MICROBIOME

Gut phages at the centre

> the positive correlation between microbiome diversity and phage diversity, and the link between phage expansion and intestinal inflammation

The human gut microbiome comprises a complex microbial community that contains bacteria, archaea, fungi and other microbial eukaryotes, as well as viruses. Whereas the bacterial community has been well studied and is well described, the human gut virome has been studied to a lesser extent. Previous studies have shown that the virome is mainly composed of phages (phage virions or integrated into their hosts as prophages). Indeed, phages are the most abundant members of the microbiota. In other ecosystems, phages were shown to have many important roles in microbial ecology, population dynamics, physiology and evolution. However, much remains to be learnt about the composition, function and dynamics of the gut phage community and the possible contribution of phages to human health and disease. Two new studies shed some more light on these open questions and report the positive correlation between microbiome diversity and phage diversity, and the link between phage expansion and intestinal inflammation.

In the first study, Ley and colleagues examined the viromes of 21 monozygotic twin pairs (thus removing host genetic relatedness as a variable) to examine the relationship between the diversity of the microbiome and the diversity of the virome. They selected twin pairs with either highly concordant microbiomes or highly discordant microbiomes. Next, using the same samples from which the microbiomes were derived, the authors determined the viromes of these twin pairs. They found that microbiome diversity was mirrored by virome diversity and that microbiome-discordant twins displayed more dissimilar viromes compared with microbiome-concordant twins. Moreover, they found that the gut virome is highly unique to each individual and is dominated by phages; Caudovirales was the most abundant order, and Microviridae and the crAssphage were also represented in the viromes. Finally, the positive relationship between the gut microbiomes and gut viromes was driven by the phages of the viromes, and not eukaryotic viruses. Future studies are now required to determine the mechanism underlying the observed correlation between the microbiome richness and diversity and the virome richness and diversity in the gut.

Previous studies indicated that changes to phage composition in the gut (for example, increased abundance of Caudovirales) are associated with disease, including ulcerative colitis. In a second study, Round and colleagues first showed that experimental phage therapy with phages against adherent invasive *Escherichia coli* isolated from the human microbiota significantly reduced colonization by those carcinogenic bacteria and prevented tumour growth and mortality in mice. However, the authors noticed that both innate and adaptive immune pathways were upregulated in phage-treated animals compared with control animals.

To test whether phages directly stimulate the mammalian immune system, they administered the purified phage cocktail or a vehicle control to germ-free mice and found that phage treatment resulted in immune cell expansion in the gut. Moreover, they were able to show that phage DNA recognition by dendritic cells stimulated the production of the cytokine interferon-γ (IFNγ) by $CD4^+$ T cells. The authors also showed that immune activation was mediated by Toll-like receptor 9 (TLR9), as incubation of purified phage DNA with dendritic cells that lacked TLR9 failed to stimulate IFNγ production.

Finally, using a phage cocktail that contained Caudovirales phages, the authors reported that increased phage abundance exacerbated intestinal colitis in a manner dependent on TLR9 and IFNγ production, as indicated by the finding that TLR9-deficient mice were protected from phage-enhanced colitis and exhibited reduced immune responses.

In sum, the study provides evidence that changes in gut phage communities can directly aggravate intestinal disease.

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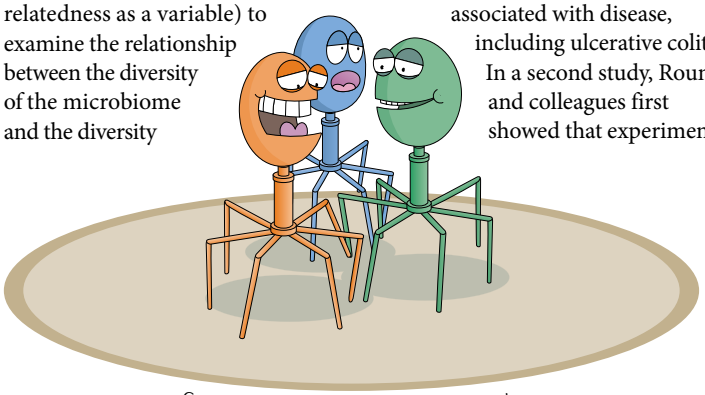

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ORIGINAL ARTICLES Moreno-Gallego, J. L., Chou, S.-P. et al. Virome diversity correlates with intestinal microbiome diversity in adult monozygotic twins. *Cell Host Microbe* https://doi.org/10.1016/j.chom.2019.01.019 (2019) | Gogokhia, L. et al. Expansion of bacteriophages is linked to aggravated intestinal inflammation and colitis. *Cell Host Microbe* https://doi.org/10.1016/j.chom.2019.01.008 (2019)

FURTHER READING Khan Mirzaei, M. & Maurice, C. F. Ménage à trois in the human gut: interactions between host, bacteria and phages. *Nat. Rev. Microbiol.* **15**, 397–408 (2017)