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LIVER

The liver as a firewall—clearance of commensal bacteria that have escaped from the gut

In a study published in *Science Translational Medicine*, Andrew Macpherson and colleagues have shown that the liver serves as a firewall to filter out commensal bacteria that have succeeded in penetrating the intestinal or systemic vascular circuits, and that this function is compromised in liver disease.

Previous work in healthy mice showed that mesenteric lymph nodes (MLNs) act as a firewall to prevent the penetration of bacteria-laden dendritic cells beyond the intestinal surface. The intestinal mucosal immune response to commensals is, therefore, compartmentalized to the intestinal mucosal immune system, and such compartmentalization is essential for host–microbial mutualism to be established.

As opportunistic bacterial infections are a frequent cause of death in patients with liver disease, Macpherson and co-workers set out to understand how liver function and dysfunction might affect the mutualism that exists between the host and the intestinal microbiota. "We started out with the question of whether the liver was also acting as a firewall and how this would affect health in the event of liver disease," explains Macpherson.

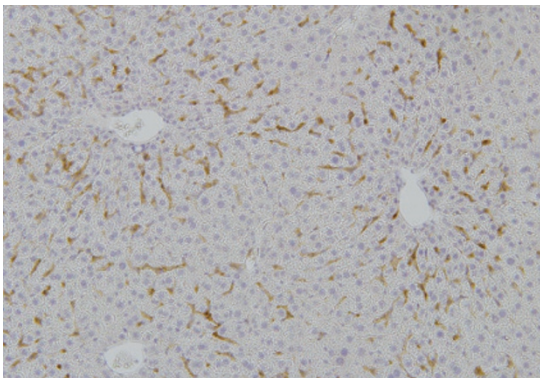
The first step was to establish the role of the liver in healthy wild-type mice. The team gavaged germ-free wild-type mice with live commensals and compared the number of culturable bacteria in MLNs and the liver at various time points. While MLNs were penetrated by live commensals, the liver was not. Live bacteria were also not detected in portal blood from germ-free mice after oral gavage or intravenous injection, though bacterial breakdown products could be found in hepatic tissue after gavage of live commensals. "We found that the liver was not an essential firewall for the dendritic cells that have sampled intestinal bacteria to induce mucosal immunity, provided the intestinal epithelial and vascular barriers are intact," explains Macpherson. The authors suggest instead that the liver has a processing and detoxifying function in healthy animals.

The team then showed that the liver cleared the majority of commensals injected into the hepatic portal venous system (some were cleared by the spleen). However, after dextran sodium sulphate treatment (to test the effect of intestinal inflammation), the liver was consistently reached by commensals; commensals were also detected in the spleen and peripheral blood of some animals. These observations confirmed that the liver acts as a vascular firewall for the mesenteric circulation when the mucosal–blood barrier function is weakened.

Next, the authors considered whether the liver was able to clear commensals in the general systemic vasculature directly (by filtering blood from the hepatic artery) or indirectly (by filtering blood from the hepatic portal vein)—it did both. "This works because the Kupffer cells that line the hepatic sinusoids (constituting over 80% of macrophages in the body) can take up and destroy these microbes that enter via the blood of either the portal vein or the hepatic artery," says Macpherson.

By using two different mouse models of liver disease, it was found that liver disease was associated with a reduced ability to clear bacteria, even though the inflammatory response to commensal bacterial challenge was increased. The presence of serum antibodies (IgG) against commensals in experimental mice also served as an indirect indication that the liver firewall had failed.

In the final part of their study, Macpherson and colleagues investigated whether early human liver disease was associated with abnormal handling and compartmentalizing of intestinal commensals. The findings were in agreement with those in the experimental mice. In the two cohorts studied—NAFLD versus matched controls and liver steatosis, NASH and cirrhosis versus controls—serum IgG and IgA responses against intestinal commensals were increased, which was independent of disease stage.



Mouse liver Kupffer cells. Image courtesy of M. L. Balmer.

The authors stress the need to now understand the mechanisms underlying the failure of liver Kupffer cells to clear intestinal microbes, particularly early in the course of NAFLD. They also plan to investigate whether emerging liver problems can be detected by the defined immune response to intestinal commensal bacteria and how the MLN and liver firewalls perform in the setting of IBD.

Macpherson believes "human health has to be seen as a harmonic relationship in the 'host–microbial superorganism,'" given the vast number of intestinal commensal microbes, the exchange of molecules between these microbes and the host—despite the filtering performed by the MLN and liver firewalls—and the fact that these molecules can penetrate organs. "We are very interested in how this molecular embrace functions in health and disease and how it may contribute to disease pathogenesis," he concludes.

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Original article Balmer, M. L. *et al.* The liver may act as a firewall mediating mutualism between the host and its gut commensal microbiota. *Sci. Transl. Med.* doi:10.1126/scitranslmed.3008618