MICROBIOME

TLR5 puts the brakes on

> motile commensal bacteria are prevented from crossing the mucosal barrier by the TLR5-induced production of anti-flagellin IgA antibodies

Getty/Photodisc

Crossing of the gut mucosal barrier by bacteria, which is often flagellum-dependent, can lead to chronic inflammation. Reporting in *Cell Host & Microbe*, Tyler Cullender and colleagues now show that, in mice, the pattern recognition receptor Toll-like receptor 5 (TLR5) has a key role in downregulating production of flagella, thus preventing this potentially harmful motility.

TLR5 is the innate immune receptor for flagellin, which is the main protein component of the bacterial flagellum. Many abundant members of the gut microbiota are capable of producing flagella; however, in the intact gut, the levels of flagellin are low. To investigate the factors that control the expression of flagellin — and thus bacterial motility — in the gut, Cullender and colleagues used a *Tlr5*$^{-/-}$ mouse strain. The main protective antibody in the mucosa is immunoglobulin A (IgA) and lower levels of anti-flagellin IgA were found in the cecum and faecal pellets of *Tlr5*$^{-/-}$ mice compared with wild-type mice. By contrast, the levels of biologically active flagellin in the gut were higher in *Tlr5*$^{-/-}$ mice than in wild-type mice. The authors then assessed flagella-related gene expression using a combined shotgun metatranscriptomics and metagenomics approach, and found that, although the overall composition of the gut microbiomes in *Tlr5*$^{-/-}$ and wild-type mice were similar, the gene expression patterns differed. The data revealed that genes encoding key elements of the flagellar apparatus were upregulated in *Tlr5*$^{-/-}$ mice and mainly belonged to members of the Firmicutes. The authors also showed that flagella that were harvested from several gut commensal Firmicutes species could stimulate TLR5.

Fluorescence-activated cell sorting was used to assess the profile of IgA-coated and uncoated bacteria in *Tlr5*$^{-/-}$ mice and wild-type mice. Although the overall ratios of coated to uncoated bacteria were similar in both, pryosequencing showed that there were phylum-level differences in coating in *Tlr5*$^{-/-}$ mice, with Firmicutes over-represented and Proteobacteria under-represented. Finally, the authors showed that antibodies against flagellin inhibit the motility of commensal species and reduce the expression of flagellin in *Escherichia coli*. Moreover, fluorescence *in situ* hybridization revealed that bacterial cells could penetrate and breach the mucosal barrier in the large and small intestines in *Tlr5*$^{-/-}$ mice but not in wild-type mice.

Together, the data suggest that, in wild-type mice, motile commensal bacteria are prevented from crossing the mucosal barrier by the TLR5-induced production of anti-flagellin IgA antibodies, which both immobilize the bacteria and, via an as yet unknown mechanism, downregulate flagellar gene expression.

Sheilagh Molloy

ORIGINAL RESEARCH PAPER Cullender, T. C. *et al.* Innate and adaptive immunity interact to quench microbiome flagellar motility in the gut. *Cell Host Microbe* **14**, 571–581 (2013)