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A Review on Various Secretion Systems: A Versatile Molecular Weapon for Bacterial Pathogenesis, Special Reference to Type 7 Secretion System (T7SS) in Multi Drug Resistance *Staphylococcus aureus.*

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Abstract

S. aureus pathogens utilize multiple methods to invade mammalian hosts, damage tissue sites, and baffle the immune system from responding. Secretion of proteins across phospholipid membranes are one of the essential strategy components in these strategies for many bacterial pathogens. Secreted proteins play many roles in promoting bacterial virulence, from enhancing attachment to eukaryotic cells, to scavenging resources in an environmental niche, to directly intoxicating target cells and disrupting their functions. Many pathogens use dedicated protein secretion systems to secrete virulence factors from the cytosol of the host environment or bacteria into host cells. In general, bacterial protein secretion apparatuses are classified into classes, based on their structures, functions, and specificity. Some systems are conserved in all classes of bacteria and secrete a broad array of substrates, while others are only found in a small number of bacterial species and/or are specific to only one or a few proteins. In this chapter, we review the canonical features of several common bacterial protein secretion systems, as well as their roles in promoting the virulence of bacterial pathogens and immune-pathogenesis. Additionally, we address recent findings that indicate that the innate immune system of the host can detect and respond to the presence of protein secretion systems during mammalian infection.

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Introduction

Staphylococcus aureus is cocci bacteria measuring about 0.8 to 1.0 µm in diameter, and it grows in clusters. Its nomenclature, broken down, means "golden cluster of grapes". It starts making sense if we look at it under a microscope-stained smear from culture- it shows that this organism grows in sticky clusters, and it stains purple when gram stained i.e. Gram positive. Facultative anaerobes, meaning that they can survive in aerobic and anaerobic environments [1]. 37°c is the optimum temperature for growth of *S. aureus*, range being 12 to 44°c, optimum pH is 7.5. It has a cell wall with a thick peptidoglycan layer and an inner lipid membrane layer. *S. aureus* has a capsule that surrounds it, which allow it to resist phagocytosis, when it invades a human body, the phagocytic cells within the body are unable to eat this bacterium up in some instances [2]. They are non-motile and don't form spores. Staphylococci produce an enzyme called catalase, which converts hydrogen peroxide to water and oxygen. *S. aureus* contains lots of virulence factors for causing infection in the human host, these types of virulence factors or proteins are synthesized by type 7 secretion (T7SSs) system [3]. The overall molecular mechanisms of virulence protein synthesis in *S. aureus* are not fully known till date. The type 7 secretion (T7SSs) system of *Staph aureus* also known as ESAT-6 secretion system and it was initially discovered in *mycobacterium tuberculosis*, where it is responsible for mycobacterium virulence [4]. Type 7 (T7SSs) is also reported in *S. aureus* and responsible for its virulence. Type 7 secretion (T7SSs) system is the orthologous system of ESX-1 initially was reported in *Mycobacterium* species [5]. *S. aureus* is a very infectious pathogen and through T7SSs secreted virulence proteins, it is able to cause infection in healthy individuals after colonization of the nares and skin [5]. Virulence proteins of T7SSs also plays a key role in long term persistence of *S. aureus* in host and promoting bacterial survival.

Background

The type VII secretion system (T7SS) was discovered in *Mycobacterium tuberculosis* (Mtb), in which core machinery components assemble in the inner membrane and utilize an ATPase to drive secretion of typically small, α-helical proteins lacking traditional signal peptides.

Secretion system of Bacteria

Secretion systems are important functions of prokaryotic cells to transport proteins from cytoplasm into other cell organelles, compartments of cell, other bacteria, and eukaryotes [6]. Prokaryotes develops several methods of protein transporting cargo between different cell organelles, Protein secretion systems are important for development and growth of bacteria.

Few secretion systems are reported in all bacteria and synthesize a wide number of proteins, while others have been present in only a small number of bacterial strains and are responsible for secreting only limited numbers of proteins [6]. In certain cases, these dedicated secretions systems were used by bacterial pathogens to manipulate the host and make a replicative niche. Other times, they are required to take advantage of an environmental niche, perhaps by secreting proteins that help to compete with nearby microorganisms. Bacteria can introduce several different classes of secretion system, and their pattern can differ based on whether their protein substrates cross a single three phospholipid membranes, two phospholipid membranes and even one phospholipid membranes [7]. Due to specificity of expression of some of these secretion systems in bacterial pathogens, antimicrobials are being designed and developed against these systems to augment our current repertoire of antibiotics. Bacterial secretion systems are protein complexes and present on cell membranes of bacteria for secretion of substances. In principle, Secretion systems are cellular devices of pathogenic bacteria to synthesize their virulence proteins to fight with host cells during infection [7]. They are classified into different classes based on structure, activity and composition. These major differences were distinguished between Gram negative and Grampositive bacteria. But classification is by no means clear and complete. There are at least eight types specific to Gram negative bacteria and four types to Gram positive bacteria, while two are common in both. Specifically, bacteria secrete proteins through two different processes, one process is a one-step mechanism in which bacteria transports proteins from our cytoplasm to the cell membrane of the host cell [7,8]. Another process is a two-step activity, in this activity proteins are first transported out of the inner cell membrane, then further deposited in periplasm, and finally goes to the outer cell membrane into the host cell [8]. The use of this dedicated secretion system is to transport proteins out of the bacterial cell and into the environment or into a targeted cell. However, protein secretion from the bacterial cytoplasmic compartment into other compartments of the cell, particularly into or across the cytoplasmic membrane. The **table 1** is containing an important overview of different classes of bacterial protein secretion systems.

Lots of secretion systems will be discussed in depth in subsequent table in this section: the Type I (T1SS), Type II (T2SS), Type III Secretion System (T3SS), T4SS, T5SS, T6SS,T7SS, T8SS and T9SS. In this Review, we provide a brief introduction to a number of protein secretion systems, including those that are not discussed in depth in succeeding chapters, in order to highlight the structural and functional similarities and differences between these systems. Our discussions will focus on the canonical features of each system and not the multitude of variations in each one. In addition, we briefly review recent findings that indicate that the innate immune system of the host can detect and respond to the presence of protein secretion systems during mammalian infection [5,6].

