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ALCOHOLIC LIVER DISEASE

Mucosal microbes exacerbate experimental alcoholic steatohepatitis

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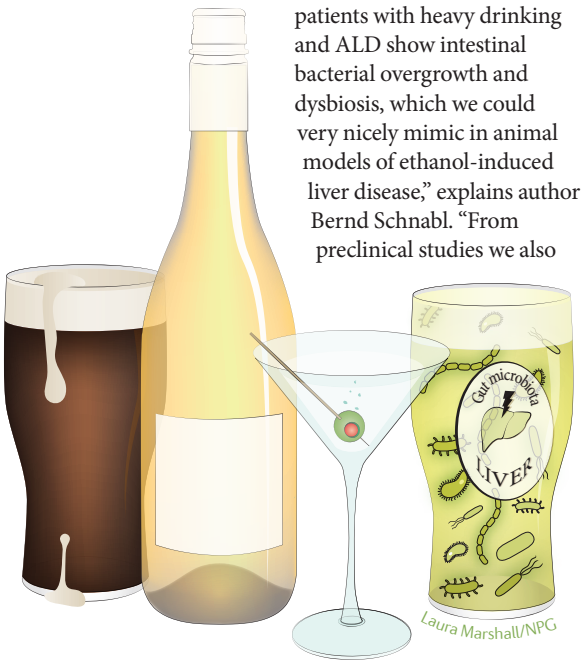
New insights into the gut–liver axis in the context of alcoholic liver disease (ALD) have been revealed in an experimental study published in *Cell Host & Microbe*. Mucosa-associated microbiota have been shown to be key to the development of liver disease associated with chronic alcohol use in mouse models. The new findings also show that boosting intestinal defence via increased expression of antimicrobial proteins reduced the numbers of these mucosa-adherent microbes and leads to a subsequent reduction in bacterial translocation and protection against alcoholic steatohepatitis in mice.

Alcohol is known to be harmful to the liver and directly causes damage — from simple steatosis to cirrhosis and end-stage liver disease — but chronic alcohol consumption has also been linked to changes in the gut microbiota.

"We knew for a long time that patients with heavy drinking and ALD show intestinal bacterial overgrowth and dysbiosis, which we could very nicely mimic in animal models of ethanol-induced liver disease," explains author Bernd Schnabl. "From preclinical studies we also knew that the gut microbiome is important, because non-absorbable antibiotics can prevent and treat alcoholic steatohepatitis," he adds, "but why changes in the intestinal microbiome occur was not known".



As such, the researchers wanted to explore the functional consequences of ALD. Previous work had already identified the association between low levels of the antimicrobial protein regenerating islet-derived protein 3 (REG3) and chronic alcoholic consumption, so the researchers focused their attention on these C-type lectins and whether absence or overexpression of these proteins affects the progression of ethanol-induced liver disease in mice.

The investigators showed that REG3B protected against ethanol-induced steatohepatitis without affecting intestinal absoprtion or hepatic metabolism of ethanol. In particular, *Reg3b*$^{-/-}$ mice developed more severe ethanol-associated liver disease than wild-type littermate mice that were also subjected to chronic ethanol feeding. Furthermore, ethanol-fed *Reg3b*$^{-/-}$ mice had increased numbers of mucosa-associated bacteria compared with ethanol-fed wild-type mice; no difference in numbers and composition of luminal bacteria were observed between the mice. Moreover, this increased colonization of the intestinal surface was also matched by increased levels of bacterial translocation to the mesenteric lymph nodes and the liver. Similar results were observed with ethanol feeding in *Reg3g*$^{-/-}$ mice versus controls.

Importantly, intestinal overexpression of REG3G protected mice from ethanol-induced liver injury, including steatosis and inflammation, compared with controls. Interestingly, this overexpression also led to markedly reduced numbers of mucosa-associated bacteria and reduced bacterial translocation to mesenteric lymph nodes and the liver after ethanol feeding. Decreased numbers of luminal bacteria were also observed, as it was believed that overexpressed REG3G can penetrate the mucus layer into the intestinal lumen, mediating its antimicrobial effects there also. Bringing the findings back to the clinic, the researchers examined whole duodenal biopsy samples from patients with alcohol dependency and found that alcohol-dependent patients had increased numbers of adherent mucosa-associated microbiota in the small intestine compared with those without alcohol dependency.

"We now provide evidence that suppression of intestinal defence mechanisms leads to increased ALD by a mechanism that involves failure to control the adherent microbiota in the intestine," says Schnabl. Further work is planned to learn more about the underlying mechanisms to determine whether other molecules or strategies can increase REG3 expression, or indeed whether specific bacteria within the mucosa-associated microbiota exacerbate ALD. Targeting these microbes in particular might alter disease susceptibility.

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ORIGINAL ARTICLE Wang, L. *et al.* Intestinal REG3 lectins protect against alcoholic steatohepatitis by reducing mucosa-associated microbiota and preventing bacterial translocation. *Cell Host Microbe* http://dx.doi.org/10.1016/j.chom.2016.01.003

FURTHER READING Louvet, A. & Mathurin, P. Alcoholic liver disease: mechanisms of injury and targeted treatment. *Nat. Rev. Gastroenterol. Hepatol.* **12**, 231–242 (2015)