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Type IV Secretion Systems

Author: Sara Morris
Major: Animal Science – Animal Biotechnology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

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The ever-present concern of antibiotic resistance and the study of horizontal gene transfer have led to recent understanding of Type IV secretion systems (T4SS). T4SSs are membrane spanning protein complexes that allow the transport of macromolecules from a cell. This transfer of macromolecules increases genome plasticity and facilitates the spread of antibiotic resistance in pathogens. The recent advancement in the study of type IV secretion systems has provided us with a better understanding of their structure, function and types of effectors. Type IV secretion systems are not the only special secretion system used by microorganisms but are one of the most versatile in the effectors they are capable of transporting and are seen in many bacteria and even a few Archaea.

Introduction

Microorganisms use special secretion systems to transport macromolecules across membranes. These special membrane spanning systems are classified into six major groups, named types I – VI. Type IV secretion systems (T4SS) are among the most versatile of these groups, capable of transporting both proteins and nucleoprotein complexes [1, 2, 3] with intra-species, inter-species and inter-kingdom recipients [1]. T4SSs aid in genome plasticity and facilitate the spread of antibiotic resistance in many common pathogens such as *Agrobacterium tumefaciens, Helicobacter pylori, Bordetella pertussis* and *Legionella pneumophila* [1, 2, 3].

Two classification systems arose due to the versatility of T4SSs. The first classification system split them into subgroups F, P and I based on their similarity to IncF (plasmid F), IncP (plasmid RP4) and IncI (plasmid R64). The second classification system splits T4SSs into Type IVA and IVB based on their resemblance to the *Agrobacterium tumefaciens (A. tumefaciens)* VirB/VirD4. The previous classification system's subgroups F and P fall under Type IVA, meaning they more closely resemble *A. tumefaciens* VirB/VirD4 than Type IVB [2, 3].

A detailed structure is only available for Type IVA secretion systems, such as those encoded by plasmids of *A. tumefaciens.* There are twelve proteins in these plasmids, VirB1-VirB11 and VirD4, commonly called the VirB/D4 proteins, other Type IVA secretion systems will have homologues for these proteins. Proteins VirB6 – VirB10, form the framework for T4SSs translocation channel. Proteins VirB7, VirB9 and VirB10 form a two layered, cylindrical core complex with a channel in the middle that is too small to allow for the passage of substrate, indicating a structural change during substrate transfer. VirB10 forms 2-helix bundles that make up the outer membrane of the core complex. VirB7 lipidation is necessary for the insertion of the core complex into the outer cell membrane. VirB1 allows for the assembly of surface structures by creating holes in the peptidoglycan of the cell wall. VirB2 and VirB5 form pilus structures and VirB2 is believed to stabilize the surface contact and create a channel for substrate transfer between the donor and host cell. VirB4, VirB11 and VirD4 are ATPases that provide energy for assembly and the movement of substrate. VirD4 couples substrate processing and translocation [3].

The general mechanism for the secretion, or transfer, of a substrate is the same across most conjugation systems. The mechanism can be broken down into a three step process. The first step of the process is the formation a relaxosome. The relaxosome is formed by proteins assembling around the origin-of-transfer (OriT) of double stranded DNA. The second step of the process is the unwinding and nicking of the double stranded DNA by relaxase bound to the 5' end of the OriT. The final step in the process is the movement of the substrate through

the secretion system. This movement begins with the transport of the substrate to the system by VirD4 and the transfer to VirB11 without the use of ATPase. ATPase is then used to hydrolyze the transfer of the substrate to VirB6 and VirB8, VirB9 and finally VirB2 [3]. From VirB2 the substrate is released either into the host cell or the extracellular matrix, depending on the effector.

Recent Progress

In the past decade significant strides have been made in identifying the role of T4SSs in pathogenesis and the identification of the diverse set of effector molecules through the study of *Agrobacterium tumefaciens*, *Helicobacter pylori*, *Bordetella pertussis* and *Legionella pneumophila*. The recent progress in genome sequencing has led to a continuous increase in the number of known homologues to T4SSs and different homologous proteins within Type IVA secretion systems. Even with all of the recent advances in the understanding of T4SSs, the structure and function has only been closely studied for Type IVA secretion systems. It is crucial to the understanding of the affects of T4SSs on pathogenesis that the structure and function of other T4SSs are studied in the coming years as well as the function of the various identified effectors [2, 3].

The T4SS of *Agrobacterium tumefaciens (A. tumefaciens)* mediates the transfer of tumor causing genes into plant cells. It is also the model for all VirB/VirD4 systems and study of this T4SS has provided our understanding of the structure and function of the systems [1, 2, 3]. *A tumefaciens* transports not only tumor producing genes to host cells but also several other effector proteins, macromolecules that change the basic processes of a host cell, to insure the success of the infection [1, 2].

Helicobacter pylori (H. pylori) T4SS encodes cytotoxin-associated genes (*cag)* A. *H. pylori* is the causative agent in ulcers, gastritis and gastric carcinoma [1, 3]. CagA interferes with elements involved in the elongation of host cells and proinflammatory genes [1]. The VirB10 homologue of cagA is believed to form an elongated pilus-like structure that is unique to the cag T4SS [3]. The cancer production of *H. pylori* is a result of β-catenin, which causes an upregulation of carcinogenic genes [1].

The T4SS of *Bordetella pertussis (B. pertussis)*, pertussis toxin liberation (Ptl), is different from other T4SSs in that it secretes its effector protein into the extracellular matrix [1, 2, 3]. Unlike other T4SSs, Ptl does not link the secretion and translocation of the pertussis toxin. Infection by pertussis toxin causes a histamine release, insulin secretion, and an increase in lymphocytes [1].

Legionella pneumophila (L. pneumophila), the cause of Legionnaire's disease, provides us with most of our knowledge about T4SSs that are capable of intracellular survival [1]. The intracellular multiplication (icm) and defective organelle trafficking (dot) genes (Dot/Icm) provide *L. pneumophila* with the open reading frames necessary for its survival [2]. After infection of macrophages upon inhalation by host, Dot/Icm inhibits the fusion of phagosomes and lysosomes and adopts the characteristics of the Endoplasmic Reticulum in order to facilitate replication.

Discussion

Type IV secretion systems are the most versatile of the membrane spanning systems used by microorganisms for transporting macromolecules between the bacteria and host cell or intracellular matrix. Though there is a large variation of T4SSs, ranging from the VirB/VirD4 system of *A. tumefaciens* to the Dot/Icm of *L. pneumophila*, they differ minimally in their structure and not at all in the mechanism for transference of substrates. Even with the recent advances in understanding of T4SSs, there is still a long way to go to fully understand them. Crucial to the understanding of the affects of T4SSs is the further study of Type IVA secretion systems and, more importantly, the study of other types of T4SSs. Areas of needed research span from the study of the structure and function of Type IVB versus Type IVA systems to the affects T4SSs have on symbiotic relationships.

References

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