Life Science & BT Pre PhD Course Work 2022

Paper I- Advance Theory

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Lecture 2:10.9.22

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Microbial Technology

- Host Microbe Interactions
- *General Secretion systems bacteria employ for pathogenesis, Diversity observed in secretion systems*
- Mechanisms of survival of *Mycobacterium*
- Enteric Infections: Cross Talk between pathogen and intestinal epithelium and how it modulate host function for its survival

Bacterial Secretion Systems

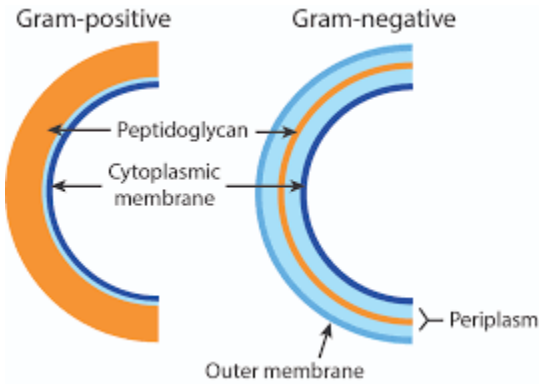
- Prokaryotes have developed numerous ways of transporting substances or effector molecules between locations, which largely involve the assistance of *dedicated protein secretion systems*.
- Bacterial secretion systems are protein complexes present on the cell membranes of bacteria for secretion of substances.
- Secreted proteins can play many roles
  - Promoting bacterial virulence,
  - Enhancing attachment to eukaryotic cells,
  - Scavenging resources in an environmental niche,
  - Directly intoxicating target cells and disrupting their functions.
- Used by pathogenic bacteria to secrete their virulence factors (mainly of proteins) to invade the host cells

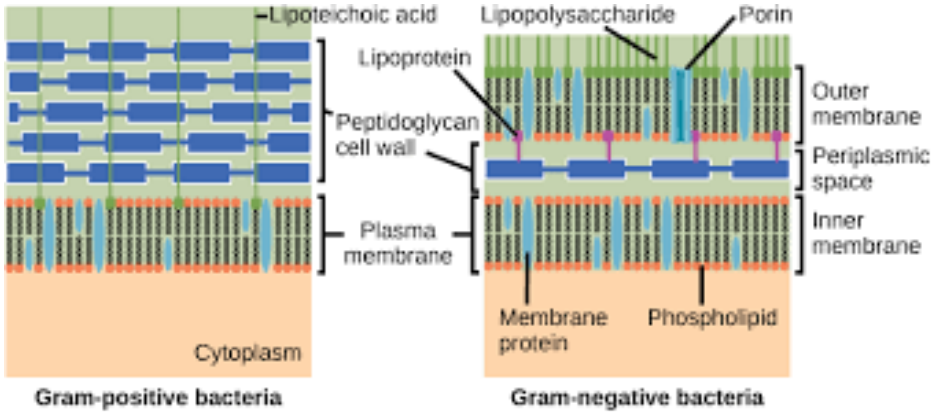
Bacterial Secretion Systems

- The secretion systems are, thus, very important virulence factors and they can be divided into different types depending on their composition, structure, mechanism and evolutionary relationship.
- Gram-negative can have (at least) eight and gram-positive bacteria (at least) four different secretion systems
- There are two fundamentally different mechanisms (one-step and two-step mechanism).
  - One-step mechanism: the effector molecules are transported directly across the bacterial cell membrane(s) into the host cell and this can occur in both gram-negative and gram-positive bacteria.
  - Two Step mechanism, the effector molecules are first transported through the plasma membrane to the periplasmic space of the bacterium and then by means of other protein complexes through the outer membrane and into the host cell. This can only happen in gram-negative bacteria.

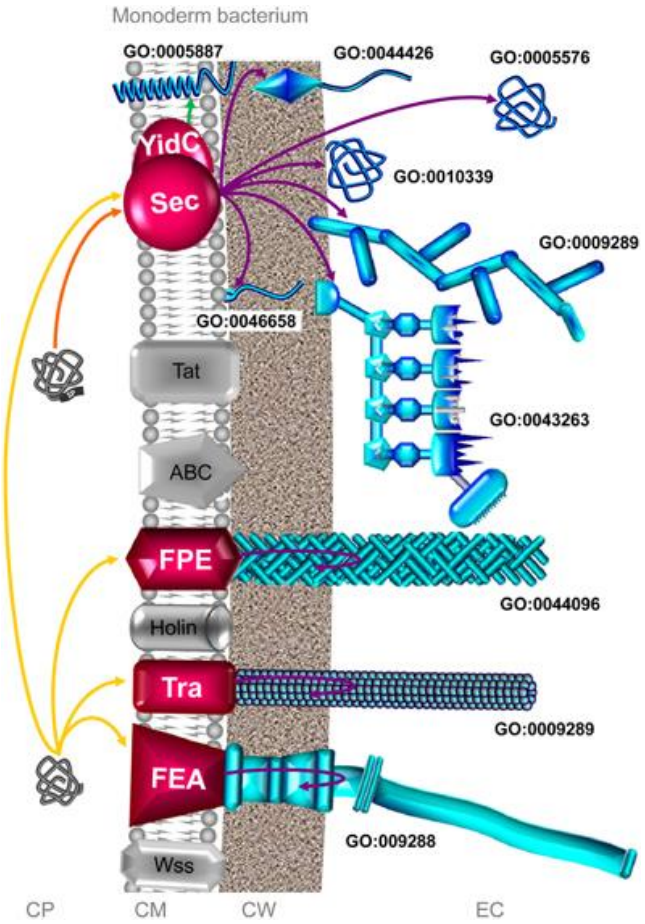
Bacterial Secretion Systems

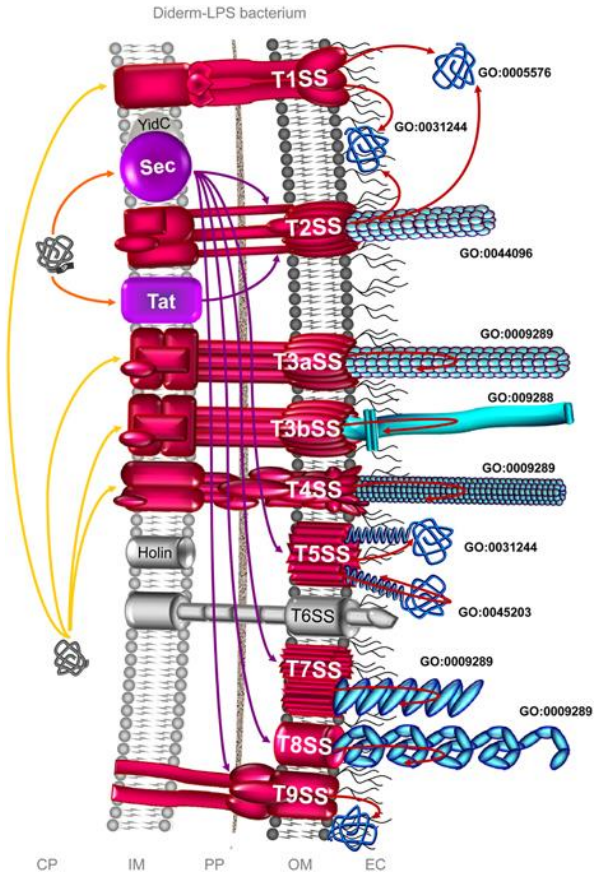
- Across Plasma Membrane
  - Secretion across the plasma membrane occurs in both gram-positive (monoderm) and gram-negative bacteria (diderm) and there are three main systems for this type of transport:
    - Sec (general secretion or GSP)
    - SRP (signal recognition particle)
    - Tat (twin arginine translocation)
- Secretion across the outer membrane only needs to occur in gram-negative bacteria and through either the one-step mechanism or the two-step mechanism.





Bacterial Secretion Systems





https://en.wikipedia.org/wiki/Bacterial_secretion_system#/media/File:Secretion_systems_in_diderm_bacteria.jpg

Bacterial Secretion Systems

- The secretion systems are usually divided into the following seven main types with subtypes:

- Type I secretion system (T1SS or TOSS)
  A simple one-step mechanism that requires only three different proteins. eg *Escherichia coli* and *Pseudomonas fluorescens*
- Type II secretion system (T2SS)
  A mechanism that only transports proteins over the outer membrane and generally transports the protein first by means of Sec across the cytoplasmic membrane.
- Type III secretion system (T3SS or TTSS)
  This type is the most complicated of all secretion systems described so far.
  - It is a one-step mechanism utilizing a cannula-like protrusion (appendix) which can make holes in the host's cell membrane so that the secreted protein can be injected.
  - This secretion system is also called **injectosome** because of its similarity to a syringe. Up to 25 different proteins are required to build up the injectosome and it has the same evolutionary origin as bacterial flagellas.
  - Certain species within the following gram-negative bacterial genera possess T3SS, for instance *Pseudomonas, Salmonella, Shigella, Vibrio* and *Yersinia*.

