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The Role of Menin-MLL Interaction in the Dissociation between Cholestatic LIver Diseases and Cholangiocarcinoma

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Multiple Endocrine Neoplasia type I (MEN1) is a familial cancer syndrome of the parathyroid glands, pituitary glands, and pancreatic islet cells. We have recently shown that menin, the protein encoded by MEN1, acts as a tumor suppressor in cholangiocarcinoma (CCA). However, recent evidence points to menin as a *positive* regulator of hepatic fibrosis. Thus, we sought to compare and contrast the role of menin in cholestatic fibrotic disease states against CCA. **Methods**: We treated bile-duct ligation (BDL) and MDR2$^{-/-}$ cholestatic mouse models with a menin-MLL (MI-2-2, 20-40 mg/kg, I.P.) or vehicle for 1 week before collecting liver samples. Immunohistochemistry was performed to measure intrahepatic bile duct mass (CK-19 staining) and Sirius Red staining to quantify collagen deposition. By real-time PCR, expression of menin and markers for proliferation (Ki67) and fibrosis (TGFbeta1, FN1, alpha-SMA, Col1alpha1) was measured. Next we sought to understand the effect of menin-MLL interaction on human CCA growth. Mz-ChA-1 cells were treated with MI-2-2 (10 microM, 24 hours) and menin expression was assessed with real-time PCR and flow cytometry. Markers of proliferation (Ki67) and angiogenesis (VEGF-A/C, VEGFR-2/3, angiopoietins Angpt1/2, and Tie1/2) were measured. **Results**: MI-2-2 treatment reduces biliary mass and collagen deposition via CK19 and Sirius Red staining in both BDL and MDR2$^{-/-}$ mice. Expression of proliferative and fibrotic markers decreased in pure cholangiocytes isolated from MI-2-2 treated livers of these mice as well. However, Mz-ChA-1 cells treated with MI-2-2 *in vitro* increased expression of proliferative and angiogenic markers. **Conclusion**: The role of menin-MLL interaction is dependent on the disease state or model. While it drives proliferation and fibrosis in fibrotic liver diseases, it inhibits human CCA initiation and progression. Understanding how menin-MLL functions in various diseases states can help us understand how cholestatic liver diseases progress to CCA.