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Review

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ATP-binding cassette (ABC) transporters: structures and roles in bacterial pathogenesis

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Abstract: Adenosine triphosphate (ATP)-binding cassette (ABC) transporter systems are divided into importers and exporters that facilitate the movement of diverse substrate molecules across the lipid bilayer, against the concentration gradient. These transporters comprise two highly conserved nucleotide-binding domains (NBDs) and two transmembrane domains (TMDs). Unlike ABC exporters, prokaryotic ABC importers require an additional substrate-binding protein (SBP) as a recognition site for specific substrate translocation. The discovery of a large number of ABC systems in bacterial pathogens revealed that these transporters are crucial for the establishment of bacterial infections. The existing literature has highlighted the roles of ABC transporters in bacterial growth, pathogenesis, and virulence. These roles include importing essential nutrients required for a variety of cellular processes and exporting outer membrane-associated virulence factors and antimicrobial substances. This review outlines the general structures and classification of ABC systems to provide a comprehensive view of the activities and roles of ABC transporters associated with bacterial virulence and pathogenesis during infection.

Key words: ATP-binding cassette (ABC) transporter; Bacterial pathogenesis; Virulence

1 Introduction

The adenosine triphosphate (ATP)-binding cassette (ABC) transport system is one of the largest and oldest protein superfamilies found in all living organisms, including archaea, bacteria, and eukaryotes. ABC transport systems are versatile systems responsible for translocating various important molecules such as monosaccharides, amino acids, peptides, iron-siderophores, metal ions, polyamine cations, vitamins, and large molecules, such as proteins, across the cellular membrane (Kanonenberg et al., 2018; Boël et al., 2019; Delepelaire, 2019; Kolich et al., 2020). By coupling the binding and hydrolysis of ATP, ABC transport systems act as active transporters that deliver substrates in a unidirectional path against a concentration gradient (Davidson and Chen, 2004; Higgins and Linton, 2004). Based on their primary functions, these systems can generally be divided into two groups: importers and exporters. ABC importers are predominantly found in prokaryotes and require a substrate-binding protein (SBP) to recognize specific substrates. The SBP then transports the substrate to the membrane-bound transporter, facilitating its delivery into the cytoplasm. In contrast, ABC exporters work in reverse by eliminating proteins, toxins, or xenobiotics from the cytoplasm and expelling them into the extracellular space (Berntsson et al., 2010; Maqbool et al., 2015; Ford and Beis, 2019). However, it has been discovered that some ABC transporter-related proteins also perform additional functions beyond substrate translocation (Davidson et al., 2008).

The number of ABC transport systems in bacteria generally correlates with the size of its genome, whereby approximately 2%–5% of the bacterial genome encodes for ABC transport system components (Giuliani et al., 2011). In some soil bacteria, such as *Agrobacterium tumefaciens* (Wood et al., 2001) and

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Streptomyces spp. (Zhou et al., 2016), these systems can make up 40%–70% of all transporter proteins encoded in their genomes. The abundant number of ABC transporters in bacterial genomes indicates their role in bacterial survival across diverse environments, particularly in host microenvironments. The importance of these systems in importing essential nutrients and exporting antibacterial agents or other toxic substances further relates to their roles in bacterial pathogenesis (Giuliani et al., 2011; Lewis et al., 2012; Murphy et al., 2016). To avoid being eradicated from the host, pathogenic bacteria adopt a series of complex mechanisms including adherence, colonization, and invasion to interact with the host immune system. These bacterial mechanisms assist pathogens in surviving and spreading within host cells, and are dependent on the ability of the bacteria to quickly sense and respond to various changes in the host environment such as host-mediated nutrient limitation, antimicrobial peptides secretion, innate and adaptive immune responses, as well as other stress (Casadevall and Pirofski, 2000; Ribet and Cossart, 2015; Paludan et al., 2021). Many recent studies have proposed that ABC systems are either directly or indirectly involved in bacterial virulence based on their roles in bacterial chemotaxis and environmental sensing (Giuliani et al., 2011; Konishi et al., 2020). Therefore, this review focuses on ABC transport systems, as these transporters are highly conserved in all living organisms and exhibit high substrate specificity to transfer molecules against concentration gradients. These characteristics provide pathogens with an advantage during bacterial infections.

2 Overview of ABC transport systems

ABC transport systems constitute one of the largest families of integral membrane proteins with a common and conserved protein fold. A complete ABC transporter consists of two nucleotide-binding domains (NBDs) and at least two transmembrane domains (TMDs) (Fig. 1a). The TMD dimer functions as a site for substrate recognition and translocation, where multiple membrane-spanning α-helices create a conduit across the membranes, facilitating substrate transport through the lipid bilayer. On the other hand, the NBD dimer is an adenosine triphosphatase (ATPase) that modifies the structure of TMDs by hydrolyzing ATP to open and close the translocation channel (Higgins and Linton, 2004; Lewinson et al., 2020).

NBDs are highly conserved in structure and include functional nucleotide-binding motifs such as Walker A, Walker B, LSGGQ, D-loop, Q-loop, and H-loop (Ford and Hellmich, 2020) (Fig. 1b). The Walker A motif (P-loop) is associated with α- and β-phosphate-binding of ATP, while the Walker B motif, featuring a glutamate residue, acts as a catalyst for a nucleophilic attack on the γ-phosphate of ATP (Leisico et al., 2020). In the α-helical domain, the LSGGQ motif plays a role in ATP hydrolysis, and the A-loop (aromatic residue interacting with the adenine ring of ATP) provides aromatic side chains that are essential for ATP binding (Thomas and Tampé, 2020). Furthermore, the H-loop, also known as the "switch histidine," catalyzes ATP hydrolysis by stabilizing the transition state geometry via placement of the attacking water, adenosine diphosphate (ADP), and the inorganic phosphatase ion. The Q-loop motif contains a conserved glutamine residue at its N-terminus, which is important for cross-talk between ATP-binding sites of the TMDs, as well as dimerization (D-loop) that couples ATP hydrolysis to substrate transport (Locher, 2016; Akhtar and Turner, 2022). These sequence motifs are important for ATP binding and hydrolysis, providing the necessary energy to facilitate substrate translocation through the TMDs.

Unlike NBDs, TMDs exhibit less conservation in both sequence and structure. TMDs are highly diverse in sequence and vary structurally in the number of transmembrane helices amongst ABC transporters (Srikant, 2020). Despite this, TMDs share a topology comparable to that of other transmembrane transport proteins. The differences in TMD structures reflect the variety of different sizes and chemical properties of the substrates transported (Fan et al., 2020).