T5SS	*Neisseria meningitidis, Pseudomonas aeruginosa, Bordetella filamentous, H. influenzae, Serratia marcescens, Yersinia enterocolitica, Y.pseudotuberculosis, P. aeruginosa, Fusobacterium nucleatum, Escherichia coli,Y. enterocolitica &H. pylori.*	Type V secretion denotes a variety of secretion systems that cross the outer membrane in Gram-negative bacteria but that depend on Sec machinery for transport through inner membrane.	Va, Vb, Vc, Vd, Ve, Vf	Outer and inner membranes.	N-terminus	2	No	1	No	Gram (-)	Yes	No	[56,57, 58,59,60]
T6SS	*Vibrio cholerae, A. hydrophila, B. cenocepacia , B. thailendensis, E. tarda, P. aeruginosa,Enterohemorragic E. coli, A. tumefaciens, D. dadantii, S. marcescens.*	The type VI secretion systems (T6SS) are react as a molecular machine used by a wide range of Gram-negative bacteria to transport proteins from the interior (cytoplasm or cytosol) of a bacterial cell across the cellular envelope into an adjacent target cell.	Ssp6,Tag,Fha ,TagJ ,PAAR ,PppA ,Ssp6 ,TagF, F TssA ,TssB ,TssC ,Hcp ,TssE ,TssF ,TssG ,TssH ,TssI TssJ ,TssK ,TssL ,TssM,Hcp, VgrG, DUF4123- , DUF1795-, DUF2169, VgrG1, TecA, VgrG-5, EvpP, VgrG2b, KatN, PldA/Tle5, PldB, VasX, TseL/Tle2, Tle1, Tse1, Tse3, TseH, VgrG-3, Tge2, Tde1, Tde2, RhsA, RhsB, Hcp-ET1, Rhs2, Tse2, Tse6, TseM, YezP, TseF	Outer and inner membrane.	No known secretion signal till date	1	Unknown till date	2-3	Yes	Gram (-)	No	Yes	[61,62, 63,64]
Sec A2	*Staphylococcus aureus, Bacillus anthracis, Streptococcus pneumoniae Listeria and Mycobacteria,Corynebacteria*	SecA2 is an auxiliary secretion of SecA2 protein through several pathogenic Gram-positive bacteria and SecA2 is required for bacterial persistent colonization in host tissues.	-	Cytoplasmic membrane	N- terminus	1	No	1	Yes	Gram (+)	Yes	No	[93,94]
Sortase	*S.aureus, E.coli, Shewanella putrefaciens, Archaea (Methanobacterium), Actinomyces naeslundii, B. anthracis, B. subtilis, Clostridium acetabutylicum, C. diphtheriae, E. faecalis, L. monocytogenes, S. mutans, S. pneumoniae and S. pyogenes.*	Sortase is refers to a group of prokaryotic enzymes that modify surface proteins by recognizing and cleaving a carboxyl-terminal sorting signal.	SrtA, SrtB, SrtC, SrtD	-	N-terminus (Sec) C-terminus (cell wall sorting)	2	Yes	1	Yes	Gram (+)	No	No	[75,76,77, 78,79,80,81]
Injectosome	*S. Typhimurium, Yersinia spp., Salmonella spp., E.coli, Shigella, Chlamydia, P. aeruginosa, P. syringae Rhizobium*	Injectosome are transmembrane complexes useful for translocation of effector proteins from bacteria to eukaryotic host cells, where the effectors influence host behaviour in favour of the bacterium.	SctF,SctC,SctI, SctRST,SctJ,SctD,SctU,SctV,SctK,SctQ,SctO,SctN,SctL.	Outer and inner membrane with peptidoglycan.	N-terminus	2	Yes	1	Yes	Gram (+)	No	Yes	[47,48, 49,50]
T7SS	*Mycobacterium tuberculosis*, *Mycobacterium smegmatis*, *Mycobacterium marinum* , *S.aureus, E.coli.*	Type VII secretion systems (T7SSs) have play a crucial role in the secretion of effector proteins in non-pathogenic bacteria and pathogenic bacteria (*S. aureus, mycobacteria*). These bacteria are the main causative agent of diseases in the human host.	EsaA, EssA, EssB ,EssC EsaB,EsaG, EsxA, EsxB, EsxC, EsxD,EsaD, and EsaE,	Outer and inner membrane.	C-terminus	1	Yes	1-3	Yes	Gram (+)	No	Yes	[65,66,67, 68, 69,70,71, 72,73,74]
T8SS	*E. coli*	The T8SS, or the curli biogenesis pathway, have played an important role employed by *Enterobacteriaceae* to secrete amyloid fibers (curli) that constitute the major protein component of their biofilms.	CsgA	Outer membrane	C-terminus	-	No	1-2	Yes	Gram(+)	-	-	[82,83]
T9SS	*Porphyromonas gingivalis*, *Flavobacterium johnsoniae and* phylum *Bacteroidetes.*	T9SS is important for the lifestyle of the bacteria. It provides movement (called gliding motility) for peace-loving environmental bacteria or a weapon for pathogens.	gldJ, gldK, gldL, gldM, gldN, porQ, porU, porV, sprA, sprT and sprE.	Outer and inner membrane including periplasm.	C-terminus	1-2	No	2-3	Yes	Gram (-)	No	Yes	[84,85]

Table 1: Classes of bacterial protein secretion systems.

