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The Important Role of Transporter Structures in Drug Disposition, Efficacy, and Toxicity[S]

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ABSTRACT

The ATP-binding cassette (ABC) and solute carrier (SLC) transporters are critical determinants of drug disposition, clinical efficacy, and toxicity as they specifically mediate the influx and efflux of various substrates and drugs. ABC transporters can modulate the pharmacokinetics of many drugs via mediating the translocation of drugs across biologic membranes. SLC transporters are important drug targets involved in the uptake of a broad range of compounds across the membrane. However, high-resolution experimental structures have been reported for a very limited number of transporters, which limits the study of their physiologic functions. In this review, we collected structural information on ABC and SLC transporters and described the application of computational methods in structure prediction. Taking P-glycoprotein (ABCB1) and serotonin transporter (SLC6A4) as examples, we assessed the

pivotal role of structure in transport mechanisms, details of ligand-receptor interactions, drug selectivity, the molecular mechanisms of drug-drug interactions, and differences caused by genetic polymorphisms. The data collected contributes toward safer and more effective pharmacological treatments.

SIGNIFICANCE STATEMENT

The experimental structure of ATP-binding cassette and solute carrier transporters was collected, and the application of computational methods in structure prediction was described. P-glycoprotein and serotonin transporter were used as examples to reveal the pivotal role of structure in transport mechanisms, drug selectivity, the molecular mechanisms of drug-drug interactions, and differences caused by genetic polymorphisms.

Introduction

Transporters are critical determinants of drug disposition (absorption, distribution, and excretion), clinical efficacy, and toxicity as they specifically mediate the influx and efflux of various substrates and drugs (DeGorter et al., 2012; Hong, 2017; Liu, 2019a,b; Yin et al., 2020; Roberts, 2021). Based on the transport mechanism, transporters can be generally divided into ATP-binding cassette (ABC) and solute carrier (SLC) superfamilies (Liu, 2019a; Bi et al., 2023). ABC transporters are

closely associated with the pharmacokinetics of many drugs, and SLC transporters are very important therapeutic targets for various diseases (Lusvarghi et al., 2020; Wang et al., 2020; Zhou et al., 2022). Over the past few decades, the study of their structure, function, and the structure-function relationship has been an important research topic in the field of medicine. Although the importance of transporters to human pharmacology has been recognized, there are many challenges in investigating their function due to the limitations of their structural information.

Transporters are membrane proteins concentrated in the intestine, kidneys, liver, and central nervous system (Girardin, 2006; Villanueva et al., 2019). It is more difficult to perform the crystallization analysis of membrane proteins than soluble proteins (Carpenter et al., 2008). Currently, atomic-resolution three-dimensional structures have only been resolved for a limited number of transporters (Fu et al., 2022). In addition, many structures are incomplete, especially multiple flexible loops. The rapid development of computational modeling and simulation methods offers new opportunities for exploring their structure and

ABBREVIATIONS: ABC, ATP-binding cassette; AI, artificial intelligence; DDI, drug-drug interaction; LeuT, leucine transporter; MFS, major facilitator superfamily; MRP1, multidrug resistance-associated protein 1; NBD, nucleotide-binding domain; NET, norepinephrine transporter; P-gp, P-glycoprotein; SERT, serotonin transporter; SLC, solute carrier; TM, transmembrane; TMD, transmembrane domain.

function. Homologous modeling (or comparative modeling), de novo methods, and artificial intelligence (AI) algorithms are widely used in structure prediction (Shen and Bax, 2015; Bienert et al., 2017; Pan and Kortemme, 2021; Tunyasuvunakool et al., 2021; Wang et al., 2022), greatly enriching the structural information of transporters and providing a basis for elucidating their function and structure-based drug discovery.