Bacterial Secretion Systems

- Type IV secretion system (T4SS or TFSS)
  Can translocate proteins through both a one-step mechanism and a two-step mechanism. *Bordetella pertussis, Helicobacter pylori* and *Legionella pneumophila*, for instance, possess T4SS. This system can also translocate DNA.
- Type V secretion system (T5SS)
  This secretion system can be divided into three main categories:autotransporter, usher protein, 2 partner secretion
- Type VI secretion system (T6SS)
  This secretion system consists of a "phage-tail-nail-like injectisome reminiscent of T3SS. T6SS has structural and functional homology with the bacteriophage T4 and is required for the following bacteria to be virulent: *Burkholderia mallei, Edwarsiella tarda, Francisella tularensis, Pseudomonas aeruginosa* and *Vibrio cholerae.*
- Type VII secretion system (T7SS)
  This type of secretion system consists of a family of similar systems, which are specialized for bacteria that have specific lipids in their cell wall (eg, mycobacteria). *Corynebacterium diphtheria* and *Nocardia* sp. have been found to possess T7SS.

Table 1: **Classes of bacterial protein secretion systems**

Green ER, Mecsas J. Bacterial Secretion Systems: An Overview. Microbiol Spectr. 2016 Feb;4(1):10.1128/microbiolspec.VMBF-0012-2015. doi: 10.1128/microbiolspec.VMBF-0012-2015. PMID: 26999395; PMCID: PMC4804464.

Secretion Apparatus	Secretion Signal	Steps in Secretion	Folded Substrates?	Number of Membranes	Gram (+) or Gram (–)
Sec	N-terminus	1	No	1	Both
Tat	N-terminus	1	Yes	1	Both
T1SS	C-terminus	1	No	2	Gram (–)
T2SS	N-terminus	2	Yes	1	Gram (–)
T3SS	N-terminus	1–2	No	2–3	Gram (–)
T4SS	C-terminus	1	No	2–3	Gram (–)
T5SS	N-terminus	2	No	1	Gram (–)
T6SS	No known secretion signal	1	Unknown	2–3	Gram (–)
SecA2	N-terminus	1	No	1	Gram (+)
Sortase	N-terminus (Sec) C-terimnus (cws)	2	Yes	1	Gram (+)
Injectosome	N-terminus	2	Yes	1	Gram (+)
T7SS	C-terminus	1	Yes	1–3	Gram (+)

Sec and Tat pathways

- Most proteins transported by the Sec and Tat pathways remain inside of the cell, either in the periplasm or the inner membrane.
- However, in Gram-negative bacteria, proteins delivered to the cytoplasmic membrane or periplasm of the cell by the Sec or Tat pathways can either stay in those compartments, or may be transported outside of the cell with the help of another secretion system.
- While the Sec and Tat systems have several common elements, they transport proteins by fundamentally different mechanisms.

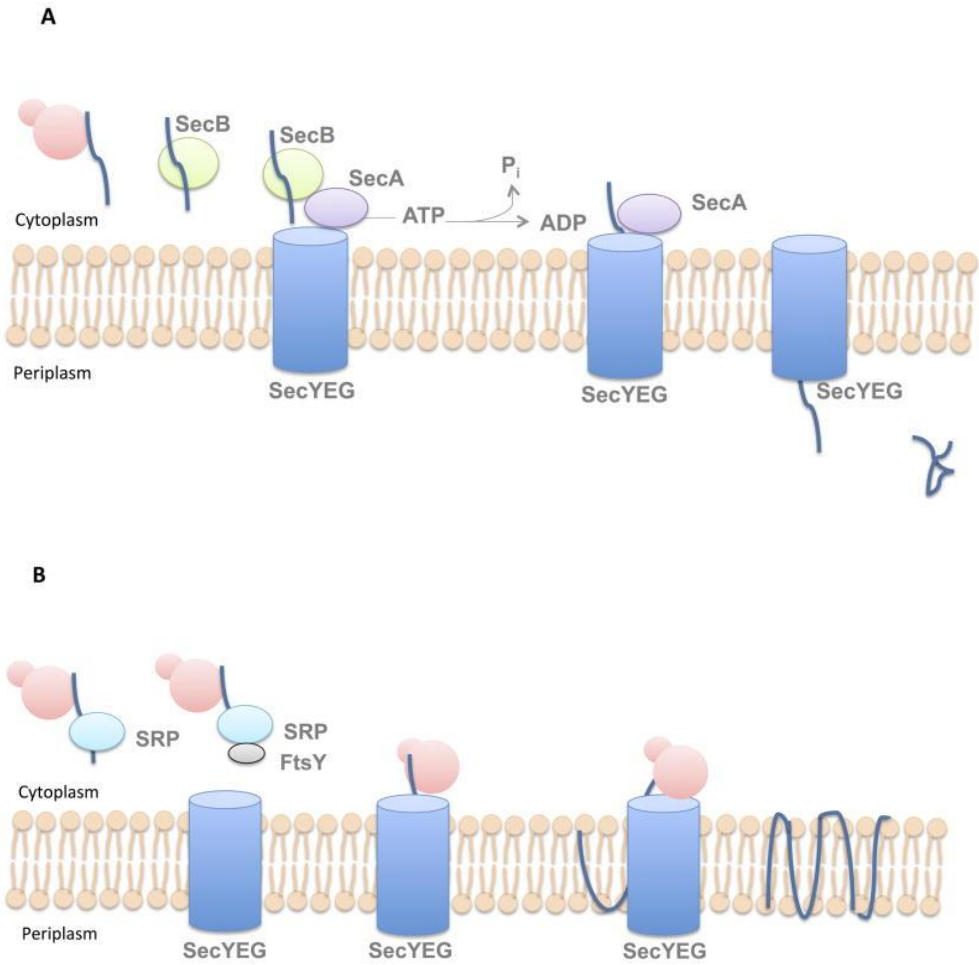
Sec secretion pathway

- Sec pathway primarily translocates proteins in their *unfolded state.*
- This system consists of three parts:
  - a protein targeting component,
  - a motor protein, and
  - a membrane integrated conducting channel, called the SecYEG translocase
- Export by the Sec pathway relies on a hydrophobic signal sequence at the N-terminus of the secreted protein, which is typically 20 amino acids in length and contains 3 regions: *a positively charged amino terminal, a hydrophobic core, and a polar carboxyl-terminal*
- a number of Gram-positive bacteria produce Sec accessory proteins that serve important roles in the secretion of specific proteins.
- The Sec system utilises two different pathways for secretion:
  - SecA : SecA is an ATPase motor protein and has many related proteins including SecD, SecE, SecF, SegG, SecM, and SecY.
  - Signal recognition particle (SRP) pathways. SRP is a ribonucleoprotein (protein-RNA complex) that recognizes and targets specific proteins to the endoplasmic reticulum in eukaryotes and to the cell membrane in prokaryotes.
- The two pathways require different molecular chaperones and ultimately use a protein-transporting channel SecYEG for transporting the proteins across the inner cell membrane.
  - SecA pathway, SecB acts as a chaperone, helping protein transport to the periplasm after complete synthesis of the peptide chains.
  - SRP pathway, YidC is the chaperone, and transport proteins to the cell membrane while they are still undergoing peptide synthesis

Sec secretion pathway

- A. Proteins for the periplasm (or extracellular release) are translocated by a *post-translational mechanism*, contain a removable signal sequence recognized by the SecB protein. SecB binds pre-secretory proteins and prevents them from folding, while also delivering its substrates to SecA. SecA both guides proteins to the SecYEG channel, and also serves as the ATPase that provides the energy for protein translocation. Following transport through the SecYEG channel, proteins are folded in the periplasm.
- (B) The Sec pathway utilizes a *co-translational mechanism of export* to secrete proteins destined for the inner membrane. These proteins contain a signal sequence recognized by the SRP particle. During translation, SRP binds target proteins as they emerge from the ribosome, and recruits the docking protein FtsY. FtsY delivers the ribosome-protein complex to the SecYEG channel, which translocates the nascent protein across the cytoplasmic membrane.

