Prophage: a crucial catalyst in infectious disease modulation

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Lysogenic conversion, in which a temperate bacteriophage sequence integrates into the bacterial genome and forms a prophage, is one of the most efficient mechanisms that bacteria use to acquire accessory traits. The contribution of prophage genetic material to the bacterial DNA might constitute up to 20% of the bacterial genome, with variation between species and strains. Furthermore, it has been suggested that approximately 25% of all the bacteriophage genomes on Earth exists in the form of a prophage.[1] These prophage sequences propagate vertically to progeny together with bacterial cell division, excise and replicate separately as a plasmid, or induce and enter the lytic cycle to form new bacteriophage particles either spontaneously or under the influence of various inducers. Prophages are capable of efficiently transferring genes vertically and horizontally. Such extrachromosomal plasmids and induced prophages can transduce to susceptible cells present in the same biome thereby disseminating their genetic material and contributing to the adaptive evolution of bacteria.[2] Induced prophages can also infect and kill competing colonisers.[3]

Lysogeny generates diversity among strains and allows bacteria to fine-tune their econiche adaptation and, at the same time, confers immunity against secondary bacteriophage attacks (appendix p 1). Both are crucially important for survival and dominance of the lysogen within its habitat. As an example, Duerkop and colleagues[4] have shown that a prophage induction from *Enterococcus faecalis* was necessary and sufficient for the lysogen to gain dominance over competing strains in a mouse model. The inducibility of a prophage is likely to be of crucial importance, at least to some pathogens, because it allows prophages to become more fit to dominate the econiche, potentially contributing to disease pathophysiology. However, prophages might gradually degrade into incomplete sequences. Although incomplete prophages cannot enter the lytic cycle anymore, potentially making their host susceptible to competition for space and nutrients from related strains, they can still contribute important remnant prophage genetic material to the host. Polylysogeny, in which a single bacterial strain carries more than one prophage sequence, is common and prophage remnants have been shown to contribute their genetic material to form hybrid novel bacteriophage particles once induced into the lytic cycle.[4] Such hybrid bacteriophage particles are used by their host as a weapon, infecting and lysing related strains during colonisation.[4]

Prophages are also known to contribute to the virulence potential of their host bacteria by encoding toxins that can cause deadly outbreaks. These include prophage-mediated toxicity in *Corynebacterium diphtheriae* (diphtheria toxin), *Clostridium botulinum* (botulinum toxin), *Vibrio cholera* (cholera toxin), *Escherichia coli* O157:H7 (Shiga toxin), and *Salmonella enterica* (SopE effector protein).[5] Apart from toxins, prophages can supply bacteria with multiple functions because they might also encode auxiliary metabolic genes, virulence factors, antimicrobial resistance genes, and immune evasion genes, which are often present in clusters. β-haemolysin-converting bacteriophages (βC-ϕs) typically encode immune evasion cluster genes in *Staphylococcus aureus* and although the presence of those genes does not assist with initial colonisation, they are associated with disease severity in chronic inflammatory diseases, such as chronic rhinosinusitis.[6,7] Immune evasion cluster genes encode various proteins that counteract the innate and adaptive immune systems in a multifaceted way, which includes inhibition of neutrophil-dependent phagocytosis and killing the βC-ϕ lysogen by blocking complement activation and reducing neutrophil chemotaxis. Immune evasion cluster genes also include the staphylococcal enterotoxin A gene, notorious for promoting a massive but inefficient polyclonal activation of the adaptive immune system, which is skewed away from a protective response against *S aureus* to benefit its own survival.[8] Whereas bacteriophages are generally considered to target only bacteria in a highly specific way, in the past decade research has shown the possibility of bacteriophage uptake and subsequent synthesis of bacteriophage mRNA by mammalian cells, which resulted in the induction of antiviral inflammatory responses that reduce the efficiency of bacterial elimination by phagocytosis leading to chronic infection and inflammation.[9,10] Targeting those prophages using active or passive immunisation could protect against lysogenic infections.[9]

In conclusion, there is increasing evidence that coexistence of bacteria and prophages is associated

See Online for appendix

with multifaceted bacterial fitness elevating the risk to human health. However, the role of lysogeny and prophage induction in immune evasion, supporting the survival and dominance of lysogens within their econiche, are poorly understood in clinical settings. Because prophages are very diverse, mosaic, and transient, they are likely to be important drivers shaping microbial ecosystems and a promising area for further investigation.

We declare no competing interests.

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1 Bondy-Denomy J, Davidson AR. When a virus is not a parasite: the beneficial effects of prophages on bacterial fitness. *J Microbiol* 2014; **52:** 235–42.

2 Silveira CB, Rohwer FL. Piggyback-the-Winner in host-associated microbial communities. *NPJ Biofilms and Microbiomes* 2016; **2:** 16010.

3 Maslov S, Sneppen K. Population cycles and species diversity in dynamic Kill-the-Winner model of microbial ecosystems. *Sci Rep* 2017; **7:** 39642.

4 Duerkop BA, Clements CV, Rollins D, Rodrigues JLM, Hooper LV. A composite bacteriophage alters colonization by an intestinal commensal bacterium. *Proc Natl Acad Sci USA* 2012; **109:** 17621–26.

5 Feiner R, Argov T, Rabinovich L, Sigal N, Borovok I, Herskovits AA. A new perspective on lysogeny: prophages as active regulatory switches of bacteria. *Nat Rev Microbiol* 2015; **13:** 641–50.

6 Verkaik NJ, Benard M, Boelens HA, et al. Immune evasion cluster-positive bacteriophages are highly prevalent among human *Staphylococcus aureus* strains, but they are not essential in the first stages of nasal colonization. *Clin Microbiol Infect* 2011; **17:** 343–48.

7 Nepal R, Houtak G, Shaghayegh G, et al. Prophages encoding human immune evasion cluster genes are enriched in *Staphylococcus aureus* isolated from chronic rhinosinusitis patients with nasal polyps. *Microb Genom* 2021; published online Dec 15. https://doi.org/10.1099/mgen.0.000726.

8 Tuffs SW, Haeryfar SMM, McCormick JK. Manipulation of innate and adaptive immunity by staphylococcal superantigens. *Pathogens* 2018; **7:** e53.

9 Sweere JM, Van Belleghem JD, Ishak H, et al. Bacteriophage trigger antiviral immunity and prevent clearance of bacterial infection. *Science* 2019; **363:** eaat9691.

10 Gogokhia L, Buhrke K, Bell R, et al. Expansion of bacteriophages is linked to aggravated intestinal inflammation and colitis. *Cell Host Microbe* 2019; **25:** 285–299.e8.