

## Bacterial Type VI secretion system could have evolved from co-opted tail sheath tube of bacteriophages

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### Abstract

Bacterial cells utilize a variety of nanomachines to secrete proteins and other molecules into the extracellular environment or target cells. One example is the Type VI secretion system (T6SS) in Gram-negative bacteria. Armed with a contractile mechanism similar to that used by bacteriophages to inject phage DNA into bacterial cells, the T6SS shares a common evolutionary origin with tail associated proteins of bacteriophages at both the structural and protein composition levels. Specifically, proteins constituting the T6SS are known to share provenance with those of the phage tail protein. More importantly, the T6SS is strikingly similar to the phage tail protein in both structure and function. However, a more important question concerns whether the T6SS evolved from the phage tail protein and if yes, what is the mechanism responsible for its development? One possibility could be the co-opt of the tail protein structure by bacterial cells through integration of the genes encoding the tail protein structure within the bacterial genome. In this case, expression of the phage tail protein genes would have resulted in a multiprotein structure without apparent function, which meant that a significant gap remains in comparison with extant T6SS that spans the inner and outer cell membrane of Gram-negative bacteria. While it is desirable to trace the evolutionary steps taken by phage tail proteins to transform into functional T6SS, multiple selection pressure and strong mutational propensity might have erased molecular evidence of such transformation. Hence, the challenge lies in uncovering as much structural and sequence evidence as possible that points to distinct steps in the evolutionary pathway towards T6SS. Structural studies offer a particularly promising route to unentangle the details but it must be augmented with sequence evidence that pins down the molecular events that shape the evolution of the complex multiprotein structure, where clefts from one protein fit into the folds of another in yielding a function that could evolve over eons. Collectively, structural and functional similarity between T6SS and phage tail protein suggests a common evolutionary origin for both macromolecular complexes, which has been established through combined structural, compositional and sequence analysis. But the steps underpinning the transformation of phage tail protein into T6SS remain unclear, which obfuscate understanding of the evolutionary forces that shape the transformation. One possible evolutionary trajectory posits that genes expressing phage tail proteins were co-opted and integrated into the bacterial genome. However, significant gap remains between a phage tail protein structure with unclear function in the cytoplasm and a functional T6SS that spans two bacterial membranes. Future detective work at the structural and sequence level might offer clues to the evolutionary path trodden by a precursor of the bacterial T6SS.

**Keywords:** Type VI secretion system, bacterial cell, outer membrane, inner membrane, bacteriophages, phage tail protein, structural similarity, evolutionary trajectory, Gram-negative bacteria, amino acid sequence,

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