Nature Reviews Gastroenterology & Hepatology | Published online 7 June 2017; doi:10.1038/nrgastro.2017.78

GUT MICROBIOTA

Intestinal fungi fuel the inflammatory fire in alcoholic liver disease

> ALD is associated with increased translocation of intestinal microbial products…

Chronic excess alcohol consumption induces intestinal mycobiota dysbiosis and hepatic inflammation in mice, worsening liver damage, according to new research. Marked intestinal fungal dysbiosis was also observed in patients dependent on alcohol.

Alcoholic liver disease (ALD), which represents a major cause of global mortality, is associated with marked changes in the gut microbiota, including intestinal bacterial overgrowth and a leaky gut barrier. Although the role of the bacterial component of the gut microbiota in ALD has been the major focus of research, the contribution of the mycobiota in this disease is of particular interest, given the increased risk of fungal infections in patients with ALD. The mycobiota is also known to be altered in other diseases, including hepatitis B and IBD. On the basis of these leads, Yang *et al.* sought to determine the effect of chronic alcohol consumption on the intestinal mycobiota and whether these changes might alter ALD development.

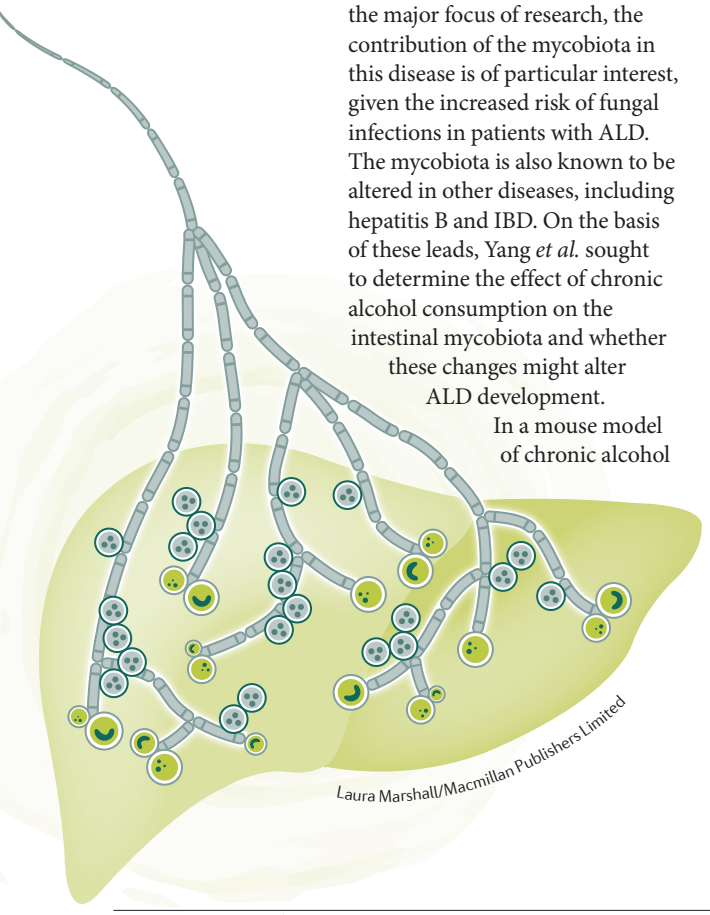
In a mouse model of chronic alcohol consumption, 8 weeks of ethanol administration increased the abundance of intestinal fungi. Sequencing of fungal internal transcribed spacer regions (equivalent to 16S ribosomal RNA sequencing in bacteria) also revealed increased fungal species richness and diversity in mice given ethanol. ALD is associated with increased translocation of intestinal microbial products as a result of impaired gut barrier integrity and dysbiosis. In the ethanol-treated mouse model, circulating levels of the fungal wall component 1,3-β-D-glucan were greater than in control mice, a finding associated with decreased intestinal expression of the tight junction protein occludin.

Next, the mouse model was treated with a nonabsorbable antifungal agent, amphotericin B. Mice given ethanol and the antifungal treatment were protected from intestinal fungal overgrowth, and had reduced plasma levels of 1,3-β-D-glucan and less severe ALD. Notably, the beneficial effects of amphotericin B treatment occurred independently of changes to gut bacteria.

To probe the effects of fungal products on hepatic innate immunity and inflammation, the researchers generated chimeric mice lacking C-type lectin domain family 7 member A (*Clec7a*, a pattern-recognition receptor that can bind 1,3-β-D-glucan) in bone-marrow-derived cells (*Clec7a*$^{\Delta BM}$ mice). Ethanol-mediated liver disease in these mice was ameliorated, despite no change to intestinal permeability or ethanol metabolism. Levels of IL-1β, a pro-inflammatory cytokine critical in the development of ALD, were found to be upregulated in Kupffer cells (liver-resident macrophages) in wild-type mice given ethanol; however, this ethanol-mediated upregulation of IL-1β was blocked in *Clec7a*$^{\Delta BM}$ mice or in wild-type mice treated with amphotericin B. Supporting the pro-inflammatory effects of CLEC7A in ALD, Kupffer cells isolated from wild-type mice and stimulated with 1,3-β-D-glucan increased *Il1b* transcription and IL-1β secretion, whereas there were was very little upregulation in *Clec7a*$^{\Delta BM}$ Kupffer cells.

Translating their findings into humans, the investigators characterized the faecal mycobiota in healthy individuals and in patients dependent on alcohol and with ALD, ranging in severity from nonprogressive disease to alcoholic cirrhosis. "We demonstrate a reduced fungal species diversity and richness in alcohol-dependent patients," explains author Bernd Schnabl. "There was also a dramatic overgrowth of *Candida* in these individuals." Finally, serum levels of anti-*Saccharomyces cerevisiae* IgG antibodies were used to determine the immune response to intestinal fungi — patients with alcoholic cirrhosis had a greater immune response than healthy individuals or those with cirrhosis resulting from hepatitis B.

Hugh Thomas



Laura Marshall/Macmillan Publishers Limited

ORIGINAL ARTICLE Yang, A.-M. *et al.* Intestinal fungi contribute to development of alcoholic liver disease. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI90562 (2017)

FURTHER READING Mukherjee, P. K. *et al.* Mycobiota in gastrointestinal diseases. *Nat. Rev. Gastroenterol. Hepatol.* **12**, 77–87 (2015)