In contrast to eukaryotic ABC transport systems, which are solely made up of TMDs and NBDs, bacterial ABC transporters include the SBP. This additional subunit enhances the transporter's specificity for the substrate it carries. This extracellular cytoplasmic anchoring SBP acts as a receptor, recognizing a particular substrate of the transporter and transferring it to the membrane-binding site (Maqbool et al., 2015). In Gram-negative bacteria, the SBP is located in the periplasmic space, whereas in Gram-positive bacteria, the

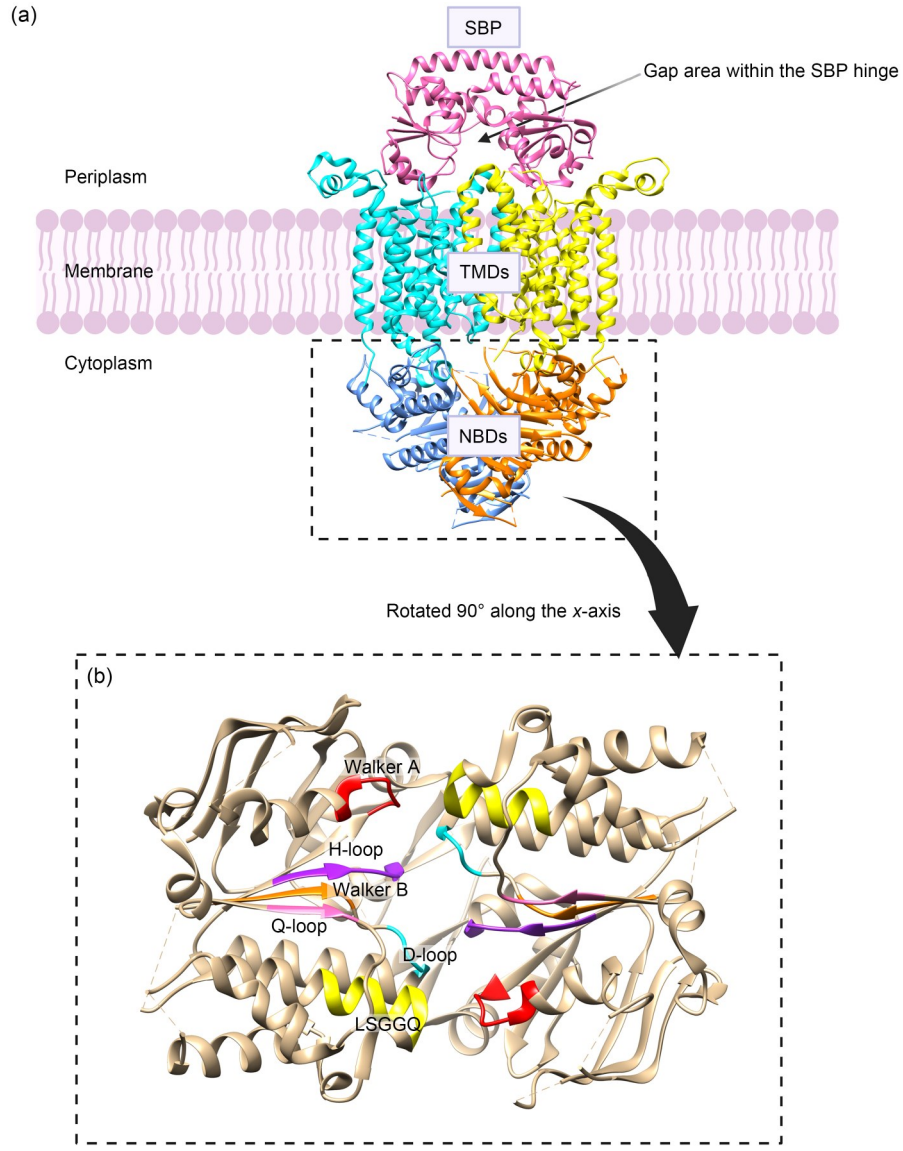

Fig. 1 An experimentally determined structure of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter (PDB ID: 5B58) derived from Naoe et al. (2016). (a) A substrate-binding protein (SBP) is situated at the periplasm, fused to the transmembrane domains (TMDs) at the surface of the inner membrane. Meanwhile, nucleotide-binding domains (NBDs), which facilitated the hydrolysis of ATP, are located in the cytoplasm. (b) The highly conserved motifs in an NBD dimer are colored: red, Walker A; orange, Walker B; yellow, LSGGQ; cyan, D-loop; purple, H-loop; pink, Q-loop. Figure created with BioRender.com.

SBP is exposed on the outer surface of the cytoplasmic membrane (Fulyani et al., 2013). Despite minimal sequence similarity among SBPs and variation in the substrates carried by each transporter, the structures of all SBPs show remarkable similarity. The SBP folds into two globular domains, each containing β-strands surrounded by α-helices. Typically, these two domains are connected by a hinge loop, and the ligand-binding site in SBP is usually found in the gap between the two globular domains (Berntsson et al., 2010; de Boer et al., 2019).

3 Structural classifications of ABC transporters

In the early 2000s, ABC transporters were initially classified into three main classes based on their structures and functions: class I exporters, class III

importers, and class II non-transport ABC system, which lacks TMDs (Davidson et al., 2008). However, in recent years, further subclassifications of ABC transporters have been proposed based on their protein structures and sequence homology. By considering TMD sequence homology and architecture, ABC transporters can now be categorized into seven distinct folds or types. Specifically, types I–III are designated as ABC importers, whereas types IV and V are involved in export processes. Type VI systems serve as extractors, and components of type VII play crucial roles in mechano-transducing tripartite efflux pumps (Thomas and Tampé, 2020). Table 1 provides an overview of the major classes and subclassifications of ABC transporters with their selected examples.

Bacterial ABC importers transport a broad range of specific substrates across the lipid bilayer into the bacterial cytoplasm. These importers are primarily prevalent in prokaryotes. The classification of these importers into type I or type II is based on the folding patterns of their TMDs and the mechanisms involved in substrate translocation (Lewinson and Livnat-Levanon, 2017; Fiorentino et al., 2019). Type I importers are responsible for the moderate- or low-affinity uptake of various small nutrient molecules such as ions, sugars, amino acids, short peptides, and oligosaccharides. The two TMD subunits in type I importers consist of 5–6 and 5–6/8 TM helices, respectively. These subunits form a homo- or heterodimer, resulting in a total of approximately 10 to 14 helices in the overall structure (Tanaka et al., 2018). On the other hand, type II importers have a greater affinity for larger substrate molecules such as cobalamin, siderophores, and chelated metals like Cu^{2+}, Zn^{2+}, or Ni^{2+} (Delepelaire, 2019; Neville et al., 2021). Compared to type I importers, each of the two identical TMDs of type II importers possesses up to 10 or more additional TM helices, allowing them to efficiently transport substantially larger substrates in a unidirectional manner (Locher, 2016; Choi and Ford, 2021).

