1

OVERVIEW OF DRUG TRANSPORTER FAMILIES

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1.1 WHAT ARE DRUG TRANSPORTERS?

Transporters are membrane proteins whose primary function is to facilitate the flux of molecules into and out of cells. Drug transporters did not evolve to transport specific drugs. Instead, their primary functions are to transport nutrients or endogenous substrates, such as sugars, amino acids, nucleotides, and vitamins, or to protect the body from dietary and environmental toxins. However, the specificity of these transporters is not strictly restricted to their physiological substrates. Drugs that bear significant structural similarity to the physiological substrates have the potential to be recognized and transported by these transporters. As a consequence, these transporters also play significant roles in determining the bioavailability, therapeutic efficacy, and pharmacokinetics of a variety of drugs. Nevertheless, because drugs may compete with the physiological substrates of these transporters, they are also likely to interfere with the transport of endogenous substrates and consequently produce deleterious effects on body homeostasis.

1.2 STRUCTURE AND MODEL OF DRUG TRANSPORTERS

Because of the involvement of transporters in all facets of drug absorption, tissue distribution, excretion, and efficacy/toxicity, characterization of transporter structure can provide a scientific basis for understanding drug delivery and disposition, as well as the molecular mechanisms of drug interaction and interindividual/interspecies differences. However, compared to soluble proteins, the atomic resolution crystal structures of membrane transporters have been extremely difficult to obtain for several reasons: first is the amphipathic nature of the surface of the transporters, with a hydrophobic area in contact with membrane phospholipids and polar surface areas in contact with the aqueous phases on both sides of the membrane; second is the low abundance of many transporters in the membrane, making it impossible to overexpress them, a prerequisite for structural studies; and third is the inherent conformational flexibility of the transporters, making it difficult to obtain stable crystals.

Due to these difficulties, high-resolution three-dimensional structures have been obtained for only a limited number of transporters. For other transporters, the three-dimensional structures have been achieved through homology modeling. In this approach, similar folding patterns between any protein and one for which the crystal structure is known enable the construction of a fairly accurate three-dimensional protein model of the unknown structure using the related crystal structure as a template and modern computational techniques. Three-dimensional structures have revealed that transporters have alpha-helical structures of the membrane-spanning domains, and some of the helices have irregular shapes with kinks and bends. Certain transporters undergo substantial movements during the substrate translocation process. Construction of three-dimensional transporter models has provided insight into functional mechanisms and molecular structures and enabled formulation of new hypotheses regarding transporter structure and function, which may be experimentally validated.

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1.3 TRANSPORT MECHANISMS

Not only different transporters reside in the membrane with different three-dimensional structures, but also they transport their substrates through different transport mechanisms. According to their transport mechanisms, transporters can be divided into passive and active transporters: passive transporters, also called facilitated transporters, allow molecules to move across the cell membrane down their electrochemical gradients. Such a spontaneous process decreases free energy, and increases entropy in a system, and therefore does not consume any chemical energy. In contrast to facilitated transporters, active transporters typically move molecules against their electrochemical gradients; such process is entropically unfavorable and therefore needs the coupling of the hydrolysis of ATP as an energy source. This coupling can be either primary or secondary. In primary active transport, transporters that move molecules against their electrical/chemical gradient hydrolyze ATP. In the secondary active transport, transporters utilize ion gradients, such as sodium or proton gradients, across the membrane produced by the primary active transporters and transport substrates against an electrochemical difference.

1.4 POLARIZED EXPRESSION OF DRUG TRANSPORTERS IN BARRIER EPITHELIUM

Most drug transporters are expressed in tissues with barrier functions such as the liver, kidney, intestine, placenta, and brain. Cells at the border of these barriers are usually polarized. For example, enterocytes of the intestine and proximal tubule cells of the kidney have an apical domain facing the lumen and a basolateral domain facing the blood circulation; hepatocytes polarize into a canalicular membrane facing the bile duct and sinusoidal membrane facing the blood circulation; syncytiotrophoblasts of placenta have an apical domain facing maternal blood and a basolateral domain facing the fetus. Brain capillary endothelial cells, which function as the blood–brain barrier, also polarize into apical and basolateral membranes. In most cases, the expression of drug transporters is highly restricted to one side (i.e., apical or basolateral domain) of polarized cells. Such polarized expression of the transporters is essential for the concerted transport of drugs in the same direction. One of the most well-studied examples of concerted transport is the kidney. Kidney proximal tubule cells play a critical role in the body clearance of drugs. These drugs are first taken up from the blood into the proximal tubule cells by transporters at the basolateral membrane. Once inside the cells, these drugs are then transported out of the cells into the tubule lumen by transporters at the apical membrane and subsequently eliminated in the urine. The alliance between transporters at both the basolateral membrane and the apical membrane of the kidney proximal tubule cells ensures the clearance of the drugs from the body.

