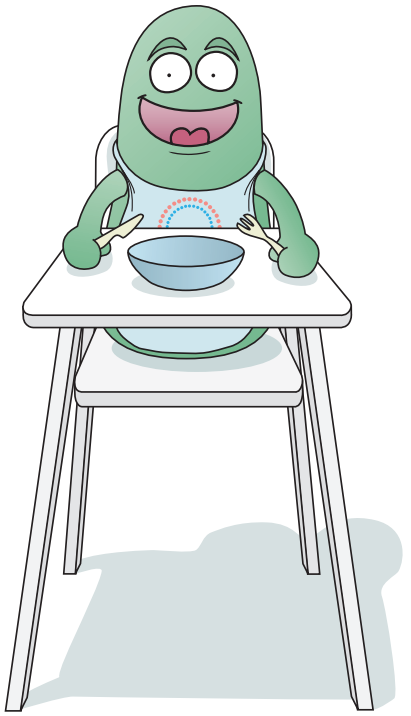
Nature Reviews Microbiology | Published online 13 Feb 2017; doi:10.1038/nrmicro.2017.9

BACTERIAL PATHOGENESIS

Microbial manipulation of the gut–brain axis



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Anorexia is a host behavioural trait that is commonly triggered by infection; however, the causes of sickness-induced anorexia, and the consequences for both the host and pathogen, are unclear. Using a mouse model of infection, Rao *et al.* now report that the intestinal pathogen *Salmonella enterica* subsp. *enterica* serovar Typhimurium manipulates the gut–brain axis to inhibit anorexia, which reduces its virulence but promotes its transmission.

S. Typhimurium causes enteric and systemic typhoid disease in humans and mice. Spread through the faecal–oral route, it establishes infection in the gut and triggers an anorexic response in the mouse host. The authors investigated the importance of the *Salmonella* effector SlrP, which is a novel E3 ubiquitin ligase, for virulence. When specific pathogen-free c57BL/6 (B6) mice were orally infected with an *S.* Typhimurium strain (SL1344) that was negative for SlrP (Δ*slrP*) they exhibited faster death kinetics, increased weight loss and more pronounced anorexia than mice that were infected with wild-type *S.* Typhimurium.

> *Salmonella enterica* subsp. *enterica* serovar Typhimurium manipulates the gut–brain axis to inhibit anorexia, which reduces its virulence but promotes its transmission

Remarkably, food-restricted mice that were infected with wild-type *S.* Typhimurium showed a similar phenotype to mice that were infected with the Δ*slrP* strain and had faster death kinetics. By contrast, force-fed Δ*slrP*-infected mice had increased survival, which was comparable to mice that were infected with wild-type *S.* Typhimurium. Together, these data suggest that the *Salmonella* effector SlrP increases survival in infected mice by inhibiting anorexia and that reduced nutrient intake is associated with increased virulence.

Interleukin-1β (IL-1β) induces sickness-induced anorexia. The authors found that IL-1β levels were increased in the small intestine of Δ*slrP*-infected mice 48 h post-infection; this correlated with the onset of anorexia. Importantly, Il-1β-deficient mice were protected from the negative effects of Δ*slrP* infection and, by contrast, mice that were infected with wild-type *S.* Typhimurium and injected with recombinant IL-1β showed increased anorexia. Thus, SlrP decreases sickness-induced anorexia in *Salmonella* infection by inhibiting IL-1β in the small intestine.

Signalling through the gut–brain axis takes place between the gut and the central nervous system (CNS). To investigate its role in sickness-induced anorexia, gene expression analysis was carried out on the hypothalamus of infected mice; genes involved in feeding and metabolism were differentially expressed between mice that were infected with wild-type and Δ*slrP S.* Typhimurium, and a subset of these genes was regulated by IL-1β. Notably, severance of the vagus nerve, which innervates the small intestine, prevented anorexia in Δ*slrP*-infected mice. Thus, pathogen-induced anorexia is dependent on signalling through the gut–brain axis.

Finally, investigating the effects of anorexia on pathogen transmission revealed that mice that were infected with the Δ*slrP* strain were more likely to have disseminated infection in secondary organs than mice infected with wild-type *S.* Typhimurium, which explains the increased virulence of this strain. Moreover, mice with disseminated infection were less likely to shed *Salmonella* in faeces. *Salmonella*-induced inhibition of anorexia may therefore promote host survival and pathogen transmission.

In summary, this study reports that the *S.* Typhimurium effector protein SlrP manipulates the gut–brain axis and prevents sickness-induced anorexia in the host. Although this reduces virulence, it is ultimately beneficial for *S.* Typhimurium as it increases pathogen transmission.

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ORIGINAL ARTICLE Rao, S. *et al.* Pathogen-mediation inhibition of anorexia promotes host survival and transmission. *Cell* **168**, 503–516.e12 (2017)