A type III importer, a subclass of energy-coupling factor (ECF) transporters, has also been identified (Xu et al., 2013; Rempel et al., 2019). As a study model, the *Lactobacillus brevis* ECF transporters specific for hydroxymethyl pyrimidine (HMP) and pantothenate were employed (Wang et al., 2013). An ECF transporter comprises two NDBs, EcfA and EcfA', which are comparable to other types of importers. However, it differs in having only one subunit of the transmembrane-coupling component (EcfT) that is coupled to the transmembrane substrate-binding component (EcfS). Unlike type I and type II importers, ECF transporters lack SBPs and, instead, contain the integral membrane protein EcfS. The EcfS component binds to the substrate and transfers it to the ECF transporters. Similar to type I and type II importers, ATP-derived energy is required to facilitate the movement of substrates across the lipid bilayer (Eitinger et al., 2011; Rice et al., 2014; Tanaka et al., 2018).

ABC exporters are found across all domains of life. In contrast to ABC importers, ABC exporters are responsible for secreting a diverse range of substances, including peptides, lipids, polysaccharides, and proteins. Additionally, they facilitate the efflux of various substrates, from small inorganic ions, drugs, and antibiotics to large protein toxins such as hemolysin and

Table 1 Classification of adenosine triphosphate (ATP)-binding cassette (ABC) transporters

Function	Type	Substrates	Example & Source	Reference
Importer	I	Small nutrient molecules: ions, sugars, amino acids, short peptides, and oligosaccharides	$MalFGK_2$, *Escherichia coli*	Oldham et al., 2013
			MetNI, *E. coli*	Kadaba et al., 2008
	II	Larger substrate molecules: cobalamin, molybdate, and siderophores	BtuCD, *E. coli*	Locher and Borths, 2004
			MolBC, *Haemophilus influenzae*	Rice et al., 2013
			HmuUV, *Yersinia pestis*	Woo et al., 2012
	III	Energy-coupling factor (ECF) transporter: vitamins, amino acids, and metal ions	Hydroxymethyl pyrimidine (HMP) ECF, *Lactobacillus brevis*	Wang et al., 2013
			FolECF, *L. brevis*	Xu et al., 2013
Exporter	IV	Diverse molecules: antibiotics, inorganic ions, drugs, and peptides	Sav1866, *Staphylococcus aureus*	Dawson and Locher, 2007
			MsbA, *E. coli*	Mi et al., 2017
	V	Lipids such as *O*-antigens	Wzm-Wzt, *Aquifex aeolicus*	Bi et al., 2018
	VI	Lipopolysaccharide molecules	$LptB_2FG$, *Pseudomonas aeruginosa*	Luo et al., 2017
	VII	Macrolide antibiotics	MacAB, *Salmonella enterica*	Bogomolnaya et al., 2013

other macromolecules (Beis, 2015; van Veen, 2016). These ABC exporters are categorized within types IV to VII of ABC transporters. Among these, type IV ABC transporters were well-documented with an array of structures and functional information, characterized by the structure of Sav1866 (Dawson and Locher, 2007). Type IV transporters structurally exhibit a conserved core of six TM helices in each TMD with a domain-swapped arrangement (Immadisetty et al., 2019). In the case of type V transporters, a well-known example is the bacterial Wzm-Wzt system responsible for the translocation of lipids. Each TMD of type V transporters is composed of six TM helices. The TMDs collectively form a continuous transmembrane channel, facilitating the open transport for bacterial biopolymer secretion including lipid-anchored *O*-antigens (Thomas et al., 2020).

The classification of type VI ABC transporters is based on the specific fold observed in lipopolysaccharide (LPS) ABC transporter $LptB_2FG$, while type VII is defined by the fold exhibited in the crystal structure of macrolide-specific MacAB ABC systems (Thomas et al., 2020). Like other types VI and V systems, type VI systems possess six TM helices in each TMD subunit. The two TMD subunits, LptF and LptG, observed in $LptB_2FG$, which belong to type VI ABC systems, exhibit an unprecedented fold without the helix swapping typically seen in other ABC transporters (Thomas and Tampé, 2018). In contrast, the TMD monomer of type VII systems consists of only four TM helices, exhibiting a unique topology. The TM1 and TM2 are elongated, extending above the inner membrane into the periplasm, whereas TM3 and TM4 are shorter, situated in the inner membrane and connected by a shoulder loop (Bilsing et al., 2023).

All substrates transported by the type VI to type VII ABC exporters mentioned above were significant for bacterial virulence, including components of bacteria peptidoglycan and the efflux of several types of antibiotics. Consequently, bacterial ABC exporters are one of the virulence factors for pathogenic bacteria, providing bacterial cells with multidrug antibiotic resistance by efficiently extruding drugs and antibiotics (Guffick et al., 2022; Huang et al., 2022). Moreover, these transporters contribute to pathogen adaptation and fitness, aiding in evading host elimination through the secretion of surface-layer proteins and polysaccharides (Hicks and Jia, 2018).

4 Roles of ABC systems in bacterial pathogenesis

Bacterial pathogens employ a variety of complex strategies and mechanisms to invade and adapt in mammalian hosts. Despite the diverse typical niches and the diseases they cause, these bacteria share common pathogenesis themes, such as their abilities to adhere to and invade host cells, inducing host cell and tissue damage, to evade host immune responses and to establish infection (Sarowska et al., 2019; Klein and Hultgren, 2020). Virulence factors are proteins or elements that assist pathogens in establishing these pathogenic lifestyles. Bacterial virulence factors or their functional characteristics are grouped into 14 categories in the virulence factor database (VFDB, http://www.mgc.ac.cn/VFs), which include biofilm formation, nutritional factors, adherence, invasion, antimicrobial activity, effector delivery systems, motility, exotoxin, exoenzyme, immune modulation, stress survival, post-translational modification, regulations, and others (Liu et al., 2022). Transporters that mediate the transfer of various chemicals required for multiple bacterial cellular processes are amongst key virulence factors. Diverse groups of bacterial transport systems, such as the phosphotransferase system, tripartite ATP-independent periplasmic (TRAP) transporters, and ABC transporter systems, assist in facilitating these transport activities (Swier et al., 2016; Rosa et al., 2018; Jeckelmann and Erni, 2020). Bacterial ABC transporters are one of the most ancient transport protein families identified and have a well-established role in bacterial virulence and pathogenesis. ABC transporter genes are abundant in bacterial genomes and the encoded proteins most likely overlap in terms of function. This has resulted in limited comprehensive functional studies of individual ABC transporters. For instance, genomic studies have shown that the presence of ABC transporter-encoding genes in pathogenic bacteria, such as *Escherichia coli* (Li et al., 2021), *Mycobacterium tuberculosis* (de la Torre et al., 2021), and *Streptococcus mutans* (Fu et al., 2017), has been found to be 5% (approximately 80 ABC systems), 2.5% (approximately 34 ABC systems), and 10% (approximately 60 ABC systems), respectively, of their total genomes.

