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MUCOSAL IMMUNOLOGY

# Tryptophan triggers tranquillity

The composition of the gut microbiota is influenced by host genetics, the environment and diet; changes in these factors can disrupt intestinal homeostasis and lead to pathologies such as inflammatory bowel disease (IBD). Reporting in *Nature Medicine*, Lamas *et al.* show that mice lacking caspase recruitment domain-containing protein 9 (CARD9) are more susceptible to colitis owing to having an altered microbiota that has impaired tryptophan metabolism and pro-inflammatory effects.

Mice lacking CARD9 have previously been shown to be more susceptible to colitis due to defective interleukin-22 (IL-22) activation. Furthermore, tryptophan metabolites generated by the microbiota can modulate the production of IL-22, which is known to be important for intestinal homeostasis. Here, the interaction between CARD9, the microbiota and tryptophan in intestinal homeostasis was investigated.

> "the microbiota of *Card9*$^{-/-}$ mice alters the IL-22 signalling pathway"

The authors compared the colon transcriptomes of *Card9*$^{-/-}$ and wild-type mice in response to dextran sodium sulfate (DSS)-induced colitis; in this model, *Card9*$^{-/-}$ mice are known to have impaired intestinal healing. During the recovery period, these mice showed decreased expression of molecules involved in epithelial cell proliferation, *Il22* and the IL-22-regulated genes *Reg3g* and *Reg3b* (encoding regenerating islet-derived 3γ (REG3γ) and REG3β, respectively). Thus, CARD9 and IL-22 seem to have a role in mediating recovery from DSS-induced colitis.

The composition of the microbiota was altered in *Card9*$^{-/-}$ mice, and these mice showed decreased levels of certain commensals such as *Allobaculum* spp. and *Lactobacillus reuteri*. To explore the impact of the microbiota in *Card9*$^{-/-}$ mice on colitis, germ-free mice were colonized with the microbiota from wild-type mice (WT→GF mice) or *Card9*$^{-/-}$ mice (*Card9*$^{-/-}$→GF mice) and exposed to DSS. Similar to *Card9*$^{-/-}$ mice, *Card9*$^{-/-}$→GF mice showed increased susceptibility to colitis and impaired recovery. Transcription analysis showed that *Il22* was one of the most downregulated genes in *Card9*$^{-/-}$→GF mice compared with WT→GF mice. Of note, *Il22*$^{-/-}$ mice have previously been shown to have increased susceptible to DSS-induced colitis and impaired intestinal healing. The production of IL-22 by T cells and innate lymphoid cells in the colon was decreased in *Card9*$^{-/-}$→GF mice but not in control mice. Thus, the gut microbiota of *Card9*$^{-/-}$ mice contributes to susceptibility to DSS-induced colitis by defective IL-22 activation.

Next, the authors investigated the metabolism of tryptophan to indole derivatives, which are ligands of aryl hydrocarbon receptor (AHR) and known to promote local IL-22 production. The levels of the bacteria-derived indole-3-acetic acid were decreased in *Card9*$^{-/-}$ and *Card9*$^{-/-}$→GF mice. Interestingly, supplementation of *Card9*$^{-/-}$→GF mice with three *Lactobacillus* strains capable of metabolizing tryptophan restored IL-22 expression and AHR ligand production and decreased susceptibility to colitis. Hence, the microbiota of *Card9*$^{-/-}$ mice alters the IL-22 signalling pathway via impaired tryptophan metabolism.

So, are these findings relevant to human disease? Indeed, the authors found that faecal samples from patients with IBD showed reduced activation of AHR compared with samples from healthy individuals. Genotyping showed that the IBD-associated single-nucleotide polymorphism within CARD9 was also associated with reduced AHR activation by microbiota-derived metabolites extracted from faecal samples from these individuals.

These results suggest a connection between CARD9, IBD and the ability of the microbiota to produce AHR agonists in humans. The authors suggest that tryptophan catabolites derived from gut microbiota could be used as biomarkers of dysbiosis and may be targeted for development of new therapeutics.

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**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)