Secretion apparatus	Bacterial Stains	Importance for bacteria	Involved Proteins	Found in/ location	Secretion signal	Steps in secretion	Folded substrates?	Number of membranes	ATP dependent	Gram(+) / Gram (-)	Auto transporters system	Conjugation-like system	Ref.
Sec	*Vibrio cholera*(-), *K. pneumoniae* (-) and *Yersinia enterocolitica* (-), *Staphylococcus aureus* (+), *Listeria monocytogenes* (+) & *E.coli (+)*	The Sec system is involved in both secretion of unfolded proteins across cytoplasmic membranes and the insertion of membrane proteins into cytoplasmic membranes.	SecY,SecE SecG, a peripheral associated ATPase, SecA,SecB.SecD, SecF, YajC, SecY,Ffh,FtsY,YajC,LepB	Cytoplasmic membrane	N-terminus	1	No	1	Yes	Both	Yes	No	[16,17,18,19 ,20,21]
Tat	*Rhodobacter capsulatus, Streptomyces coelicolor, halophilic archaea, Streptomyces coelicolor, Halobacterium sp, B. subtilis, H. volcanii, Rickettsia prowazekii ,Staphylococcus aureus, Legionella pneumophila, Streptomyces lividans, S. coelicolor,H. volcanii , A. tumefaciens, Helicobacter pylori, P. aeruginosa, M. tuberculosis & smegmatis.*	The Tat pathway catalyses export of proteins from the cytoplasm across inner/cytoplasmic membrane (IM).	TatA and TatC or TatA, TatB, TatC,	Cytoplasmic membrane	N-terminus	1	Yes	1	No	Both	Yes	Yes	[23,24,25]
T1SS	*E. coli, Vibrio cholerae, Bordetella pertussis. S. marcescens, P. aeruginosa & N. meningitid*	Type-1 secretion systems (T1SSs) represent a wide- spread mode of protein secretion across cell envelope.	hlyC, hlyA, hlyB, hlyD hasA.hasB, hasR,hasD, slaA,lipB, lipC,lipD, lipA, prtA	Inner-membrane ABC transporter, a periplasmic membrane-fusion protein, and outer-membrane porin.	C-terminus	1	No	2	Yes	Gram (-)	No	Yes	[33,34,35, 36,37]
T2SS	*Vibrio cholerae , enterotoxigenic and Escherichia coli, Pseudomonas aeruginosa, Klebsiella spp., Legionella pneumophila and Yersinia enterocolitica, Aeromonas hydrophila.*	Type II secretion system (T2SS) to translocate folded proteins from periplasm through outer membrane and into extracellular milieu.	GspS,GspK, GspI GspH GspJ GspG GspF GspD GspE GspL GspM GspC	Inner and outer membranes.	N-terminus	2	Yes	1	Yes	Gram (-)	Yes	No	[38,39,40, 41,42]
T3SS	*Yersinia species (Y. pestis, Y. enterocolitica, Y. pseudotuberculosis), Salmonella enterica serovars (Typhimurium, Typhi, Paratyphi, Sendai, Dublin, Shigella species, Bordetella species, Pseudomonas aeruginosa, Burkholderia pseudomallei, Vibrio parahaemolyticus, V. cholerae, Chlamydia species*	The type III secretion system (T3SS) is an important virulence factor that enables some bacteria to directly inject effector proteins into host cells, facilitating colonization.	**For Yersinia species-**Ysc injectisome, YopB, YopD, LcrV **For Salmonella species -** SPI1, PrgK, PrgH, InvG , PrgI , SipB/C/D , SPI2, Ssa proteins, Ssc proteins, SsrAB , SseB/C/ D. **For Shigella species**- Mxi/Spa, IpaB/C , IpgC (IpaB/C chaperone) BopB, BopD **For *Pseudomonas aeruginosa*** -PopB, PopD , PcrV, SpcU.	Outer and inner membranes including peptidoglycan layer.	N-terminus	1-2	No	2-3	Yes	Gram (-)	No	Yes	[43,44, 45,46]
T4SS	*H. pylori, Bordetella pertussis, Legionella pneumophila, Brucella spp., Bartonella spp. Agrobacterium tumefaciens, Stenotrophomonas, Lysobacter, Luteimonas, Pseudoxanthomonas, Rhodanobacter, Luteibacter, Dyella, Frateuria, Aquimonas and L. pneumophila, C. burnetii, & Rickettsiella grylli*	T4SSs are thus important virulence factors in a variety of human diseases, including whooping cough (Bordetella pertussis), cat-scratch fever (Bartonella henselae), brucellosis (Brucella spp.), Legionnaire's pneumonia (Legionella pneumophila), Q fever (Coxiella burnetii) and peptic ulcer and gastric cancer (Helicobacter pylori)	VirB7, VirB9, VirB10, VirB4, VirB11, VirD4 VirB8, VirB6, VirB3, VirB2, VirB5, VirB1	Outer membrane and inner membrane including periplasm.	C-terminus	1	No	2-3	Yes	Gram (-)	Yes	Yes	[51,52,53, 54,55]

Localization process of proteins in bacteria

Localization processes exist in all cells and affect where protein ends up after translation, placing proteins in different parts of the cell. There are five readily distinguishable compartments (Cytoplasmic, inner membrane, periplasmic, outer membrane & secreted) in a Gram negative bacteria such as *E.coli* defined by presence of contiguous bilayer membranes that prevent free exchange of biomolecules [8,9]. There is cytoplasm in the innermost compartment where all central dogma processes and most of metabolism takes place, there is periplasm between two membranes and an extracellular environment accessible only by secretion. Two membranes also present distinct compartments to the cell, where proteins can be inserted. All proteins start their life in cytoplasm, so cytoplasm is the default location of a new protein in absence of targeting mechanisms [9].

Two pathways exist for periplasmic localization *Tat* and *Sec*

Sec secretion involves a signal sequence also called a leader sequence or pre sequence. After a gene will employ a pre-pro sequence on n-terminus which is cleaved after transport completes, pre-pro sequences are typically 18 to 30 amino acids long and contain one or more basic residues near N terminus and central seven amino acids have hydrophobic core [10]. If a protein just contains a pre-sequence it will remain anchored into the membrane after translation or it has a pre - pro sequence it will be proteolytically cleaved off releasing protein to periplasm. During the export of protein is in an unfolded state and is often secreted coincident with translation popular parts for pre-pro sequences that find in many common expression systems are pelB and ompT leakers leader sequences [10]. The *Tat* secretion system similarly involves a signal sequence but it doesn't need to be on n-terminus, it is sequence: ((S/T) RRXFLK) [11]. During *Tat* secretion system protein first folds in cytoplasm and is subsequently transported the system will not transport non folded proteins, which is a useful trick in various assays. Getting a protein to the outer membrane or extracellular environment is more challenging but possible. Several *E. coli* systems have been examined extensively including OmpA, OmpT, OmpG and LamB shown in table-1 [11,12]. The process starts with *Sec* secretion to periplasm and then spontaneously fold and insert themselves into the outer membrane.

Popular strategy for targeting a protein in prokaryotes

The most popular strategy for targeting a protein to the outer membrane and prokaryotes is to fuse protein to another protein that already goes there. Most popular fusion based targeting systems include AmpA and a structurally dissimilar one called ice nucleation protein [12]. In Gram positive bacteria there is no outer membrane and thus there are only three vesicular compartments including cytoplasm, inner membrane and extracellular environment. The same basic set of proteins and localization signals that directed proteins to periplasm in gram negative will target a protein for extracellular secretion in a gram positive bacteria thus secreting proteins is usually much easier to achieve in a gram positive rather than a gram negative bacteria [13,14]. Industrially commodity proteins like proteases that are used as detergent are usually produced in gram positive bacillus strain various fungi are also good protein secretors, these are useful for industry. Targeting proteins for secretion is more challenging in gram negative bacteria There are at least six distinguishable types of secretion systems that cluster based on sequence homology in consistent aspects of function, the type 5 and type 2 secretion systems are *Sec* dependent this means that proteins being secreted will need to contain a pre-pro sequence on their N terminus and first step of crossing inner membrane involves *Sec* apparatus [14]. Type 1, 3 and 4 don't employ *Sec* and they form a contiguous conduit for secretion of protein from cytoplasm to extracellular environment [14]. The most commonly used secretion systems for transport of proteins across the cytoplasmic membrane are general secretion (*Sec*) and twin arginine translocation (*Tat*) .*Tat* and *Sec* are highly conserved pathways for protein secretion in bacteria and have been discovered in all domains of life included bacteria, archaea and eukaryote [15]. Most proteins transported through *Sec* and *Tat* pathways remain inside of the cell, either in periplasm or inner membrane. However, in gram negative bacteria proteins delivered to the cytoplasmic membrane or periplasm of cell through *Sec* and *Tat* pathways, can either stay in those compartments or may be transported outside of the cell with the help of another secretion system [15]. While *Sec* and *Tat* pathways have several common elements, they transport proteins through fundamentally different mechanisms.

