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Loss of Histamine Signaling Reduces Biliary and Hepatic Damage, Mast Cell Migration and Tumor Formation in 52 wk Old Multidrug Resistance-2 Knockout Mice

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Background: Primary sclerosing cholangitis (PSC) is characterized by biliary damage and liver fibrosis. The multidrug resistance-2 gene knockout (*Mdr2*^{-/-}) mouse (i) develops cholestasis; (ii) mimics some characteristics of human PSC; and (iii) develops hepatocellular cancer (HCC) within one year. We have demonstrated that depletion of the l-histidine decarboxylase/histamine (HDC/HA) axis using 12 week old HDC/*Mdr2* double knockout (DKO) mice results in decreased (i) hepatic damage; (ii) mast cell (MC) infiltration and activation; (iii) biliary proliferation; (iv) inflammation and (v) liver fibrosis when compared to *Mdr2*^{-/-} mice. The **aim** of our study was to evaluate the effects of the loss of the HDC/HA axis on biliary and hepatic damage, MC infiltration/activation and tumor formation in older *Mdr2*^{-/-} and DKO mice. **Method:** 52 week old homozygous DKO mice and aged matched *Mdr2*^{-/-} mice were utilized. Livers were evaluated for tumor formation and lobular damage by H&E staining. In total liver we evaluated: (i) HDC/histamine receptor (HR) expression by qPCR, (ii) MC infiltration by staining for mouse mast cell protease-1, (iii) MC activation by qPCR for chymase, tryptase and c-Kit expression, (iv) ductular reaction by CK-19 and Ki67 immunohistochemistry and (v) biliary senescence by SA- β -galactosidase activity and staining for p16, p18, p21 and p53. Changes in liver fibrosis were evaluated by Sirius red staining in liver sections, and staining for α -SMA and collagen-1a. Hepatic stellate cell (HSC) activation was determined by immunofluorescence and qPCR for SYP-9. Inflammation was evaluated by staining for IL-6, TNF- α and F4/80. HA serum levels were measured by EIA. In livers and tumors (when present), we evaluated angiogenesis by VEGF and vWF gene expression. **Results:** Loss of the HDC/HA axis in 52 week old DKO mice resulted in little to no tumor formation compared to age-matched *Mdr2*^{-/-} mice, which displayed large HCC tumors. The HDC/HA/HR axis and MC infiltration/activation were reduced in DKO mice compared to age-matched *Mdr2*^{-/-} mice. Infiltrating MCs were found near bile ducts. Ductular reaction, biliary senescence and hepatic fibrosis were increased in *Mdr2*^{-/-} mice, but were reduced in DKO mice. Furthermore, angiogenesis and inflammation were all reduced in DKO when compared to age-matched *Mdr2*^{-/-} mice. **Conclusion:** Our data demonstrates that depletion of the HDC/HA axis blunts tumor growth and progression in *Mdr2*^{-/-} mice, which is coupled with reduced biliary and hepatic damage, and MC infiltration/activation. The HDC/HA axis may be a critical therapeutic target for patients with cholestasis or liver cancer.

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