ABC transporters are primary active transporters using the energy of ATP hydrolysis to drive the transmembrane transport of structurally diverse molecules (Hong, 2017; Kroll et al., 2021). In this superfamily, ABCB1 [P-glycoprotein (P-gp)], ABCC1 [multidrug resistance-associated protein 1 (MRP1)], and ABCG2 [breast cancer resistance protein (BCRP)] mediate the efflux of various anticancer drugs with different scaffolds, which are closely related to multidrug resistance and drug-drug interactions (DDIs) (Choi and Yu, 2014; Chufan et al., 2015; Robey et al., 2018; Liu, 2019b; Sun et al., 2023). DDIs mediated by ABC transporters may occur when drug disposition (absorption, distribution, and excretion) is altered by another drug, leading to an enhancement in its efficacy or toxicity (Liu, 2019b). Additionally, the pharmacokinetic difference caused by genetic factors is another reason why these ABC transporters have received so much attention in the last decades (Iram and Cole, 2012; Shukalek et al., 2016; Sarkadi et al., 2020). Due to the function of ABC transporters in regulating drug concentration, much effort has been focused on developing their potential inhibitors (Mollazadeh et al., 2018; Silbermann et al., 2019; Moinul et al., 2022). Recently, a series of potential inhibitors were developed, but most have not passed the clinical trial due to low efficacy, poor selectivity, or excessive toxicity (Crowley et al., 2010). Based on the structures of ABC transporters, clarification of their physicochemical properties, transport mechanisms, ligand-receptor interactions, and differences caused by genetic factors can help clarify the microscopic processes involved in drug disposition and are crucial for drug development and optimization.

SLC members are secondary active transporters that carry endogenous and exogenous molecules across membranes utilizing the electrochemical potential or ion gradients (Bai et al., 2017; Hong, 2017). Some of them are important drug targets relevant to drug efficacy, and the investigation of their structure, transport mechanism, and ligand-receptor interaction are significant for treatment of various diseases (Lin et al., 2015; Zheng et al., 2017; Wang et al., 2020; Xue et al., 2020). For instance, the SLC6 family (monoamine transporters) reuptake endogenous neurotransmitters into neurons, and modulating their function can provide treatment for many psychiatric disorders (Baumann et al., 2014; Zeppelin et al., 2019; Xue et al., 2020). The structures of SLC transporters are more diverse than those of the ABC superfamily, which can be divided into many different protein folds (Ferrada and Superti-Furga, 2022). Another important structural feature is the allosteric site (Coleman et al., 2019; Xue et al., 2022). Effector molecules in the allosteric

site of SLC transporters impact the binding of drugs in the central site. In addition, extensive computational and experimental studies were performed to investigate the effects of residue mutation on transport activity and drug efficacy, but the molecular mechanism needs to be further elucidated. (Chen et al., 2005; Bhat et al., 2019; Zwartsen et al., 2019).

In this review, we collected structural information on ABC and SLC transporters and described the application of computational methods in structure prediction. Taking P-gp and serotonin transporter (SERT) as examples, we assessed the pivotal role of the structure to clarify transport mechanisms, drug selectivity, and the molecular mechanisms of DDIs, as well as genetic polymorphism-induced individual differences. The above information provides insight into the role of transporter structure in drug disposition, efficacy, and toxicity, with positive implications for pharmacological treatment.

Drug Transporter Families and Structures

Transporters can be generally divided into ABC and SLC superfamilies based on their sequence homology and transport mechanism (Liu, 2019a; Bi et al., 2023). From 2006 to 2022, approximately 90 experimental structures of the ABC superfamily have been reported; these structures are distributed in five families (Supplemental Table 1), which mediate the efflux of a wide range of lipids, drugs, and other molecules (Thomas and Tampé, 2020; Juan-Carlos et al., 2021). As shown in Supplemental Table 1, 10 ABC transporters (ABCA3, ABCB1, ABCB4, ABCB6, ABCB8, ABCB11, ABCC1, ABCC6, ABCC8, and ABCG2) have been reported to mediate the translocation of approved drugs. Crystallographic data show that the general topologies of ABC transporters have two transmembrane domains (TMDs) and two nucleotide-binding domains (NBDs) (Fig. 1). There are usually 12–20 transmembrane helices in the TMDs, which recognize and bind compounds, and the NBDs, which bind nucleotides and are associated with ATP hydrolysis. (Wilkens, 2015; Lusvarghi et al., 2020; Juan-Carlos et al., 2021).

