Bacterial peptide transporters: Messengers of nutrition to virulence

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ABSTRACT
Bacteria possess numerous peptide transporters for importing peptides as nutrients. However, these peptide transporters are now consistently reported to play a role in the virulence of various bacterial pathogens. Their ability to transport peptides has implications in antibacterial therapy as well. Therefore, it would be instrumental to have complete knowledge about the role of peptide transporters in mediating this cross connection between metabolism and pathogenesis. Studies on various peptide transporters in bacterial pathogens have improved our understanding of this field. In this review, we have given an overview of the functioning of bacterial peptide transporters and their contribution in virulence of major bacterial pathogens.

Potential of peptide transporters in antimicrobial therapy

The general strategy of complete elimination of the pathogen for antimicrobial therapy is associated with the drawback of emergence of resistance. An alternate strategy involves targeting of metabolism associated genes. This may slow down the growth but does not affect survival and therefore leave little scope for the development of resistance. Metabolism associated genes of pathogens have been consistently linked with virulence of major pathogens, such as, role of carbon metabolism related pathways like glycolysis and TCA cycle in virulence of Salmonella Typhimurium and requirement of metabolism associated pathways for protection of Mycobacterium tuberculosis from host immune system. Salmonella is even known to modulate host to exploit the limited supply of nutrients.

Coupling of nutrition with virulence reveals metabolism associated genes that can be targeted for antimicrobial therapy. Peptide transporters represent one such class of genes known to be required for virulence of Gram negative as well as Gram positive pathogens. Uptake of extracellular peptides is important for the growth of bacteria in peptide rich medium as they are a major source of amino acids, carbon and nitrogen. Peptides can also perform several alternate cellular functions ranging from modulation of stability of membrane proteins to regulation of function of 2 component systems. This has led researchers to search for novel transporters in the genomes of pathogens like M. tuberculosis.

Hijacking of bacterial transporters for delivering antimicrobial agents is an upcoming strategy to circumvent infectious diseases. They can also act as potential therapeutic targets for treating infectious diseases or development of vaccines. Emergence of antimicrobial peptides as potent therapeutic agents against bacterial pathogens adds to the importance of these transporters in treating infectious diseases. Clearly, the knowledge of peptide transporters and their connection with virulence is essential in microbiological research today. This review gives an overview of the role of peptide transporters in virulence of major pathogens while describing the distinct features of the major categories of peptide transporters on one platform. It further describes the methodology required to identify and characterize unknown peptide transporters and their regulatory network in the context of pathogenesis.

The distinct mode of function of bacterial peptide transporters

Peptide transporters are located in the plasma membrane of Gram positive bacteria and inner membrane of Gram negative bacteria to acquire specific peptides from the periplasm. There are 2 major categories of peptide transporters.
transporters known so far depending on the mode of transport. The proton motive force driven transporters (POT or PTR family transporters) capitalize on import of protons for the transport whereas the ATP binding cassette containing transporters (ABC transporters) hydrolyse ATP by coordination between multiple proteins (Table 1). The ability of these proteins to transport peptides is demonstrated frequently.

**Proton coupled peptide transporters**

The proton coupled transporters are also known for their pharmacological importance as they aid in uptake of drugs that have steric resemblance with substrate peptides.

They belong to the major facilitator family (MFS) of transporters as they typically contain 12–18 transmembrane domains which derive their energy of transport from the import of proton. Despite their huge size (600 to 900 amino acids), they are commonly reported to transport small peptides like di- and tripeptides (Table 1). The ability of these proteins to transport alanine as well as trialanine was also reported to transport tetraalanine, whereas YjdL from *Escherichia coli* was reported to transport tetraalanine, whereas YjdL could transport the amino acid alanine as well as trialanine. Therefore, these transporters behave promiscuously toward their substrates, while being conserved in their structure, from bacteria to mammals.

