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Sinusoidal Endothelial Cells as Orchestrators of the Gut Liver Immune Axis

The paper by Gola and colleagues published recently in *Nature* uses an array of state-of-the-art techniques to demonstrate how commensal organisms shape protective immunity in the liver by organizing immune cells into anatomical zones that are closely related to blood flow into the liver from the gut through the portal venous system.⁽¹⁾ Sophisticated confocal imaging is used to map leukocyte distribution within the liver, targeted disruption of critical signaling pathways, and RNA sequencing of specific cell types to determine molecular and cellular mechanisms and murine models of bacterial and malarial infection to demonstrate functional relevance. The authors show that localization of Kupffer cells and lymphocytes is dependent on the ability of sinusoidal endothelial cells to sense bacteria and activate myeloid differentiation protein 88 (MyD88)-dependent signaling, which in turn regulates local extracellular matrix deposition and the presentation of chemokine gradients that attract and retain leukocytes in the periportal region. Although the authors do not specify the bacteria responsible, by comparing germ-free mice (in which bacteria are completely absent) with specific-pathogen free mice (in which only pathogens have been eliminated), they are able to show that the effect is mediated by commensal bacteria, i.e., those that exist in harmony with the host. They then show that this zonation provides more efficient protection against infection when compared with a more random distribution of intrahepatic immune cells. It is an extremely thorough and elegant study that provides important mechanistic insights into how the liver regulates local responses to infection and immunity.

It has been known for many years that resident leukocytes show regional distributions in the liver and that the periportal region appears to be particularly important with a high concentration of Kupffer cells associated with innate lymphoid cells and dendritic cells within

the portal tracts.⁽²⁾ Furthermore, previous studies have proposed that these cells are recruited and retained by chemokine gradients. The paper by Gola et al. provides a detailed mechanism that links this to specific signals activated by commensal bacteria in the gut. The distribution of Kupffer cells in the periportal region is consistent with high levels of exposure to bacterial products entering the liver through the portal blood and is a component of what Andrew MacPherson et al. have described as the gut's second fire wall, providing protection in response to pathogens that have escaped detection in the gut.⁽³⁾ The current study suggests that this firewall is shaped and maintained by responses to products from commensal bacteria sensed by sinusoidal endothelial cells. Sinusoidal endothelial cells are ideal candidates for this role. They display a particularly dense network in periportal regions, maximizing their exposure to antigens entering from the portal blood; and they express an array of scavenger and toll-like receptors (TLRs), allowing them to detect and respond to bacteria and microbial products not only by removing them but also by secreting inflammatory mediators and modulating the extracellular matrix.⁽⁴⁾

Chemokines that bind to chemokine (C-X-C motif) receptor 3 (CXCR3) have been shown to play an important role in the recruitment and positioning of a range of leukocytes in and around portal tracts. In the present study one of the CXCR3 ligands, chemokine (C-X-C motif) ligand 9 (CXCL9), was shown to play a critical role in the zonal positioning of Kupffer cells and lymphocytes in periportal areas. However, Gola et al. show that increased secretion *per se* is not the important mechanism resulting in local periportal chemokine gradients. Rather, this is a consequence of changes in glycosaminoglycans (GAGs) such as hyaluronic acid and heparan sulfate in the glycocalyx that promote enhanced binding of cationic chemokines including CXCL9. The ability of chemokines to be retained and presented by the glycocalyx and within the extracellular matrix is critical for their functioning in lymphoid tissues. Such binding presents the chemokine to local leukocytes, establishes a gradient to guide cellular migration, and prevents diffusion and degradation. Enzymes that modulate matrix to change

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chemokine presentation thus have a critical role in shaping local immunity. They are also potential targets to disrupt chemokine gradients that drive inflammation and fibrogenesis. Therapies aimed at modulating the presentation of chemokines may be more selective and effective than those aimed at inhibiting their secretion or blocking cognate G protein-coupled receptors (GPCRs), an approach which has been problematic. Alternative strategies could target the enzymes that modulate the glycocalyx or target chemokine binding by GAGs using microbial products that block chemokine-GAG binding or chemokine mimetics that display strong binding to GAGs but weak binding to GPCRs. These can displace chemokines from the glycocalyx and thereby disrupt chemokine gradients.⁽⁵⁾

The authors go on to show the functional importance of this zonation by demonstrating that it is critical for protection from systemic infection with listeria and malaria through Kupffer cells and cluster of differentiation 8 T cell-dependent mechanisms, respectively. This zonal barrier not only removes pathogens but also limits harmful inflammatory responses to the periportal regions and prevents damage spreading to the metabolically critical cells around the central vein in acinar zone 3. Pathological disruption of this sophisticated system might thus be expected to contribute to changes in immune cell distribution, potentially explaining some histological features of liver inflammation such as interface and lobular hepatitis and perivenular inflammation.

Although the study focuses on protection against microbial pathogens, it also provokes important questions about immune mechanisms underlying liver diseases. Changes in the microbiome have been associated with a wide range of immune-mediated or inflammatory liver diseases including alcohol-associated steatohepatitis and NASH, primary sclerosing cholangitis, and liver cancer.⁽⁶⁾ Increased exposure to microbial products, including TLR-4 agonists, has been proposed as a trigger for pathological liver inflammation, as has dysregulated MyD88 signaling; but how these pathways drive disease remains to be elaborated. Understanding whether disruption of the protective zonal immunity in the liver triggers or exacerbates these conditions will be important and could suggest approaches to therapy. The authors observe that not only are intrahepatic myeloid and lymphoid cells enriched around portal tracts but this immune zonation constrains inflammatory responses to the periportal region, preventing spread throughout the

lobule. This may help us understand the distribution of inflammatory damage in liver diseases and the drivers that lead to persistent hepatic inflammation and fibrogenesis. One of these drivers could be dysbiosis, adding to the evidence that in some diseases changes in the microbiome may be pathogenic triggers rather than consequences of liver disease.

Finally, the critical role for sinusoidal endothelial cells in this process puts these complex and still poorly understood cells at the center of the gut liver immune axis. Understanding how these cells are maintained and how phenotypic changes such as capillarization that accompany disease progression alter their function should be priorities for researchers aiming to understand hepatic immune networks and their roles in driving inflammatory liver disease.

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