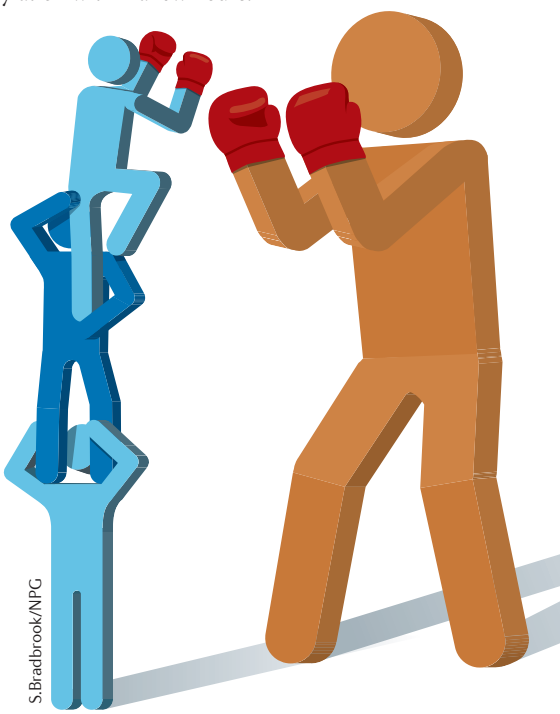
MICROBIOTA

Support your friends to resist your enemies

Reporting in *Science*, *Nature* and *Cell Host & Microbe*, three studies show that intestinal epithelial cells (IECs) supply fucosylated substrates to be metabolized by the commensal gut microbiota. The maintenance of host–commensal relationships in this manner improves host fitness through increased pathogen resistance and disease tolerance.

Goto *et al.* observed constitutive expression of the α(1,2)fucosyltransferase gene *Fut2* in mouse IECs and their fucosylation, which depended on the commensal microbiota, specifically segmented filamentous bacteria (SFB). Pickard *et al.* did not observe constitutive fucosylation of IECs in their mice (possibly resulting from a lack of SFB), but systemic injection with Toll-like receptor (TLR) agonists such as lipopolysaccharide (LPS) — to mimic systemic infection — led to IEC fucosylation within a few hours.

> “ILCs have a crucial role in inducing epithelial fucosylation”



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These two studies also showed that innate lymphoid cells (ILCs) have a crucial role in inducing epithelial fucosylation. Goto *et al.* showed that type 3 ILCs (ILC3s) produce interleukin-22 (IL-22) in response to commensal bacteria, which stimulates *Fut2* expression by IECs. In the study by Pickard *et al.*, IL-23 production by TLR-stimulated dendritic cells led to IL-22 production by ILCs and consequently *Fut2* induction by IECs.

To show that fucosylated IECs can provide fucose to the intestinal microbiota, Pickard *et al.* used a reporter system in which *Escherichia coli* expresses green fluorescent protein (GFP) under the promoter control of the fucose metabolism operon. In LPS-injected germ-free mice, the reporter *E. coli* expressed significantly more GFP when co-colonized with the commensal bacterium *Bacteroides acidifaciens*, which provides the α(1,2)fucosidase activity that is required to cleave fucose from fucosylated substrates. Furthermore, *Fut2* was required for GFP expression in LPS-treated specific pathogen-free reporter mice. The results show that epithelial fucosylation, which can be increased by infection (LPS) stress, leads to the increased supply of fucose as a substrate for the gut microbiota.

So what is the effect of fucose metabolism by commensal bacteria? Compared with wild-type mice, *Fut2*$^{-/-}$ mice in the study by Goto *et al.* had greater levels of inflammatory damage in response to infection with *Salmonella enterica* subsp. *enterica* serovar Typhimurium. *S.* Typhimurium titres in caecal contents were comparable between wild-type and *Fut2*$^{-/-}$ mice, but increased numbers of *S.* Typhimurium infiltrated the caecal tissue of *Fut2*$^{-/-}$ mice. In the study by Pickard *et al.*, *Fut2*$^{-/-}$ mice had greater weight loss after infection with *Citrobacter rodentium* followed by LPS treatment. Pham *et al.* showed that mice lacking the IL-22 receptor subunit α1 (IL-22RA1) are more susceptible to systemic breakthrough infection by the resident opportunistic pathogen *Enterococcus faecalis* after disruption of the normal microbiota by *C. rodentium* infection or administration of dextran sodium sulphate. Intestinal dysbiosis resulting from *C. rodentium* infection was significantly exacerbated in *Il22ra1*$^{-/-}$ mice, which led to overcolonization by *E. faecalis*. Using RNA sequencing of primary colonic organoids from wild-type and *Il22ra1*$^{-/-}$ mice, they showed that *Fut2* is highly upregulated by IL-22RA1 signalling, and in the absence of such signalling, there is a decreased level of fucosylation.

So, IEC fucosylation in response to commensal or systemic bacterial exposure is a host-protective mechanism to increase disease tolerance and resistance by providing support to beneficial commensals. In support of this conclusion, Pham *et al.* showed the beneficial effect of administering physiologically relevant doses of fucosylated molecules orally to *Il22ra1*$^{-/-}$ mice during *C. rodentium* infection. Such treatment increased the richness and diversity of commensal bacterial species, which in turn restricted colonization by *E. faecalis*.

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ORIGINAL RESEARCH PAPERS Goto, Y. *et al.* Innate lymphoid cells regulate intestinal epithelial cell glycosylation. *Science* **345**, 6202 (2014) | Pickard, J. M. *et al.* Rapid fucosylation of intestinal epithelium sustains host–commensal symbiosis in sickness. *Nature* http://dx.doi.org/10.1038/nature13823 (2014) | Pham, T. A. N. *et al.* Epithelial IL-22RA1-mediated fucosylation promotes intestinal colonization resistance to an opportunistic pathogen. *Cell Host Microbe* **16**, 504–516 (2014)