholino (AANAT down regulator)-treated rats; and (iii) the decrease in AANAT expression and subsequent lower melatonin secretion by cholangiocytes is associated with increased biliary proliferation and increased expression of Secretin Receptor (SR) and VEGF-A/C. In vitro, we observed that overexpression of AANAT in large cholangiocyte (LC) decreased proliferation and ablated secretin-stimulated biliary secretion. These results indicate that: in vivo down-regulation of biliary AANAT stimulates cholangiocyte proliferation by an autocrine loop, and in vitro overexpression of AANAT in LC decreases proliferation. Local targeting of AANAT in cholangiocytes may be important for the management of cholangiopathies.

References

- Alpini et al. (1994) Upregulation of Secretin Receptor Gene Expression in Rat Cholangiocytes After Bile Duct Ligation. *Am J Physiol Gastrointest Liver Physiol.* 266: G922-928.
- Renzi et al. (2011) Melatonin exerts by an autocrine loop antiproliferative effects in cholangiocarcinoma: its synthesis is reduced favoring cholangiocarcinoma growth. *Am J Physiol Gastrointest Liver Physiol.* 301(4): G623-33.

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