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NON PARENCHYMAL WNTS REGULATE BETA-CATENIN SIGNALING IN MURINE LIVER ZONATION AND REGENERATION

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β-Catenin in hepatocytes, under the control of Wnts, regulates pericentral gene expression and contributes to liver regeneration (LR) after partial hepatectomy (PH) by regulating cyclin-D1 gene expression as shown in b-catenin and Wnt co-receptors LRP5-6 conditional knockouts (KO). However, conditional deletion of Wntless (Wls), required for Wnt secretion, in hepatocytes, cholangiocytes, or macrophages lacked any impact on zonation, while Wls deletion in macrophages only marginally affected LR. Here, we address the contribution of hepatic endothelial cells (EC) in zonation and LR by characterizing EC-Wls-KO generated by interbreeding Wls-floxed and Lyve1-cre mice. While Lyve1 expression in adult liver was limited to sinusoidal EC only, Lyve1-cre mice bred to ROSA26-Stop$^{flox/flox}$-EYFP mice showed EYFP labeling in sinusoidal and central vein EC. EC-Wls-KO mice showed notable decreases in liver weights; lacked glutamine synthetase, Cyp2e1 and Cyp1a2 in pericentral hepatocytes; and were resistant to acetaminophen-induced liver injury. After PH, EC-Wls-KO failed to optimally induce cyclin-D1 expression at 24-48 hours, which led to lower hepatocyte proliferation at 48 hours, and rebound by 72 hours. EC and macrophages isolated from regenerating livers at 12 hours showed significant upregulation of Wnt2 and Wnt9b mRNA expression, the same 2 Wnts involved in baseline b-catenin activity in pericentral hepatocytes. Further, we show shear stress can induce Wnt2 and Wnt9b mRNA production in endothelial cells *in vitro*, suggesting an initiating mechanism after partial hepatectomy. In *conclusion,* our studies validate that at baseline, EC secrete Wnt proteins essential for b-catenin activation in pericentral hepatocytes. During LR, primarily EC and secondarily macrophages, secrete Wnt2 and Wnt9b, to spatiotemporally regulate β-catenin activation and cyclin-D1 expression in hepatocytes to induce cell proliferation.

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