1.5 CLASSIFICATIONS OF DRUG TRANSPORTERS

Drug transporters can be classified in a number of different manners, including as efflux transporters versus influx transporters, secretory transporters versus absorptive transporters, and ATP-binding cassette (ABC) transporters versus solute carrier (SLC) transporters.

1.5.1 Definition of Efflux and Influx Transporters

Drug transporters can be categorized as efflux or influx transporters according to the direction they transport substrate across the cell membranes. This classification is often observed in the literature where drug transport studies are performed at the cellular level. With this definition, transporters that pump the substrates out of the cells are called efflux transporters, whereas transporters that transfer substrates into cells are called influx transporters.

1.5.2 Definition of Absorptive and Secretory Transporters

The other way of classifying drug transporters is from a pharmacodynamic or pharmacokinetic point of view. In such a classification, the transporter that transfers its substrates into the systemic blood circulation is called an absorptive transporter, whereas the transporter that excretes its substrates from the blood circulation into the bile, urine, or gut lumen is known as a secretory transporter. However, when absorptive or secretory transporters in the blood–brain barrier and placenta are discussed, the definition needs to be modified. The brain and fetus have been traditionally considered as two “isolated” compartments in the human body. In drug therapy, many strategies have been utilized to achieve either enhanced or reduced penetration of drugs into these two compartments. Conventionally, the transporters facilitating drug penetration into the brain or fetus are referred to as absorptive transporters.

1.5.3 Relationship between Influx/Efflux and Absorptive/Secretory Transporters

An absorptive transporter does not necessarily mean that it influxes a substrate. Similarly, a secretory transporter does not have to be an efflux pump. For example, organic anion transporter (OAT) OAT1, present at the basolateral membrane of the kidney proximal tubule, is an influx transporter based on its role of taking up drugs from the blood into the proximal tubule cells for their subsequent exit across the apical membrane into the urine for elimination. However, considering its overall role of removing drugs out of the blood circulation into the urine, OAT1 is a secretory transporter. Intestinally expressed organic anion-transporting polypeptide

TABLE 1.1 Classifications of representative drug transporters

Transporter family	Family member	Gene name	Human chromosome locus	References[a]
Organic cation transporter (OCT)	hOCT1	*SLC22A1*	6q26	[1]
	hOCT2	*SLC22A2*	6q26	[1]
	hOCT3	*SLC22A3*	6q26-q27	[2]
Organic cation/carnitine transporter (OCTN)	OCTN1	*SLC22A4*	5q31.1	[3]
	OCTN2	*SLC22A5*	5q31	[4]
	OCTN3	*SLC22A21*	5q31	[5]
	CT2	*SLC22A16*	6q22.1	[6]
OAT	OAT1	*SLC22A6*	11q13.1-q13.2	[7]
	OAT2	*SLC22A7*	6p21.2-p21.1	[8]
	OAT3	*SLC22A8*	11q11.7	[9]
	OAT4	*SLC22A11*	11q13.1	[10]
	URAT1	*SLC22A12*	11q13.1	[10]
Organic anion-transporting polypeptides (OATP)	OATP1C1	*SLCO1C1*	12p12.2	[11]
	OATP1B1	*SLCO1B1*	12p12.2	[12]
	OATP1A2	*SLCO1A2*	12p12	[11]
	OATP1B3	*SLCO1B3*	12p12	[13]
	OATP2A1	*SLCO2A1*	3q21	[14]
	OATP2B1	*SLCO2B1*	11q13	[15]
	OATP3A1	*SLCO3A1*	15q26	[16]
	OATP4A1	*SLCO4A1*	20q13.33	[16]
	OATP4C1	*SLCO4C1*	5q21.2	[17]
	OATP5A1	*SLCO5A1*	8q13.3	[18]
	OATP6A1	*SLCO6A1*	5q21.1	[19]
Peptide transporter (PEPT)	PEPT1	*SLC15A1*	13q33-q34	[20]
	PEPT2	*SLC15A2*	3q21.1	[21]
	PHT1	*SLC15A4*	12q24.32	[22]
	PHT2	*SLC15A3*	11q12.2	[23]
Monocarboxylate transporters (MCT, sMCT)	MCT1	*SLC16A1*	1p12	[23]
	MCT2	*SLC16A7*	12q13	[24]
	MCT3	*SLC16A8*	22q12.3-q13.2	[25]
	MCT4	*SLC16A3*	17q25	[26]
	SMCT1	*SLC5A8*	12q23	[27]
	SMCT2	*SLC5A12*	11p14	[28]
Nucleoside transporters (CNT, ENT)	CNT1	*SLC28A1*	15q25-26	[29]
	CNT2	*SLC28A2*	15q15	[30]
	CNT3	*SLC28A3*	9q22.2	[31]
	ENT1	*SLC29A1*	6p21.1-p21.2	[32]
	ENT2	*SLC29A2*	11q13	[33]
	ENT3	*SLC29A3*	10q22.1	[34]
	ENT4	*SLC29A4*	7p22.1	[35]
Bile acid transporters	NTCP	*SLC10A1*	14q24.1	[36]
	ASBT	*SLC10A2*	13q33	[37]
	BSEP	*ABCB11*	2q24	[38]
	OST-alpha		3q29	[39]
	OST-beta		15q22.31 (Mapview)	[39]
P-Glycoprotein	MDR1	*ABCB1*	7q21.1	[40]
MRP	MRP1	*ABCC1*	16p13.1	[41]
	MRP2	*ABCC2*	10q24	[42]
	MRP3	*ABCC3*	17q22	[43]
	MRP4	*ABCC4*	13q32	[44]
	MRP5	*ABCC5*	3q27	[45]
	MRP6	*ABCC6*	16p13.1	[46]
	MRP7	*ABCC10*	6p21.1	[47]
	MRP8	*ABCC11*	16q12.1	[48]