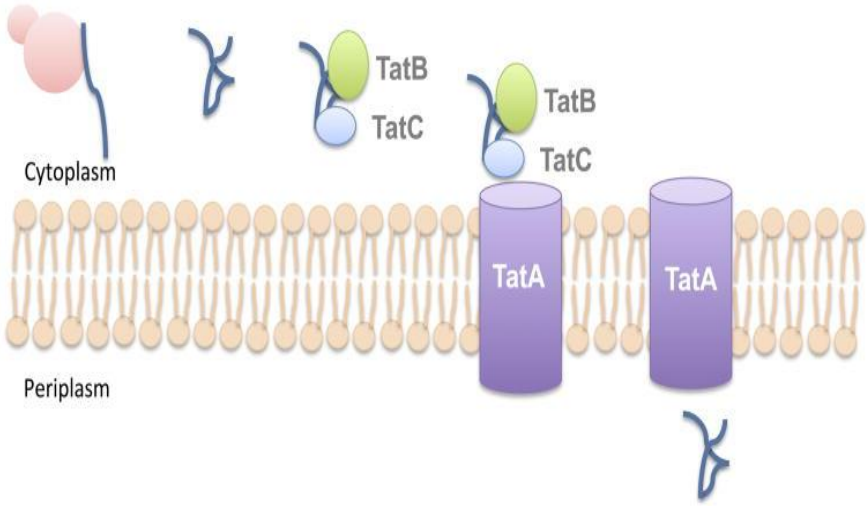
During translocation across the channel, the transmembrane domain is able to escape through the side of the channel into the membrane, where the protein remains attached.



Tat- twin arginine translocation Secretion Pathway

- Tat pathway primarily secretes folded proteins

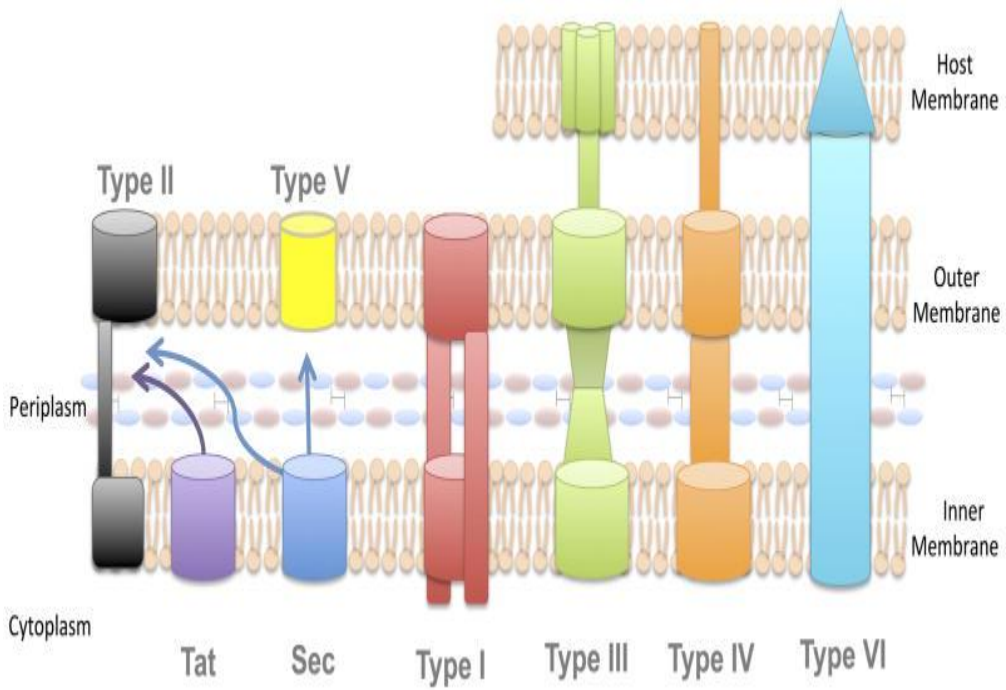
- Found in bacteria, archae and plants
- Consists of 2–3 components (TatA, TatB, and TatC).
- In Gram-negative bacteria, TatB and TatC bind a specific N-terminal signal peptide containing a “twin” arginine motif on folded Tat secretion substrates.
- TatB and TatC then recruit TatA to the cytoplasmic membrane, where it forms a channel. Folded proteins are then translocated across the channel and into the periplasm. In Gram-negative bacteria, these proteins may remain in the periplasm, or can be exported out of the cell by the T2SS.
- Eg. phospholipase C: *P. aeruginosa* , *Legionella pneumophila*, and *Mycobacterium tuberculosis*

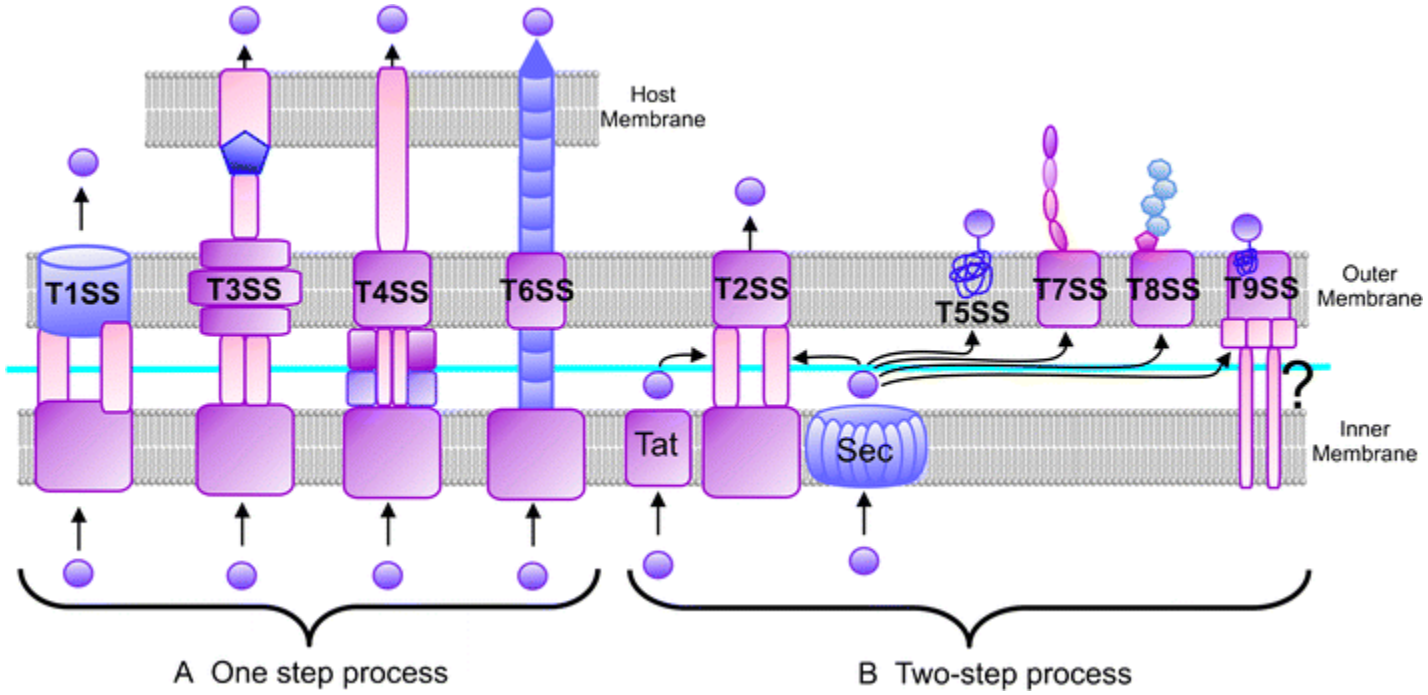


Gram Negative Bacterial Secretion Types

- In Gram-negative bacteria, secreted proteins must cross two (and, in some cases, three) phospholipid membranes in order to reach their final destination.
- Sec- or Tat-dependent protein secretion : Some secreted proteins in Gram-negative bacteria traverse these membranes in two separate steps, where they are first delivered to the periplasm through the Sec or Tat secretion systems and are then transferred across the outer membrane by a second transport system.
- Sec- or Tat-independent protein secretion : Other proteins are secreted through channels that span both the inner and outer bacterial membranes.
- The dedicated secretion systems in Gram-negative bacteria are numbered Type I through Type VI, with each system transporting a specific subset of proteins.

