Transcriptional Regulation of Solute Carrier (SLC) Drug Transporters

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Abbreviations:
SLC, Solute carrier; ABC, ATP-binding cassette; OATPs, Organic anion-transporting polypeptides; OATs, Organic anion transporters; OCTs, Organic cation transporters; OCTNs,
Organic cation/carnitine transporters; PEPTs, Peptide transporters; MATEs, Multidrug and toxin extrusion proteins; HATs, Histone acetylases; HDACs, Histone deacetylases; BBB, Blood-brain barrier; NRs, Nuclear receptors; PXR, Pregnane X receptor; AhR, Aryl hydrocarbon receptor; CAR, Constitutive androgen receptor; FXR, Farnesoid X receptor, LXR, Liver X receptor; HIF-1α, Hypoxia-inducible factor 1 alpha; HNFs, Hepatocyte nuclear factors; Nrf2, Nuclear factor erythroid 2-related factor 2; RXR, Retinoid X receptor; RAR, Retinoic acid receptor; VDR, Vitamin D receptor; PPARα, Peroxisome proliferator-activated receptor alpha; PCN, Pregnenolone 16α-carbonitrile; SHP, Small heterodimer partner 1; CDCA, Chenodeoxycholic acid; TNF-α, Tumor necrosis factor alpha; UDCA, Ursodeoxycholic acid; HCC, Hepatocellular carcinoma; atRA, All-trans retinoic acid; BCL6, B-cell CLL/lymphoma 6; CBF, CCAAT-box-binding transcription factor; HNRNPK, Heterogeneous nuclear ribonucleic protein K; USF, upstream stimulating factor; RCC, Renal cell carcinoma; MLL1, Mixed-lineage-leucemia 1; H3K4me3, Lysine 4 on histone 3; H3K9me3, Lysine-9 on histone H3; H3K27me3, Lysine 27 trimethylation; SRC-1, Steroid receptor coactivator 1; CML, Chronic myeloid leukemia; ERE, Estrogen-responsive element; AREs, Antioxidant response elements; AP-1, Activating protein-1; AP-2rep, Activating protein-2 repressor.
Abstract

Facilitated transport is necessitated for large size, charged, and/or hydrophilic drugs to move across the membrane. The drug transporters in the solute carrier (SLC) superfamily, mainly including organic anion-transporting polypeptides (OATPs), organic anion transporters (OATs), organic cation transporters (OCTs), organic cation/carnitine transporters (OCTNs), peptide transporters (PEPTs), and multidrug and toxin extrusion proteins (MATEs), are critical facilitators of drug transport and distribution in human body. The expression of these SLC drug transporters is found in tissues throughout the body, with high abundance in the epithelial cells of major organs for drug disposition, such as intestine, liver, and kidney. These SLC drug transporters are clinically important in drug absorption, metabolism, distribution, and excretion. The mechanisms underlying their regulation have been revealing in recent years. Epigenetic and nuclear receptor-mediated transcriptional regulation of SLC drug transporters have particularly attracted much attention. This review focuses on the transcriptional regulation of major SLC drug transporter genes. Revealing the mechanisms underlying the transcription of those critical drug transporters will help us understand pharmacokinetics and pharmacodynamics, ultimately improving drug therapeutic effectiveness while minimizing drug toxicity.
Significance Statement

It has become increasingly recognized that solute carrier (SLC) drug transporters play a crucial, and sometimes determinative, role in drug disposition and response, which is reflected in decision-making during not only clinical drug therapy but also drug development. Understanding the mechanisms accounting for the transcription of these transporters is critical to interpret their abundance in various tissues under different conditions, which is necessary to clarify the pharmacological response, adverse effects, and drug-drug interactions for clinically used drugs.
1. Introduction

Drug transporter is a general term for proteins that undertake the function of transporting drugs across the cell membrane (International Transporter et al., 2010). These proteins usually belong to two super families: solute carrier (SLC) and ATP-binding cassette (ABC) proteins. Although there are exceptions, most SLC transporters are influx transporters, which mostly mediate the uptake of their substrates into cells, and ABC transporters are usually efflux transporters which transport substrates out of cells by hydrolyzing ATP (Hediger et al., 2004). SLCs are widely distributed in various tissues and organs in human body. They usually utilize the ion concentration gradient across the cell membrane as the driving force to transport their substrates (Anderson and Thwaites, 2010). Most SLC transporter proteins contain 7-14 transmembrane helices and have an intracellular and/or extracellular flexible domain, which can assist transmembrane helices to form transmembrane channels (Anderson and Thwaites, 2010). The SLC proteins include over 400 members belonging to 66 families (Perland and Fredriksson, 2017).

