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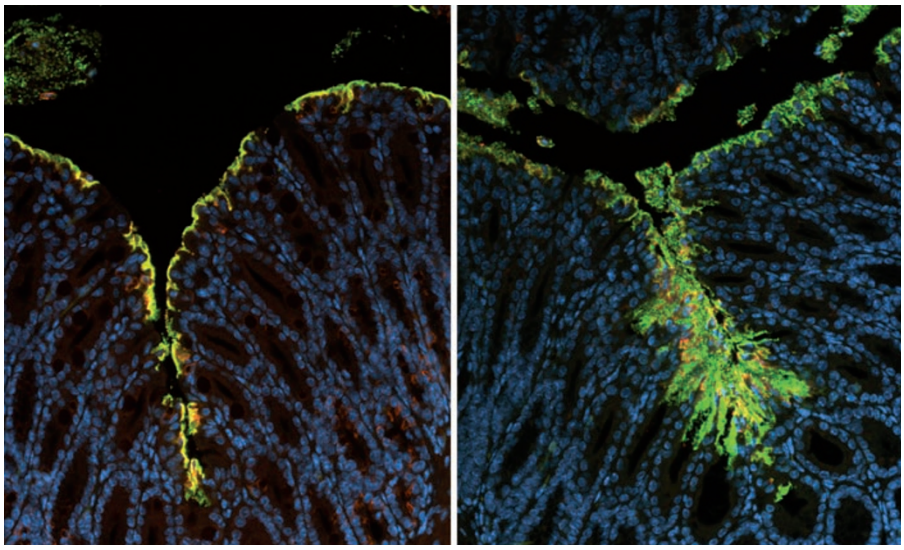
INNATE IMMUNITY

Stuck to MUC2

A new report in *PLoS Pathogens* by Bergstrom and colleagues provides a detailed look at the role of mucin 2 (MUC2) in protection against enteric pathogens.

Mucins are high-molecular-mass glycoproteins that are produced by epithelial cells in secreted and membrane-bound forms. Previous studies have indicated that the absence of membrane-bound mucins exacerbates infection with enteric bacterial pathogens, but how secreted mucins protect the host remained unknown. In this study using *Citrobacter rodentium*, a common model organism for pathogenic *Escherichia coli* infections in mice, the authors investigated the role of the major colonic secretory mucin MUC2. MUC2 is synthesized by goblet cells in the intestinal epithelium, ultimately forming a mucus gel layer up to 800 μm thick. The authors found that *C. rodentium* was sporadically detected in the MUC2 layer of infected wild-type animals, indicating that the mucus layer must be penetrated by the pathogen. To confirm a protective function for MUC2, they showed that mice deficient in MUC2 (*Muc2*$^{-/-}$) lost more weight, had an approximately four-fold higher mortality rate, displayed worsened colonic disease and harboured more total *C. rodentium* than wild-type mice.

Interestingly, the number of *C. rodentium* that adhered tightly to the epithelium was similar in *Muc2*$^{-/-}$ and wild-type mice, but the mutant mice harboured more pathogens in their intestinal lumen.



Localization of *Citrobacter rodentium* on the mucosal epithelium of a wild-type mouse (left panel) and a mucin 2-deficient mouse (right panel). Visualized are bacterial lipopolysaccharide (green), the secreted effector Tir (a marker for bacterial adherence) (red) and nuclei of host cells (blue). Image is reproduced, with permission, from Bergstrom, K. S. B. *et al.*

A closer look at the bacteria in the intestine revealed that in *Muc2*$^{-/-}$ mice *C. rodentium* formed microcolonies on the surface of the epithelium. Commensal bacteria could also be detected in these microcolonies, but they were not detected with the pathogen in wild-type mice. Therefore, MUC2 provides a barrier function that prevents commensal bacteria from interacting with the epithelium.

To determine how the lack of MUC2 results in increased pathogenesis, the authors tested which bacterial factors were required for infection. Interestingly, the type III secretion system (T3SS) effector EspF, an important virulence factor in infection of wild-type mice, was dispensable for infection of *Muc2*$^{-/-}$ mice, although the T3SS was required. In addition, more dextran passed across the epithelium in infected *Muc2*$^{-/-}$ mice than in uninfected *Muc2*$^{-/-}$ or wild-type mice. More bacteria penetrated the epithelium in *Muc2*$^{-/-}$ mice, leading to bacteraemia and *C. rodentium* infection of various organs, which is the likely cause of the increased mortality of the mutant. Therefore, MUC2 reduces the increased permeability of the intestinal epithelium that is induced by the pathogenic bacteria.

The total number of enteric bacteria was similar in uninfected wild-type and *Muc2*$^{-/-}$ mice; however, following infection with *C. rodentium*, the total level of commensal bacteria dropped in wild-type mice but not in mutant mice. Therefore, MUC2 probably protects the host by flushing out both commensal and pathogenic enteric bacteria during an infection.

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ORIGINAL RESEARCH PAPER Bergstrom, K. S. B. *et al.* Muc2 protects against lethal infectious colitis by disassociating pathogenic and commensal bacteria from the colonic mucosa. *PLoS Pathog.* **6**, e1000902 (2010)
FURTHER READING Hooper, L. V. Do symbiotic bacteria subvert host immunity? *Nature Rev. Microbiol.* **7**, 367–374 (2009)