Gram Negative Bacterial Secretion Types

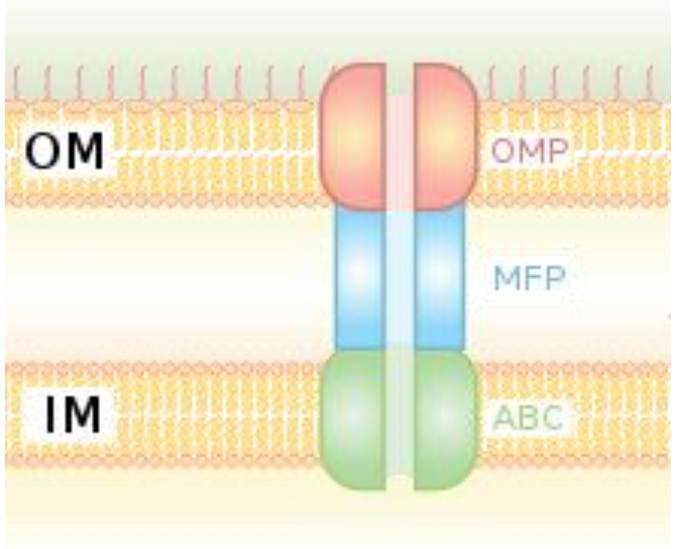




Type 1 secretion

- known as ABC protein secretion pathway
- ABC: ATP-binding cassette Secretion
- These substrates range in function and include digestive enzymes, such as proteases and lipases, as well as adhesins, heme-binding proteins, and proteins with repeats-in-toxins (RTX) motifs.
- T1SSs have three essential structural components:
  - ABC transporter protein in the inner membrane:it catalyzes ATP to provide the energy to transport the substrate, interacts with the MFP, and participates in substrate recognition
  - Membrane fusion protein (MFP) that crosses the inner membrane and
  - Outer membrane factor (OMF) in the outer membrane-OMF generates a pore in the outer membrane, through which the substrate passes in an unfolded state

  Eg. hemolysin A (HlyA), named after its ability to lyse erythrocytes from uropathogenic *Escherichia coli* strains

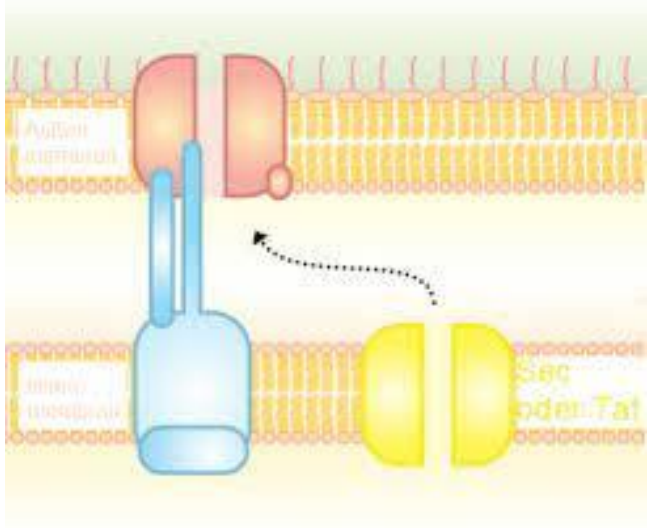


Type 2 secretion system (T2SS)

- Gram negative bacteria
- T2SS channel is only found in the outer membrane
- Type II (T2SS) secretion system depends on the Sec or Tat system for initial secretion inside the bacterial cell.
- Broad specificity and are capable of secreting a diverse array of substrates outside of the bacterial cell, some of which contribute to the virulence of bacterial pathogens-proteases, lipases, and phosphatases
- From the periplasm, proteins are secreted out of the outer membrane secretins.

Type 2 secretion system (T2SS)

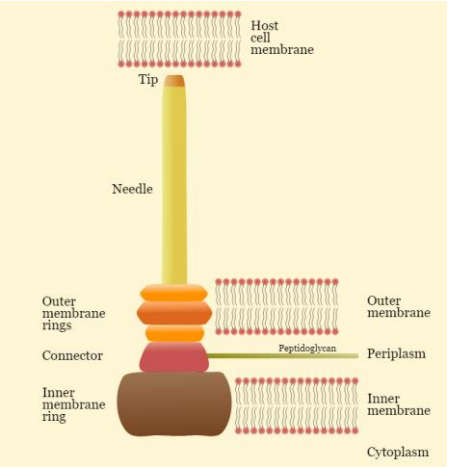
- T2SSs are complex and consist of as many as 15 different proteins, which can be broken into four subassemblies:
  - **Outer-membrane complex**-it serves as the channel through which folded periplasmic T2SS substrates are translocated. This channel is composed of a multimeric protein called the secretin. Secretins are multimeric (12–14 subunits) complex of pore-forming proteins. Secretin is supported by 10–15 other inner and outer membrane proteins to constitute the complete secretion apparatus
  - The secretin has a long N terminus, that extend all the way to the periplasm to make contact with other T2SS proteins in the inner membrane
  - **Inner-membrane platform** -is composed of multiple copies of at least 4 proteins, is embedded in the inner membrane and extends into the periplasm, contacting the secretin. This platform plays a crucial role in the secretion process, by communicating with the secretin, pseudopilus, and the ATPase to coordinate export of substrates
  - Secretion ATPase:located in the cytoplasm and provides the energy
  - Pseudopilus-structurally similar to proteins that comprise type IV pili , pseudopili retract in order to push the folded T2SS substrate through the outer membrane channel
  - Eg. Cholera toxin of *V. cholerae,* exotoxin A of *P. aeruginosa*
  - Enzyme secretion by enterotoxigenic and enterohemorrhagic *E. coli* (ETEC and EHEC), *K. pneumonia, Legionella pneumophila*

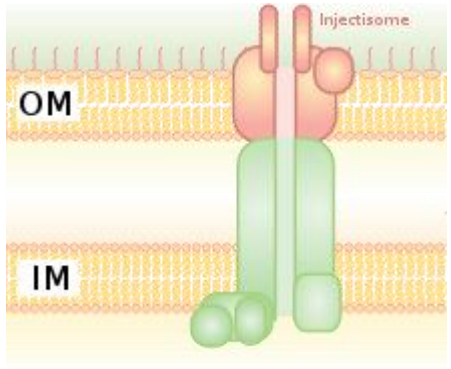


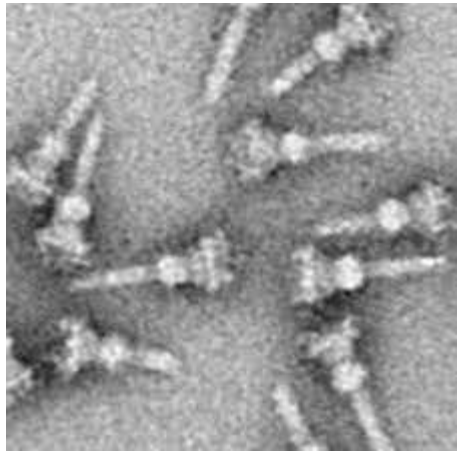
https://en.wikipedia.org/wiki/Bacterial_secretion_system