There are approximately 52 families in the SLC superfamily (Lin et al., 2015; Xie et al., 2018). Approximately 250 protein structures of 53 transporters in 24 SLC families have been resolved by experimental methods (Supplemental Table 2). Notably, the structures of SLC transporters are more diverse than those of the ABC superfamily. According to structural similarity and topology criteria of SLC transporters, the structures can be divided into the major facilitator superfamily (MFS) fold, leucine transporter (LeuT) fold, mitochondrial carrier fold, and others (Ferrada and Superti-Furga, 2022). The availability of fold information for SLC transporters may be valuable for structure prediction as well as functional knowledge. Figure 2 depicts the structural topologies of the MFS and LeuT folds, which are the two largest folding categories. As shown, the MFS fold has 12 transmembrane (TM) helices,
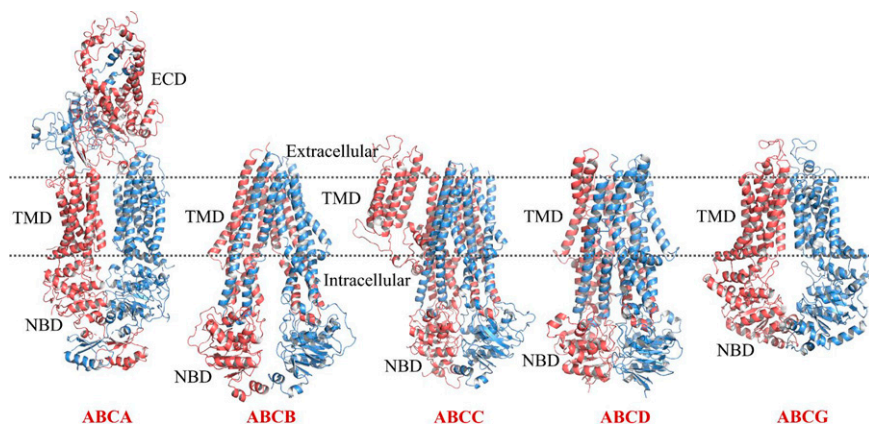
Fig. 1. The general topologies of ABC transporters. From left to right, the protein data bank (PDB) IDs are 7M1P, 7A69, 7S5V, 7VX8, and 6ETI. The N-terminal halves of the TMD and NBD (including the TMD0 of the ABCC family) are colored red, and the corresponding C-terminal TMD and NBD are colored blue. The parallel dashed lines indicate the position of the membrane; the top and bottom are the extracellular and intracellular sides, respectively.
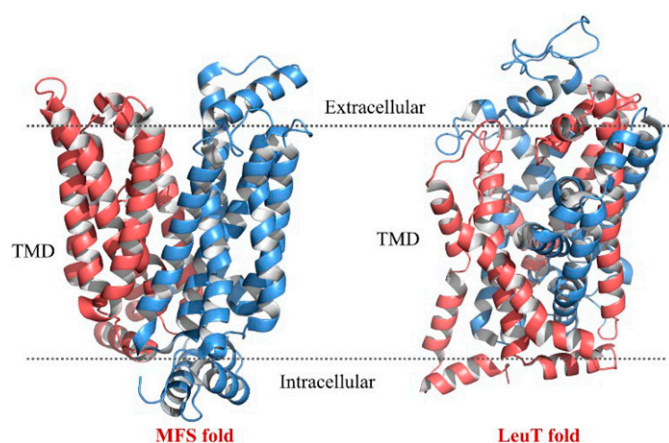
Fig. 2. The structural topologies of the two largest folding categories in the SLC superfamily. On the left is the MFS fold [SLC2A3; protein data bank (PDB) ID: 4ZW9], and on the right is the LeuT fold (SLC6A4; PDB ID: 5I73). TM1–6 are highlighted in blue, and TM7–12 are highlighted in red. The parallel dashed lines indicate the position of the membrane; the top and bottom are the extracellular and intracellular sides, respectively.

including the amino-terminal domain (NTD, TM1-6) and the carboxyl-terminal domain (CTD, TM7-12). The LeuT fold is characterized by a core containing two inverted (5 + 5 TM) repeats. In addition, the central binding site and ion binding site are located between the TM helices and are specific among the different families (Bai et al., 2017).