To overcome this challenge, bioinformatics approaches and transcriptome studies play a crucial role in screening and predicting significant ABC transporters

involved in bacterial virulence. In *Porphyromonas gingivalis*, a total of 18 ABC transporter genes were significantly regulated in a real-time polymerase chain reaction (PCR) screen of differentially expressed genes during the invasion process (Gao et al., 2020). Six ABC transporter genes exhibited more than two-fold changes in expression levels and were correlated with biofilm development, bacterial invasion, and the infection of gingival epithelial cells (Gao et al., 2020). In a comparison between *Brucella melitensis* and *Brucella ovis* transcriptomes, it was revealed that several ABC transport proteins in *B. melitensis* are partially active or inactive in less virulent *B. ovis*. This resulted in the poor translocation of essential nutrients like polyamines, nickel, thiamine, glycine, betaine, erythritol, xylose, and molybdenum. The uptake of these substrates by ABC systems is expected to be implicated in *B. melitensis* pathogenesis and virulence towards the host (Paci et al., 2020). Furthermore, various ABC transporters have been linked to multiple bacterial pathogenic mechanisms, including colonization processes, heme uptake, and the utilization, formation, and morphology of biofilms, adhesion, invasion, and colonization (Lewis et al., 2012). This suggests that ABC transport systems play a significant role in bacterial virulence and pathogenesis, but the precise mechanism remains a mystery.

4.1 Biofilm formation

Biofilms are clusters of bacteria embedded in a self-produced matrix and attached to a surface. The biofilm matrix is made up of substances including water, proteins, lipids, extracellular polymeric substance (EPS), and extracellular DNA (eDNA) (Allison, 2003). Many pathogenic bacteria, including *Staphylococcus aureus*, *S. mutans*, *E. coli*, and *Pseudomonas aeruginosa*, can cause biofilm-associated infections in various internal host systems including auditory, cardiovascular, digestive, integumentary, reproductive, respiratory, and urinary systems (Fahmy et al., 2016; Vestby et al., 2020). The ability of bacterial pathogens to form biofilm greatly improves disease-causing capacity, as biofilms protect the bacterial cells from elimination by host immune responses such as cytokine release, complement activation, and antigen phagocytosis, antimicrobial stress, or treatment with chemicals or antibiotics (Gupta et al., 2016). This cluster of bacterial cells is likely to be a bacterial fortress that enables the pathogen to thrive in hostile environments because the persister cells formed within the biofilm have a slower growth rate than planktonic bacteria (Khan et al., 2020).

Bacterial biofilm development is dependent on their quorum sensing (QS) system. QS systems promote the production of extracellular polysaccharides and extracellular proteins (the main components of biofilm) by interacting with ABC transporters. A transcriptomic study demonstrated that QS systems may modulate the activities of various bacterial ABC transporters for substrate translocation to adapt to biofilm formation. In this context, ABC importers collaborate with QS systems to deliver proteins and carbohydrate molecules required for the secretion of EPS during biofilm formation. On the other hand, ABC exporters are involved in the translocation of signaling transition molecules or a wide range of structurally unrelated toxins (Vijayababu et al., 2018; Zaynab et al., 2021; Wang et al., 2022).

Autoinducers are small signaling molecules released by bacteria to recognize and respond to extracellular factors. One such autoinducer is autoinducer-2 (AI-2), which most likely acts as a QS communication mediator for biofilm formation and accelerates biofilm maturation (Song and Wood, 2021). An LsrABCD transporter positively regulates its ATP-binding protein LsrA to translocate AI-2 during *E. coli* biofilm formation (Alav et al., 2018). Additionally, the *lsrA* gene is found in the genome of *Salmonella* sp., where it plays a similar role in modulating biofilm formation. To boost biofilm formation in bacteria, the transfer of AI-2 driven by the LsrA protein in *Salmonella* sp. is required to increase the bacterial population density within the biofilm (Vijayababu et al., 2018; Cui et al., 2020).

ABC transporters have been identified as a positive regulator for biofilm formation in various bacteria. Transporters have important functions in nutrient absorption; hence, a particular transporter's specific role(s) in biofilm formation are determined by the substrates delivered. Numerous proteomics studies have demonstrated that different bacterial pathogens express ABC transporter proteins at different expression levels. For example, in *Cronobacter* sp., several ABC transporter proteins, including the maltose transporter MalE (UniProt ID: K8CYM9), putative ABC transporter (UniProt ID: I2EGX2), and arginine transporter

ArtP (UniProt ID: K8CYA0), were up-regulated during biofilm formation (Yang et al., 2016). Furthermore, a proteomics study of various stages of *S. aureus* biofilm formation, reported by Rahman et al. (2022), revealed that ABC transporter proteins are responsible for early biofilm development. The proteins SACOL0187 (heme ABC transporter protein) and SACOL0779 (protein component of a peptide ABC transporter) were highly elevated, demonstrating the significance of the ABC system in the development of *S. aureus* biofilm. During the early stages of biofilm development, bacteria within the biofilm have a higher metabolic and nutritional need for biofilm formation; therefore, the up-regulation of genes encoding ABC transport proteins can provide the bacteria with a consistent supply of nutrients to maintain cellular functions (Rahman et al., 2022). Similarly, in *Streptococcus pneumoniae*, the production of biofilm has been associated with the up-regulation of an ATP-binding protein and a sugar-binding protein from a sugar ABC transporter, and maltose/maltodextrin-binding protein from a multi-substrate transporter. These findings indicate that sugars are crucial for the adaptation of *S. pneumoniae* to biofilm formation, and ABC transporters are critical in ensuring sufficient sugar intake for cellular metabolism (Allan et al., 2014).

