

MICROBIOME

With a little help from my phage friends

Mounting evidence suggests that the gut microbiota has a considerable impact on host physiology, but how the functional capacity of the microbiota is maintained after exposure to environmental stresses is unclear. Now, Collins and colleagues report that following antibiotic perturbation, the resident phage population provides the microbiota with a reservoir of advantageous genes, suggesting that the phage metagenome preserves the functional robustness of the microbiota on exposure to environmental stress.

In the complex ecosystem of the gut, gene exchange is likely to be widespread. Because phages can contribute beneficial genes to their bacterial hosts, the authors reasoned that these viruses might have an important role in the adaptation of the microbiota to stressful conditions. To test this, mice were treated with ciprofloxacin (a quinolone that inhibits DNA synthesis) or ampicillin (a β -lactam that inhibits cell wall synthesis) for 8 weeks, and phage DNA was subsequently purified from faecal samples and sequenced.

To determine whether antibiotic exposure selected for phage-encoded drug resistance genes, the phage metagenomes were compared to an assembled database of antibiotic resistance genes. This analysis showed that the phage metagenomes of antibiotic-treated mice were highly enriched for resistance genes compared with those of non-treated control mice. Interestingly, in addition to drug-specific resistance genes, both treatments led to the enrichment of multidrug resistance genes, suggesting that the phage metagenome

contributes to the emergence of multidrug resistance. Furthermore, the authors demonstrated that *ex vivo* infection of a naive microbiota with phages from antibiotic-treated mice resulted in a 2–3-fold increase in the frequency of bacterial resistance compared with infection with phages from the untreated control group, confirming that the phage metagenome can transfer beneficial traits to their bacterial hosts.

In addition to resistance genes, other genes encoding proteins that could potentially modulate susceptibility to antibiotics were also enriched. For example, phages from ciprofloxacin-treated mice were enriched for genes belonging to DNA repair pathways, such as nucleotide excision repair and homologous recombination. Furthermore, there was an enrichment for genes encoding diverse bacterial functions that are important for maintaining the stability of the host–microbiota relationship in the gut. These included genes belonging to pathways needed for the metabolism of vitamins, such as thiamine, which is an essential nutrient provided by the microbiota. In addition, there was an increase in the number of genes encoding bacterial carbohydrate-active enzymes, which are needed for fermentation of dietary- and host-derived glycans. Because a particular bacterium generally expresses a limited subset of such enzymes, the authors propose that the phage metagenome provides a resource for the acquisition of additional carbohydrate-degrading genes to maximize metabolic adaptation to the changing gut environment following antibiotic-mediated perturbation.



IMAGE SOURCE

These data show that the phage metagenome acts as a repository of beneficial genes, but how accessible are they to the gut microbiota? Because phage genomes contain an assortment of bacterial genes that have been acquired from their hosts, the reconstruction of individual phage genomes allowed the authors to infer putative phage–bacterium associations. They found that drug treatment resulted in increased connectivity of the phage–bacterium ecological network, such that more bacterial species were associated with a given phage.

Together, these findings show that antibiotic perturbation leads to the enrichment of beneficial genes in the intestinal phage metagenome and to an expanded phage–bacterium interaction network for gene exchange. Thus, the phage metagenome seems to increase the resilience of the gut microbiota to environmental stresses, which could have implications for host physiology.

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ORIGINAL RESEARCH PAPER Modi, S. R. *et al.* Antibiotic treatment expands the resistance reservoir and ecological network of the phage metagenome. *Nature* <http://dx.doi.org/10.1038/nature12212> (2013)

FURTHER READING Sommer, F. & Bäckhed, F. The gut microbiota — masters of host development and physiology. *Nature Rev. Microbiol.* **11**, 227–238 (2013)

“the resident phage population provides the microbiota with a reservoir of advantageous genes”

