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NASH

CX3CR1—a direct line to gut–liver crosstalk?

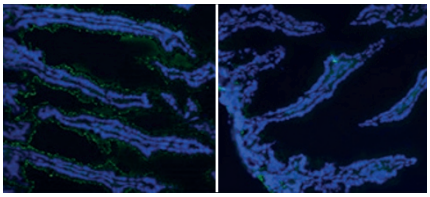
Deleting CX3C chemokine receptor 1 (Cx3cr1) negatively affects intestinal barrier function and exacerbates steatohepatitis in a mouse model NASH, according to a study from Christian Trautwein's group published in *Hepatology*.

"The observation that patients suffering from IBD often also present elevated liver transaminases and show signs of mild steatohepatitis, caught our interest into how the immunological status of the intestine influences the liver," explains first author Markus Schneider. CX3CR1 has previously been shown to have a role in both the liver and intestines, and so the authors hypothesized that it might also have a role in gut–liver crosstalk.

Wild-type and *Cx3cr1*$^{-/-}$ mice were fed a high-fat diet (HFD) or a methionine choline deficient diet to induce NASH. *Cx3cr1*$^{-/-}$ mice developed more severe disease, as indicated by lipid accumulation and higher levels of alanine aminotransferase, than wild-type mice. The knockout mice also had a higher number of infiltrating inflammatory cells (predominantly macrophages) and levels of pro-inflammatory cytokines (Tnf and Ccl2 [also known as Mcp1]) compared with wild-type mice.

Genomic analysis of the gut microbiota revealed that the HFD led to more changes in microbial composition in *Cx3cr1*$^{-/-}$ mice than wild-type mice. *Cx3cr1*$^{-/-}$ mice also had a thinner mucus layer in the colon than wild-type mice. In the ileum and colon, *Cx3cr1* deletion and HFD feeding resulted in decreased expression of two tight-junction proteins, zonula occludens 1 (see image) and occludin. More endotoxins were found in portal vein serum from *Cx3cr1*$^{-/-}$ mice than serum from wild-type mice, indicating that Cx3cr1 is involved in maintaining barrier function and protecting the liver from microbial toxins.

Bone-marrow-derived macrophages from *Cx3cr1*$^{-/-}$ mice released more Il-1β and had higher expression of *Il1b*, *Nlrp3* and *Casp1* than those from wild-type mice, indicating the involvement of Cx3cr1 in innate immune signalling. A broad-spectrum antibiotic treatment of both groups of mice on the HFD improved liver disease and decreased activation of the innate immune system.



Zonula occludens 1 expression (green) in ileum of wild-type (left) and *Cx3cr1*$^{-/-}$ (right) mouse on a high-fat diet. Courtsey of M. Schneider.

"Future experiments should focus on the gut–liver crosstalk and homeostasis during steatohepatitis progression," concludes joint first author Veerle Bieghs.

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Original article Schneider, K. M. *et al.* CX3CR1 is a gatekeeper for intestinal barrier integrity in mice: limiting steatohepatits by maintaining intestinal homeostasis. *Hepatology* doi:10.1002/hep.27982