The development of bacterial biofilm has also been linked to peptide or amino acid ABC transport systems. The *P. aeruginosa* DppBCDF transporter, which is responsible for assimilating dipeptides and tripeptides, contributes to the production of biofilms by coordinating with the periplasmic dipeptide-binding protein DppA1, a significant SBP component (Lee et al., 2018). This study revealed that DppA1 regulates biofilm formation by controlling the concentration of its substrate in bacterial cells. Under nutrient deprivation, the dipeptides transported by DppA1 decrease, leading to cell evolution that results in biofilm dispersal and active cell lysis in the presence of *P. aeruginosa* Pf phage. Moreover, the arginine ABC transporter genes *artM* and *artQ*, which encode ABC transmembrane proteins, were overexpressed during biofilm formation. These ABC permeases act as a channel for the transport of positively charged substrates, such as arginine or histidine, and may control biofilm through substance metabolism (Jiang et al., 2021). When compared to wild-type *Cronobacter sakazakii*, a glutathione transporter SBP (*gsiB*) mutant exhibited a deficiency in biofilm development. In addition to GsiB, the mutant of a *C. sakazakii* excinuclease ABC subunit A gene (*uvrA*) also showed a reduction in biofilm formation. UvrA is a dimeric protein belonging to the ABC ATPase family but is primarily involved in nucleotide excision repair (Du et al., 2012). However, further research is required to better understand how GsiB and UvrA regulate *C. sakazakii* biofilm production. In *Listeria monocytogenes*, the UvrA protein is similarly associated with bacteria biofilm formation most likely due to its role in activities related to DNA metabolism (Piercey et al., 2016).

4.2 Adherence and invasion of host cells

For many pathogenic bacteria, the ability to adhere is an important step in establishing successful invasion and colonization of host cells. The initial stage of infection involves bacteria attaching to the host's mucosal surface as an entry point into host cells. Upon contact with host cells, bacteria are sensitive to changes in the physicochemical properties of their environment and can modify their physiology to respond and adapt within the host cells (Sansonetti, 1993). These changes in the environment are triggered by the host's immunological response, such as nutritional immunity or host-induced metal toxicity for bacterial clearance. As a result, bacteria must be able to adapt to host microenvironments and mechanisms to overcome host immune defenses in order to evade eradication. This adaptability enables effective invasion and rapid colonization, leading to the development of disease (Alteri and Mobley, 2012; Kalita et al., 2014).

During host–pathogen interactions, host cells often scavenge different nutrients such as carbohydrates, proteins, and metal ions, including iron, cobalt, nickel, copper, zinc, and manganese, for their own metabolism. This results in limited availability of these nutrients for bacterial pathogens, particularly trace elements, in the host environment. Bacterial pathogens have to overcome this situation at the early stage of infection to ensure their survival in the host environment by acquiring nutrients through various nutrient acquisition systems (Begg, 2019; Antelo et al., 2021). The function of bacterial ABC importers as a substantial group of transport proteins in bacteria is critical for acquiring vital nutrients in the host environment. These nutrients are important for regulating

bacterial metabolic processes and proliferation such as glycolysis, oxygen transport, and gene regulation, as well as DNA biosynthesis to enhance bacterial adherence to, and invasion of, host cells (Gomes et al., 2018; Murdoch and Skaar, 2022).

Metal ions, which are necessary cofactors for protein structural stability, particularly bacterial surface components such as pili, fimbriae, and adhesins, have emerged as the most important transported substrates involved in bacterial adhesion mechanisms (Izoré et al., 2010; Honsa et al., 2013). Previous studies demonstrated that SBPs, also known as lipoprotein components of various metal ions' ABC transport systems, functioned as an adhesin in host–pathogen interactions that were regulated by the concentration of metal ions transported (Sheldon and Heinrichs, 2012; Patel et al., 2017). In *Streptococcus pyogenes*, the heme iron transporter, HtsABC, was shown to be involved in bacterial adherence. When compared to wild type, a deletion mutant of *htsA* that lacks an SBP component of the HtsABC transporter was less competent in adhering to Hep-2 cells and had lower resistance to phagocytosis in human blood and rat neutrophils (Song et al., 2018). Moreover, in *S. pneumoniae*, a mutant of a putative novel ABC transporter lipoprotein SPD_1609 implicated in iron uptake demonstrated reduced adhesion and ability to invade host cells. This study once again highlighted the importance of iron acquisition in bacterial pathogenicity during infections (Yang et al., 2019). The adherence of *P. gingivalis* in the early stages of infection is influenced by two ABC proteins, namely PG_RS04465 and PG_RS07320, encoding the ATP-binding protein and permease, respectively, from distinct ABC transporters. Although the precise substrate of these transport proteins remains unknown, the knockout mutants of these genes exhibit a significant reduction in enzymatic activity, impairing the bacteria's ability to adhere to and invade gingival epithelial cells during infection. This observation indicated the involvement of the ABC transporter genes *PG_RS04465* and *PG_RS07320* in the virulence of *P. gingivalis* (Gao et al., 2020).

Several ABC transporters that transfer other substrates were shown to be involved in metal ion translocation under metal-limited conditions in the host environment. An example is the dipeptide transporter DppABCD in *M. tuberculosis*, which can mediate the binding of dipeptides and heme simultaneously (Mitra et al., 2019). This condition was clearly observed in *Haemophilus influenzae*, from the study conducted by Rodríguez-Arce et al. (2019) on a series of ABC transport proteins from different uptake systems. These ABC systems have been shown to aid in bacterial adhesion and the invasion of host cells by facilitating iron/heme acquisition. For example, DppBCDF, an amino acid-related glutathione uptake system, has been demonstrated to have a role in heme import. The SBP of HbpA is able to bind and transport heme, and inactivation of the component resulted in a significant decrease in bacterial adhesion and the invasion of lung epithelial cells (Rodríguez-Arce et al., 2019). Similarly, the potassium transporter, SapABCDFZ, has been implicated in heme scavenging. The absence of the SapA SBP in *H. influenzae* resulted in reduced bacterial adhesion to epithelial cells but enhanced invasiveness. A multi-substrate importer with substrates that differ in structure and chemical properties is rarely identified. However, in a study on heme auxotrophs, the *H. influenzae* ABC transporter was shown to enable heme uptake during heme starvation, and the underlying mechanism is still unclear (Rodríguez-Arce et al., 2019). The molecular processes involved in the transport of these compounds and how they relate to bacterial pathogenicity should be further studied. In summary, metal uptake has been classified as a subcategory of virulence factors, with its main category belonging to nutritional/metabolic factors in the virulence factors database (Liu et al., 2022). Hence, metal ion translocation promoted by ABC transporters is critical in bacterial pathogenesis, where the metal mediates bacterial adherence to and invasion of host cells.

In *Moraxella catarrhalis*, nine ABC transporters were identified and involved in bacterial adhesion and invasion of epithelial and lymphoid cells. Two of these ABC transporters carry metal ions (iron and zinc) and three transport amino acids or peptides (lysine, ornithine, and oligopeptides), while three others transport inorganic ions (sulfate/thiosulfate, molybdate, and nitrate), and the last one is an uncharacterized ABC transporter with an unknown substrate. These different *M. catarrhalis* ABC transporters operate as nutritional virulence factors, promoting bacterial adhesion and invasion in the varied milieu of host respiratory cells (Murphy et al., 2016). Liu et al. (2017) discovered the oligopeptide importer OppABCDF of *Vibrio alginolyticus*. This transporter was involved in the

pathogenesis of *V. alginolyticus* through a number of mechanisms, including peptide uptake, bacterial adherence, and hemolytic activity. The oligopeptide uptake by the ABC systems functioned as a signal to activate bacterial expression of a specific gene to induce adhesion to host cells. Once the bacterial population had grown to a substantial size, the oligopeptide was utilized to regulate hemolytic activity in order to promote bacterial proliferation in the host (Liu et al., 2017). Fig. 2a provides a concise summary of bacterial adherence to and invasion of host cells, both of which are connected with ABC importers.