Obtaining a high-resolution protein structure is fundamental for determining its function. Structural data of the ABC and SLC superfamilies show that only a few transporters have atomic-resolution structures (Supplemental Tables 1 and 2). Thus, computational techniques are an important way to enrich protein structures. The popular structure prediction approaches AlphaFold and AlphaFold2 have changed the biomedical research landscape and can predict the protein structure of almost the complete human proteome based on AI algorithms (Jumper et al., 2021; Tunyasuvunakool et al., 2021; Huang and Ecker, 2023). Prior to the development of AlphaFold, homology modeling was the most commonly used method for predicting transporters structures (Shen and Bax, 2015; David et al., 2022). In our previous study, we constructed extensive structural variability data for transporters by homology modeling and added the results to the VARIDT database (http://varidt.idrblab.net); these results included residue mutations, species differences, different intermediate states, and xenobiotics-driven conformational alterations (Fu et al., 2022). The SWISS-MODEL Repository also deposits a large number of transporter structures obtained by homology modeling (Waterhouse et al., 2018). These computational structures can be used as a complement to the experimental structures and greatly enrich the structural information of transporters which provides opportunities to clarify the mechanism of interaction between transporters and small molecules, reveal the pharmacophore region, binding affinity, and selectively of ligands, and study the mechanism of DDIs (Le et al., 2021; Namasivayam et al., 2021; Liu et al., 2022b; Mora Lagares and Novič, 2022). The absorption, distribution, metabolism, excretion, and toxicity properties can also be predicted based on the computational structure of ABC transporters to assess the pharmacokinetic properties of lead compounds or candidates (Demel et al., 2009; Yalcin-Ozkat, 2021; Yin et al., 2021). Moreover, there are several studies based on computational structures for mutation studies of transporters (Becerra et al., 2021; Onnée et al., 2021).

Transporter Structure Is the Basis for Elucidating the Transport Mechanism

ABC and SLC transporters are of considerable pharmacological significance; revealing their transport mechanisms has positive implications for drug development and disease treatment. The transport processes of ABC and SLC transporters often undergo highly diverse conformational changes, including local rearrangement of ligand binding site and global conformational transition (Vermaas et al., 2016). Several key intermediate states of transporters in the transport cycle have been experimentally resolved in recent years, such as the inward-facing, outward-facing, and occluded conformations. These structures are the prerequisite for us to determine their transport mechanisms.

To elucidate the transport mechanisms of ABC transporters, their different intermediate conformations must be linked to the dynamic transition process (Thomas and Tampé, 2020). Multiple structures or homologous structures of ABC transporters have been resolved by experimental methods, including inward-facing, outward-facing, and occluded conformations, with and without ATP/substrate/inhibitor binding (Johnson and Chen, 2017; Manolaridis et al., 2018; Lusvarghi et al., 2020; Orlando and Liao, 2020). Based on these structures, the transport mechanisms can be generally summarized as follows: ligand binding starts the transport process, and ATP binding induces dimerization of NBDs, driving conformational transitions of the TMDs (Choi and Yu, 2014; Alam et al., 2019; Lusvarghi et al., 2020; Nosol et al., 2020; Yee and Giacomini, 2021; Jones and George, 2023). Taking P-gp as an example, the binding of ATP causes NBDs to move and form a closed dimer, driving the rigid modules (several TM helices move as rigid entities in the transporter cycle) to move closer to the vertical pseudosymmetry axis, which further triggers large-scale conformational changes in the mobile helices. Subsequently, P-gp gradually undergoes conformational transitions from the inward-facing to the occluded, outward-facing, and collapsed states (Fig. 3). Through this process, compounds can be translocated across biologic membranes.