Most of the knowledge of the functioning of the proton family of peptide transporters comes from the studies on the mammalian peptide transporters PepT1 and PepT2. While PepT1 is present in the small intestine to obtain broad range of peptides from dietary proteins, PepT2 works in kidney to prevent loss of specific substrates, while being conserved in their structure, from bacteria to mammals.

| mRNA          | Functional protein | Source of energy for transport | Common peptide substrates | Proton coupled peptide transporters | ABC peptide transporters |
|---------------|--------------------|-------------------------------|---------------------------|------------------------------------|--------------------------|
| Monocistronic | Single protein as monomer | Proton import                 | Dipeptides, Tripeptides   | PTR peptide transporters           | ABC peptide transporters |
| mRNA Functional protein | Source of energy for transport | Common peptide substrates | Proton coupled peptide transporters | ABC peptide transporters |
are multi-subunit protein pumps that couple ATP hydrolysis with the movement of peptides across the inner membrane. In Gram negative species, the substrate peptides are usually accessible through an extracytoplasmic receptor, called solute-binding protein (SBP), whereas the Gram positive species contain a lipoprotein subunit that extend beyond the extracellular face of the cell membrane. These transporters are also involved in peptide export as observed in the case of pheromone peptide secretion by ABC transporter in Enterococcus faecalis, required for conjugation and biofilm formation.

A typical ABC transporter has 4 functional domains or subunits including 2 nucleotide binding domains (NBD1 and NBD2) and 2 transmembrane domains (TMD1 and TMD2). NBDs and TMDs are held together with the help of a terminal coupling helix of the TMDs. In prokaryotes, these domains are synthesized from polycistronic mRNA and can be present as individual domains or in fused form of NBD-TMDs. For example, in E. coli, the TMDs and NBDs are fused as TMD-NBD-TMD-NBD in the exporter protein haemolysin B (HlyB). In eukaryotes, the transporter is synthesized from a monocistronic mRNA mostly as a single peptide chain containing all 4

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**Figure 1.** Proton coupled peptide transporters (PTR or POT transporters). A. General structure of PTR transporters. A representation of single PTR transporter showing number of transmembrane domains (TM 1–12) spanning the inner membrane and the final arrangement of these domains into monomeric functional unit. The arrangement of the transmembrane domains is not accurate. For exact structure of PTR transporters refer to Newstead, S. 2015 [27]. B. Mechanism of peptide transport by PTR transporters. The outward open conformation allows for the binding of proton and the peptide. Upon binding of the proton to TM7, the peptide binds to TM 1 and 10, forming the occluded conformation. Finally the inward open state leads to release of peptide and proton in the cytoplasm.
domains, or as homodimeric or heterodimeric halves. The TMDs or the integral membrane protein subunits of ABC exporters differ in the number of transmembrane segments. Each of the TMDs or membrane-spanning domains (MSDs) typically contains 6–10 membrane-spanning $\alpha$ helices constituting each TMDs are shown in enlarged view, showing a rough arrangement of the transmembrane domains. B. Mechanism of peptide transport by ABC transporters in Gram negative bacteria. The outward conformation allows the binding of 2 ATP molecules on the cytosolic face and SBP bound peptides on the extracellular face that leads to formation of the occluded conformation. ATP hydrolysis changes the conformation to the inward open state releasing the peptide in the cytoplasm.

Link of peptide transporters with virulence

Gram positive pathogens

Of the many ABC and PTR transporters known, only few ABC peptide transporters are known to affect pathogenesis in major Gram positive pathogens. To highlight the connection between nutritional peptide transporters and
virulence, we have excluded the examples of bacterial pheromone peptides. *Streptococcus* sp. represents the group of opportunistic Gram positive pathogens that cause diseases like meningitis, pneumonia and pharyngitis. The significance of peptide transporters in virulence of various species of *Streptococcus* has been demonstrated in the past. The peptide permeases Ami (or AmiACDEF) and PlpA affect recognition of host cell receptor glycoconjugates GalNAcβ1-4Gal and GalNAcβ1-3Gal by *Streptococcus pneumoniae*. \(^{48}\) Genome wide Tn-seq screen revealed that *S. pneumoniae* requires its peptide transport system AmiACDEF for survival in human saliva, an essential strategy for transmission. \(^{49,50}\) Regulation of transcription of the adherence mediating cell surface polypeptide CshA by hexa-hepta peptide permease HppA in *S. gordonii* shows another example. \(^{51}\) The Gram positive cocci, *S. agalactiae*, responsible for causing major invasive infection in human newborns, requires 4 peptide permeases for attachment to the host cells and to express its virulence determinants. \(^{14}\) In *S. pyogenes*, Dpp transporter system controls the expression of cysteine protease SpeB, a virulence factor required for attachment to the host. \(^{52}\)