ABC exporters are also important for the interaction between bacterial pathogens and the host's immune system during adhesion and invasion. ABC exporters promote the extrusion of glycoconjugates, surface layer proteins, and polysaccharides, all of which are required for the synthesis of bacterial outer membranes or adhesins, which are essential for host detection, bacterial protection, and infection (Fig. 2b). The thin outer membrane of Gram-negative bacteria and the thick peptidoglycan layer of Gram-positive bacteria provide an important barrier against harmful compounds such as host immune molecules or antimicrobial peptides. The export of substrates such as lipid A, core oligosaccharide, *O*-antigen, or teichoic acids, which are required for the formation of the bacterial outer layer, are associated with bacterial adhesion and invasion of host cells (Cuthbertson et al., 2010; Lewis et al., 2012).

The outer membrane of Gram-negative bacteria typically constitutes LPS, which is a glycolipid composed of lipid A, core oligosaccharides, and *O*-antigen. This glycolipid has numerous functions in bacterial pathogenicity: modulating bacterial adherence, attenuating phagocytosis, and inducing the host inflammatory response during invasion (Pier, 2007). The two ABC transporters MsbA and $LptB_2FGC$ interact with one another to facilitate LPS export in several pathogenic bacteria, including *E. coli* (Li et al., 2019), *P. aeruginosa* (Luo et al., 2017), *Klebsiella pneumoniae* (Dong et al., 2017), *Enterobacter cloacae* (Owens et al., 2019), and *Vibrio cholerae* (Owens et al., 2019). Spectroscopic studies on the protein structure have revealed the interaction and export mechanism between MsbA and $LptB_2FGC$. The lipid A and core oligosaccharides are synthesized within cytoplasmic space, and MsbA translocates the resulting molecule through the inner membrane into the periplasm. In the periplasmic region, the lipid A and core oligosaccharides bond with *O*-antigen to form the LPS. The newly synthesized LPS complex is then extruded from the periplasm by an $LptB_2FGC$ exporter (Thélot et al., 2020). The importance of ABC transporters in LPS exportation was clearly demonstrated, where MsbA was involved in the export of key membrane lipid components in bacteria, and the deletion of MsbA was deadly to *E. coli* and *P. aeruginosa* (Doerrler et al., 2001; Ghanei et al., 2007).

To protect their internal organelles from host immune system eradication, Gram-positive bacteria synthesize a cell envelope that includes a sturdy peptidoglycan layer. Teichoic acids, the primary component of this peptidoglycan cell wall, are transported to the extracellular space by ABC exporters and subsequently attached to the peptidoglycan layer (Swoboda et al., 2010). In *S. aureus*, the ABC exporter TarGH is involved in teichoic acid translocation (Chen et al., 2020). The effective transport of teichoic acids by ABC exporters enables the required cell wall assembly and maintenance, thus improving bacterial resistance towards host defenses to establish the infection. Teichoic acids also act as a non-proteinaceous adhesin, facilitating *S. aureus* adhesion to host tissues (França et al., 2021; Pietrocola et al., 2022).

4.3 Antimicrobial activities and drug resistance

Bacterial efflux is a crucial process that significantly contributes to bacterial drug resistance, thereby increasing pathogenicity and virulence. Bacterial efflux pumps belong to several protein families, including the resistance-nodulation-division (RND) family, the multidrug and toxic compound extrusion (MATE) family, the small multidrug resistance (SMR) family, the major facilitator superfamily (MFS), and the ABC superfamily (Delmar et al., 2014). Bacterial ABC exporters were first identified in the early 1980s and, up to this point, various studies have demonstrated their ability to transport drugs and antimicrobial substances (Holland, 2019).

In comparison to ABC importers, ABC exporters play a more direct role in bacterial pathogenicity by actively extruding antimicrobial peptides or antibiotics. These exporters are capable of transporting a variety of substrates with variable structures and sizes, linking them to numerous pathogenic mechanisms.