The SLC superfamily contains multiple protein folds that may mediate transmembrane transport through multiple different mechanisms (Coleman et al., 2019; Liu et al., 2022a). Taking SERT (SLC6A4) as an example, the transport mechanism of transports with the LeuT fold can be illustrated. In 2019, Coleman et al. (2019) successfully resolved the structures of SERT bound with ibogaine in the inward-facing, outward-facing, and occluded conformations (Fig. 4). These critical intermediate structures describe conformational rearrangements from the outward-facing state to the inward-facing state, providing insight into the transport cycle of neurotransmitters. The process of neurotransmitter transport by SERT can be further described as follows: 1) ligand binding to the central site (outward-facing conformation) from the extracellular side of SERT, 2) closing the extracellular gate by inducing the structural rearrangements of TM1b and 6a (occluded conformation), and 3) driving the movements of TM1a and 5 to open the intracellular gate (inward-facing conformation) and creating a pathway that allows substrate and ion influx into the cytoplasm.

Despite this progress, many mechanisms in the transport process remain unclear, such as regulatory mechanisms and energy coupling. Many high-resolution experimental structures provide structural information for elucidating transport mechanisms, but it is challenging to clarify the dynamic process of global conformational change only by experimental methods. To address this challenge, computational simulation methods are used, which enable comprehensive sampling of large-scale conformational transitions in the transport process to obtain dynamic information at the atomic level (Barducci et al., 2008; Decherchi and Cavalli, 2020; Célerse et al., 2022). AI algorithms have a significant advantage in addressing massive, high-dimensional, dynamic information
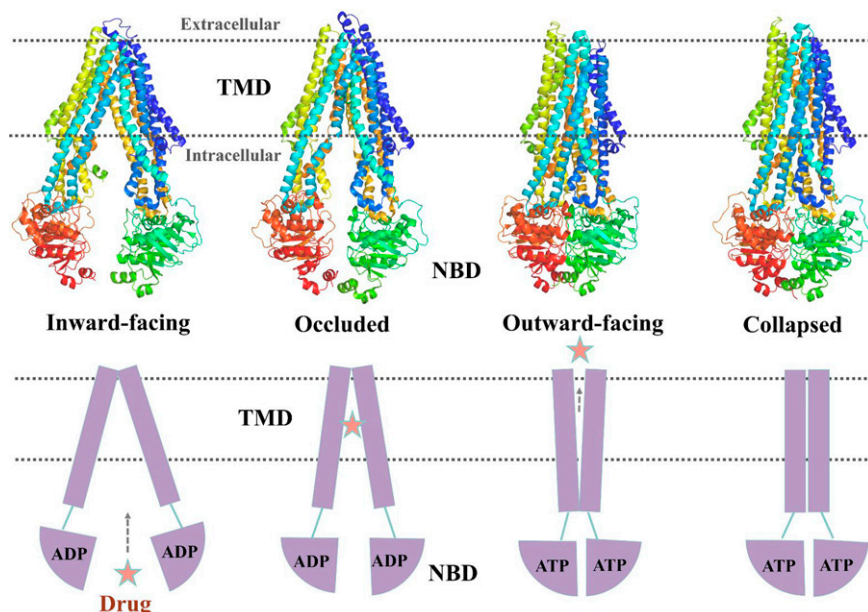
Fig. 3. The proposed transport mechanism of P-gp based on multiple experimental structures and homologous structures. From left to right, the protein data bank (PDB) IDs are 4M1M (*mouse*), 6QEX, 2HYD (*Staphylococcus aureus*), and 6C0V. The arrows represent the direction of drug transport. The parallel dashed lines indicate the position of the membrane; the top and bottom are the extracellular and intracellular sides, respectively.

(Hong et al., 2020a,b; Wang et al., 2023; Zhang et al., 2023). Recently, computational simulation methods combined with AI algorithms have been used to identify key conformational states and present the dynamic transformation of membrane proteins, which may provide a new opportunity for obtaining in-depth knowledge on the transport mechanisms of transporters (Do et al., 2022; Yao et al., 2022).

