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IMMUNOLOGY

Starve a fever, feed the microbiota

A study finds that the cells lining the gut are modified in response to systemic infection, increasing the host's tolerance to infection in a manner that is dependent on the microorganisms that inhabit the gut.

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Mammals have a mutualistic relationship with the consortium of microorganisms that inhabit their intestines, collectively known as the gut microbiota. The microbiota profits from an environment that is rich in dietary and host-derived nutrients, and provides its host with numerous benefits, ranging from immune and digestive capabilities to resistance to pathogen colonization. In a paper published on *Nature*'s website today, Pickard *et al.*[1] describe another facet of this mutualism. They show that in a model of systemic infection, the host modifies the surface molecules of the epithelial cells lining its intestine, which increases host fitness in a microbiota-dependent manner.

The authors began their study with the question of how the beneficial microbiota is maintained during the period of diminished food consumption — known as anorexia — associated with systemic infection in the host. Host-derived sugars such as fucose are present on the intestinal epithelium and serve as an alternative to dietary food sources for the gut microbiota. Pickard and colleagues therefore evaluated fucosylation (the addition of fucose to molecules that are then secreted to the cell surface) of the small intestine following systemic administration of bacterial-derived molecules, such as lipopolysaccharide (LPS), which are recognized by Toll-like receptor proteins (TLRs). This administration mimics a bacterial infection and induces symptoms of sickness, including anorexia. The researchers showed that systemic LPS administration leads to rapid and sustained fucosylation of glycoproteins throughout the small intestine. These fucosylated glycoproteins are released into the intestinal lumen where the fucose residues are liberated and consumed by the resident bacteria in the colon.

Pickard *et al.* found that systemic administration of LPS induces release of the cell-signalling molecule interleukin-23 (IL-23) from dendritic cells of the innate immune system, which in turn activates innate lymphoid cells to release IL-22. This induces expression of a specific fucosyltransferase gene, *Fut2*, in epithelial cells of the small intestine, resulting in addition of fucose to their surface molecules (Fig. 1).

Next, the authors demonstrated that mice lacking *Fut2* recovered weight more slowly after LPS-induced anorexia than did control mice, indicating that under these conditions, fucosylation is beneficial to the host. Furthermore, this benefit is dependent on the presence of the microbiota, because germ-free or microbiota-depleted mice also showed impaired weight gain in LPS-induced anorexic conditions, despite the fact that their epithelial cells were fucosylated.

Finally, to investigate whether fucosylation improves the host's fitness during infection, Pickard and co-workers infected *Fut2*-deficient or control mice with the intestinal bacterial pathogen *Citrobacter rodentium*. They showed that inducible fucosylation in response to LPS is crucial for limiting both proliferation of colonic cells (hyperplasia), which is indicative of tissue damage, and weight loss during infection. This benefit is probably not due to increased resistance to infection, because the total levels of *C. rodentium* in the small intestine were similar in mice with or without *Fut2*. Because the damage to the host is independent of pathogen burden, it is probable that this microbiota-dependent effect improves host fitness through disease tolerance[2,3].

Recently, Goto *et al.*[4] identified a molecular pathway involved in microbiota-triggered fucosylation on the small intestinal epithelium in normal, 'steady-state' conditions, which shares similarities with the systemic-LPS-inducible pathway described by Pickard and colleagues. Both studies provide evidence that fucosylation is dependent on a subset of IL-22-producing innate lymphoid cells. Similar to Pickard *et al.*, Goto and colleagues show that fucosylation is important for host defence