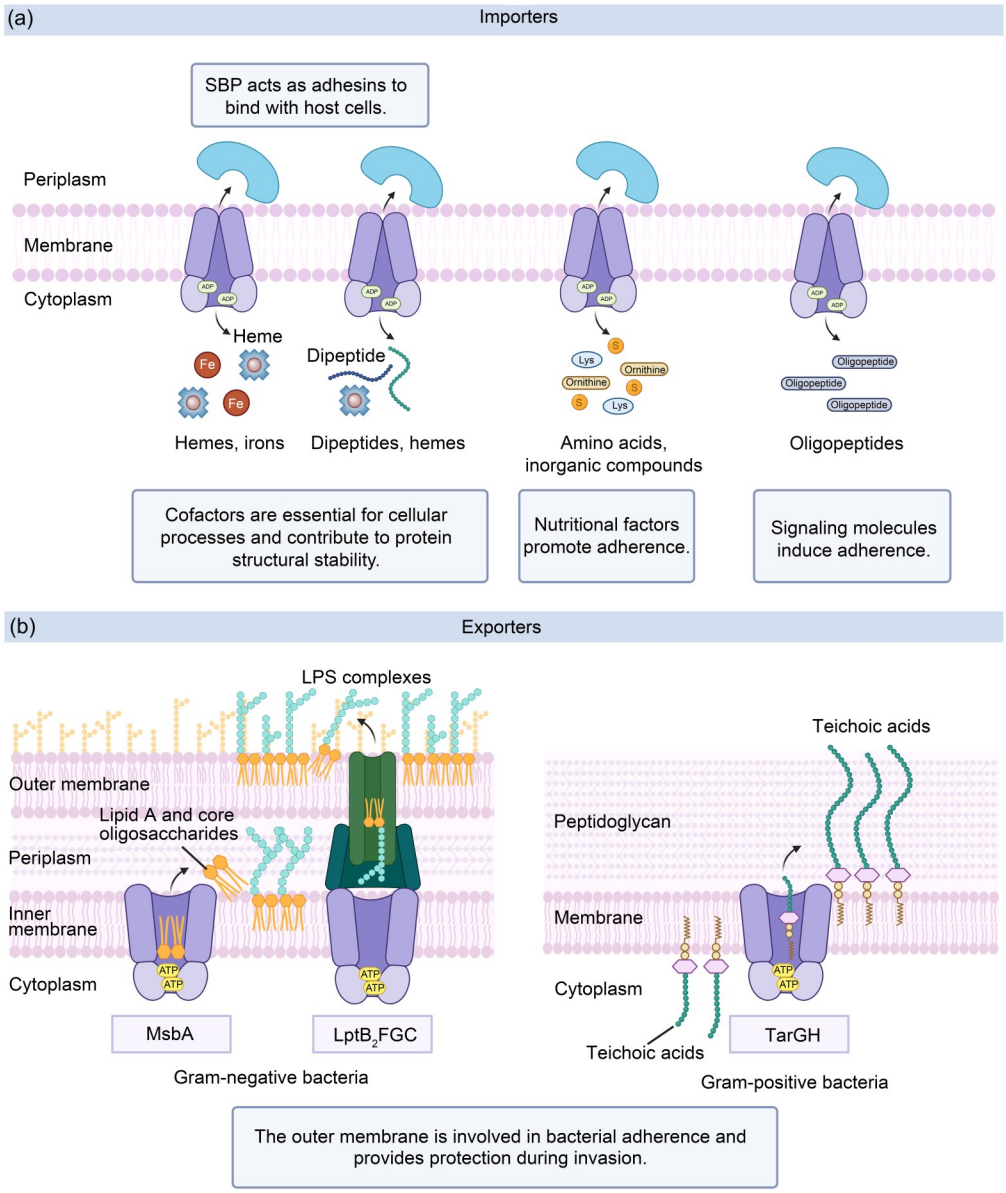

Fig. 2 Roles of adenosine triphosphate (ATP)-binding cassette (ABC) importers and exporters in bacterial adherence. (a) ABC importers import metal ions that act as cofactors for various cellular process and protein structural stability, including the production of adhesins and pili involved in bacterial adherence (Izoré et al., 2010; Honsa et al., 2013). Some substrate-binding lipoproteins of ABC systems serve as adhesins for bacterial attachment to host cells, for example, *Streptococcus pyogenes* HtsABC (Song et al., 2018) and *Streptococcus pneumoniae* SPD_1609 (Yang et al., 2019). Certain dipeptide transporters are also involved in heme transport during iron starvation, thereby contributing to the structure of adherence proteins, for instance, DppABCD in *Mycobacterium tuberculosis* (Mitra et al., 2019) and DppBCDF in *Haemophilus influenzae* (Rodríguez-Arce et al., 2019). ABC importers of essential nutrients, such as amino acids and inorganic compounds, are also important for bacterial metabolism and the synthesis of biomolecules for bacterial survival during host invasion. In particular, ABC systems facilitate the transportation of sulfate/thiosulfate, molybdate, nitrate, lysine, and ornithine in *Moraxella catarrhalis* (Murphy et al., 2016). Oligopeptides imported by ABC systems function as signaling molecules that regulate the expression of genes participating in adherence, for example, OppABCDF of *Vibrio alginolyticus* (Liu et al., 2017). (b) ABC exporters that export substrates involved in the formation of the outer membrane. In Gram-negative bacteria, MsbA and $LptB_2FGC$ work together to translocate lipopolysaccharide (LPS) (Doerrler et al., 2001; Ghanei et al., 2007), while in Gram-positive bacteria, the ABC exporter (TarGH) promotes export of teichoic acids, which make up peptidoglycans in the cell wall. Teichoic acids not only protect the bacteria from phagocytosis but also act as an adhesin that is conducive to bacterial adherence (França et al., 2021; Pietrocola et al., 2022). Figures created with BioRender.com.

The ABC-type efflux pump MacAB from *E. coli* collaborates with outer membrane porins (e.g., TolC) to transport macrolide antibiotics (Miryala and Ramaiah, 2019). The mechanotransmission mechanism used by this transporter was discovered by studying its assembled crystal structure. Unlike other ABC transporters that move substrates across the inner membrane, MacB (transmembrane domain) uses transmembrane conformational changes to couple with cytoplasmic ATP hydrolysis, driving the substrates from the periplasm to the extracellular space via the TolC exit channel (Crow et al., 2017). Later studies revealed that this tripartite pump associated with macrolide export is present in many other Gram-negative bacteria, including *Vibrio vulnificus* and *Salmonella enterica* (Lee et al., 2013; Yamagishi et al., 2020). Aside from antibiotics, it has been proposed that this ABC efflux system is involved in the extrusion of several substrates, including heat-stable enterotoxin II (STII) and protoporphyrin. STII is a virulence factor produced by enterotoxigenic *E. coli* that causes watery diarrhea in the host, whereas protoporphyrin is a by-product of bacterial heme biosynthesis (Yamanaka et al., 2008; Turlin et al., 2014). ABC exporters' roles in eliminating these substrates further helped bacteria to avoid intracellular toxin accumulation that can significantly impact bacterial growth such as slowed growth rate or faster bacteria cell death (Alcalde-Rico et al., 2016). Moreover, MacAB was found to confer resistance against different classes of antibiotics, instead of macrolides, for distinct bacterial species reported in several other studies. For example, the MacAB efflux pump mediated tetracycline-related antibiotic resistance in *K. pneumoniae* and *Acinetobacter baumannii* (Lin et al., 2017; Zheng et al., 2018). Shirshikova et al. (2021) reported that MacAB in *Serratia marcescens* contributed to the extrusion of aminoglycoside antibiotics and demonstrated intrinsic resistance to polymyxin antimicrobial peptides, which protected the bacteria from elimination during an infection.

In Gram-positive bacteria, ABC family efflux pumps related to antibiotic resistance, such as the PatAB exporter, contributed to quinolone antibiotic resistance through the ability to transport norfloxacin, ciprofloxacin, and levofloxacin in *S. pneumoniae*. The quinolone antibiotic class is a broad-spectrum antimicrobial agent previously used to treat pneumococcal infections caused by *S. pneumoniae*. However, treatment failure was observed shortly after levofloxacin and ciprofloxacin therapy (Low, 2004). The drug resistance in *S. pneumoniae* leading to therapy failure was found to be associated with the presence of the PatAB transporter, which provides intrinsic resistance to these quinolone antibiotics. The study by el Garch et al. (2010) demonstrated that exposure to fluoroquinolones induced the expression of the *patAB* gene in *S. pneumoniae*, while the inactivation of *patA* and *patB* genes caused an increase in the susceptibility of mutant strains towards fluoroquinolones. *patAB* gene expression is regulated by a Rho-independent terminator, and the disruption of this transcriptional attenuator located upstream of *patA* resulted in the overexpression of *patAB* and increased resistance against fluoroquinolones (Baylay and Piddock, 2015; Amblar et al., 2022). These findings regarding the transcriptional regulation and roles of the PatAB efflux pump in antibiotic resistance are crucial for the development of new antibiotics due to the rapid emergence of antibiotic resistance in *S. pneumoniae*.

