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EDITORIAL

Of Sugar and Fat: How Protein Glycosylation in Sinusoidal Cells Controls Lipid Metabolism in Liver

The liver sinusoidal endothelial cells (LSECs) are highly adapted to control the organ's metabolic functions.[1] A wealth of information, including from multiomic and spatial analyses, has been obtained on the biochemical properties of the LSECs, revealing that they are compartmentalized along the axis of the liver lobule from the portal to the central vein.[2] Such compartmentalization of LSECs is referred to as *zonation*, and parallels the zonation of the hepatocytes, which is characterized by the partitioning of their metabolic processes in periportal, intermediate, and pericentral zones. Hepatocytes acquire specific metabolic functions at distinct stages of development and maturation. Their zonation becomes detectable before birth in mice and matures postnatally under the control of growth factors released by the LSECs.[3,4] Although disrupted lobular zonation in diseases such as metabolic dysfunction–associated steatotic liver disease has raised questions about the dialogue between LSECs and hepatocytes in lipid homeostasis, significant gaps remain in our knowledge of lipid metabolism zonation in hepatocytes. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, the team led by Lijun Xia has taken an original approach to unravel a crosstalk between LSECs and hepatocytes.[5]

Intercellular control of lobular zonation mainly has been addressed by focusing on ligands, receptors, and effectors of signaling cascades, and their organization into gene and protein networks. In this context, and with the notable exception of protein phosphorylation, less emphasis has been placed on post-translational modifications.[6] Sialylation is a glycosylation process in which sialic acids are bound to N- and O-linked glycans. Sialylation influences the affinity of ligands for their receptor and modulates cell–cell interactions involving endothelial cells.[7] Therefore, Xia et al[5] postulated that sialylation plays a role in LSECs and addressed this issue in mice by deleting the *Slc35a1* gene. *Slc35a1* codes for a transporter that carries CMP-sialic acids between the cytoplasm and the Golgi apparatus. *Slc35a1* inactivation was obtained through recombination of a floxed allele using *Tie2-Cre*, which is active in endothelial and hematopoietic cells. This resulted in a dramatic phenotype. Mutant mice failed to thrive postnatally and died before 10 weeks of age. They presented with dyslipidemia and focal areas of necrosis in the liver. Their hepatocytes displayed abundant lipid droplet deposition. In homeostatic conditions, LSECs are fenestrated and specifically express Lyve1; they normally lack a basement membrane and do not express the endothelial cell marker CD34. In contrast, LSECs in the mutant mice had lost part of their identity as evidenced by the loss of fenestrae and Lyve1 expression; they expressed CD34 and deposited a basement membrane. LSECs also displayed perturbed zonation and down-regulation of Wnts, which are notable regulators of hepatocyte zonation. Thus, hepatocyte zonation was impacted, as evidenced by reduced expression of genes typical of pericentral hepatocytes. Lipid droplet accumulation was not distributed evenly in the liver lobules but was predominant in pericentral hepatocytes, again confirming profound alteration of lobular zonation.

What is the link between sialylation in LSECs and perturbed lipid metabolism in hepatocytes? The absence of Slc35a1 resulted in vascular endothelial growth factor receptor 2 (VEGFR2) desialylation, as expected, but also in enhanced VEGFR2 phosphorylation and strong activation of downstream signaling genes, revealing overstimulated VEGF signaling. This was in line with earlier observations that enzymatic removal of VEGFR2 N-glycans enhances ligand-mediated–receptor activation.[8] The next experiment that had to be performed became obvious: blocking VEGFR2 signaling in Slc35a1-deficient livers. This was performed by administering the VEGFR2 inhibitor SU5416 a few days before birth and collecting the livers 1 or 2 weeks later. The results were spectacular: endothelial cell identity and hepatocyte zonation were partially restored, lipid accumulation was attenuated, and survival of the animals was improved significantly. Therefore, normal lipid metabolism in liver requires a dialogue between LSECs and hepatocytes involving signaling via sialylated VEGFR2.

The data from Xia et al[5] are consistent with earlier findings that a lack of VEGF produced by hepatocytes causes a loss of LSEC identity and enhances expression of pericentral genes.[9] However, how lipid accumulates in Slc35a1-deficient livers is not fully clear. Inhibiting VEGF signaling in the prenatal period is known to disrupt sinusoidal architecture and to reduce lipid levels in the liver.[10] In Slc35a1-deficient livers, lipid deposition in newborns was normal, but its resolution was inhibited, leading to steatosis. This reveals the existence of stage-dependent control of lipid metabolism by the LSECs. Loss of LSEC fenestrae may impede the transit of lipoproteins from hepatocytes to the sinusoidal lumen, as suggested by the authors.

Can we transpose the findings of Xia et al[5] to human beings? Not at this stage of our knowledge. Patients with deficient SLC35A1 display congenital disorder of glycosylation type II, but no liver anomaly has been reported. Still, the new findings on the role of sialylation already represent a conceptual advance that must be taken into account in future studies of liver pathophysiology.

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