The pathogen *Staphylococcus aureus* possesses one oligopeptide transporter system Opp and one di- as well as tripeptide permease namely DtpT. \(^{53}\) *S. aureus* was found to be attenuated in multiple animal models, after mutation in the oppC gene, a permease subunit of Opp peptide transporter assembly. \(^{54}\) In *Corynebacterium pseudotuberculosis*, which causes caseous lymphadenitis (CLA) in small ruminants, the peptide transporter system Opp is required for adhering to host cells. \(^{15}\) The oligopeptide permease systems, Opp and App, of the gastrointestinal pathogen *Clostridium difficile*, transport oligopeptides for nutrition. These transporters were found to inversely regulate sporulation, and thereby virulence, of *C. difficile* in hamster model. Unlike other sporulating Gram positive pathogens, *C. difficile* genome has not revealed the presence of any pheromone peptides in its genome. It is speculated that oligopeptides taken up as nutrients are responsible for this inverse regulation of virulence of *C. difficile*. \(^{55}\) In case of the facultative intracellular pathogen *Listeria monocytogenes*, the gene oppA is required for survival inside macrophages besides providing nutrition. \(^{56}\)

**Gram negative pathogens**

Gram negative bacteria, like *E. coli* and *Salmonella* sp. can utilize small peptides for carbon and nitrogen sources, \(^{57}\) imported by transport systems like Dpp, Tpp and Opp. Dpp and Tpp are specific for dipeptides and hydrophobic tripeptides, whereas Opp can transport oligopeptides. \(^{30,58,59}\) While Dpp and Opp belong to ABC transporters, Tpp belongs to PTR family of transporters. Opp is the major peptide transporter in *E. coli* and *S. Typhimurium*, as strains with mutation in Opp were unable to transport peptides, whereas, strains with mutation in Dpp and Tpp, did not show any defect in transport of peptides. \(^{57}\) Surprisingly, there is poor information available on the role of peptide transporters in the virulence of Gram negative pathogens, where most of the knowledge comes from the studies carried out on *S. Typhimurium* (Table 2).

The enteropathogen *Salmonella* sp. colonizes the intestine of the host wherein the digestion of dietary proteins by host generates large amount of peptides. In fact, the PTR transporters are reported to be highly induced in the gut of Atlantic salmon. \(^{60}\) This gives the hint that bacteria residing in the gut may also express their counterpart PTR transporters to import peptides. *In vitro*, in peptide rich medium LB, the virulence associated genes encoded in the pathogenicity island SPI 1, are expressed only during the transition between exponential and stationary growth phases, i.e., late exponential phase. \(^{61}\) The stationary growth phase dependent expression of virulence factors is accompanied by decrease in amino acid biosynthesis. \(^{12}\) However, the concentration of amino acids is maintained in the stationary phase as well as during the later stage of infection inside host cell. \(^{12}\) This suggests parallel import of amino acids or peptides containing the required amino acids. Hence, peptide transporters of *Salmonella* may provide for the amino acids required for survival inside host and thereby play a role in the establishment of infection. The PTR transporters known in *S. Typhimurium* include tripeptide transporter (tpp) \(^{58}\) and carbon starvation genes *i.e.* *cstA* and *yjiY*. \(^{13}\) While CstA and YjiY are required for virulence of *S. Typhimurium* in *Caenorhabditis elegans* and mouse model respectively, \(^{13,62}\) tripeptide permease (TppB) is shown to be required for resistance against antimicrobial peptides. \(^{58}\) YjiY affects the transcription of flagellar class III genes, which explains the mechanism behind the reduced colonization of *yjiY* mutant in mouse model. \(^{13}\) However, the role of CstA in colonization of host is not addressed completely. The ABC peptide transporter system Dpp codes for proteins that can act as chemoreceptors and help the bacterium to move toward the source of peptides, showing peptide chemotaxis. \(^{30}\) Other ABC peptide transporter systems YejABEF and SapABCDF confer resistance against antimicrobial peptides. \(^{63,64}\) The probable mechanism behind this kind of resistance is that the antimicrobial peptides are transported inside cytoplasm, away from their targets and
exposed to digestion inside the cytoplasm. The YejABEF operon also plays role in the virulence of S. Typhimurium in mouse model.63