The Type III Secretion System

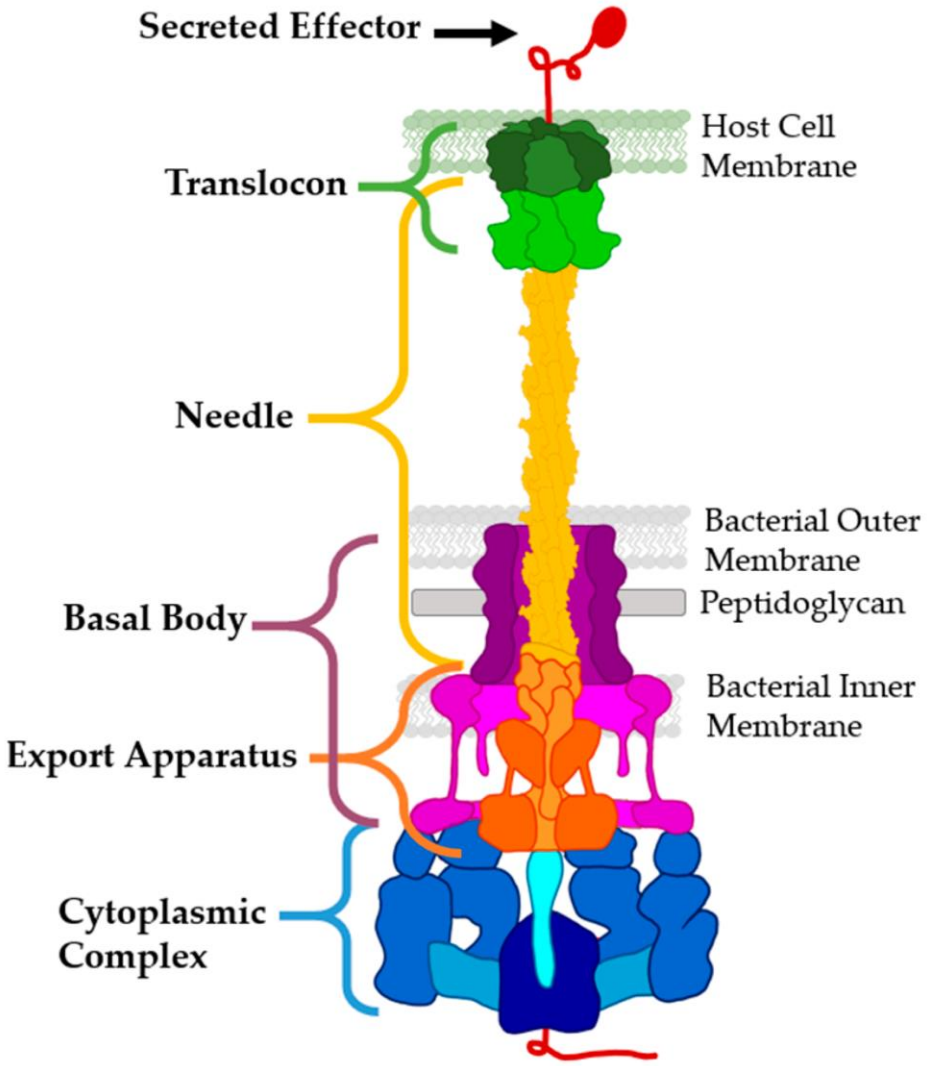
- T3SSs have been described as “injectisomes” and “needle and syringe”-like apparatuses because of their structure
- Type III secretion system (T3SS or TTSS) is structurally similar and related to the basal body of bacterial flagella
- Discovered in *Yersinia pestis*, it was found that T3SS can inject toxins directly from the bacterial cytoplasm into the cytoplasm of its host's cells. Also seen in *Shigella*, EHEC, *Salmonella*, *Shigella*
- T3SS has a core of 9 proteins that are highly conserved among all known systems. 8 of these proteins with the flagellar apparatus found in many bacteria and are evolutionarily related to flagellin.
- T3SSs have an additional 10 to 20 proteins that play either essential or important roles in their function.
- The structural components of T3SSs are typically encoded in a few operons, which can be found either in pathogenicity islands in the bacterial chromosome or on plasmids
- The T3SS can be broken down into three main components:
  - Base complex or basal body,
  - Needle component-bacteriumsensing contact with host cells and regulating secretion of effectors, also necessary for insertion of the translocon into host cell membranes
  - Translocon-essential for passage of effectors through host cell membranes, but not for secretion of effectors outside of the cell







The Type III Secretion System

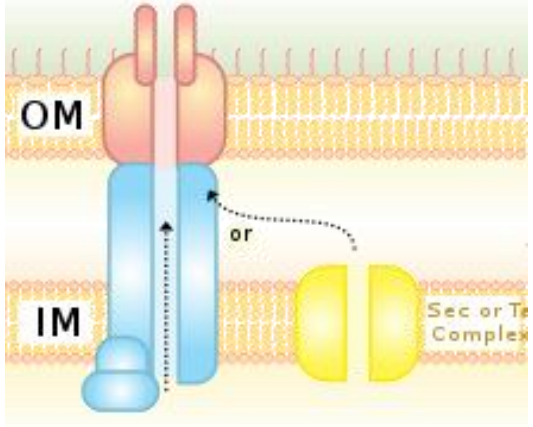


Section	Unified Name	Function
Translocon	SctE	Translocon (Major)
	SctB	Translocon (Minor)
Needle	SctA	Needle Tip
	SctF	Needle Component
	SctI	Needle Adaptor/Inner Rod
Basal Body	SctC	Upper Ring
	SctD	Outer Lower Ring
	SctJ	Inner Lower Ring
Export Apparatus	SctR	Export Component
	SctS	Export Component
	SctT	Export Component
	SctU	Autoprotease/Switch
	SctV	Gate
Cytoplasmic Complex	SctK	Cofactor
	SctQ	Cytoplasmic Ring
	SctL	Linker/Stator
	SctO	Stalk
	SctN	ATPase

Hotinger, J.A.; Pendergrass, H.A.; May, A.E. Molecular Targets and Strategies for Inhibition of the Bacterial Type III Secretion System (T3SS); Inhibitors Directly Binding to T3SS Components. Biomolecules 2021, 11, 316. https://doi.org/10.3390/biom11020316

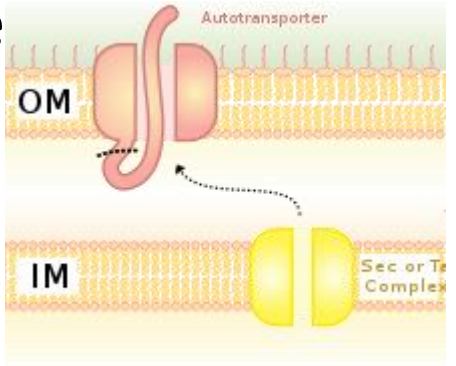
Type IV secretion system (T4SS or TFSS)

- Type IV secretion system (T4SS or TFSS) is related to bacterial conjugation system, by which different bacteria can exchange their DNAs and with eukaryotes
- *Agrobacterium tumefaciens*, from which it was originally discovered, uses virB/D system to send the T-DNA portion of the Ti plasmid into plant cells, in which a crown gall (tumor) is produced as a result.
- *Helicobacter pylori* uses it for delivering CagA into gastric epithelial cells, to induce gastric cancer.
- *Bordetella pertussis*, the causative bacterium of whooping cough, secretes its pertussis toxin partly through T4SS.
- *Legionella pneumophila* that causes legionellosis (Legionnaires' disease) has a T4SS called icm/dot (intracellular multiplication/defect in organelle trafficking genes) that transport many bacterial proteins into its eukaryotic host



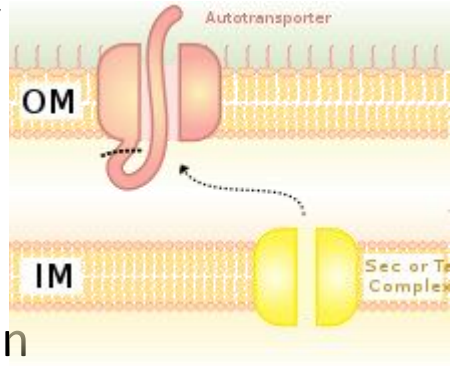
Trimeric autotransporter adhesion Type 5 secretion system (T5SS)

- T5SS substrates (unique) which cross the bacterial membrane with the help of a dedicated secretion apparatus or membrane channel, they secrete themselves.
- These proteins or groups of proteins carry their own β-barrel domain, which inserts into the outer membrane and forms a channel
- 3 categories
- ***1. Autotransporters*** they contain 3–4 domains:
  - a translocator domain at the C-terminus that forms the outer membrane channel,
  - a linker domain, a passenger domain that contains the functional part of the autotransporter protein,
  - a protease domain (optional) that cleaves off the passenger domain once it passes through the channel



Trimeric autotransporter adhesion Type 5 secretion system (T5SS)