Importance of the Transporter Structure for Understanding Drug Selectivity

ABC transporters regulate intracellular drug concentrations by driving the translocation of various drugs across biologic membranes. Clarifying the selectivity of drugs to ABC transporters is important for characterizing the pharmacokinetics of drugs. To date, P-gp, MRP1, ABCC2, ABCC4, and BCRP in the ABC superfamily have been reported to be closely related to multidrug resistance due to their overexpression in many drug-

resistant tumors and act as efflux pumps (Juan-Carlos et al., 2021). Selectively inhibiting the function of these transporters is an effective strategy to promote the accumulation of many anticancer drugs in target tissues and improve their bioavailability. Therefore, many studies have been conducted to study ligand-receptor interactions based on structures of ABC transporters and to further design selective inhibitors. These studies suggested that the substrate binding site of P-gp does not involve positively or negatively charged residues (Chufan et al., 2015). Thus, inhibitors that can form hydrogen bonds, van der Waals interactions, hydrophobic interactions, and π-π interactions with P-gp may exhibit higher selectivity (Chufan et al., 2015; Mollazadeh et al., 2018; Zhang et al., 2021). For MRP1, many charged residues affect the selectivity of inhibitors, such as arginine, histidine, and lysine located in the binding site (He et al., 2011). Hydrophilic inhibitors, especially amphipathic organic acids, may have higher selectivity for MRP1 (Gottesman et al., 2002). Moreover, different inhibitors stably bind in the substrate binding site
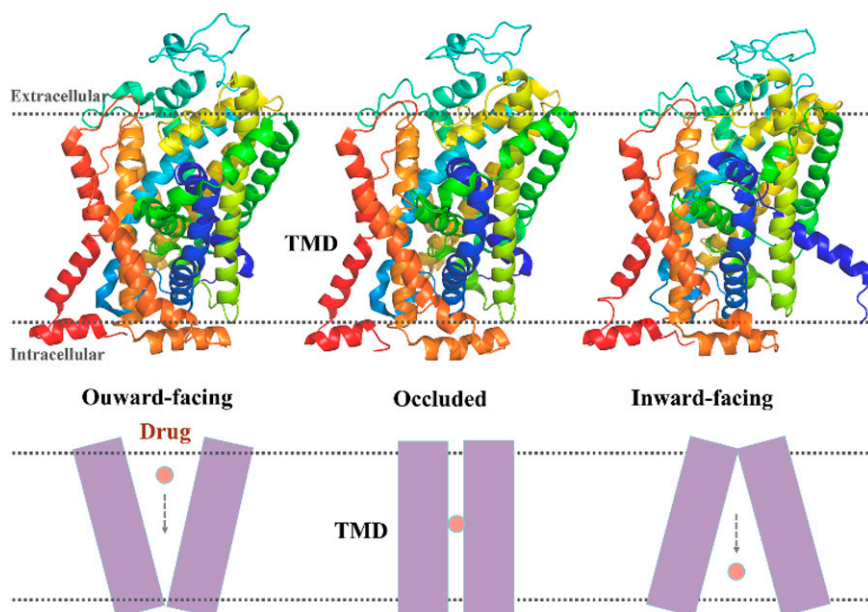

Fig. 4. The proposed transport mechanism of SERT based on multiple experimental structures. From left to right, the protein data bank (PDB) IDs are 6DZY, 6DZV, and 6DZZ. The arrows represent the direction of drug transport. The parallel dashed lines indicate the position of the membrane; the top and bottom are the extracellular and intracellular sides, respectively.

by interacting with different key residues; thus, we can speculate that the selectivity is related to the physicochemical characteristics of the inhibitor and the binding site. Altogether, the structure of ABC transporters is critical to the understanding of drug selectivity, which provides significant insights into the function of these transporters in multidrug resistance and positively contributes to effective pharmacological treatments.

