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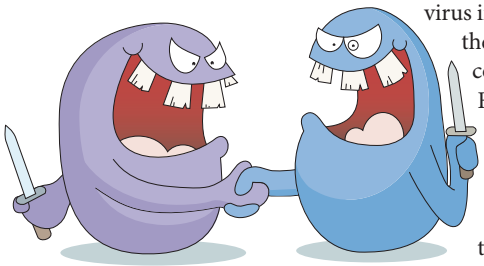
VIRAL INFECTION

The gut microbiota: friend or foe?

We normally think of the gut microbiota as the 'friendly' bacteria that carry out many beneficial functions, including protecting us from infection. But two studies now identify a different side to the gut microbiota, showing that it can actually facilitate viral infection and promote transmission.

In the first study, Kane *et al.* used mouse mammary tumour virus (MMTV), which is transmitted through mucosal surfaces, to determine how retroviruses evade host immune responses to establish chronic infections. They found that, whereas the offspring of antibiotic-treated, MMTV-infected mice could mount an immune response to viral antigens, antibiotic-free, MMTV-infected mice transmitted the virus to their progeny; this indicates a crucial role for the gut microbiota in this process.

Similar observations were made in the second study by Kuss *et al.*, who investigated the role of the gut microbiota in the transmission of poliovirus, an enteric pathogen. Using a mouse strain that is susceptible to human poliovirus, they found that antibiotic-treated mice showed lower mortality following oral poliovirus infection than their untreated counterparts. Furthermore, re-introduction of faecal bacteria into the antibiotic-treated mice restored the susceptibility of the mice to the disease. Interestingly, poliovirus replicated more efficiently in the intestines of untreated mice than in mice that had been treated with antibiotics, owing to the presence of the microbiota. Furthermore, incubation of the virus with faeces from antibiotic-treated mice significantly decreased its viability *in vitro* compared with culture in the presence of untreated faeces, which suggests that bacteria have a direct effect on the infectivity of the virus.



So how does the gut microbiota promote virus replication and transmission? To dissect the mechanism, Kane *et al.* used mice lacking Toll-like receptor 4 (TLR4), which induces the production of the anti-inflammatory cytokine interleukin-10 (IL-10), thereby dampening the immune response and allowing MMTV to become persistent. Following injection with MMTV virions, germ-free TLR4-deficient mice did not pass the virus to their offspring, unlike TLR4-sufficient mice, indicating that TLR4 has a role in promoting virus replication.

TLR4 binds to lipopolysaccharide (LPS) secreted by bacteria; Kuss *et al.* found that poliovirus also binds to LPS and that this interaction increases viral infectivity. Consistent with this, Kane *et al.* observed that MMTV binds and sequesters LPS *in vitro* and that this stimulates the production of IL-10 by splenocytes in culture. When they dissected the pathway further, Kane *et al.* observed that the induction of IL-10 depended on the secretion of IL-6, which is, in turn, produced in response to signalling through TLR4 and its co-receptor, CD14, following TLR4 binding to LPS. Indeed, mice deficient in IL-6, IL-10, TLR4 or CD14 did not efficiently transmit MMTV through successive generations, highlighting the importance of this pathway in virus persistence and transmission. Based on this, Kane *et al.* propose that, to establish a chronic infection and transmit to the following generation, MMTV requires LPS secreted by the gut microbiota, which it binds to and uses to dampen the immune response by triggering the secretion of the anti-inflammatory cytokine IL-10.

Together, these studies reveal that, in the case of MMTV and poliovirus, the gut microbiota has a detrimental effect towards the host by interacting with the virus and, consequently, promoting infection or transmission. Other viruses may promote their replication and transmission in a similar way — Kuss *et al.* find that reovirus also requires the gut microbiota to establish infection — so further work is required to understand the interaction of viruses with the host microbiota.

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ORIGINAL RESEARCH PAPERS Kane, M. *et al.* Successful transmission of a retrovirus depends on the commensal microbiota. *Science* **334**, 245–249 (2011) | Kuss, S. K. *et al.* Intestinal microbiota promote enteric virus replication and systemic pathogenesis. *Science* **334**, 249–252 (2011)