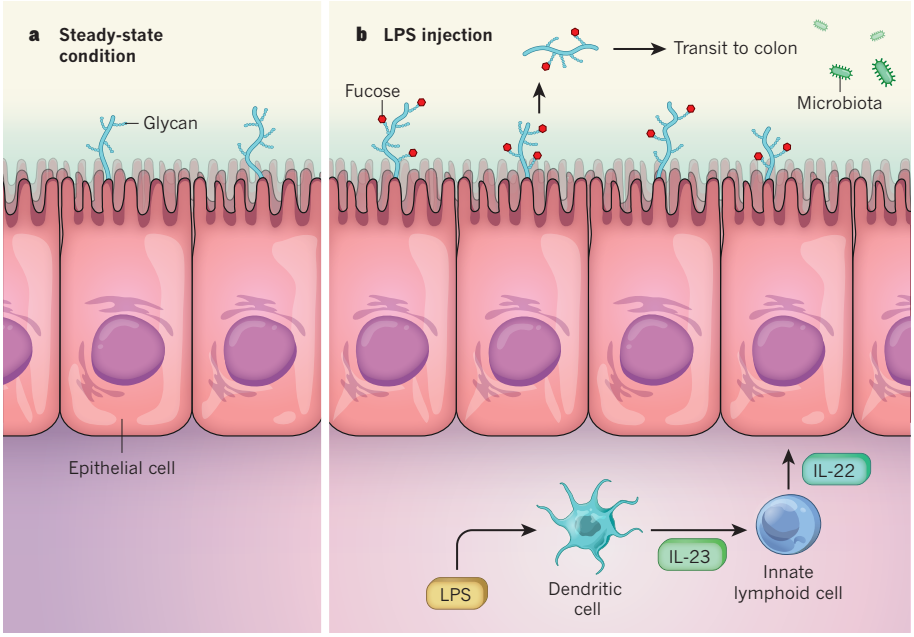

Figure 1 | Making a meal of disease. **a**, In steady-state conditions, fucosylation (the addition of fucose groups to the glycan chains of molecules secreted to the cell surface) is not induced in the small intestine. **b**, Pickard *et al.*[1] injected mice with lipopolysaccharide (LPS), which mimics systemic infection, including diminished food consumption. They report that this leads to the release of the cell-signalling molecule interleukin-23 (IL-23) from dendritic cells of the immune system. IL-23 drives IL-22 production from innate lymphoid cells, inducing expression of the gene encoding the fucosyltransferase enzyme Fut2 (not shown) in the epithelial cells of the small intestine. Fut2 catalyses fucosylation, and fucose-containing molecules are then released into the gut lumen where they transit to the colon. Here, fucose is liberated and consumed by members of the microbiota. This process correlates with an increased tolerance to infection in the host.

against an intestinal bacterial pathogen, *Salmonella typhimurium*. However, in this second study, fucosylation inhibited bacterial invasion of intestinal tissues and, therefore, host protection seems to be due to pathogen resistance rather than disease tolerance.

An apparent discrepancy in Pickard and colleagues' study is that they did not detect fucose on small intestinal epithelial cells in mice that had not been treated systemically with LPS, whereas Goto and colleagues' and other studies[5,6] showed steady-state fucosylation in the distal small intestine of mice. This may be accounted for by differences in the intestinal microbiota of the mice used in each study. Pickard and co-workers used mice from the Jackson Laboratory whose microbiota does not contain segmented filamentous bacteria[7], which Goto *et al*. identify as potent inducers of fucosylation. It will be interesting to determine the factors derived from the microbiota (and, in particular, from the segmented filamentous bacteria) that mediate intestinal fucosylation, which may act independently of Toll-like receptors[7]. It is likely that the steady-state fucosylation of the distal small intestine observed by Goto and colleagues would be augmented if mice were injected with LPS, because the fucosylation reported in the current study[1] occurred not only in this distal region, but throughout the small intestine.

Perhaps the most exciting aspect of Pickard and colleagues' work is what it adds to our understanding of beneficial interactions between the host and its microbiota. Although there is a growing list of host factors, cells and conditions that shape the microbiota, little is known about whether, under certain conditions, the host can select for a beneficial microbiota that increases the host's own fitness. This study suggests a mechanism by which such selection may occur. An outstanding question is how the microbiota contributes to disease tolerance.

Furthermore, the benefit to the host of fucosylation of intestinal epithelial cells shown by the authors sheds light on potential trade-offs with the known negative consequences of fucosylation. These include the use of fucosylated receptors by viruses[8], and the use of liberated fucose by bacterial pathogens[9]. The complex interactions between the host, its microbiota and pathogens, especially regarding fucose, will continue to be a stimulating area for investigation. ■

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