The Gram negative diplococcus Moraxella catarrhalis causes otitis media in children and exacerbations of chronic obstructive pulmonary disease in adults. The oligopeptide transporter system Opp was found to be required for nutrition as well as fitness of M. catarrhalis in the host animal.45 Campylobacter jejuni, another Gram negative enteropathogen, requires peptide transporters for transport of peptides as a compensation for restricted growth in the host.66 Therefore, it is safe to say that peptide transporters in Gram negative pathogens hold importance in pathogenesis.

**Other bacterial pathogens**

**Mycobacterium tuberculosis**

As Mycobacteria cannot be categorized on the basis of Gram staining, it is discussed separately in this section. Mycobacterium tuberculosis poses biggest challenge in infectious diseases due to the emergence of multi drug resistant (MDR) and extensively drug resistant (XDR) strains causing tuberculosis. As a potential tool for delivery of therapeutic agents, transporters were identified across the genome of M. tuberculosis. Above 10% of a total of 171 transport systems were found to be peptide transporters in M. tuberculosis.17 The Opp system of peptide transport was shown to be required for chronic infection and expression of virulence associated surface lipids.67 The importance of peptide transporters in the pathogenesis of M. tuberculosis also gets emphasized by the finding that ABC peptide transporter system OppABCD is required for glutathione import in M. tuberculosis to regulate the detoxification of methyl glyoxal, cytokine release and apoptosis of macrophages.68

**Borrelia burgdorferi**

Borrelia burgdorferi is a spirochete that causes Lyme disease in human when bitten by the infested tick, Ixodes ricinus. The pathogen propagates through blood and lymphatics and causes persistent infection like M. tuberculosis. There is limited information available about the virulence factors in B. burgdorferi that help the pathogen to adapt to host environment. Transposon mutagenesis has been used to understand the biology and identify factors that contribute to virulence of B. burgdorferi.69 Such Tn-Seq data has revealed that the oligopeptide permease OppA2 is required for its infectivity in mouse model.70

**Regulatory network of peptide transporters in pathogenic bacteria**

There is limited information available about the environmental stimuli required for the expression of peptide transporters in pathogens. Commencement of nutrient starvation in stationary phase of growth is reported to induce carbon starvation (Cst) family of PTR peptide transporters, i.e., CstA and YjiY, via CAMP, in E. coli and Salmonella.13,71-73 In E. coli, the exponential phase specific global regulator protein CsrA negatively regulates the translation of CstA by binding to cstA mRNA.74 Nutrient

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**Table 2. Peptide transporters in bacterial pathogens.**

