Review

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VgrG, Tae, Tle, and beyond: the versatile arsenal of Type VI secretion effectors

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The type VI secretion system (T6SS) is a macromolecular machine that delivers protein effectors into both prokaryotic and eukaryotic cells, therefore participating in interbacterial competition and virulence. The T6SS is functionally and structurally similar to the contractile bacteriophage cell puncturing device: the contraction of a sheath-like structure is believed to propel an inner tube terminated by a spike towards target cells, allowing the delivery of effectors. In this review, we summarize recent advances in the identification and characterization of T6SS effector proteins, highlighting the broad repertoire of enzymatic activities, and discuss recent findings relating to the secretion mechanisms.

The type VI secretion system: a bacteriophage-like structure expelling toxin effectors

The T6SS recently garnered much attention because it emerged as one of the key players for both pathogenesis and interbacterial competition due to its ability to mediate toxin delivery into both eukaryotic and prokaryotic cells. The genes encoding the T6SS are widely distributed and found in approximately one-third of sequenced Gram-negative genomes, primarily in the *Proteobacteria* phylum. The T6SS comprises 13 core proteins, named type six secretion (Tss) [1]. The TssL, TssM, and TssJ subunits interact to form a complex that crosses the cell envelope [2–4]. Bioinformatic and structural evidence showed that several other T6SS subunits are related to bacteriophage tail components [5,6]. Hemolysin-coregulated protein (Hcp) forms hexameric rings and shares a common fold with the major tail tube protein gpV [7,8]. Indeed, Hcp rings stack on each other to assemble tubular structures with a central lumen of 40 Å [9,10]. The trimeric valine-glycine repeat (VgrG) structure is reminiscent of the bacteriophage gp27/gp5 spike complex [11]. Recently, Shneider *et al.* showed that a small protein of the Pro-Ala-Ala-Arg repeats containing protein (PAAR) family forms a conical structure at the tip of the VgrG protein, thus sharpening the VgrG spike complex and likely contributing to the piercing of the target cell [12]. The TssB and TssC subunits assemble dynamic cytoplasmic tubules that undergo cycles of assembly, contraction, and disassembly [13–16]. These structures are structurally and mechanistically similar to the sheath of contractile bacteriophages, in which the sheath wraps the tail tube and, upon bacterial infection, contracts to inject the tail tube into the bacterial cell [17]. Based on these homologies, it has been proposed that contraction of the T6SS sheath propels the Hcp internal tube towards the target cell, piercing the membrane using the VgrG–PAAR complex. The VgrG protein of *Vibrio cholerae* comprises an additional C-terminal domain that carries an actin cross-linking activity and, therefore, was the first T6SS effector identified [18]. However, effectors are not only restricted to catalytic domains fused to the structural element of the VgrG protein. Recent breakthrough studies have identified toxin proteins encoded by independent genes. In this review, we focus on the toxins secreted by the T6SS machinery and the molecular mechanisms developed for their delivery into target cells.

T6SS activities

The T6SS is versatile due to its ability to modulate bacterial relations, as well as to maintain pathogenic or symbiotic interactions with eukaryotic organisms.

The T6SS modulates bacterial interactions

Several studies revealed that the activity of the T6SS helps to reshape microbial communities, either by promoting biofilm formation or by competing with neighboring bacteria. Since the first report of a role of the *Pseudomonas aeruginosa* H1-T6SS in interbacterial competition [19], a similar function has been shown in *Burkholderia thailandensis* (T6SS-5), *V. cholerae*, *Serratia marcescens*, enteroaggregative *Escherichia coli* (EAEC, Sci-2), *Citrobacter rodentium* (CTS-1), and *Acinetobacter baumanii* [20–24]. It is now known that the T6SS is used to deliver antibacterial toxins directly inside neighboring bacterial cells. Beside its role in interbacterial competition, it has been shown that different isolates produce different sets of toxin effectors and, therefore, competition occurs between different strains of the same species (intraspecific competition

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