Nature Reviews Gastroenterology & Hepatology | Published online 18 May 2016; doi:10.1038/nrgastro.2016.82

IBD

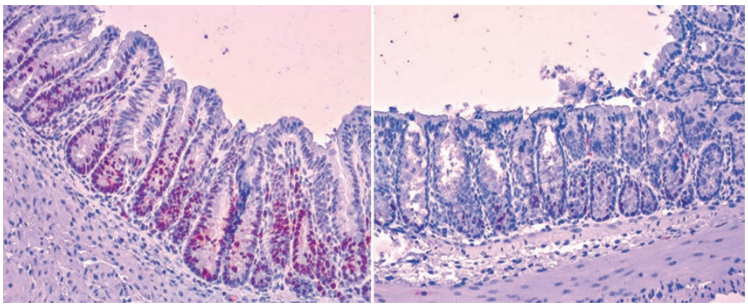
Dysbiosis underlies CARD9 risk alleles in colitis

> *Card9*$^{-/-}$ mice have a defective activation of the IL-22 pathway

Knockout of caspase recruitment domain-containing protein 9 (*Card9*), an IBD susceptibility gene, exacerbates colitis in mice by impairing microbial production of ligands critical for immune regulation that act via the aryl hydrocarbon receptor (AHR), according to a new study.

Whether dysbiosis is a cause or consequence of IBD is unclear. CARD9 plays a part in the innate immune response to fungi and promotes recovery from colitis by activating IL-22 production, but certain *CARD9* polymorphisms favour IBD pathogenesis. In addition, *Card9*-knockout (*Card9*$^{-/-}$) mice have increased vulnerability to colitis.

Harry Sokol and colleagues investigated how *Card9* and the gut microbiota might interact to affect IBD pathogenesis. In *Card9*$^{-/-}$ mice, the researchers detected impeded recovery from induced colitis in addition to altered gene expression in the colon. "*Card9*$^{-/-}$ mice have a defective activation of the IL-22 pathway," explains Sokol. "We then compared the faecal microbiota of wild-type and *Card9*$^{-/-}$ mice and observed several differences both at the bacterial and fungal level".



Cross-sections of proximal colon from wild-type (left) and *Card9*$^{-/-}$ (right) mice immunostained for proliferation marker Ki67. Image courtesy of H. Sokol.

To isolate the effect of the altered microbiota on intestinal inflammation, the team colonized germ-free, wild-type mice with microbiota from *Card9*$^{-/-}$ mice and found that increased susceptibility to colitis and reduced IL-22 production was recapitulated in these animals. AHR activation can modulate IL-22 production, and microbiota-mediated metabolism of tryptophan is a crucial step in generating AHR ligands. Interestingly, the researchers observed impaired tryptophan metabolism in microbiota from *Card9*$^{-/-}$ mice. Furthermore, AHR agonist treatment or supplementation with tryptophan-metabolizing *Lactobacillus* strains rescued susceptibility to colitis in *Card9*$^{-/-}$ mice. Sokol and colleagues also found reduced AHR activation in patients with IBD compared with healthy individuals, a defect exacerbated in those with disease-associated *CARD9* polymorphisms.

"The next steps would be to try to correct this impaired microbiota function," concludes Sokol.

Charlotte Ridler

ORIGINAL ARTICLE Lamas, B. *et al.* CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. *Nat. Med.* http://dx.doi.org/10.1038/nm.4102 (2016)