In *S. aureus*, the multidrug-resistance ABC transporter AbcA promotes antibiotic resistance by exporting β-lactam antibiotics and moenomycin. Gene expression of the AbcA efflux pump is regulated by a small number of transcriptional regulators, including MgrA, NorG, SarA, and SarZ, with up-regulation of the *abcA* gene observed during starvation and antibiotic exposure (Villet et al., 2014). Each of these regulators, but not AbcA, is also associated with the expression of other virulence factors involved in autolysis, capsule biosynthesis, and toxin secretion (Jenul and Horswill, 2019), indicating the crucial role of AbcA in bacterial virulence. Yoshikai et al. (2016) discovered the significant role of AbcA transporters in the exportation of the endogenous cytolytic toxin phenol-soluble modulin (PSM), which is secreted by *S. aureus* to facilitate the expansion of bacterium colonies. PSM aids the bacterium in lysing the host cells during bacterial spread, but an accumulation of PSM in the bacterial cytoplasm can be lethal. A knockout mutant of *abcA* was unable to export the accumulated PSM from its cytoplasmic space, resulting in the autolysis of bacterial cells (Yoshikai et al., 2016).

Overall, the active efflux of structurally diverse antibiotics by ABC exporters provides the bacteria with intrinsic resistance towards a broad range of antibiotics, contributing to the persistence of bacterial infections

(Hernando-Amado et al., 2016). Bacterial pathogens can develop resistance against multiple antibiotics simultaneously (Biondo, 2023), further contributing to increased bacterial virulence and fitness. The direct involvement of ABC efflux pumps in conferring bacterial antibiotic resistance is a key factor in bacterial colonization and infection of the host (Beceiro et al., 2013). To combat this issue, further research is needed to investigate the regulation and mechanisms of these drug resistance transporters to develop effective strategies that inhibit extrusion and restore the effectiveness of antibiotics.

4.4 Future perspectives

Omics studies, including genomics, transcriptomics, and proteomics, driven by the development of next-generation sequencing, have become crucial in the study of ABC transporters, particularly in the context of bacterial pathogenesis (Ohashi et al., 2015). By comparing transcriptome or proteome profiles of various bacteria, omics studies can identify ABC transporters with variable expression patterns in pathogenesis, highlighting potential candidates with essential roles in pathogenesis and virulence. For example, the proteomic study carried out by Abril et al. (2022) successfully identified 70 ABC transporter peptides related to *Enterococcus* virulence factors. These transporters were predominantly associated with metal uptake, peptide transport, and antibiotic efflux pumps. Further characterization of these ABC transporters is needed to elucidate their high-resolution three-dimensional (3D) structures, substrate specificity, and translocation mechanisms as well as their role(s) in host–pathogen interactions.

Thorough investigations into the roles of ABC transporters in bacterial pathogenesis have increased the promise of novel therapies for bacterial infections. ABC importers are one of the virulence factors in bacterial infections because they aid in the uptake of essential nutrients that enable bacteria to survive within the host environment. The absence of an importer protein in the genomes of most eukaryotic hosts, including humans, and its location in the bacterial cell membrane suggest that it could be a viable target for antimicrobial treatments. The components of the ABC importer could serve as potential drug targets, limiting nutrient uptake and thereby disrupting the virulence pathways of pathogens (Soni et al., 2020). For example, the SBP components of ABC importer systems, responsible for substrate identification and binding, have the potential to be used in blocking ABC transporter functions, which can affect bacterial growth and disease manifestation (de la Torre et al., 2021). Recent studies on SBP structures and conformation in different states have provided new insights into SBP dynamics and the plasticity of ligand binding, as well as the interaction with TMDs and NBDs to activate transport (de Boer et al., 2019). This knowledge opens the possibility of finding substrate mimic inhibitors using a high-resolution SBP structure complexed to ligand and transport mechanisms, thereby blocking the transport of native substrates critical for bacterial growth or virulence. For instance, in a study performed by Ilari et al. (2016) on *S. enterica* ZnuABC importers, two zinc-binding compounds, RDS50 and RDS51,were found to bind with ZnuA (SBP) and suppress the transport of zinc in *S. enterica*, resulting in reduced invasion of human Caco-2 cells.

Aside from SBP, other ABC transporter components such as ATP-binding proteins have been identified as possible therapeutic targets. Molecular docking analysis discovered that patulin, a naturally occurring structural AI-2 analogue, showed a greater binding affinity to the ATP-binding protein LsrA than AI-2 in *Salmonella typhi*. The binding of patulin at the AI-2 interaction site in LsrA resulted in lower bacterial cell density and biofilm formation (Vijayababu et al., 2018). Although studies on ABC transporter protein inhibitors are still in the early stages, there have been recent reports on crucial roles of ABC transporters in pathogenic bacteria. The inactivation of these transporters led to a decrease in bacterial virulence, indicating a novel trend in antimicrobial drugs development by targeting ABC transporter proteins (Varela and Kumar, 2019). Understanding the complex structures and regulatory and transport mechanisms of ABC transporters associated with bacterial pathogenicity is essential for identifying specific inhibitors and, consequently, for the development of novel antimicrobial treatments to combat bacterial infections.

5 Conclusions

Numerous transport activities of bacterial ABC transporters can be associated with bacterial

pathogenicity, both directly and indirectly, through various mechanisms. ABC importers facilitate nutrient uptake, particularly iron or metal ions, from the host microenvironment, which is crucial for bacterial growth and disease manifestation in mammalian hosts. On the other hand, ABC exporters are responsible for the translocation of surface layer components, enhancing the formation of the bacterial outer membranes, which protect against the host immune responses. Furthermore, ABC exporters play a significant role in antibiotic efflux and the extrusion of endogenous toxins, aiding bacterial escape from antimicrobial agents or stimulating bacterial proliferation within the host. Some bacterial ABC transporters not only participate in transport activities but also regulate a wide range of events associated with bacterial pathogenicity. This versatility has been observed in both Gram-positive and Gram-negative bacteria. All of these ABC transporters may one day serve as therapeutic targets for bacterial infections.

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Author contributions

Shu Sian HOW was responsible for conceptualization, writing – original draft, and visualization. Sylvia CHIENG played roles in supervision, writing – review & editing, and funding acquisition. Sheila NATHAN participated in writing – review & editing, resources, and supervision. Su Datt LAM contributed to visualization, writing – review & editing, and supervision. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Shu Sian HOW, Sheila NATHAN, Su Datt LAM, and Sylvia CHIENG declare that they have no conflict of interest.

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