In recent years, many SLC members have been characterized as drug transporters because their substrates include a structurally diverse of clinically used drugs. The genes encoding these SLC drug transporters mainly include SLC21/SLCO gene family (encoding for organic anion-transporting polypeptides, OATPs), SLC22A gene subfamily (for organic anion transporters, OATs; organic cation transporters, OCTs; and organic cation/carnitine transporters, OCTNs), SLC15A gene subfamily (for peptide transporters, PEPTs), and SLC47A gene subfamily (for multidrug and toxin extrusion proteins, MATEs) (Liu, 2019) (Fig. 1). It is notable that although MATEs belong to the SLC superfamily, they may function
as efflux transporters in polarized epithelia cells such as hepatocytes and renal proximal tubular cells (Loncar et al., 2016). Due to their critical role in drug absorption, distribution, and elimination, alteration in the activities of these SLC drug transporters may result in changes in pharmacokinetics and consequently in drug response, potentially leading to reduced therapeutic effectiveness, developed drug resistance, increased susceptibility to drug-induced tissue injuries, and endogenous toxin-mediated diseases (Niemi, 2010; Huang et al., 2020; Yang and Shu, 2021). The activity of a drug transporter is subject to regulation by various factors such as genetic polymorphisms, co-medication, environmental toxins, food, and disease conditions.

The molecular biology, substrates, inhibitors, and role in drug disposition and response of these SLC drug transporters have been comprehensively reviewed elsewhere (Roth et al., 2012; Cesar-Razquin et al., 2015; Lin et al., 2015; Bhutia et al., 2016; Murray and Zhou, 2017; Rives et al., 2017; Nigam, 2018; Schlessinger et al., 2018; Liu, 2019; Ayka and Sehirli, 2020; Bednarczyk and Sanghvi, 2020; Huang et al., 2020; Koepsell, 2020; Pacha et al., 2021; Pizzagalli et al., 2021; Yang and Shu, 2021). These major SLC drug transporters are also briefly summarized in Table 1. In contrast to their well-recognized clinical importance, the regulatory mechanisms accounting for the activities of SLC drug transporters remain less characterized in general. However, there have been important progresses in recent years on regulation of individual SLC drug transporters via the mechanisms at different levels including transcription, post-transcription, translation, and post-translation. Herein we choose to review the transcriptional regulation of those major SLC drug transporters. Currently, the evidence supporting various transcriptional regulation of an individual SLC drug transporter
is predominantly obtained from cellular studies and animal models. Although further clinical studies with a sufficient sample size are needed to validate those preclinical findings, certain transcriptomic analyses with patient tissue samples, pharmacogenetic studies, and characterization of probe drug disposition and effects in human subjects have begun to reveal clinical relevance of such transcriptional regulation. Below we first provide a brief overview of the general mechanisms involved in transcriptional regulation of SLC drug transporters, which is followed by our review on the research progress of transcriptional regulation on those important SLC drug transporters and then our prospective on future research in this area.

2. Overview of the mechanisms involved in transcriptional regulation of SLC drug transporters

Transcriptional regulation refers to alteration in the level of gene expression by changing the rate of transcription. It is a vital process in regulation of gene function in eukaryotes that plays an important role in the accuracy and diversity of genetic information transmission. Transcriptional regulation in eukaryotes includes various processes that are highly related to each other, such as DNA methylation, histone modification, chromatin remodeling, and control of transcription via different regulatory factors (Miller and Grant, 2013).

DNA methylation is a form of chemical modification for DNA that alters gene expression without altering the DNA sequence (Fig. 2). The process results in the addition of methyl (CH$_3$) groups to the DNA strands, often to the fifth carbon atom of a cytosine ring (Jin et al., 2011). DNA methylation can be found in all vertebrates. The methylation of specific
cytosines can be determined by using bisulfite sequencing. In eukaryotes, DNA methylation predominantly occurs at the dinucleotide CpG. The methylation of CpG dinucleotides in the promoter region may suppress the transcription of the corresponding gene (Sperling, 2007). Sometimes, it may fully silence gene expression, which in turn can render functional deficiency of the corresponding gene.