| Peptide substrates | Bacterial pathogen | Role in virulence |
|--------------------|--------------------|------------------|
| **PTR peptide transporters** | | |
| Tpp | Triptides | Salmonella Typhimurium | Antimicrobial resistance58 |
| CstA | Dipeptides & Tripeptides | Salmonella Typhimurium | Virulence in Caenorhabditis elegans62 |
| YjiY | Dipeptides & Tripeptides | Salmonella Typhimurium | Induction of class III flagellar genes and virulence in Balb/c mouse model13 |
| DtpT | Dipeptides & Tripeptides | Staphylococcus aureus | Unknown |
| **ABC peptide transporters** | | |
| Opp operon | Oligopeptides | Salmonella sp Mycobacterium tuberculosis | Glutathione import for methyl glyoxal detoxification, Induction of cytokine release and apoptosis in macrophages68 |
| | | Staphylococcus aureus | Bacteremia64 |
| | | Corynebacterium pseudotuberculosis | Adhesion to host cells15 |
| | | Clostridium difficile | Sporulation and virulence in hamster model15 |
| | | Listeria monocytogenes | Survival inside macrophages56 |
| | | Campylobacter jejuni | Growth inside host66 |
| | | Moraxella catarrhalis | Fitness inside host46 |
| | | Borrelia burgdorferi | Infectivity in mouse model39 |
| | | Staphylococcus pyogenes | Chemotaxis30 |
| Dpp operon | Dipeptides | Salmonella Typhimurium | Expression of cysteine protease62 |
| | | Streptococcus pneumoniae | Survival inside human saliva and transmission49,50 |
| | | Clostridium difficile | Sporulation and virulence in hamster model15 |
| Ami operon | Oligopeptides | Streptococcus pneumoniae | Antimicrobial resistance62 |
| App operon | Oligopeptides | Clostridium difficile | Survival inside human saliva and transmission49,50 |
| Yej operon | Oligopeptides | Salmonella Typhimurium | Antimicrobial resistance63 |
| Sap operon | Oligopeptides | Salmonella Typhimurium | Antimicrobial resistance64 |
| HppA | Hexapeptides | Streptococcus gordonii | Adhesion to host51 |
starvation also induces the expression of YehU/YehT, the only 2 component system known to regulate cst genes, in E. coli as well as in Salmonella. TtpB is transcriptionally regulated by leucine and anaerobiosis in Salmonella, whereas in E. coli, the ttpB homolog ydgR is regulated by EnvZ/OmpR 2 component system, showing its involvement in stress response. The stationary phase specific sigma factor RpoS, which is known to regulate several virulence factors required in mammalian host, induces the expression of OppA2 in B. burgdorferi.

The nutritional status is also required for the expression of ABC peptide transporters. For example, the amino acid leucine is known to induce the expression of OppA peptide transporter in E. coli. The exponential phase specific small RNA GcvB inhibits the binding of ribosome to the transcripts of ABC transporters OppA and DppA in S. Typhimurium. The expression of these peptide transporters may depend on the presence of specific substrate peptides. One example includes induction of dppA-E operon and repressed or unchanged expression of oppA1-F operon during growth of the fastidious organism S. agalactiae in media containing mixture of di- and oligopeptides. In case of S. pyogenes, repression of expression of peptide transporters dppA-E occur in free amino acid containing, di- and oligopeptide rich THY media.

Presence of peptides is also shown to induce the expression of peptide transporters in E. coli. One of the mechanisms behind this regulation is addressed in an industrially important species Lactococcus lactis, which is commonly studied for peptide transport. L. lactis depends on its peptide transporters DtpT from the PTR family and Opp and Opt from the ABC transporter family, for growth during the manufacturing of various fermented dairy products. The PTR transporter DtpT in Lactococcus lactis transports di- and tripeptides and is shown to be expressed constitutively, except for heat shock and acidic stress, showing its essentiality in the growth of L. lactis. DtpT also causes repression of proteinase PrtP. OptS, on the other hand, in response to the import of peptides from milk, regulates the expression of another peptide transport system Opp. The mechanism behind is speculated to be the binding of peptides or amino acids generated from these peptides to certain transcription regulators.

Clearly, the nutritional status of the bacteria and presence of peptide substrates or amino acids in the surroundings are important factors for the expression of peptide transporters. This gives an idea of the mode of function of peptide transporters in the context of virulence as well. For instance, the transcription of class III flagellar genes in Salmonella is shown to be dependent on the PTR peptide transporter YjiY (Table 2).

However, the role of peptides in regulating transcription of virulence associated genes is not established. The host certainly provides a plethora of peptide substrates to the pathogen during infection. Once peptides are being imported, they may get degraded to generate amino acids. Also, antimicrobial peptides produced by the host, upon bacterial infection, can be digested by the pathogen generating amino acids. Besides serving as essential building blocks of cells, these amino acids may also play a more direct role in virulence. One recent example includes the transcriptional regulation of the virulence factor MgtC by the amino acid proline in Salmonella. The oligopeptide permeases of Bacillus cereus and B. thuringiensis, regulate the expression of a virulence regulator plcR, by transporting the pentapeptide PapR through Opp transport system. The first residue of this peptide determines strain specificity, suggesting that amino acid composition of the peptide substrates matters for virulence. However, this is an example of phenome peptides which are different from the nutritional peptides in their origin and function. It is conceivable that peptide transporters affect pathogenesis probably by providing the regulatory amino acids. Therefore, similar phenomena should be displayed by amino acid transporters.

