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MICROBIOME

A viral understudy for commensal bacteria

A body of work has highlighted the crucial role of the intestinal microbiota in promoting the maturation of the immune system. Most studies have explored the contribution of commensal bacteria, but a new study by Kernbauer *et al.* shows that enteric viruses can have a supporting role too.

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Murine norovirus (MNV) is a positive-strand RNA virus of the Caliciviridae family that is endemic in mouse facilities. In a previous study, the CR6 strain of MNV (MNV.CR6) was found to drive intestinal pathology in mice lacking the gene encoding ATG16L1, which is associated with inflammatory bowel disease in humans. To address if MNV also has symbiotic effects, the authors infected germ-free breeding pairs with MNV.CR6 and generated mono-associated mice. They found that these mice did not show the immunological and anatomical defects that are typically observed in the germ-free intestine. Whereas germ-free mice had narrow villi, abnormal crypts and few lamina propria T cells, the MNV.CR6-associated mice had a normal intestinal architecture and similar T cell numbers to conventionally housed mice. MNV.CR6 also regulated the development of innate lymphoid cells (ILCs); type 2 ILC (ILC2) populations were expanded in the intestine of germ-free mice, but not in mice that were mono-associated with MNV.CR6.

S.Bradbrook/NPG

These effects were not specific to MNV.CR6, as mono-association with other strains of MNV also supported immune maturation and the development of a normal intestinal tissue structure. Furthermore, conventionally housed mice that were treated with antibiotics for 2 weeks developed intestinal defects similar to those seen in germ-free mice, but infection with MNV.CR6 reversed these abnormalities. The inoculation of antibiotic-treated mice with the commensal bacteria *Bacteroides thetaiotamicron* or *Lactobacillus johnsonii* also protected the architectural integrity of the intestine, but had varying effects on intestinal T cell populations. This strengthens the idea that different components of the microbiota have overlapping, but not identical, effects on host physiology.

Indeed, RNA deep-sequencing analyses identified sets of shared and unique host genes that are regulated by commensal bacteria and MNV.CR6. The overlapping gene set contained genes that regulate the development and function of immune cells, which is consistent with the results from the microbiota repletion experiments. Unique genes regulated by MNV.CR6 included those associated with the type I interferon (IFN) response and, notably, MNV.CR6 could not reverse intestinal defects in antibiotic-treated mice that lacked the IFN receptor. The authors also examined how MNV.CR6 colonization affects intestinal inflammation, using models of chemically induced colitis and *Citrobacter rodentium* infection. In both of these settings, antibiotic treatment exacerbated disease symptoms, but infection with MNV.CR6 was found to have a protective effect.

Therefore, enteric viruses seem to function in an analogous way to their better understood bacterial neighbours, providing both beneficial and detrimental effects in a context-dependent manner. The authors propose that rapid technological developments in the field of viral discovery will help unearth symbiotic viruses in the mammalian intestine.

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