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Hepatic Stellate Cell-Derived Cancer Associated Fibroblasts Sustain Tumor Growth in Intrahepatic Cholangiocarcinoma

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Background: Cholangiocarcinoma (CCA) is characterized by abundant cancerassociated fibroblasts (CAF). Clinical data suggest an inverse correlation between αSMA-positive CAF and survival in CCA. However, functional in vivo studies that determine whether CAF promote or restrict CCA are lacking. Objectives: To determine the cellular source and functions of CAF in intrahepatic CCA (ICC) in vivo. Methods and Results: Sleeping beauty-mediated overexpression of HAtagged pT3-myr-AKT and pT3-EF1aH-YapS127A in the liver resulted in desmoplastic ICC with abundant αSMA-positive CAF and significant upregulation of fibrogenic genes Acta2 (34-fold) and Col1a1 (125-fold). Expression of hepatic stellate cell (HSC) markers Des and Lrat mRNA was significantly increased in ICC (11- and 3-fold, respectively). HSC origin of CAF was further supported by tracing studies in triple transgenic mice expressing LratCre and Cre reporter TdTom, which label >99% of HSCs in the liver, in combination with Col1a1-GFP, which labels collagen-producing fibroblasts. 92.95± 5.27% (n=10) of CAF were TdTompositive, i.e. derived from LratCre+ HSC. To functionally manipulate HSC-derived CAF in vivo, we employed triple transgenic mice expressing LratCre, Creinducible iDTR and Cre reporter TdTom. By this approach, we depleted >90% CAF, as determined by TdTom fluorescence, qPCR for HSC markers *Lrat*, *Lhx2* and Des, as well as Col1a1, but not portal fibroblast marker Msln. Short-term CAF depletion reduced fibrosis, tumor proliferation, as determined by Ki67 staining and qPCR for mKi67 and Ccnb1, and increased cell death in ICC. Conclusion: Our study suggest that the majority of CAF are HSC-derived, and HSC-derived CAF support the development of ICC by promoting tumor cell proliferation and survival.

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