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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Heart-of-Glass: A Regulator at the Heart of Liver Morphogenesis and Metabolic Zonation

Liver development requires a well-orchestrated dialog among the vasculature, bile ducts, and hepatocyte cords. Yet, the molecular mechanisms driving formation of the 3-dimensional (3D) architecture of the liver remain largely unknown.[1] In this issue of *Cellular and Molecular Gastroenterology and Hepatology* a team led by Xiangjian Zheng sheds new light on how liver endothelial cells shape the liver vasculature, the biliary network, and the metabolic functions of hepatocytes.[2]

The authors addressed the function of *Heart-of-glass* (*Heg*), a gene that was originally identified in a zebrafish (*Danio rerio*) genetic screen as a mutation causing enlarged heart. Subsequently, *Heg* was shown to encode a transmembrane protein linked with cerebral cavernous malformation signaling.[3] Following up on these observations, its function in zebrafish liver was studied by Didier Stainier's team who uncovered that *Heg* expression in endothelial cells is required for normal hepatocyte polarization and biliary morphology.[4] Xiangjian Zheng and coworkers now further investigated the function of *Heg* and focused on mammalian liver.[2] Starting with the phenotypic analysis of $Heg^{-/-}$ mice, they showed that the absence of *Heg* significantly reduces the vascular network's density, affecting the portal and central veins, as well as the sinusoids. Endothelial cells lining these blood vessels are the predominant cell type expressing *Heg* in the liver. This prompted the authors to derive mice with an endothelial cell-specific deletion of *Heg*. Using the Lyve1-Cre driver to recombine floxed *Heg* alleles, they inactivated the *Heg* gene in the entire venous system of the liver. The phenotype of the mutant mice was again characterized by reduced density of the liver vascular network. A reduction of the biliary tree, paralleling that of the portal vein's network, was also observed.

The reduced vascular density in *Heg*-deficient livers was clearly of developmental origin. Indeed, when the authors used tamoxifen-inducible $Cdh5\text{-}Cre^{ERT2}$, which enables postnatal inactivation of *Heg* in the vasculature, morphologic anomalies of the vascular network were no longer detected. How *Heg* controls the morphogenesis of the vasculature during development was not further studied by the authors. However, considering that development of the bile ducts is critically dependent on the periportal mesenchyme,[5,6] the authors speculate that the reduced biliary network in the absence of *Heg* is a consequence of the reduced portal vein network. In the zebrafish liver, inhibition of *Heg* perturbs hepatocyte polarity and development of the biliary network. The zebrafish and mouse biliary trees bear numerous similarities, yet they significantly differ in their 3D morphology. Therefore, the morphogenic mechanism by which *Heg* controls biliary development is probably not fully conserved among the 2 species. Still, *Heg* may illustrate how a gene controls similar biologic process in zebrafish and mammals, although via distinct molecular mechanisms.

Zheng and coworkers were intrigued by their observation that *Heg*-deficient livers display abnormal zonation. Normally, the liver lobule is partitioned into 3 zones from the portal to the central vein, each zone exerting specific metabolic functions: zones 1, 2, and 3 are the periportal, intermediate, and pericentral zones, respectively.[7] Zonation depends on several factors. The critical role of Wnt signaling in establishing metabolic zonation was uncovered several years ago by the team of Sabine Colnot, and further investigated in depth by several groups.[8,9] Zonation is not restricted to hepatocytes because endothelial cells also display zone-specific gene expression.[10] Mice with *Heg*-deficient endothelial cells displayed an enlarged zone 1, and this resulted in part from transient postnatal hyperproliferation of zone 1 hepatocytes. Furthermore, Zheng and coworkers found that *Heg* controls zonation of both endothelial cells and hepatocytes. They provide strong evidence that expression of *Wnt2*, *Wnt9b*, and *Rspo3* is downregulated in *Heg*-deficient pericentral endothelial cells. These 3 genes code for ligands that activate canonical Wnt signaling in adjacent target cells. Consistently, zone 3 pericentral hepatocytes displayed reduced expression of Wnt target genes.

But what about *Heg* and liver function? Strikingly, under homeostatic conditions, *Heg* mutant mice did not display obvious functional defects, thus serum levels of liver enzymes, hepatic proteins, and bilirubin were normal. However, when the animals were challenged with xenobiotic compounds, such as CCl_4, thioacetamide, or with an acetaminophen overdose, the lack of *Heg* protected the livers from toxic or drug-induced damage. This correlated with reduced expression of the enzymes that convert the xenobiotics and acetaminophen to toxic metabolites in zone 3.

As usual in good science, solving one problem raises more questions. Zheng and coworkers uncovered that *Heg* regulates liver zonation by stimulating Wnt expression. How *Heg* is controlled and how it stimulates the expression of Wnt ligands are the next obvious questions. Also, the increasing quality of imaging provides the hepatology community with splendid 3D pictures of bile ducts and vasculature. The finding that *Heg* shapes the vascular and biliary network now nicely paves the way to the study of mechanisms driving formation of the 3D liver architecture.

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