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HOST RESPONSE

Fungal safeguards in the gut

Commensal gut bacteria have important roles in modulating health and disease by providing protection against infections and regulating immune homeostasis. The gastrointestinal tract is also colonized by numerous fungal species; however, as the field has mostly focused on bacterial species, the protective benefits of commensal fungi and whether they can influence disease outcomes have been unknown. In a recent study, Jiang *et al.* report that commensal enteric fungi provide protection in local intestinal and non-intestinal systemic tissues.

To test whether commensal fungi could functionally recapitulate the protective benefits of commensal bacteria, the authors administered *Candidia albicans* to mice that had been treated with broad-spectrum antibiotics and were housed in a pathogen-free facility. *C. albicans* mono-colonization was sufficient to protect these mice from fatal intestinal injury and inflammation as a consequence of dextran sodium sulfate (DSS)-induced colitis. *C. albicans* also increased the survival of germ-free mice, which are particularly susceptible to DSS-induced intestinal injury. The authors then tested whether *Saccharomyces cerevisiae* — an unrelated fungus that is also naturally found in the mammalian gut — could influence disease susceptibility. Similar to *C. albicans*, *S. cerevisiae* colonization reduced susceptibility to DSS-induced colitis in antibiotic-treated mice.

Next, the authors investigated immune modulation by commensal fungi in extra-intestinal tissues, given that enteric bacteria have been shown to enhance systemic immunity. The authors used influenza A virus to test whether *C. albicans* and *S. cerevisiae* could reduce susceptibility to respiratory infection. Mono-colonization by either of these fungi significantly reduced mortality after influenza A virus infection and strengthened virus-specific $CD8^+$ T cell responses in antibiotic-treated mice. Based on these observations, the authors conclude that commensal fungi can functionally replace commensal bacteria by preventing local tissue injury and enhancing systemic immunity.

To investigate the molecular basis for the protection that was conferred by *C. albicans* and *S. cerevisiae* to the antibiotic-treated mice, the authors tested whether major fungal cell wall components were sufficient to functionally replace whole intact fungi. Intrarectal administration of purified mannan (to recapitulate mannan that is naturally released by commensal enteric fungi) was sufficient to reduce the susceptibility of antibiotic-treated mice to DSS-induced colitis and influenza A virus infection. Importantly, administration of other fungal cell wall components, including curdlan and zymosan, failed to improve mortality.

> “commensal fungi can functionally replace commensal bacteria by preventing local tissue injury and enhancing systemic immunity”

To identify which host receptor was responsible for recognizing mannan, the authors neutralized a panel of pattern recognition receptors on a macrophage nuclear factor-κB (NF-κB) reporter cell line and tested their responsiveness to mannan stimulation. Neutralization of DECTIN1 and Toll-like receptor 4 (TLR4) significantly reduced mannan-induced NF-κB levels. As expected, susceptibility to DSS-induced colitis was increased in both DECTIN1-deficient and TLR4-deficient mice after antibiotic treatment; however, the protective benefits against DSS that had been previously observed with *C. albicans* mono-colonization were selectively overturned in TLR4-deficient mice, suggesting that TLR4 recognizes fungal mannan to confer protective benefits to the host.

In this series of experiments, Jiang *et al.* have shown that two unrelated species of commensal fungi can each reverse the susceptibility to intestinal injury and extra-intestinal infection that is caused by an absence of commensal bacteria, thus revealing a heretofore unappreciated role of commensal fungi in modulating susceptibility and host responses to disease.

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ORIGINAL ARTICLE Jiang, T. T. *et al.* Commensal fungi recapitulate the protective benefits of intestinal bacteria. *Cell Host Microbe* http://dx.doi.org/10.1016/j.chom.2017.10.013 (2017)
FURTHER READING Budden, K. F. *et al.* Emerging pathogenic links between microbiota and the gut–lung axis. *Nat. Rev. Microbiol.* **15**, 55–63 (2017)