***Sec* System**

The general secretion (*Sec*) system is a specified system for the secretion of unfolded proteins that first remains inside the cell [16]. In Gram negative bacteria, the secreted proteins are sent to either the inner membrane or the periplasm. But in the case of Gram-positive bacteria, the proteins may stay in the cell and are mostly transported out of bacteria using other secretion systems. *Sec* system is reported in these gram-negative bacteria *Vibrio cholera, Klebsiella pneumoniae* and *Yersinia enterocolitica* but *sec* mediated Protein secretion is best studied in only *E.coli*. Till date [16,17]. Among gram positive bacteria, *Staphylococcus aureus* and *Listeria monocytogenes* use the *Sec* System. Type 1, 3, 4 are *sec* independent secretion systems and are Type 2, 5 *Sec* dependent secretion systems [16,17].

The *Sec* system deals with two different pathways for secretion: *Sec* A and signal recognition particle (SRP) pathways are two arms of the *Sec* system. *Sec* A is an ATPase motor protein and has many related proteins including *Sec*D, *Sec* E, *Sec*F, *Sec*G, *Sec*M and *Sec*Y [17,18]. SRPs are ribonucleoproteins (Protein RNA complexes) that recognize and target specific proteins to ER in multicellular organisms and to the cell membrane in single cell organisms. *Sec*A and SRP pathways require different molecular chaperons and also wanted a protein transporting channel *Sec*YEG for transporting the proteins across the inner membrane [18]. *Sec*B acts as a molecular chaperone in *Sec* pathway provides help for protein transport to periplasm after complete synthesis of the peptide chains. Whereas YidC acts as a molecular chaperone in SRP pathway and transports proteins to cell membranes while they are still undergoing peptide synthesis [19].

***Sec A* or post translational pathway:** Protein synthesis machinery are ribosomes by a process of serially adding amino acids, called translation. In *Sec* A pathway, a molecular chaperone trigger factor (TF) first binds to uncover N-terminal signal sequence of peptide chain [19,20]. As elongation of the peptide chain continues, TF is replaced by *Sec*B. *Sec*B specifically maintains peptide in an unfolded state, and aids in binding of *Sec*A. The complex can then bind to *Sec*YEG, by which *Sec*A is triggered by binding with ATP. Driven by ATP energy, *Sec*A pushes the protein through the *sec*YEG

channel. The *Sec*D/F complex also helps in pulling of protein from the other side of the cell membrane . On the basis of amino acid level, *Sec*A1 and *Sec*A2 are about 50% similar to each other in *M. tuberculosis* and both have 61% and 50% similar to *E. coli Sec*A, respectively [20]. *Sec*A1 protein is an important protein of mycobacteria and it has functional similarity to single *Sec*A proteins of *E.coli* and *B. subtilis*. *Sec*A2 protein of mycobacteria is not essential for growth in culture but it plays a very pretty crucial role for exporting a subset of proteins [21]. *Sec*A2 protein of mycobacteria is important for virulence. In a single bacterial species the functional dissimilarity between *Sec*A1 and *Sec*A2 proteins are not known till date due to lack of functional features [21].

SRP Pathway

In this pathway, SRP competes with TF and binds to N-Terminal signal sequence [22]. Proteins from the inner membrane block the process of chain elongation. The SRP then binds to a membrane receptor, FtsY [22]. The peptide chain SRP-FtsY complex is then transported to SegY, where peptide elongation resumes.

***Tat* System:** The twin arginine translocation (*Tat*) system is like *Sec* in process of secretion, however, it sends proteins only to their folded (Tertiary) state [23]. It is used by all types of bacteria, as well as archaea, chloroplasts and plants mitochondria. In case of bacteria, *Tat* system exports proteins from cytoplasm across the inner cell membrane, whereas in chloroplasts, it is present in thylakoid membrane where it aids import of proteins from stroma [23,24]. That proteins have highly variability in different bacterial strains and are distributed into major types namely *Tat*A, *Tat*B and *Tat*C. For example, while there are only two functional *Tat* proteins in *Bacillus subtilis* there can be over a hundred in *Streptomyces coelicolor* [24]. Signal peptides that can recognise *Tat* proteins are characterized by a consensus motif Ser/Thr-Arg-Arg-XPhe-Leu-Lys (where X can be any polar amino acid) [24,25] It is two successive arginines from which the name twin arginine translocation came from. Replacement of any leads to slow down or failure of secretion.

