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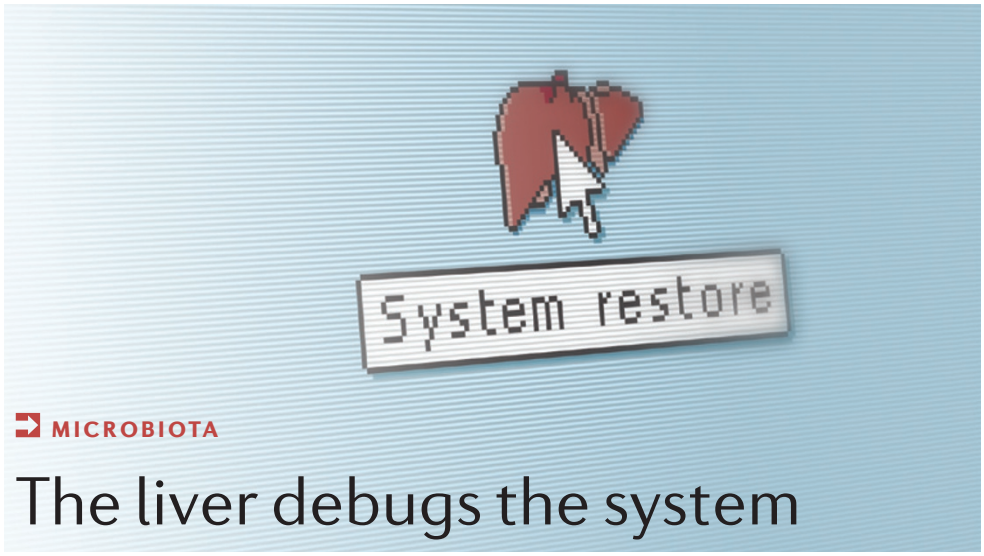

MICROBIOTA

The liver debugs the system

Patients with terminal liver failure most commonly die as a result of overwhelming infections, many of which are caused by commensal bacteria. Andrew Macpherson and colleagues now describe a role for the liver in clearing the blood of commensal microorganisms that have penetrated intestinal defences.

The mesenteric lymph nodes (MLNs) serve as a 'firewall' between the intestinal and systemic immune systems; live commensal bacteria that have been sampled by migratory intestinal dendritic cells are contained here and do not normally gain access to systemic compartments. Accordingly, when the authors administered commensal bacteria to germ-free mice by oral gavage, they could subsequently obtain live bacteria from the MLNs but not from the liver or spleen, although bacterial breakdown products could be detected in the liver. This suggests that in healthy animals, the liver does not limit the spread of intestinal commensals but instead has a role in the processing and detoxification of bacterial breakdown products. However, when the authors induced intestinal inflammation in mice by administering dextran sodium sulphate (DSS), they found that live commensal bacteria could now be cultured from the liver. Thus, the liver seems to function as a vascular firewall that clears commensals from the circulation when intestinal defences are overwhelmed.

> "the liver can serve as a vascular firewall"

To further explore the capacity of the liver to clear commensal bacteria, the authors depleted Kupffer cells (the macrophages of the liver) from splenectomized mice and intravenously administered commensal bacteria. Compared with controls, mice lacking Kupffer cells had a decreased capacity to clear commensal bacteria from the blood circulation. In addition, in different models of liver disease, mice experiencing liver dysfunction showed reduced clearance of intravenously administered commensal bacteria compared with healthy controls, despite showing evidence of an increased inflammatory response to the bacteria.

Finally, to determine the impact of liver dysfunction on host–commensal interactions independently of systemic bacterial challenge, the authors measured IgG production against intestinal commensals. The premise of these experiments is that the containment of commensals in the MLNs will generally only lead to IgA induction, whereas the spread of commensal bacteria to systemic sites will lead to specific IgG production. Indeed, serum from healthy mice or mice with early-stage liver disease did not contain IgG specific for intestinal commensals. By contrast, as liver disease progressed, IgG specific for commensals could be detected in the serum. Importantly, the authors found that patients with different forms of liver disease also had higher serum levels of IgG specific for intestinal commensals compared with healthy humans.

The authors conclude that the liver can serve as a vascular firewall and that the failure of this function could promote the systemic spread of commensal bacteria in patients with liver disease. Their results also suggest that monitoring specific IgG production against commensal bacteria could be useful for diagnostic purposes in patients with liver disease.

Yvonne Bordon

ORIGINAL RESEARCH PAPER Balmer, M. L. *et al.* The liver may act as a firewall mediating mutalism between the host and its gut commensal microbiota. *Sci. Transl. Med.* **6**, 237ra66 (2014)