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The role of the secretin/secretin receptor axis in the modulation of liver fibrosis via changes in TGF-1β-mediated biliary senescence

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The biliary epithelium and its cells, cholangiocytes, are the target in several human cholangiopathies including primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), which are diseases characterized by extensive fibrosis (1). Proliferating cholangiocytes display neuroendocrine characteristics and secrete and respond to several neuropeptides and gastrointestinal hormones that modulate cholangiocyte responses to injury via autocrine/paracrine mechanisms (2). Secretin (Sct) exerts its effects through secretin receptor (SR), which is expressed in the liver by large cholangiocytes. Enhanced biliary proliferation during cholestasis is associated with increased SR expression on cholangiocytes and increased cAMP dependent secretin-stimulated ductal secretion (3). Our aim was to define the role of Sct-regulated cellular senescence and demonstrated that liver fibrosis is significantly reduced in Sct-/-, SR-/- and Sct-/-/SR-/- BDL mice compared to BDL wild-type (WT) mice. The reduction in hepatic fibrosis in Sct-/-, SR-/- and Sct-/-/SR-/- BDL mice was accompanied by reduced TGF-β1 levels in serum and cholangiocyte supernatant as well as decreased expression of markers of cellular senescence in cholangiocytes in contrast to increased expression of cellular senescence in hepatic stellate cells (HSCs) compared to BDL WT mice. Sct directly stimulated the senescence of cholangiocytes and regulated by a paracrine mechanism the senescence of HSCs and liver fibrosis via modulation of TGF-β1 biliary secretion. Targeting senescent cholangiocytes may represent a novel therapeutic approach for ameliorating hepatic fibrosis during cholestatic liver injury.

References

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Key words

Biliary epithelium, cholangiocytes, fibrosis, secretin.