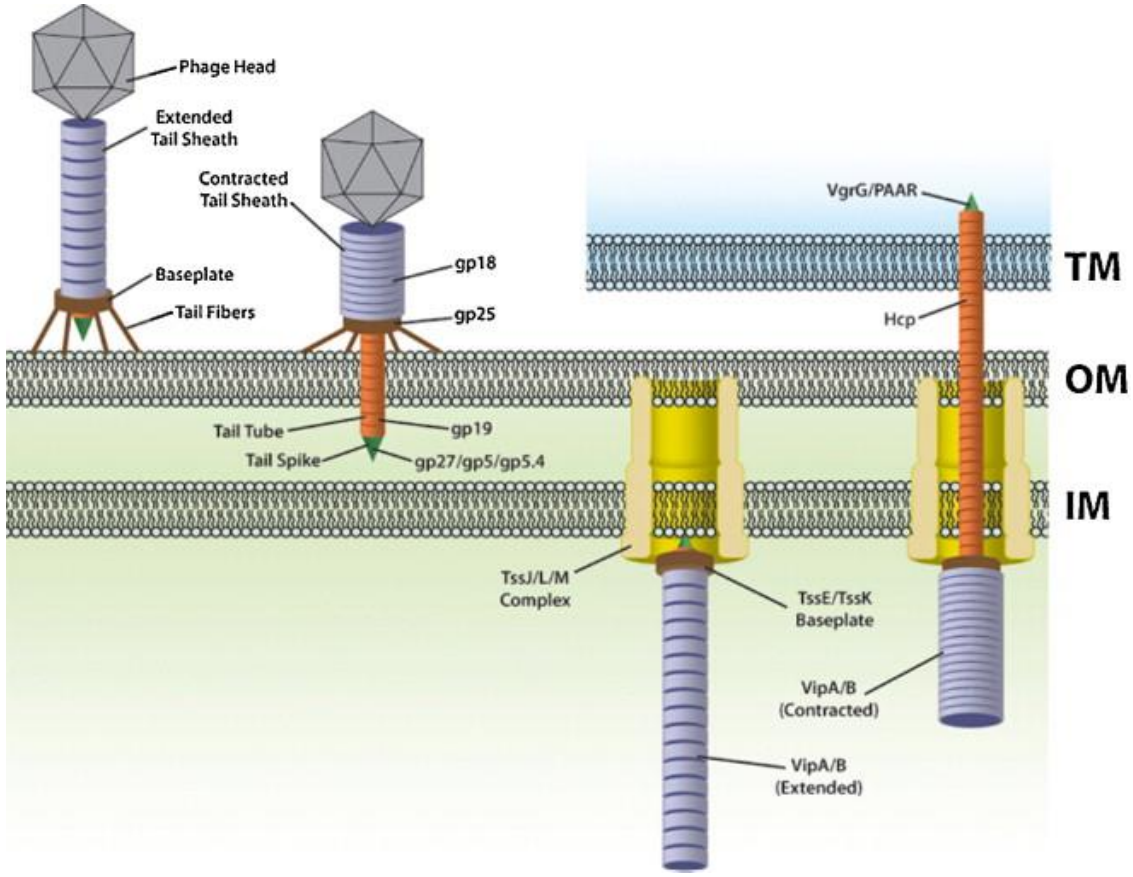
- Eg. immunoglobulin A protease of *N. gonorrhoeae*, which cleaves host antibodies
- IcsA protein of *Shigella flexneri* which promotes actin-based intracellular motility and also serves as an adhesion
- YadA of *Y. enterocolitica* which helps to promote translocation of T3SS substrates into host cells, and assists in mediating resistance to attack by the host complement system
- Protein secretion by T5SSs only occurs in the outer membrane, these proteins must first be translocated across the inner membrane and into the periplasm in an unfolded state by the Sec apparatus- protein carry an N terminal Sec sequence



- 2. ***Two-partner secretion***, a pair of proteins participates in the secretion process, in which one partner carries the β-barrel domain, while the other partner serves as the secreted protein primarily responsible for transporting large virulence proteins, such as the filamentous haemagglutinin of *Bordetella pertussis* and the high-molecular weight adhesins HWM1 and HWM2 of *Haemophilus influenzae*
- 3. ***Usher Proteins***: which forms the β-barrel channel in the outer membrane, and the chaperone, a periplasmic protein that facilitates folding of the secreted protein prior to delivery to the channel. Chaperone-usher systems are commonly used to assemble pilins on the surface of Gram-negative bacteria, such as the P pilus of uropathogenic *E. coli*

Type VI secretion systems (T6SS)

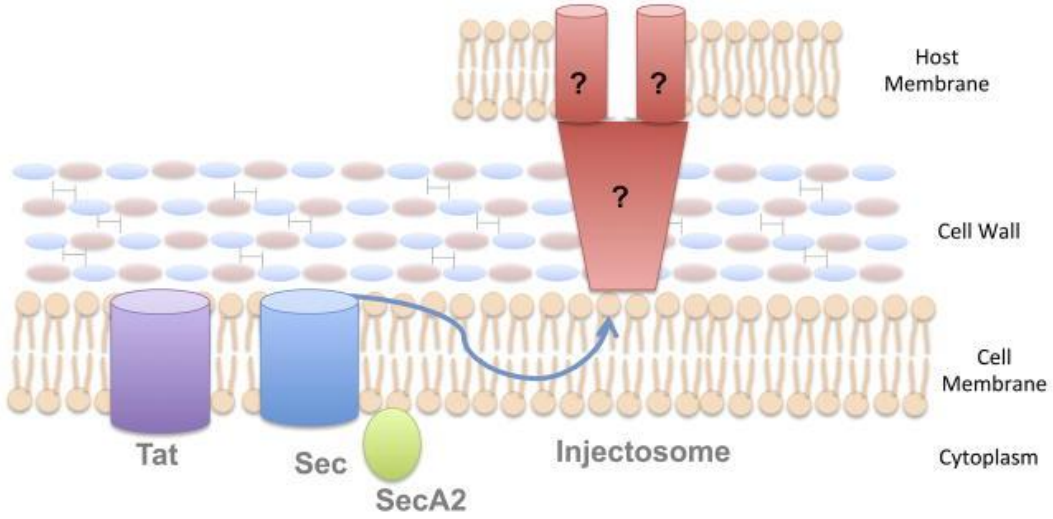
- Discovered by the team of John Mekalanos at the Harvard Medical School in 2006 from *Vibrio cholerae* and *Pseudomonas aeruginosa*- mutations in the *Vibrio Cholerae Hcp* and *VrgG* genes caused diminished virulence and pathogenicity
- gene for T6SS form a gene cluster that consists of more than 15 genes. *Hcp* and *VgrG* genes are the most universal genes
- T6SSs share structural homology to T4 phage tails



Chen *et al*. Microbiological Res.2015, 172:19-25
https://doi.org/10.1016/j.micres.2015.01.004

Gram Positive Bacterial Secretion system

- Gram-positive bacteria contain thick Cell wall of peptidoglycan
- GPB secrete proteins across the cell membrane using the Tat and Sec secretion systems but require additional systems particularly in CW modified GPB and *Mycobacteria*
- Sec A2: additional factor for Sec secretion of a smaller subset of proteins, called SecA2.
- Dedicated secretion apparatuses, called “injectosomes” to transport proteins from the bacterial cytoplasm into the cytoplasm of a host cell in a 2-step process.



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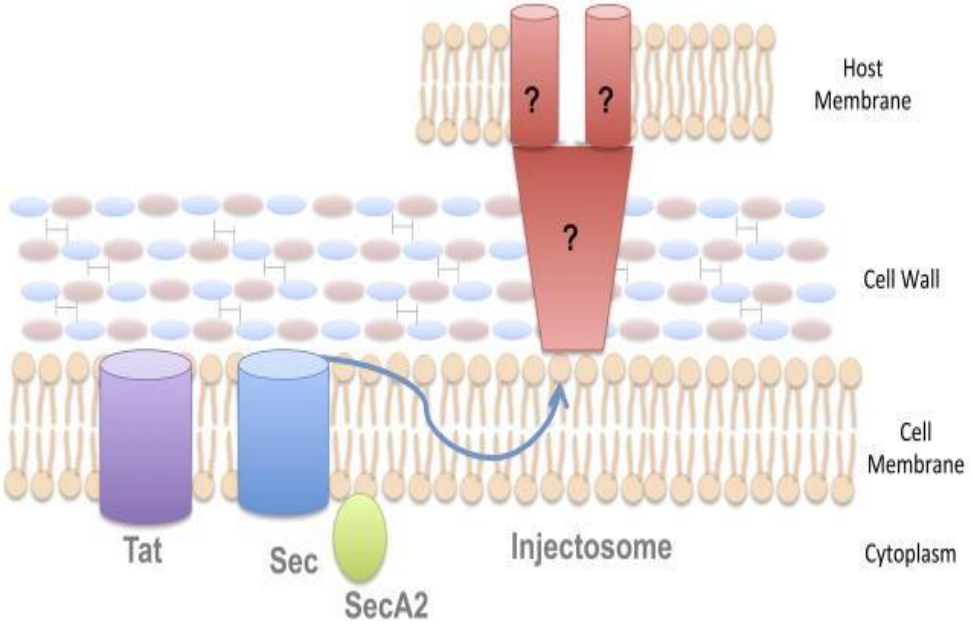
Gram Positive Bacterial Secretion system