The chromosomes of eukaryotes are mainly composed of DNA and proteins that include histones and non-histones. Posttranslational modification of the DNA-binding histones has been characterized as a common mechanism in regulation of gene expression (Fig. 2). It refers to chemical modification of histones, such as methylation, acetylation, phosphorylation, adenylation, ubiquitination, and ADP ribosylation, under the action of related enzymes such as histone acetylase (HAT), deacetylase (HDAC), methyltransferase, and demethylase (Wang et al., 2016; Zhang et al., 2021). Histone modification could regulate gene expression by affecting the binding between histones and DNA double strands and altering the conformation of nucleosomes, which may result in chromatin remodeling, or by affecting the binding between transcription factors and the promoter of a gene (Moore et al., 2013).

Chromatin remodeling refers to the molecular mechanism by which the packaging state of chromatin, histones in nucleosomes, and the corresponding DNA molecules are changed during the replication and recombination (Lorch and Kornberg, 2017). ATP-dependent chromatin remodeling factors play a critical role in this process. They regulate chromatin conformation by altering the assembly, disassembly, and rearrangement of nucleosomes on chromatin, thereby improving the accessibility of transcription factors and other
transcription-related factors to local chromatin DNA (Hota and Bruneau, 2016).

Transcription factors are a set of proteins that bind to specific regions of DNA molecules that control transcription, such as the sequences of promoters and enhancers, promoting or suppressing the transcription of genetic information from DNA into RNA (Lambert et al., 2018). The function of transcription factors can be accomplished alone or by forming complexes with other proteins or molecules. The transcriptional factors are encoded by a variety of genes. About 1600 genes have been predicted in the human genome to encode transcription factors. The nuclear receptors (NRs) are a group of transcription factors in cells. Members of the nuclear receptor superfamily play important roles in cell growth, development, differentiation, metabolism and are particularly known to positively or negatively regulate the transcription of SLC drug transporter genes (Geier et al., 2007; Stieger and Geier, 2011; Svoboda et al., 2011; Stieger and Hagenbuch, 2014).

The transcriptional regulation of a transporter gene could be complicated. Multiple mechanisms described above could be involved in regulation of an individual transporter gene. For example, a single NR may be involved in the regulation of multiple hepatic transporter genes, while a transporter gene can be regulated by multiple NRs in the liver (Staudinger et al., 2013; Amacher, 2016). Those major regulatory mechanisms and/or the related regulatory molecules for transcription of major SLC drug transporter genes are briefly summarized in Table 2.

### 2.1 Transcriptional regulation of OATPs

Studies have shown that the expression of OATPs is subject to the regulation via DNA
methylation and histone modification (Imai et al., 2013a). A recent analysis on DNA methylation of SLCO genes showed that the CpG dinucleotides around the transcription start site (TSS) of SLCO1B3 have multiple methylation patterns (Ichihara et al., 2010). These methylation patterns have differential impact on the expression of SLCO1B3 in various human cancer cell lines (Imai et al., 2013b). Furthermore, it has been reported that the promoter region of SLCO3A1 was hypermethylated while that of SLCO4A1 hypomethylated in colorectal cancer tissues and cell lines, which resulted in a low mRNA expression of SLCO3A1 and high expression of SLCO4A1, respectively (Rawluszko-Wieczorek et al., 2015). In addition, in prostate tumor tissues, the promoter region of SLCO4C1 was found to be significantly hypermethylated, which was negatively correlated with the expression of SLCO4C1 and the prognosis of patients after radical prostatectomy (Li et al., 2019). Interestingly, the use of demethylating agents or histone deacetyslase inhibitor could partially restore the expression of some SLCOs, such as SLCO2A1 in colorectal neoplasia (Holla et al., 2008) and in human head and neck squamous cell carcinoma (Zolk et al., 2013), and SLCO1B3 in hepatic carcinoma (Ichihara et al., 2010). A genome-wide DNA-methylation profiling has revealed that the expression of Slco1b2 in mouse liver was regulated by DNA methylation in the promoter and by histone acetylation (Imai et al., 2009). In subsequent analyses, the epigenetic profiles of DNA methylation and histone acetylation around the TSS of mouse and human SLCOs (Slco1a1, Slco1a6, Slc16a2, Slco1a4, SLCO1B1 and SLCO1B3) were found to be associated with tissue-specific expression of these transporters (Imai et al., 2013a). The DNA methylation may be a determinant of the specific tissue distribution of OATPs.
The role of transcription factors in regulation of OATP expression has been widely characterized. The NRs involved in the transcription of SLCO genes include: the typical xenobiotic responsive NRs, such as pregnane X receptor (PXR), aryl hydrocarbon receptor (AhR), and constitutive androgen receptor (CAR), and other NRs of both physiological and pharmacological importance, such as farnesoid X receptor (FXR), liver X receptor (LXR), hypoxia-inducible factor 1 alpha (HIF-1α), hepatocyte nuclear factors (HNFs), the nuclear factor erythroid 2-related factor 2 (Nrf2), retinoid X receptor (RXR), retinoic acid receptor (RAR), vitamin D receptor (VDR), and peroxisome proliferator-activated receptor alpha (PPARα) (Guo et al., 2002a; Cheng et al., 2005; Jigorel et al., 2006; Meyer zu Schwabedissen and Kim, 2009; Klaassen and Aleksunes, 2010; Aleksunes and Klaassen, 2012; Eloranta et al., 2012; Wang et al., 2012b).

