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BACTERIAL TOXINS

Strain competition keeps a lid on gut pathogens

> secretion of Bte2 by NTBF T6SS is able to reduce disease burden by targeting ETBF

One role of the commensal gut microbiota is to exclude pathogenic bacteria, such as enterotoxigenic *Bacteroides fragilis* (ETBF), from the gut but little is known about the mechanisms that underlie this exclusion. Using co-colonization of specific pathogen-free (SPF) mice, Hecht *et al.* show that an ETBF strain can be excluded from the gut by an effector that is secreted by a non-toxigenic *B. fragilis* (NTBF) strain, which demonstrates the potential of strain-specific competition to shape the composition of gut microbial communities.

B. fragilis populations in the gut microbiota of individual humans are known to be predominantly composed of either ETBF or NTBF, which suggested to the authors that ETBF and NTBF might compete in the gut, and thus represent a useful model for the study of pathogen exclusion by the commensal microbiota. As *B. fragilis* type VI secretion systems (T6SSs) have previously been shown to mediate interstrain competition, exclusion of ETBF was compared between wild-type, T6SS-deficient (in which the gene that encodes the essential T6SS component TssC had been deleted) and T6SS-complemented strains (in which *tssC* was deleted from the genome but expressed from a plasmid) of NTBF. In co-colonization experiments using SPF mice, the strain dominance over ETBF that was observed for wild-type NTBF and T6SS-complemented NTBF was abolished in mice that were co-colonized with T6SS-deficient NTBF. That the phenotype of T6SS deficiency was caused by the failure to exclude ETBF, rather than arising from a loss of fitness of NTBF, was confirmed by showing that monocolonization by NTBF was indistinguishable between wild-type and T6SS-deficient strains.

To assess whether the exclusion of ETBF, which secretes the colitis-inducing *B. fragilis* toxin (BFT), reduced the disease burden, the authors measured the levels of BFT transcript in faeces and injury and inflammation in the colon and caecum. Interstrain competition enabled wild-type NTBF to provide complete protection from ETBF-induced colitis, whereas T6SS-deficient NTBF only provided partial protection. To identify the T6SS effector, or effectors, that contributed to interstrain competition, mass spectrometry of wild-type and T6SS-deficient NTBF was used to characterize the T6SS secretome, which identified Bte2 as the most abundant effector. Importantly, examination of a *bte2*-deficient NTBF strain confirmed that Bte2 is the effector that mediates exclusion of ETBF, and thus reduction of disease burden, in the mouse gut.

Finally, a comparison of the ability of three NTBF and two ETBF strains to establish secondary colonization in monocolonized SPF mice showed that interstrain exclusion of secondary challenge was not specific to the exclusion of ETBF by NTBF. Instead, NTBF secondary challengers could also be excluded in mice that were monocolonized with ETBF or even by other NTBF strains, which suggests a broader role for interstrain competition in shaping the microbiota than pathogen exclusion. Furthermore, although the potency of interstrain competition varied between individual strains, the secondary challenge experiments indicate that a priority effect of the order of colonization is important in determining the outcome of interstrain competition between primary and secondary colonizers. Similarly to interstrain competition during co-colonization, this priority effect was abolished in primary colonizers deficient for T6SS.

Together, the findings reported in the study show that the secretion of Bte2 by NTBF T6SS is able to reduce disease burden by targeting ETBF and shape the microbiota by establishing a priority effect when competing with secondary NTBF challengers.

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ORIGINAL ARTICLE Hecht, A. *et al.* Strain competition restricts colonization of an enteric pathogen and prevents colitis. *EMBO Rep.* http://dx.doi.org/10.15252/embr.201642282 (2016)