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How viruses infect bacteria?

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Viruses are minuscule infectious particles composed of a protein coat and a nucleic acid core. They exist in a huge variety of forms and infect practically all living creatures: animals, plants, insects and bacteria. Insight into the infection process could facilitate new therapeutic strategies for viral and bacterial diseases as well as food preservation. An article by Aksyuk *et al* (2009) published in this issue sheds light on the still mysterious infection process. It reports the first crystal structure of a significant portion of the bacteriophages T4 tail sheath protein. Together with fittings into existing cryo-EM reconstructions, it suggests a mechanism of genome delivery into the host cell for the Myoviridae phages.

Viruses can be considered as mobile genetic particles, containing instructions for reproducing themselves using foreign cellular resources. The amount of viruses that exist in the biosphere is enormous, varying in their virion shapes, genomes and lifestyles. Classification of viruses is defined by host preference, viral morphology, genome type and auxiliary structures such as tails or envelopes. Viral particles outside a host cell (so called virions) are inert entities with a genome surrounded by a protective coat.

Viruses that attack bacteria were named 'bacteriophages'. The term *phage* originates from Greek *phagein*, which translates as 'to eat'. The phage infection cycle seems to be simple but extremely efficient: a single phage injects its genome into a bacterial cell, switching the cells' programme in its favour so the host cell will eventually die and release about 100 new phage particles. Studies of bacteriophages became an essential part of biology because their omnipresence was tightly linked to bacteria. Analyses of bacteriophage genome sequences provide the opportunity to identify basic principles of genome organisation, co-evolution, as well as model and modify their genome. Novel studies on the phage life cycle will not only reveal its interaction with biological barriers during viral transmission and high-level adaptation but might also help to overcome serious clinical problems caused by the occurrence of multi-resistant bacteria, the so-called 'superbugs'. This presumption is based on the fact that phages infecting certain bacteria may recognise and infect these despite their antibiotic(s) resistance. Indeed, exponential effects of phage growth in cells has proven very important in combating bacterial diseases.

The *Caudovirales* order of bacteriophages is characterised by double-stranded DNA (dsDNA) genomes, which can be of the size from 18 to 500 kb in length. The phages, belonging to *Caudovirales*, account for 95% of all the phages reported in the scientific literature, and most likely represent the majority of phages on the planet (Ackermann, 2006). Although genome sequences vary quite significantly, the virus particles of this group have a quite similar organisation: each virion has a polyhedral, predominantly icosahedral, head (capsid) that contains a genome. The head is bound to a tail through a connector, and the distant end of the tail is equipped with a special system for piercing a bacterial membrane. The bacteriophage tail and its related structures are essential tools of the phage during infectivity process securing the entry of the viral nucleic acid into the host cell.

Rossmann's group has been involved for many years with analysing different viruses and a significant part of their research is dedicated to the bacterial virus T4 that belongs to the *Myoviridae* family (Ackermann, 2006). *Myoviridae* are a family of bacteriophages with contractile tails, comprising ~25% of all known phage populations. Tail contraction is an essential phase of cellular infection by these phages, resulting in pressing the central tail tube through the outer cell membrane similar to a syringe, thereby creating a channel for DNA ejection from the capsid and into the host cell (Figure 1; Leiman *et al*, 2003).

Tailed dsDNA phages are characterised by their futility for crystallisation trials, although crystal structures of some individual protein components have been determined for T4 bacteriophage by the Rossmann lab. Structural studies of other phages from the Myoviridae family were hampered by variation and diversity in the amino-acid sequences among the tailed bacteriophages, making prediction of the structural organisation of phage elements unreliable. Cryo-EM became the only available tool that allowed structural insight at subnanometer resolution (6–10 Å; Jiang *et al*, 2006; Lander *et al*, 2008). Combining EM and crystallography also allowed the identification of the T4 bacteriophage baseplate proteins, long and short fibres as well as the capsid protein (Leiman *et al*, 2004; Kostyuchenko *et al*, 2005).

The new work by Aksyuk and co-authors published in this issue of *The EMBO Journal* further advances our understanding of this complex biological system. Using a similar hybrid approach, Aksyuk *et al* (2009) solve here the crystal structure of a small protease-resistant fragment (gp18PR) of the sheath protein gp18. Using molecular replacement, they further determine the structure

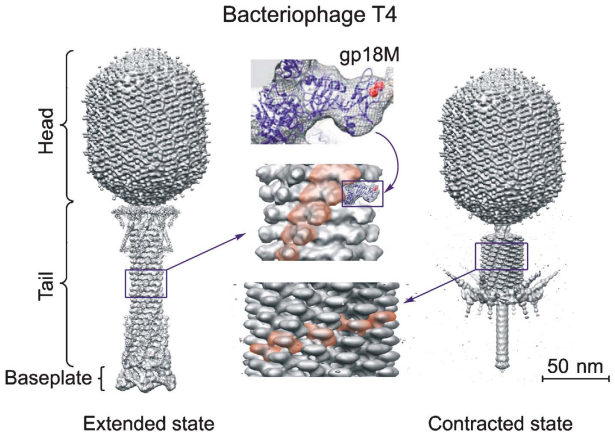

Figure 1 Bacteriophage T4. The left panel illustrates the phage in the extended state, whereas the right panel shows the phage in the contracted state. The middle panel shows enlarged fragments of the tail both in extended and contracted states; the upper part of the middle panel demonstrates the fitting of the X-ray structure into EM map. Subunits shadowed in red show their rearrangement in the same helical strand (adapted from figures kindly provided by Petr Leiman and Michael Rossmann).

of the larger gp18M protein comprising three of the four domains of the protein. Fitting of the gp18M atomic model into existing EM maps allowed localisation of the individual protein subunits within the tail sheath and also identified conformational changes during tail contraction (central panel in Figure 1). These results suggest the interactions of subunits within the tail, and provide a mechanistic view on the phage tail contraction during the infection process.

This first tail sheath protein structure determination, together with the comparative modelling approach, sheds light on the process of T4-bacteriophage infection and might similarly be applied to related structural studies.

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