(*Continued*)

TABLE 1.1 (Continued)

Transporter family	Family member	Gene name	Human chromosome locus	References[a]
	MRP9	*ABCC12*	16q12.1	[48]
BCRP	BCRP1	*ABCG2*	4q22	[49]
Multidrug and toxin extruders	MATE1	*SLC47A1*	17p11.2	[50]
	MATE2	*SLC47A2*	17p11.2	[50]

[a]References where the human chromosome locus can be found.

1A2 (OATP1A2) is localized on the apical domain of enterocytes. It can take up (i.e., influx) orally administered drugs into the enterocytes for their subsequent exit across the basolateral membrane into the bloodstream, so OATP1A2 is considered an absorptive transporter. Therefore, influx transporters can function as either absorptive or secretory transporters depending on the tissue and on the membrane domain where they are expressed.

1.5.4 ABC Transporters and SLC Transporters

Most of the drug transporters can also be molecularly and mechanistically classified as a member of the ABC transporter family or the SLC transporter family (Table 1.1).

ABC transporters are a family of membrane transport proteins that require ATP hydrolysis for the transport of substrates across membranes. Therefore, ABC transporters are primary active transporters. The protein family derives its name from the ATP-binding domain found on the protein. The best studied drug transporters that are classified as ABC transporters are multidrug resistance protein (MDR), multidrug resistance-associated protein (MRP), and breast cancer resistance protein (BCRP).

Some of the SLC transporters utilize an electrochemical potential difference of the transported substrate and are therefore classified as facilitated transporters; other SLC transporters utilize an ion gradient, such as sodium and proton gradients across the membrane produced by the primary active transporters, and transport substrates against an electrochemical difference. These transporters are classified as secondary active transporters. In contrast to ABC transporters, SLC transporters do not possess ATP-binding sites. Most drug transporters belong to the SLC transporter family.

1.6 REGULATION OF DRUG TRANSPORTERS

Given the importance of drug transporters in the absorption, distribution, and excretion of a diverse array of environmental toxins and clinically important drugs, alteration in the function of these transporters plays a critical role in intra- and interindividual variability of the therapeutic efficacy and the toxicity of the drugs. As a result, the activity of drug transporters must be under tight regulation so as to carry out their normal duties. Key players involved in the regulation of transporters are hormones, protein kinases, nuclear receptors, scaffolding proteins, and disease conditions. These players may affect transporter activity at multiple levels, including (i) when and how often a gene encoding a given transporter is transcribed (transcriptional control), (ii) how the primary RNA transcript is spliced or processed (RNA processing control), (iii) which mRNA in the cytoplasm is translated by ribosomes (translational control), (iv) which mRNA is destabilized in the cytoplasm (mRNA degradation control), and (v) how a transporter is modified and assembled after it has been made (posttranslational control). Posttranslational modification may alter physical and chemical properties of the transporters, their folding, conformation, distribution, stability, and their activity. Because of such loops and layers of regulation, the functional diversity of these transporters often far exceeds the considerable molecular diversity of the transporter genes, which may help in utilizing identical transporter proteins for different cellular functions in different cell types.

Regulation of transporter activity at the gene level usually occurs within hours and days and is therefore classified as long-term or chronic regulation. Long-term regulation usually occurs when the body undergoes massive change, such as during development or the occurrence of disease. Regulation at the posttranslational level usually occurs within minutes or hours and is therefore classified as short-term or acute regulation. Short-term regulation usually occurs when the body has to deal with rapidly changing amounts of substances as a consequence of variable intake of drugs, fluids, or meals, as well as metabolic activity.

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