Monoamine transporters belonging to the SLC6 family are very important therapeutic targets for many psychiatric disorders; they are norepinephrine transporter [(NET) SLC6A2], dopamine transporter (SLC6A3), and SERT (SLC6A4) (Zeppelin et al., 2019; Xue et al., 2020). Their physiologic function is to reuptake neurotransmitters into the presynaptic neuron, which can be modulated by a variety of compounds. To date, many inhibitors of monoamine transporters have been designed as potential therapeutic agents for neurologic disorders, including selective reuptake inhibitors of serotonin and norepinephrine, reuptake inhibitors of both serotonin and norepinephrine, and the multitarget inhibitors (Xue et al., 2020; Santra et al., 2021). Many psychoactive compounds are also substrates of monoamine transporters, such as amphetamine and its congeners (Baumann et al., 2014; Sitte and Freissmuth, 2015). Currently, multiple high-resolution experimental structures of inhibitors with monoamine transporters or homologous proteins provide information on binding sites, key residues, ligand-receptor interactions, and conformational rearrangements of inhibitor binding, which are prerequisites for determining the drug selectivity (Coleman et al., 2016; Coleman and Gouaux, 2018; Coleman et al., 2019, 2020; Pidathala et al., 2021; Plenge et al., 2021). Based on these structures, the members of Zhu's group have made significant efforts to investigate the interaction details between psychotropic drugs and monoamine transporters, identifying the key factors that determine selectivity through molecular docking, molecular dynamics simulation, and binding-free energy calculation. They suggested that inhibitors can form salt bridges with residues (Asp98/Asp75/Asp79) in the central site of SERT, NET, and dopamine transporter, as well as identified a large number of residues as key determinants of inhibitor selectivity (Xue et al., 2016; Zheng et al., 2016; Wang et al., 2017b; Xue et al., 2018a,b; Zheng et al., 2018; Xue et al., 2020; Zhang et al., 2020; Tu et al., 2021; Li et al., 2023). For example, resides Ala73, Tyr151, Ala477, and Ile481 in NET and Ala96, Ala173, Thr439, and Leu443 in SERT were identified as the key factors that determine the selective binding of escitalopram to NET and SERT (Zheng et al., 2018). They also explored the selectivity and structural characteristics of dual- and triple-target inhibitors to monoamine transporters, providing important theoretical support for the development of antipsychotic drugs (Wang et al., 2017a; Xue et al., 2018b; Tu et al., 2021). In-depth knowledge of the selectivity of drugs based on the structure of transporters is essential for screening and optimizing lead compounds.

Importance of the Transporter Structure for Understanding Drug-Drug Interactions

Drugs can compete with each other for binding to ABC transporters, resulting in DDIs, since ABC transporters recognize and transport a series of structurally diverse drugs (Chufan et al., 2015; Liu, 2019b). In the process of DDIs, the pharmacokinetics of the drug are altered by another drug, leading to an enhancement in its efficacy or toxicity (Liu, 2019b). For instance, the combination of the selective P-gp inhibitors zosuquidar and nelfinavir significantly improves the distribution of nelfinavir in the brain (Kaddoumi et al., 2007). In addition, P-gp can also mediate the risk of DDIs between rivaroxaban and many tyrosine kinase inhibitors (axitinib, dabrafenib, idelalisib, and others) (Lafaie et al., 2022). Based on the structure or homologous structure of ABC transporters, many experimental and computational methods were applied to

determine the interaction between ABC transporters and the drugs, which can help researchers predict DDIs, investigate the molecular mechanism, and provide solutions to the enhanced drug efficacy or therapeutic failure caused by DDIs (Hong, 2017; Silbermann et al., 2019; Elmeliegy et al., 2020; Yalcin-Ozkat, 2021; Moinul et al., 2022).

In addition to competitive binding of drugs in the substrate binding site, DDIs may affect the interactions between transporters and drugs in an allosteric manner. For SERT, the central site is roughly halfway across the TM helices, and an allosteric site is at the extracellular vestibule consisting of extracellular loops 4 and 6, TM1, 6, 10, 11 (Coleman et al., 2016; Coleman and Gouaux, 2018; Coleman et al., 2019, 2020). Effectors in the allosteric site of SERT can enhance the binding of escitalopram in the central site and block its dissociation (Xue et al., 2022). The allosteric effect of escitalopram makes it an effective and fast-acting medication for psychiatric disorders. DDIs between the allosteric site and central binding site may have effects on the efficacy and toxicity of SERT inhibitors, which has the potential to be a new therapeutic strategy.