PXR is a ligand-dependent transcription factor with a broad spectrum of ligands, including many endogenous and exogenous compounds (Masuyama et al., 2005). After binding with ligand, PXR experiences conformation change and binds to the promoter region of target genes to regulate gene expression (Wang et al., 2014). In animals, it was reported early that treatment with PXR ligand pregnenolone 16α-carbonitrile (PCN) could induce the protein level of rat Oatp2 by more than three folds (Guo et al., 2002b). In addition, the mRNA expression of rodent Slco1a4 and the hepatic uptake of OATP substrates could be up-regulated by several PXR ligands (phenobarbital, PCN and spironolactone) (Hagenbuch et al., 2001; Cheng et al., 2005). In human subjects, carbamazepine (CBZ), which is a PXR agonist, was reported to increase the mRNA expression of OATP-A (SLCO1A2), OATP-B (SLCO2B1), OATP-C (SLCO1B1), and OATP-8 (OATP1B3) in the livers of CBZ-treated
patients (Oscarson et al., 2006). Atorvastatin, a possible PXR agonist, has been shown to increase the mRNA expression of \( SLCO2B1 \) in patient livers as well (Björkhem-Bergman et al., 2013). The \textit{in vivo} findings are supported by abundant \textit{in vitro} evidence. For example, treatment with the PXR ligand rifampicin was found to upregulate the mRNA expression of \( SLCO1B1, SLCO1B3 \) and \( SLCO2B1 \) in human primary hepatocytes (Rodrigues et al., 2020). PXR also plays a significant role in regulating the mRNA expression of OATPs in certain cancer cells, such as \( SLCO2A1 \) in head and neck squamous cell carcinoma cells (Zolk et al., 2013), \( OATP-A \) (\( SLC21A3 \)) in breast carcinoma (Miki et al., 2006), and \( SLCO1A2 \) in breast cancer cells (Meyer zu Schwabedissen et al., 2008). Notably, as a possible effect of OATP induction on drug disposition, rifampicin administration could alter the pharmacokinetics of statins that are OATP substrates (Rodrigues et al., 2020). However, we should be careful while interpreting the DDIs involved those PXR ligands that may have multiple pharmacological mechanisms or targets in different species. For example, there are controversial reports in which rifampicin had no direct effect on the gene expression of \( SLCO \) in hepatocytes \textit{in vitro} and in monkey livers (Meyer Zu Schwabedissen et al., 2010; Benson et al., 2016; Niu et al., 2019). The molecular mechanism of PXR signaling and the effects by PXR ligands in regulation of \( SLCO \) transcription \textit{in vivo} thus remains to be fully characterized.

