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The Host Cell Recognition and Penetration Apparatus of Staphylococcal Bacteriophages

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Staphylococcus aureus is an opportunistic pathogen responsible for a wide range of infections in humans and livestock. Most resistance and virulence factors in *S. aureus* are encoded on mobile genetic elements (MGEs), including bacteriophages, genomic islands and plasmids. Transduction by bacteriophages provides the main means for horizontal transfer of MGEs in *S. aureus*, which is not naturally transformable and rarely undergoes conjugation. The emergence of virulent, antibiotic resistant strains of *S. aureus* is a considerable public health concern, and has re-ignited interest in the use of bacteriophages for therapeutic use against these pathogens.

Tailed bacteriophages with double-stranded DNA genomes (order *Caudovirales*) have icosahedral or prolate heads (capsids) with long or short tails attached at one vertex, capped by a baseplate and frequently decorated with one or more tail fibers. The baseplate provides the main point of contact with the host, and is involved in host recognition and adsorption, cell wall penetration and degradation, and DNA ejection. Most staphylococcal bacteriophages bind to wall teichoic acid (WTA), a variable carbohydrate polymer present on the surface of most Gram-positive cells.

80α is a typical example of a staphylococcal siphovirus, having a T=7 icosahedral capsid and a long, flexuous tail. We previously determined cryo-EM structures of 80α capsids [1, 2] and have now determined the structure of the 80α baseplate at 3.7 Å resolution (Fig. 1A) [3]. The 80α baseplate structure has several unique features, including the presence of three tail fiber/receptor binding proteins (Fig. 1B), but also displays striking similarities to other phage baseplates, indicating a mix-and-match strategy for baseplate evolution across the phages of the Firmicutes.

The main receptor binding protein (RBP) of 80α forms six trimers that each consists of a kinked α-helical stem domain, a platform domain and two tower domains (Fig. 1C). The 80α RBP is strikingly similar to the RBP from other phages that infect *S. aureus*, even those belonging to different viral families, such as the podovirus P68 [4]. In contrast, phages of *Staphylococcus epidermidis* or *Listeria* encode RBPs of a different structure. This suggests that the RBP structure is correlated with the distinct WTA present in different bacterial species [5].

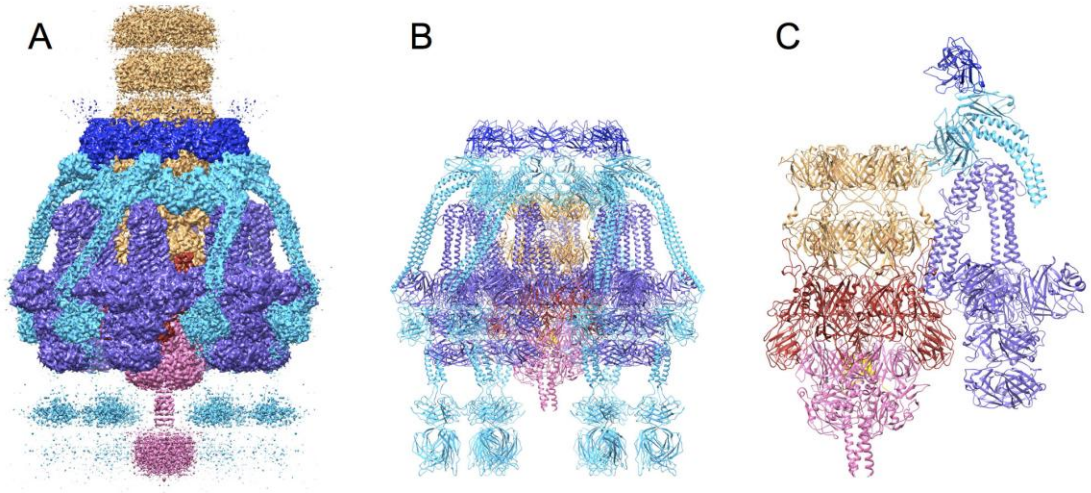

Figure 1. (A) Isosurface representation of cryo-EM reconstruction, and (B) atomic model of the bacteriophage 80α baseplate, colored according to protein: gold, major tail protein (MTP); red, Dit; pink, Tal; purple, RBP; cyan, FibL; blue, FibU. (C) Closeup view of the baseplate core (MTP, Dit, Tal) with all but one of the six peripheral structures (RBP, FibL, FibU) removed [3].

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