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Regulation of Biliary Progenitor Cell Proliferation by Hedgehog Signaling in *In Vivo* and *Ex Vivo* Organoid Models

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Background: Cholangiopathies are a group of chronic progressive diseases with poor outcomes, and include primary sclerosing cholangitis and cholangiocarcinoma (CCA). Hedgehog (Hh) signaling mediates biliary repair in injury and is activated in CCA. The steps from chronic inflammation to CCA are not well defined, but are thought to include hyperplasia of the PBGs, the niche for biliary progenitor cells (BPCs). **Objectives:** To elucidate the effects of Hh signaling on the BPCs. **Methods:** We used wild type (WT) mice, and mice with Hh pathway activation (*pCMV-Shh^{HA}*) and inhibition (*Gli1^{-/-}*). We assessed the mouse bile ducts (BDs) for proliferation (BrdU) and expression of differentiated cell markers *in vivo*. We used the novel 3-D biliary organoid (BO) model and evaluated effects of genetic and pharmacological Hh signaling activation [recombinant Shh (rShh)] and inhibition (GANT-61) *ex vivo*. **Results:** We demonstrated that Shh expression in the *pCMV-Shh^{HA}* mice localized to the PBGs and Gli1 was expressed in the *Gli1^{-/-}* mice stroma in homeostasis. Hh signaling did not affect PBG cell proliferation but rather promoted PBG cell differentiation in homeostasis *in vivo*. However, the *pCMV-Shh^{HA}* mice-derived organoids and BOs treated with rShh demonstrated increased BO growth and proliferation *ex vivo*. Pharmacological Gli inhibition significantly decreased growth and proliferation in the BOs from the WT and *pCMV-Shh^{HA}* mice. **Conclusions:** Hh signaling regulates PBG proliferation, which can contribute to PBG hyperplasia, in a paracrine and autocrine manner. The cross-talk between the Shh ligand-producing PBGs and Gli1+ stromal cells is required to control BPC proliferation.