- GPB including L. *monocytogenes, Bacillus subtilis, Clostridium difficile, M. tuberculosis,* and *Corynbacteria glutamicum*, actually contain two SecA homologues, called SecA1 and SecA2
- SecA1 is essential, and aids in the secretion of proteins via the canonical Sec pathway
- SecYEG core transporter transports SecA2 substrates and that SecA2 provides an additional means of regulation of specific substrates.
- The SecA2 protein, contains two nucleotide-binding domains, a pre-protein cross-linking domain, a helical wing and helical scaffold domain, and a C- terminal domain



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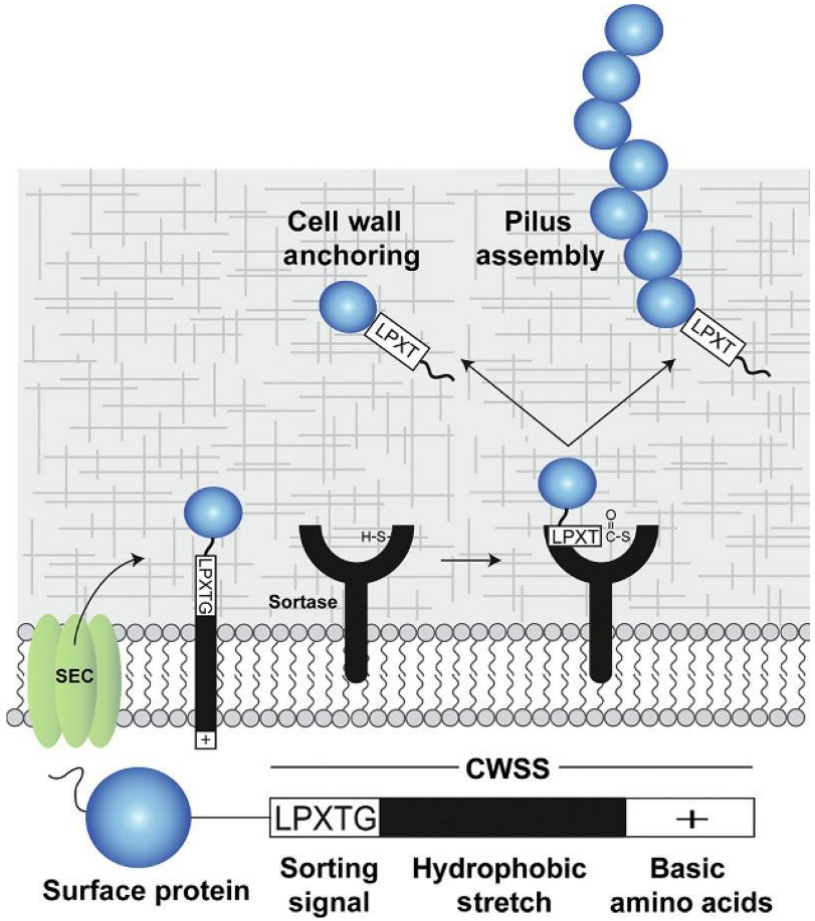
Sortase

- Sortases: Gram-positive bacterial extracellular transpeptidases responsible for covalently attaching secreted proteins to the peptidoglycan cell wall and assemble pili
- promoting bacterial adhesion, nutrient acquisition, and the evasion and suppression of the immune response
- *Staphylococcus aureus* Sortase A (SaSrtA) enzyme has been developed into a valuable biochemical reagent because of its ability to ligate biomolecules together in vitro via a covalent peptide bond.



Sortase enzymes attach proteins to the cell wall and assemble pili. (A) Overview of anchoring and pilus assembly reactions. A protein that is to be displayed (blue) contains an N-terminal secretion signal and a C-terminal cell wall sorting signal (CWSS). The CWSS contains an LPXTG-like sorting signal sequence that is processed by the sortase, a nonpolar polypeptide segment (black), and a C-terminal segment of positively charged residues (+).

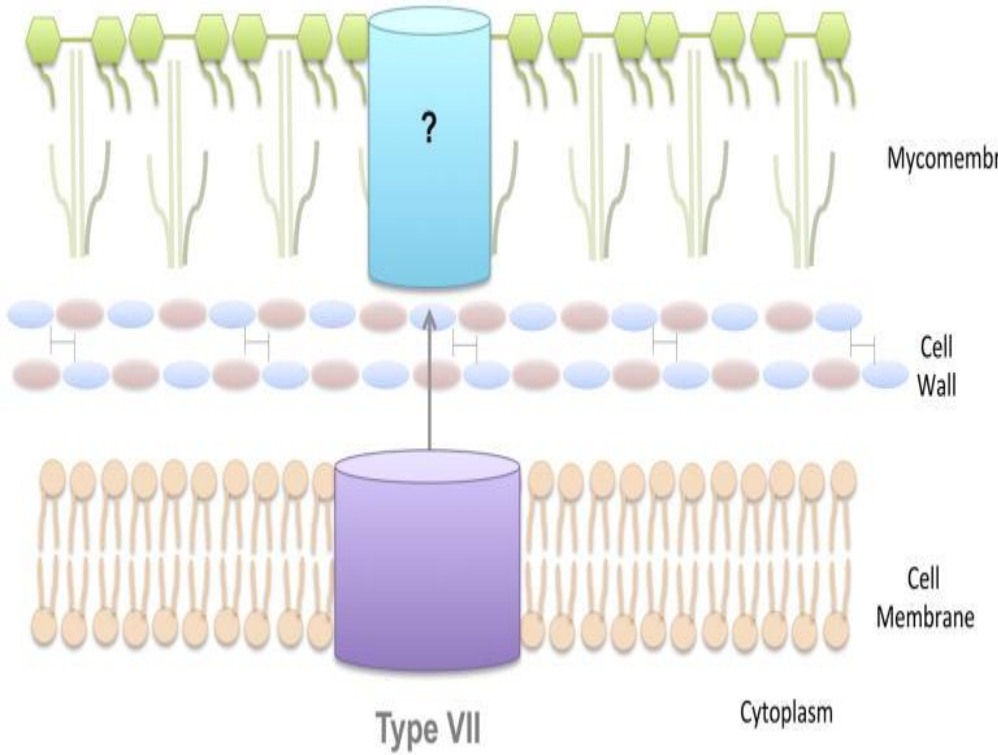
After secretion through the Sec translocon, the protein remains embedded in the lipid bilayer via the nonpolar segment within the CWSS.

The sortase enzyme then cleaves between the threonine and glycine residues to form a sortase–protein thioacyl intermediate in which the active site cysteine is covalently linked to the carbonyl carbon atom of the threonine. There are two basic types of sortases: (1) cell wall anchoring sortases that attach protein to the crossbridge peptide of the cell wall and (2) pilin polymerase sortases that covalently link pilin subunits together via lysine–isopeptide bonds. In both cases, the enzymes function as transpeptidases. Some sortases are capable of performing both functions, attaching proteins to the cell wall and polymerizing pili.

Jacobitz AW, Kattke MD, Wereszczynski J, Clubb RT. Sortase Transpeptidases: Structural Biology and Catalytic Mechanism. Adv Protein Chem Struct Biol. 2017;109:223-264. doi: 10.1016/bs.apcsb.2017.04.008

Type VII secretion systems (T7SS)

- 2003. *M. tuberculosis* refered to as ESX systems
- *Mycobacteria* and *Corynebacteria*, contain a heavily lipidated cell wall layer called a mycomembrane. These lipids form a very dense, waxy, hydrophobic layer on the outer surface of the bacteria
- Also identified in *S. aureus*, *Bacillus anthracis*, and *L. monocytogenes*
- Five core structural proteins appear in most of these gene clusters. EccB, EccC, EccD, EccE and MycP in the ESX systems, are all membrane proteins
- All except EccD have hydrophobic domains and thus all may interact with various other accessory components in the cytoplasm or peptidoglycan layer, such as chaperones or the cytosolic protein
- EccA, supply the source of energy for substrate transport
- The four membrane associated Ecc proteins from ESX-5 form a large inner membrane complex, which presumably contains a channel through which the substrates traverse
- The fifth component, MycP, is a mycosin, or subtilisin-like protease. The role of MycP in protein translocation through the T7SS is not completely understood, however, it is believed to play an important role in the regulation of secretion



Green ER, Mecsas J. Bacterial Secretion Systems: An Overview. Microbiol Spectr. 2016 Feb;4(1):10.1128/microbiolspec.VMBF-0012-2015. doi: 10.1128/microbiolspec.VMBF-0012-2015. PMID: 26999395; PMCID: PMC4804464.