Relation of Type 7 Secretion system with other bacterial secretions

Bacteria has seven (Type 1 to 7) different types of secretion systems, T7SS is one of specialised systems for secretion of extracellular proteins across bacterial cell membranes and it is associated with virulence in *S. aureus*. The synthesis of virulence factors is dependent upon genetic diversity of ess locus, which encodes T7SS and the mode of action of encoded proteins within it are not fully characterized [26]. Type 7 Secretion system is an important mechanism to make a bridge between prokaryotic and eukaryotic cells. For the better understanding about T7SS, we can first understand Type 1 to Type 6 secretion systems because these are all evolutionary interconnected to each other and have evolutionary relationships between them for survival of the fittest of microorganisms [26,27]. Type 1 and Type 4 secretion systems are present in both gram positive and gram-negative bacteria, most of other all types of secretion systems are reported only in gram negative bacteria, while T7SS is reported in *S. aureus* a gram-positive bacterium. Secretion system in *S. aureus* has long been known to play principal roles in bacteria host interactions. By the secretion system bacteria secret effectors proteins into the extracellular environment or directly into the host cytoplasm [28]. The secreted proteins then interact with the host cellular processes to elicit a defence response, or promote disease. In gram negative bacteria, these proteins must pass through two membranes: the inner membrane, which surrounds the cytoplasm, and the outer envelope, which enclose the periplasm and acts as a barrier to the environment [29]. The general secretory pathway transports proteins to the periplasm. Proteins and other biomolecules targeting the mechanism of Gram-negative bacteria is too difficult, because it has to pass two hydrophobic barriers, the inner and outer membrane (IM or OM), before they achieve their final destination [29,30] Obviously, during evolution bacteria have to find lots of solutions to the same fundamental problem. These mentioned the Type 1 to 7 secretion systems and it is included that further systems will be discovered in the future. Updating secretion systems inside the bacteria is an essential part of defence and survival of the fittest of bacteria. Type 1, Type 3 and Type 4 (conjugation-like systems) are the part of one class and deal with onestep secretion direct to the medium, while Types 2, 4 and 5 (auto transporters) are the examples of two-step procedure to shuttle the transport substrate to the outside [30,31]. Most secretion systems are principally based on membrane transport mechanisms. Type 4 secretion systems intriguingly have a dual role. So, here we will discuss all secretion systems in brief and try to connect evolution with T7SS. Type 1 secretion system is an important example of the haemolytic toxin HlyA secretion from uropathogenic strains [31]. Type 1 systems are typified by the haemolysin secretion system from *E. coli* adding this functionality to *E. coli* requires three transport proteins and ATP binding ABC transporter an adaptor protein that bridges both inner and outer membranes [32]. Outer membrane pore secretion of a protein through this apparatus doesn't involve any periplasmic intermediate, the protein is shuttled straight through the channel and targeting signal is a short 20 amino acid peptide on c-terminus of protein [32,33].

Type 1 secretion system

T1SS is the combination of three indispensable membrane proteins, two inner membrane proteins and one outer membrane protein, T1SS is achieved by a single step directly from the cytosol to the extracellular space [33,34]. The inner membrane proteins are the members of ABC transporter family and membrane fusion protein families (MFPs), respectively, while the outer membrane component belongs to porin-like protein [35,36]. Gathering of the three proteins are operated by accretion of the transport substrate (HlyA) in the cytoplasm, to form a continual channel from the inner membrane, fly covering the periplasm and finally to the outside [37].

Type 2 secretion system

T2SS system is present in gram negative bacteria include *Vibrio cholerae*, enter-toxigenic and enter-haemorrhagic *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Legionella pneumophila* and *Yersinia enterocolitica* [38]. *Aeromonas hydrophila*, a pathogen of fish and *amphibia Vibrio cholerae,* enterotoxigenic and enterohaemorrhagic *Escherichia coli* (ETEC and EHEC, respectively), *Pseudomonas aeruginosa, Klebsiella spp, Legionella pneumophila* and *Yersinia enterocolitica* [38,39]. T2SS is useful for translocation of unfolded proteins from periplasm through outer membrane and into extracellular milieu in gram negative bacteria. T2SS is present in both pathogenic and non-pathogenic species of gram negative bacteria. Plant pathogens that also contain T2SS include *Dickeye dadantii, Erwinia carotovora* and *Xanthomonas campestris* among others [40]. Non-pathogens with a T2SS gene cluster include metal-reducing bacteria such as *Shewanella oneidensis*. It has also become ap-

parent that the T2SS, the type IV pilus system (T4PS) [40,41]. The T2SS are sophisticated multiprotein machinery containing 12-15 different proteins, it is generally encoded in a single operon [41]. T2SS was reported as a terminal branch of the general secretory pathway. T2SS is the protein complex of 40-70 proteins of 12-15 different types that have to come together to form final machinery [42]. Owing to this complexity, many questions regarding the biogenesis of the T2SS are still unanswered till date.

Type 3 secretion system

T3SS is important for interactions with host cell membranes in which virulence factors are directly injected into the host cell. T3SS is responsible for making better understanding about bacterial pathogenesis and developing possible antibiotics, which target T3SS components [43]. T3SS are native to many clades of bacteria and are usually associated with bacteria host interaction, in addition to directing proteins across to inner membranes. T3SS systems usually have the ability to secrete proteins across a host cell outer membrane, those hosts include plant cells, mammalian cells and different type 3 systems are specialized for host cell surface structure [44,45]. The genes of T3SS are usually encoded as clusters and contain around 20 proteins with extensive internal regulation; they are both evolutionarily and functionally related to flagella [45]. Flagella can be repurposed for T3SS in *E.coli*, The signal sequence does not appear to map onto a primary sequence instead it is propagated in 3D structure of the secreted proteins [46]. However, it can often target other proteins for secretion by fusion to a native effector that is normally secreted by T3SS and like T1SS. Other additional T3SS secretion system information refers to table.1.

Injectisome

Injectisome is a major structural component of the type III secretion system, it is a multiprotein structural complex composed by extracellular, envelope-associated, and cytoplasmic elements or substructures [47]. Each element facilitates different functions in a separate and scientific manner. It is reported in many Gram negative bacteria that contain a sustained long-standing close relationship with eukaryotes. Type III secretion machinery most of works strongly depends upon injectiosome. It acts as a single functional structural unit in T3SS and its separation into different subcomponents, while useful, is somewhat arbitrary [48,49]. Till date injectisome structural organization is not fully characterized and it is too confusing. Lots of researchers are working on finding the full structural organization (specific components) of inject some with universal nomenclature. Furthermore, the plethora of gene names has made comparison of systems across species somewhat challenging; thus, when referring to specific components of the injectiosome [49]. The assembly of injectisome are made by export apparatus components SctR, SctS, and SctT and SctU and SctV (two additional membrane proteins) [50]. Injectiosome overview is summarized in table.1 with additional information.

Type 4 secretion system

T4SS resembles the conjugation machinery of bacteria. T4SS is capable of transporting both Proteins and DNA [51]. Through T4SS Agrobacterium tumefaciens is introduced Ti plasmid and proteins into the plant host that causes crown gall disease [52]. T4SSs is the type of highly diverse superfamily of secretion systems reported in many bacterial species. T4SS diversity are responsible for recognition and translocate single-stranded (ss) DNA substrates (conjugation machines) to bacterial recipients, deliver effector proteins (effector translocator systems) to eukaryotic target cells, exchange DNA with the milieu, contribute to biofilm development, and deliver a killing toxin to bacterial neighbors [53,54]. Many pathogenic bacteria are used T4SSs as virulence determinants aiding their colonization and propagation in the eukaryotic host. Most if not all T4SS-carrying species alternatively utilize these machines to disseminate mobile genetic elements, often rife with antibiotic resistance genes and other fitness traits, for enhanced survival in clinical and other environmental settings [55]. T4SS overview is summarized in table.1.

