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Knockout of the Neurokinin-1 Receptor Reduces Cholangiocyte Proliferation in Bile Duct Ligated Mice

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Background and aims. Cholangiocytes, the cells that line biliary ducts, have the capacity to respond to a variety of hormones and neuropeptides, regulating their surrounding cell functions and proliferative activity1. There is no evidence that the sensory neuropeptide substance P (SP) regulates cholangiocyte hyperplasia interacting with its endogenous neurokinin 1 receptor (NK1-R)2.

Methods. To shed light on this interaction, Wild-type (WT, +/+) and NK-1 receptor (NK-1R) knock-out (NK-1R -/-) mice underwent sham or BDL for 1 week. Then, we evaluated: (i) NK-1R expression by immunohistochemistry, (ii) necrosis, apoptosis, steatosis and the number of cholangiocytes positive for citokeratin-19 (CK-19) in liver sections; (iii) PCNA expression and PKA phosphorylation by western blots. In vitro, we determined the effects of SP on growth by MTS proliferation assay, cAMP intracellular levels and PKA phosphorylation by western blots.

Results. Cholangiocytes express NK-1R with upregulation following BDL. In normal NK-1R (-/-) mice, there was higher apoptosis and scattered steatosis compared to controls. In NK-1R -/- BDL mice, there was a decrease in the number of CK-19-positive cholangiocytes and enhanced biliary apoptosis compared to controls. In cholangiocytes from BDL NK-1R -/- mice there was decreased PCNA expression and PKA phosphorylation. In vitro, SP increased cAMP levels, proliferation and PKA phosphorylation of cholangiocytes.

Conclusion. In the present study we have demonstrated that modulation of SP, by NK-1R, such as other neuroendocrine factors, may offer a new target in the inhibition and in the regulation of biliary functions during cholangiopathies.

Keywords: biliary epithelium, sensory innervation, cholangiopathies