Type VIII secretion systems (T8SS)

- Extracellular nucleation-precipitation (ENP) pathway or Type VIII secretion system (T8SS) in GNB (diderm) is responsible for the secretion and assembly of prepilins for fimbiae biogenesis, the prototypical curli
- The curli, also called thin aggregative fimbriae (Tafi), are the only fimbriae dependent on the T8SS.
- Tafi were first identified in *Salmonella* spp and the controlling operon termed *agf* (2002)
- Homologous operon in *E coli* led to its being called csg (2007). In the absence of extracellular polysaccharides Tafi appear curled, although when expressed with such polysaccharides their morphology appears as a tangled amorphous matrix. CsgF is one of three putative curli assembly factors appearing to act as a nucleator protein.
- https://www.ebi.ac.uk/interpro/entry/InterPro/IPR018893/

Type IX secretion systems (T9SS)

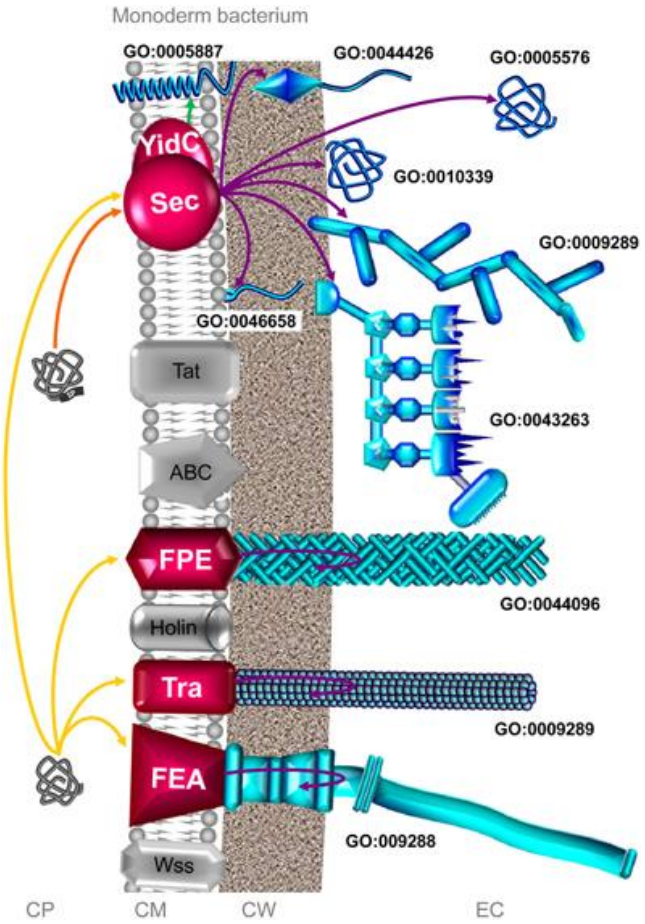
- Type IX secretion systems (T9SS) are found regularly in the Fibrobacteres-Chlorobi-Bacteroidetes lineage of bacteria, where member species include an outer membrane.
- Used in gliding motility, in the proper targeting of certain virulence factors to the cell surface, and the degradation of complex of biopolymers.
- Gliding motility is the ability of certain rod-shaped bacteria to translocate on surfaces without the aid of external appendages such as flagella, cilia, or pili.
- T9SS has also been known as Por (porphyrin accumulation on the cell surface) secretion, after the oral pathogen *Porphyromonas gingivalis*.
- At least sixteen structural components of the system have been described, including PorU, a protein-sorting transpeptidase that removes the C-terminal sorting signal from cargo proteins and mediates their attachment instead to lipopolysaccharide.

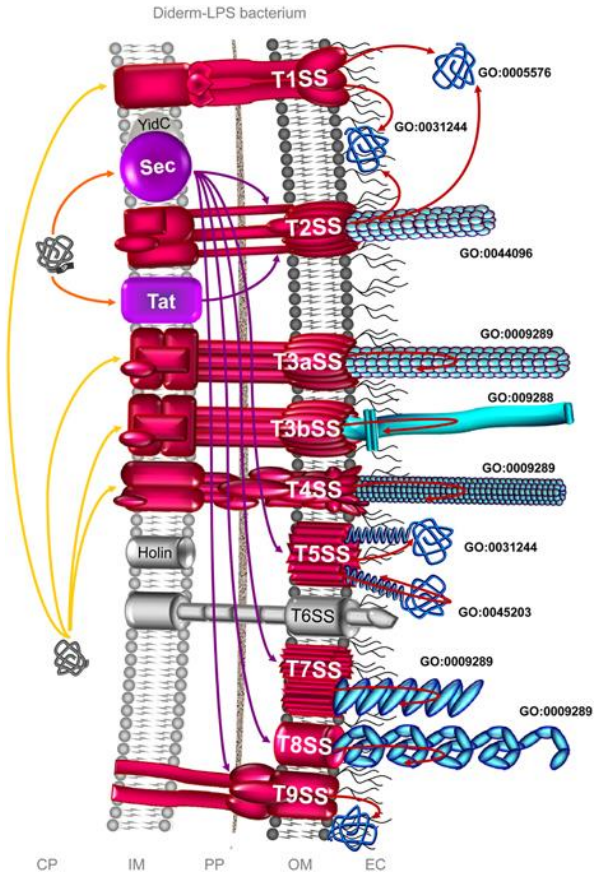
Veith PD, Glew MD, Gorasia DG, Reynolds EC (October 2017). "Type IX secretion: the generation of bacterial cell surface coatings involved in virulence, gliding motility and the degradation of complex biopolymers". Molecular Microbiology. 106 (1): 35–53.

Classes of bacterial protein secretion systems

Secretion Apparatus	Secretion Signal	Steps in Secretion	Folded Substrates?	Number of Membranes	Gram (+) or Gram (−)
Sec	N-terminus	1	No	1	Both
Tat	N-terminus	1	Yes	1	Both
T1SS	C-terminus	1	No	2	Gram (−)
T2SS	N-terminus	2	Yes	1	Gram (−)
T3SS	N-terminus	1–2	No	2–3	Gram (−)
T4SS	C-terminus	1	No	2–3	Gram (−)
T5SS	N-terminus	2	No	1	Gram (−)
T6SS	No known secretion signal	1	Unknown	2–3	Gram (−)
SecA2	N-terminus	1	No	1	Gram (+)
Sortase	N-terminus (Sec) C-terimnus (cws)	2	Yes	1	Gram (+)
Injectosome	N-terminus	2	Yes	1	Gram (+)
T7SS	C-terminus	1	Yes	1–3	Gram (+)

Bacterial Secretion Systems





https://en.wikipedia.org/wiki/Bacterial_secretion_system#/media/File:Secretion_systems_in_diderm_bacteria.jpg

Secretion system inhibitors

- Secretion system inhibitors are **a novel class of anti-infectives that do not inhibit bacterial growth and therefore do not cause selection for mutations causing resistance**.
- Another advantage is the fairly high degree of conservation of these systems between a whole range of Gram-negative pathogens
- Major cause of antibiotic resistance is bacterial conjugation mediated by the versatile type IV secretion system (T4SS)- develop drugs against the secretion systems

Reading Material

- Green ER, Mecsas J. Bacterial Secretion Systems: An Overview. Microbiol Spectr. 2016 Feb;4(1):10.1128/microbiolspec.VMBF-0012-2015. doi: 10.1128/microbiolspec.VMBF-0012-2015. PMID: 26999395; PMCID: PMC4804464.
- Prescott Microbiology Book by Christopher J. Woolverton, Joanne Willey, and Linda Sherwood
- https://www.microbiologyresearch.org/content/journal/micro/10.1099/mic.0.001193?crawler=true
- https://en.wikipedia.org/wiki/Bacterial_secretion_system
- https://bio.libretexts.org/Bookshelves/Microbiology/Book%3A_Microbiology_(Boundless)/*14%3A_Pathogenicity/14.4%3A_Damaging_Host_Cells*

- **THANK YOU**