Type 5 secretion system

T5SS is referred to as an auto transporter system, this system was first reported as an auto transporter of proteins. It can transport the proteins in an automatic way [56]. Proteins that are being transported through this system have capability to form a beta barrel with their C- terminus which inserts into the outer membrane, allowing the rest of peptide (the passenger domain) to reach outside of the cell [57]. Autotransporters are sometimes cleaved, freeing the passenger domain outside the membrane and leaving the beta barrel domain in the outer membrane. Remnants of the autotransporters are trusted to be porins which form similar beta barrel structures. T5SS systems come in two types autotransporters proteins involve a single two domain polypeptide one of these domains is an outer membrane barrel protein and other is a passenger protein a well-studied example of this is Ag43 protein in *E.coli* [57,58]. The process begins with *Sec* secretion to periplasm as an unfolded protein it then spontaneously inserts itself into outer membrane pulls passenger domain through to cell surface, some auto transporter proteins remain this way while others undergo cleavage of passenger to secreted state both proteases and spontaneous processes can cause cleavage of extracellular domains from membrane bound barrel [59]. So, sometimes autotransporters result in secretion and other times they result in displaying two partner secretion systems that are very similar to autotransporters, but each is composed of two genes like autotransporters. Tps systems involve dedicated secretion proteins for singular proteins [60]. While they are genetically encoded as two proteins instead of a fusion protein, Tpp transport results in secretion of passenger protein. T5SS other additional information is mentioned in table.1.

Type 6 Secretion System

T6SSs was first found in two bacterial strains *Vibrio cholerae* and *Pseudomonas aeruginosa* [61]. T6SSs secreted proteins lack N- terminal signal sequences and can't enter in the *Sec* pathway. T6SS are now known to be widespread in Gram negative bacteria. T6SS acts as a protein that is found in Gram-negative bacteria and is used to translocate effector proteins directly into neighbouring cells [62,63]. It presented a versatile bacterial weapon that delivers effectors into distinct classes of target cells, playing key roles in inter-bacterial competition and bacterial interactions with eukaryotic cells [63]. This versatility is underpinned by the ability of the T6SSs to deliver a vast array of effector proteins, with many distinct activities and modes of interaction with the secretion machinery [64]. Ongoing work on T6SS has highlighted the importance and diversity of interactions mediated by T6SS within polymicrobial communities, and offers new molecular insights into effector delivery and action in target cells [64]. T6SS additional information is summarized in table.1.

Type 7 Secretion System

T7SS was commonly discovered in Gram positive actinobacteria and in firmicutes like *S. aureus*. *S. aureus* can code a single T7SS, which plays a very pretty crucial role for virulence in mouse models of infection [65]. The T7SS is mostly characterized in the low G + C Grampositive phylum Firmicutes that have an evolutionarily distant subfamily of this pathway referred to as T7SSb. The Type 7 Secretion system (T7SS) was reported in different strains of *S. aureus* like COL, RN6390, USA300 and Newman. T7SS has four integral membrane proteins (EsaA, EssA, EssB and EssC) (table-1), two cytosolic proteins (EsB and EsaG), five secreted substrates (EsxA, EsxB, EsxC, EsxD and EsaD), and EsaE, which interconnect with the T7SS substrates to attack them to the secretion system [66,67]. EssA, EssB and EssC are well reported proteins in secretion of *S.aureus*. The synthesis of T7SS proteins are activated by *S. aureus* interaction with host tissues like blood serum, nasal secretions and pulmonary surfactant. T7SS secretory proteins are responsible for *S. aureus* virulence, environmental adaptation and competition to other bacteria. Virulence proteins with lack of cleavable Nterminal signal peptides are also secreted by T7SS in *S. aureus* [67]. T7SS is a combination of multiple proteins of *S. aureus* dedicated to the synthesis of several virulence proteins during host interaction. Most substrates of T7SS exist in α helical structure and might be variable in size. Lots of proteins (EsxA & EsxB), that are belongs to WXG100 Protein superfamily are also secretory part of T7SS. WXG 100 superfamily proteins are present in the form of helical hairpins, that contains conserved WXG amino acid motif [68]. These WXG-100 proteins are secreted by *S. aureus* in the form of folded dimers. Recently, EssH, a peptidoglycan hydrolase enzyme within *S. aureus*, was described to regulate T7SS transport over the bacterial cell wall envelope [68,69]. The molecular pattern of *S. aureus* type 7 secretion system (T7SS) has not yet been completely known. According to current studies haemin (haem B) enhances T7 secretion in *S. aureus* (RN6390) strain. In type 7 secretion systems EsaA, EssA, EssB and EssC are the main part of the secretion machinery, with the EssC substance of central membrane transporter. In *S.aureus*, three additional membrane proteins-EsaA, EssA, and EssB-function alongside the EssC ATPase to mediate T7 protein secretion [69]. *S. aureus* EssC proteins contain 1480 amino acids in length and it has a common organization domain. EssD is secreted by *S. aureus* ESS, EssD acts as a nucleus to cleave DNA. EssD nuclease activity is blocked by EssI in bacterial cytoplasm, EssI is a small cytoplasmic protein that is attached with the nuclease domain of EssD and whose gene is located adjacent to essD [69,70]. During host and *S. aureus* interaction EssD stimulates immune signalling to support the pathogenesis of *S. aureus* infection. In T7SS, EsaD proteins are made detoxified during its biosynthesis with help of its counterpart antitoxin EsaG and furthermore EsaD makes a complex with EsaG and then binds with EasE [70]. The EsaE portion is bound to EssC, which is an ATPase switch enzyme of T7SS protein complex. EssC membrane bound ATPase protein in *Staphylococcus aureus*, is the part of the heart of secretion machinery [70]. EssC proteins are showing different variants (EssC1-EssC4) within different strains of *S. aureus*; those variants are responsible for Cterminal region variability. During secretion EsaG proteins are left in cytoplasm and only EsaE and EsaD both are proteins secreted together [71]. Some strains of *S. aureus* can't synthesize EsaD protein, but two copies of EsaG like proteins are synthesized instead. *S. aureus* pathogenesis totally depends upon its virulence factors and *S. aureus* have developed various systems by the help of virulence proteins, these proteins can be secreted into the surroundings or injected inside the host cells [71,72]. Structural discovery suggested that EssC, a potent family member of the AAA+ Superfamily, proteins are important for the formation of secretion pore [72]. Most of *S. aureus* strains are showing sequence variability in the lots of C- terminal ATPase domain of EssC and proof suggested that this part of protein participates in substrate recognition. Few strains of *S. aureus* are responsible for the large number of nuclease toxin secretion through T7SS, which is very potent and highly functional against chromosomal DNA. S. aureus can block the activity of nuclease by producing an antitoxin for self-protection, anti-toxin tightly binds to nuclease and stops its catalytic activity [72,73]. Nuclease also makes an interaction with a specified chaperone that participates to attack the nuclease anti-toxin complex to the secretion network [73,74]. At the time of Type 7 secretion system (T7SSs), the Anti toxin is most probably separated from the nuclease and remains inside the cell while the nuclease is secreted [74]. Sub culture experiments give important information about T7 based nuclease mediated competition between closely related *S. aureus* strains, which play an important role during the colonization process. As per current studies all researchers are doing work on the identification of T7 substrate protein, this protein encoded by all strains of *S. aureus* as well as in *Enterococci* and *Listeria*. T7 substrate protein contains a toxic C-terminal domain that is responsible for depolarization of bacterial cytoplasmic membrane [74]. Toxic activity is stopped through a membrane bound anti toxin. Zebrafish hindbrain ventricle infection model is suitable for the demonstration, T7 substrate protein is essential for complete virulence. T7SS system overview is summarized in table.1 with additional information.