There is a growing body of evidence that lipid molecules play a critical role in regulating transporter function (Li et al., 2015; Corradi et al., 2019). The effects of lipids on ABC transporters appear to be more complex than those of the SLC superfamily as they can mediate the efflux of multiple exogenous drugs and endogenous lipids, which can easily mediate drug-lipid interactions (Muller et al., 2019; Kroll et al., 2021). Although mechanisms of drug-lipid interactions have not been extensively investigated, the binding sites, binding pathways, and conformational changes induced by lipids have been preliminarily explored based on transporter structures using computational simulation methods (Omote and Al-Shawi, 2006; Mayne et al., 2016; Barreto-Ojeda et al., 2018; Domicevica et al., 2018; Immadisetty et al., 2019). Moreover, drug-metabolite interactions and drug-food interactions have also been reported for transporters, which may influence the pharmacokinetic profile of drugs in vivo (Nakanishi and Tamai, 2015; Nigam, 2015).

Importance of Structure in the Study of Transporter Gene Polymorphisms

The interindividual variability in the pharmacological treatment between patients may be related to the genetic factor of transporters (Zhou et al., 2017; Juan-Carlos et al., 2021). Residue mutations of transporters usually change the charge environment, hydrophobic property, and volume of residues, causing spatial variations in structures (Fu et al., 2022). Understanding the variability in transporter structure caused by genetic factors can help clarify changes in drug disposition and provide safer and more effective drug treatments. For example, molecular dynamics simulation results suggested that the Arg538Ser and Met701Arg mutations in the P-gp structure have effects on P-gp function by changing protein dynamics (Chakraborty et al., 2018). In addition, residue mutations of Phe978 (located in TM12), Pro223(located in TM4), Phe777 (located in TM8), and Pro866 (located in TM10) in P-gp also have effects on the binding of many drugs, including vinblastine, colchicine, adriamycin, and others (Loo and Clarke, 1993a,b; Hong, 2017).

For the SLC superfamily, extensive computational and experimental studies have reported that residue mutations have important effects on their function. In brief, residue mutations associated with psychiatric diseases lead to dysfunction of SLC transporters by reducing ligand binding affinity, altering the electrochemical potential and the sensitivity of sodium and chloride ions to transporters, and affecting transport activity (Ivancsits et al., 2003; Chen et al., 2005; Mazei-Robison et al., 2008; Wendland et al., 2008; Hamilton et al., 2013; Fraser et al., 2014; Mergy et al., 2014; Herborg et al., 2018; Reith et al., 2018; Quinlan et al., 2019; Zwartsen et al., 2019; Strauss et al., 2022). For example,

Gly56Ala, Lys605Asn, and Ile425Val of SERT are associated with psychiatric disorders by enhancing their function (Ozaki et al., 2003; Quinlan et al., 2019). Taking into account the importance of structural variability in transporters, the VARIDT database (http://varidt.idrblab.net) collects 145 mutation structures originating from 42 transporters of 16 subfamilies, which contributes to knowledge on the critical role of transporter structures in drug disposition, efficacy, and toxicity (Fu et al., 2022).

Summary and Prospect

In this review, we collected structural information on the ABC and SLC transporters and found that only a few transporters have atomic-resolution three-dimensional structures. Combining experimental structures and methods with computational techniques to predict protein structures, studying the binding sites, key residues, ligand-receptor interactions, protein conformational changes, and the development of potential regulatory molecules are the most common research topics for transporters. Despite the apparent progress, many mechanisms still need to be clarified regarding the structure-function relationship of transporters; the main focus should be the dynamic transport process and its regulatory mechanism. For example, energy-coupling mechanisms and the modulation of transport activity by gene polymorphisms and other molecules. The functional processes of transporters involve highly diverse conformational changes; however, it is difficult to capture dynamic information in a comprehensive manner. The combination of computational simulation methods with AI algorithms may offer a new opportunity to further examine the function of transporters, allowing the conformational changes that occur during dynamic transport to be effectively identified.

Data Availability

The authors declare that all the data supporting the findings of this study are contained within the paper.

Authorship Contributions

Participated in research design: Fu, Zeng, Zheng, Zhu.

Performed data analysis: Fu, Zhu.

Wrote or contributed to the writing of the manuscript: Fu, Zeng, Zheng, Zhu.

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