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INFECTIOUS DISEASE

# IL-22 complements protection

Pathobionts such as *Clostridium difficile* can cause severe disease when intestinal homeostasis is disrupted; however, the immune response to pathobionts is poorly defined. Reporting in *Immunity*, Inohara and colleagues show that interleukin-22 (IL-22) regulates the complement system to eliminate pathobionts that enter the systemic circulation.

*C. difficile* commonly overgrows in the intestine of patients who have received broad-spectrum antibiotics and this dysbiosis can lead to colitis. The authors investigated whether IL-22 — which controls the microbiota by enhancing the expression of antimicrobial peptides and by regulating the repair of damaged intestinal epithelium — has a role in *C. difficile*-induced colitis. Indeed, *C. difficile* infection of antibiotic-treated mice led to increased levels of IL-22 in the intestine, lungs and liver, and *Il22*$^{-/-}$ mice showed higher mortality rates than wild-type mice. Of note, *Il22*$^{-/-}$ and wild-type mice showed similar numbers of intestinal neutrophils and macrophages, and a comparable degree of intestinal damage after *C. difficile* infection. Thus, IL-22 contributes to protection against *C. difficile* through mechanisms that are independent of the recruitment of inflammatory cells.

> “injection of recombinant IL-22 induced *C3* expression”

Given that the composition of the faecal microbiota and the numbers of *C. difficile* were similar in wild-type and *Il22*$^{-/-}$ mice after infection, the authors tested whether IL-22 could have a role in the systemic clearance of commensal bacteria that translocate to extraintestinal organs after *C. difficile* infection. Indeed, *Il22*$^{-/-}$ mice showed increased numbers of commensal bacteria in the liver, spleen, kidneys and lungs compared with wild-type mice, but similar numbers of bacteria were found in faecal samples. Notably, treatment with ciprofloxacin — which kills many commensals but not *C. difficile* — reduced the number of translocated bacteria and thereby protected the *Il22*$^{-/-}$ mice from lethality induced by *C. difficile* infection. Hence, IL-22 is important for the clearance of bacteria that translocate to extraintestinal sites after *C. difficile* infection.

As intestinal pathobionts and nonpathobionts showed similar induction of cytotoxicity and cytokine induction in host tissue cells *in vitro*, the authors hypothesized that pathobiont strains evade host immune responses. In fact, pathobionts isolated from *C. difficile*-infected *Il22*$^{-/-}$ mice were more resistant to neutrophil killing and phagocytosis by macrophages than commensal strains. Phagocytosis was dependent on complement factor C3, and C3 deposition on *C. difficile* was lower than on commensal strains although pathobionts and nonpathobionts elicited similar levels of complement activation. These results indicate that pathobionts have increased resistance to complement-mediated phagocytosis.

Finally, the authors investigated whether IL-22 regulates the complement system. In accordance with IL-22-induced gene expression profiles, the authors found that the expression of *C3* was increased in the liver and intestine after *C. difficile* infection but the induction of *C3* was substantially lower in *Il22*$^{-/-}$ mice than in controls. Furthermore, injection of recombinant IL-22 induced *C3* expression in wild-type mice and increased the expression of *C3* in the liver of *Il22*$^{-/-}$ mice after *C. difficile* infection.

This study indicates that by regulating the expression of *C3*, IL-22 has a protective role in host defence against pathobionts that translocate systemically after *C. difficile* infection.

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**ORIGINAL RESEARCH PAPER**
Hasegawa, M. *et al.* Interleukin-22 regulates the complement system to promote resistance against pathobionts after pathogen-induced intestinal damage. *Immunity* **41**, 620–632 (2014)
**FURTHER READING** Kamada, N. *et al.* Role of the gut microbiota in immunity and inflammatory disease. *Nature Rev. Immunol.* **13**, 321–335 (2013)