Sortase

Sortase is a group of enzymes synthesized by gram positive bacteria and occasionally synthesized by gram negative bacteria. Sortase enzymes are cysteine peptidase and belongs to MEROPS peptidase C60 family [75]. These enzymes are responsible for the modification of surface proteins by cleaving and recognizing a carboxyl terminal sorting signal. The most of substrates of sortase enzymes are consist recognition signal motif LPXTG (Leu-Pro-Thy-ThrGly) with highly hydrophobic transmembrane sequence followed by a bunch of basic residues such as arginine [76]. Cleavage by sortase enzyme perform between Thr and Gly with transient attachment through Thr residue to active Cys residue, followed by transpeptidation that attaches protein covalently to cell wall components [77]. Cell wall LPXTG mediated decoration are not reported till date. Although sortase A is a "housekeeping" sortase typically perform cleavage on many protein target and other form of sortase recognized variant forms of cleavage motif and catalyse assembly of pilins into pilli [77,78]. *S. aureus* sortase has transpeptidase activity that is binds surface of proteins on cell wall and it is perform cleavage between Gly and Thr of LPXTG motif [78]. *S. aureus* sortase participate in amide bond formation between carboxyl group of threonine and amino group cell wall peptidoglycan [78]. Sortase enzymes are highly sensitive to newly generated antibiotics. Sortase additional information is summarized in table 1.

Biological role of sortase: The attachment of substrate proteins on bacterial cell walls are done in the presence of sortase enzymes, pilins and adhesion mediated large surface glycoproteins [79]. Such types of proteins are valuable for virulence of bacteria, infection and colonization by pathogens.

Surface proteins are not only specific for promotion and in-

teraction between invading pathogens and animal tissues, but also provide ingenious pathways for bacterial masking from host immune response [79,80]. In the case of *S. aureus* protein a, antibodies are captured on the microbial surface and camouflage bacteria during invasion of host tissues. *S. aureus* mutants do not have srtA gene, fail to anchor and show few surface proteins, are impaired in ability to cause animal infections [81]. Sortase performs its own function on surface proteins that are initiated into the secretion (*Sec*) pathway and have their signal peptide eliminated by signal peptidase [81]. Two sets of sortase and secretion genes are encoded by the *S. aureus* genome. It is imaginable that *S. aureus* has evolved more than one pathway for transport of 20 surface proteins to cell wall envelopes (table-1). Exosortase and archaeosortase can perform functional analogue, while not in any way homologous to sortase.

Type 8 secretion system: The T8SS is reported as an extracellular nucleation precipitation (ENP) pathway involved in the outer membrane secretion [82]. T8SS contained an assembly of thin and aggregative pilli called curli. Curli are made of amyloid fibers and most of the time it is present in the form of functional amyloid fibers. They play a very pretty crucial role in cell aggregation, bacterial adhesion and the formation of mature biofilms [82,83]. They actually change bacterial surface properties thereby enhancing adherence and attachment to surfaces. In the course of sessile development they constitute a significant part of the proteinaceous component of the biofilm matrix [83]. During infection curli mediates bacteria and host cell interactions. T8SS additional information is summarized in table.1.

Type 9 secretion system: The T9SS is a well-known Por (porphyrin accumulation on the cell surface) secretion system and it is found in *Porphyromonas gingivalis* and *Flavobacterium johnsoniae* [84]. T9SS appears restricted to members of the phylum Bacteroidetes. T9SS play an important role for bacteria to surface colonization process on host cell and it is also required for secretion of cell-surface motility adhesins, namely SprB (colony spreading protein B) and RemA (redundant motility protein A), but also some hemin-binding proteins [84,85]. The cell surface adhesin SprB allows attachment to the substratum but is also required for efficient gliding as it is propelled along a closed helical loop track, generating rotation and translation of the bacterial cell. While SprB is involved in movement over agar, RemA is involved in movement over surfaces coated with F. johnsoniae polysaccharide [85]. Gliding involves the rapid movement of the semi redundant motility adhesins SprB and RemA along. T9SS additional information is summarized in table.1.