Several amino acid transporters are indeed reported to be related to pathogenesis. For instance, glutamine transporter GlnQ is required for the fitness of S. pneumoniae during infection. Mutation in GlnQ of group B streptococci, shows reduced attachment and invasion of the pathogen in vitro and reduced virulence in vivo. The transporter of the amino acid arginine, ArgT, is required for survival of S. Typhimurium inside host cells. Francisella tularensis depends on amino acid importers for adaptation to intracellular life. Transcriptome analysis shows that transporters of amino acids like glutamine and proline get upregulated in the uropathogenic E. coli during urinary tract infection. Therefore, there is certainly an overlap in the functions of peptide transporters and amino acid transporters. It is noteworthy that peptides provide a combination of amino acids and therefore may hold more importance during infection. Nevertheless, these transporters could also function completely independent of their peptide substrates to bring about virulence associated phenotypes. Therefore, a complex network of gene regulation connects peptide transporters with pathogenesis (Fig. 3).

**Characterization of unknown peptide transporters**

Keeping the medical importance of peptide transporters in mind, there is strong requirement of identification
and characterization of novel peptide transporters in pathogens. Genome of major bacterial pathogens may have several annotated peptide transporters which are yet to be characterized. Peptide transporters can be identified in the bacterial genome based on the similarity in the nucleotide sequence with previously characterized transporters in different bacterial species. Identification of transporters can be done with the help of Transporter Classification Database (TCDB; www.tcdb.org) along with prediction of transmembrane domains using programs like HMMTOP, TMHMM, MEMSAT3 and OCTOPUS. For the purpose of exploitation of these peptide transporters as drug delivery systems, it is necessary to have the knowledge of their peptide substrates. Structural studies of transporters in model pathogenic organisms would shed light on this. To establish the function of many unknown or putative peptide transporters, several direct and indirect peptide uptake assays have been designed in the past. Indirect methods include assessment of growth or expression of inducible enzymes in physiological auxotrophs in presence of candidate peptides. Phenotype microarray has turned out to be one of the most useful high throughput method for preliminary indirect assessment of function of peptide transporters. Direct methods like microscopic examination of fluorescently labeled peptides taken by bacterial cells, use of radiolabeled substrates and chromatography mediated analysis of the peptides present inside the cell would describe the function of the transporter more specifically. Use of proton ionophores or measuring alkalization as a result of proton translocation would be helpful to study PTR peptide transporters. Mammalian peptide transporters have been exogenously expressed in Xenopus oocytes to characterize their function and determine the nature of peptide substrates. Similar studies are carried out by expressing bacterial transporters in laboratory bacterial strains like E. coli BL21. Thus, with the help of these methodologies it is possible to characterize many unknown peptide transporters from the genome of pathogenic bacteria.

**Conclusion and future perspectives**

The research related to the link of peptide transport and pathogenesis is in its beginning phase, leaving us with several intriguing questions. For example, what are the...
environmental cues for the expression of peptide transporters by pathogens during infection? How do these transporters regulate expression of specific virulence associated genes and are these mechanisms conserved in all pathogens? How important is the sequence of peptide substrate for virulence? Interestingly, most of these transporters impact the step of adhesion of pathogen to the host, thereby its colonization, indicating toward a possible common modality of function. Although, the significance of peptide transporters in multiple steps of bacterial pathogenesis including adhesion, motility and biofilm formation, is reported, the mechanisms behind these phenotypes are never completely addressed. Also, there is less focus on identification and characterization of novel transporters of peptides in important pathogens. It is important to identify peptide transporters that hold maximum potential in delivering antimicrobial agents or serving as therapeutic targets. In conclusion, there is a wide avenue left for research regarding peptide transporters and their contribution in bacterial pathogenesis.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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