The role of T7SSs for *Staphylococcus aureus* to cause infection in humans

The *S. aureus* infection-causing mechanism in the human host is highly scientific because its virulence factors are evading and masking the activity of the host immune system. Clinical management of *S. aureus* infection at the community level is too difficult because it has a prevalence of multi drug resistance [86]. *S. aureus* is extremely common and about a quarter of the population is colonized by it, usually in their nostrils, groin, armpits, and other parts of skin . As per an idea 30% of the population is world-wide colonized by *S. aureus* [86,87]. But, most of the time it's a normal part of our skin flora, and doesn't cause trouble. *S. aureus* also contains adhesion protein molecules and carbohydrates that bind on two latches onto cells within the human body allowing it to invade the cell, these adhesions include fibronectin binding protein and collagen binding protein. In virulence pathway of *S. aureus* host specific cis unsaturated fatty acids plays important role as the major stimulatory factors [87]. The synthesis of virulence proteins through T7SS is required to host fatty acid internalization into bacterial biosynthetic pathways by *S. aureus* fatty acid kinase (FAK) complex and FaKA is important for virulence [87,88]. The internalized cis unsaturated fatty acids are reduced *S. aureus* membrane fluidity and make alterations to membrane dynamics are partially responsible for T7SSs expression. Different types of *S. aureus* cells sense the host environment and modify suitable virulence pathways on the basis of their T7SS molecular mechanism [88]. The skin flora is a complex ecosystem of different bacterial species and occasionally, *Staph aureus* can begin to dominate that ecosystem. In individuals that have *Staph aureus* colonization, a number of factors like pH, humidity, sweat levels of the skin, as well as presence of other bacteria on our skin, all affect the amount of *Staph aureus* that's present. If more and more *Staph aureus* is around on the skin, it begins to penetrate through tiny micro fissures in the skin, like get with eczema, as well as larger breaks in the skin like might get after shaving [88,89]. It's particularly troublesome in terms of causing wound infections where there is a large break in the skin either from trauma or after a surgery. So low levels of *staph aureus* with intact skin leads to colonization, whereas high levels of *Staph aureus* with breaks in the skin lead to infections. When staph aureus invades into the skin it can lead to localized skin infections like a pimple which can evolve in a furuncle, or a boil [89]. A bunch of furuncles clustered together make a carbuncle. There can also be diffuse skin infections, like superficial impetigo which is an infection of the epidermis, or deeper reaching cellulitis, which is an infection of the dermis and can spread over larger surfaces rapidly [89,90]. If the infection goes deeper, it can develop into a subcutaneous abscess - a collection of pus that's walled off and sometimes develops thin walls within it - called septations. These abscesses can occur all over the body including in the mouth where they are called dental abscesses, and they can develop within various organs like the liver, kidney, spleen and brain [91]. Abscess of the skin is a common infection characterized by localized accumulation of neutrophils with tissue necrosis and it's mainly caused by the bacteria *S. aureus*. If the infection is overlying a muscle, it can spread into the muscle causing pyomyositis [91,92,93]. If it gets into the bone, it can cause osteomyelitis and if it gets into the joint space it can cause septic arthritis. *Staph aureus* gets into the bloodstream, it can cause a septic thrombophlebitis - an infected blood clot. In addition, bacteria in the blood are called bacteraemia and it can lead to a number of serious health problems [92,94]. There is typically a widespread immune reaction that causes the blood vessels to expand and the blood pressure to fall. The result is hypotension and poor perfusion to various organs - a process called sepsis. Once it's in the blood, *Staph aureus* can also get to various parts of the body. It can get into the central nervous system - causing bacterial meningitis or an epidural abscess in the spine [92,94].

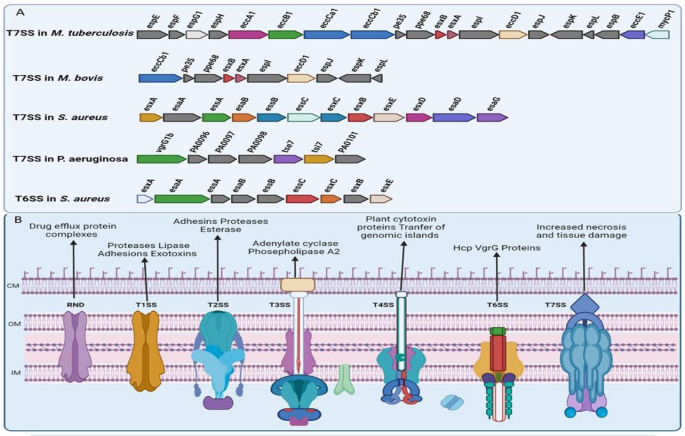

Figure 1: Mechanisms of bacterial secretions systems in different gram positive and gram negative bacterial cells.

Mechanisms of bacterial secretions systems in different gram positive and gram negative bacterial cells to the TssB–TssC tail sheath and the haemolysin co-regulatedprotein inner tube through the baseplate. The tail sheath is ~25 times longer than depicted, and its disassembly involves the ClpV ATPase. The T7SS of diderm-LPS bacteria is the chaperone-usher pathway A. Genetic arrangements of four chromosomally encoded secretion system gene clusters in gram negative and gram positive bacteria [86,87,88]. B. structural organization of bacterial secretion system. Resistance–Nodulation–Division (RND) pumps and the Type I Secretion System (T1SS) share an Outer Membrane (OM) TolC component, a periplasmic membrane fusion protein (MFP) and an inner Membrane Component (IM) that supplies energy for transport [34,36]. The T2SS consists of an OM complex, a periplasmic pseudopilus and an IM platform that is tightly associated with the cytoplasmic ATPase GspE [38,40]. The T3SS cytoplasmic domain includes a hexametric ATPase (InvC) and a sorting platform [45]. The secretin InvG extends from the bacterial OM to the IM base, forming a series of protective rings that surround the needle. Outside the bacterial cell, the needle tip complex mediates – host cell contact and assists in pore formation.The T4SS is composed of three ATPases that, together with VirB3, VirB6 and VirB8, form the IM complex. VirB7, VirB9 and VirB10 form the core–OM complex, with VirB10 extending from the IM to the OM [53]. The conjugative pilus is composed of VirB2 and VirB5. The T6SS TssJ–TssL–TssM membrane complex is connected.

Conclusion

The secretion systems in bacteria are protein complexes present on the cell membranes of bacteria for secretion of pathogenic proteins. Specifically, they are the cellular devices used by pathogenic bacteria to secrete their virulence factors (mainly of proteins) to invade the host cells. There are two pathways which are the bacterial secretion systems most commonly used to transport proteins across the cytoplasmic membrane: the general secretion (Sec) and twin arginine translocation (Tat) pathways. The secretion system exports several proteins that are pivotal for bacterial virulence. Bacterial pathogens utilize a multitude of methods to invade mammalian hosts, damage tissue sites, and thwart the immune system from responding. One essential component of these strategies for many bacterial pathogens is the secretion of proteins across phospholipid membranes. Secreted proteins can play many roles in promoting bacterial virulence, from enhancing attachment to eukaryotic cells, to scavenging resources in an environmental niche, to directly intoxicating target cells and disrupting their functions. Nevertheless, structural and molecular advances in the past few years have greatly improved our mechanistic understanding of bacterial secretion systems and have led to the emergence of new drug design efforts. Although secretion systems are essential for bacteria to adapt to the wide range of environmental conditions that they encounter in nature, their diversity in terms of structures and mechanisms of action poses challenges for the development of vaccines or ant virulence compounds that target these systems. As we discussed in this review, these secretions of bacteria may be transferred out of the bacterial cytoplasm through a variety of mechanisms, usually involving the use of dedicated protein secretion systems. For this reason, the study of secretion systems has been an important focus in the field of bacterial pathogenesis. The remaining in this review section will offer a more detailed focus on the molecular and functional characteristics of some of these secretion systems in gram negative and gram positive bacterial cell.

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