AhR and CAR are also ligand-dependent transcription factors that regulate the transcription of downstream target genes, and particularly those xenobiotic response genes including \( SLCO \) genes (Kawamoto et al., 1999; Murray et al., 2014; Kersten and Stienstra, 2017). The effects of AhR and CAR activation on specific \( SLCO \) gene expression may be
opposite. Studies have shown that AhR ligands (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD; polychlorinated biphenyl 126; beta-naphthoflavone, and 3-methylcholanthrene) could increase the mRNA expression of certain OATPs, such as Slco2b1 and Slco3a1 in mouse liver (Cheng et al., 2005). Treatment with statins, which have not been characterized as direct AhR ligands, were reported to induce the mRNA expression of SLCO4C1 through AhR activation in human kidney proximal cells (Toyohara et al., 2009; Suzuki et al., 2011). Furthermore, treatment with the natural product shikonin has been reported to effectively upregulate the transcription of SLCO1B1 and SLCO2B1 through activation of AhR in hepatocytes as well (Huang et al., 2018). On the other hand, it has been reported that TCDD could repress the mRNA expression of SLCO2B1 (Le Vee et al., 2015), Slco1a1 (Aleksunes and Klaassen, 2012), and Slco1a4 (Guo et al., 2002a). Whereas CAR activation has been reported to cause decreased expression of SLCO1B3, SLCO2B1 (Jigorel et al., 2006), and Slco1a1 (Cheng et al., 2005; Aleksunes and Klaassen, 2012), it results in an enhanced activity of SLCO1A2 gene promoter (Meyer zu Schwabedissen et al., 2008) and an increased expression of Slco1a4 (Aleksunes and Klaassen, 2012). In addition, the CAR ligand diallyl sulfide could increase the mRNA expression of mouse Slco1a4 (Guo et al., 2002a) but decrease that of SLCO1B3 in human liver slices (Jigorel et al., 2006).

FXR acts as an intrahepatic "bile acid receptor", regulating bile acid synthesis, detoxification and transport, and maintaining the homeostasis balance between bile acid and liposome (Glastras et al., 2015). FXR can also regulate the transcription of SLCO, indirectly or directly (Ohtsuka et al., 2006; Godoy et al., 2013). On the one hand, the accumulation of bile acids can activate FXR, which in turn promotes the transcription of the FXR-responsive
gene encoding small heterodimer partner 1 (SHP) protein. The SHP could repress the expression of HNF4α, eventually reducing HNF4-mediated expression of *SLCO1B1* and *SLCO1B3* (Kullak-Ublick et al., 2004). On the other hand, the activated FXR could directly bind to the promoter of *SLCO* genes and regulate its transcription. This is exemplified by several lines of evidence. The genetic polymorphism of FXR promoter has been associated with a decreased expression of *SLCO1B1* (Marzolini et al., 2007). Treatment with the bile acid chenodeoxycholic acid (CDCA), an FXR ligand, could increase the mRNA expression of *SLCO1B3* in human hepatocellular carcinoma cells (Jung et al., 2002). The synthetic FXR agonists GW4064 and fexaramine could significantly increase the transcription activity of *SLCO1B1* gene (Meyer Zu Schwabedissen et al., 2010). In addition, berberine could induce the nuclear translocation of FXR and LXRα, which in turn increased the expression of *SLCO1B1* (Liu et al., 2020). Both agonists and antagonists of FXR could also regulate the transcription of other *SLCO* such as *SLCO1A2, SLCO1B3-1B7* (*LST-3TM12*) (Yang et al., 2014; Malagnino et al., 2019). *SLCO1B3-1B7* is a splice variant of *SLCO1B3* and *SLCO1B7*. For OATP1B3–1B7 protein, the N-terminal part of its mRNA derives from *SLCO1B3*, whereas the remaining part of the transcript originates from the neighboring *SLCO1B7* gene locus. Notably, the regulation of *SLCO* transcription by FXR signaling is often involved with other NRs.

LXR is also activated by ligands, which could consequently initiate and regulate the transcriptional expression of its target genes that are important in endogenous metabolism (Wang et al., 2015). It has been reported that treatment with the LXRα agonists TO-901317 and GW3965 could up-regulate the mRNA expression of *SLCO1B1* in Huh-7 cells (Meyer Zu
Schwagedissen et al., 2010). LXRα collaborates with FXR to co-regulate \textit{SLCO1B1} transcription. There is an interaction among LXRα, FXR and the specific DNA binding module of the 5' non-coding region of the \textit{SLCO1B1} gene.

HIFs are transcription factors that respond to oxygen content in cellular environment and are activated in the presence of reduced oxygen levels or hypoxia (Ziello et al., 2007). Several lines of evidence have indicated that a role of HIF1α in \textit{SLCO} transcriptional regulation. Studies have shown that HIF1α could bind to the promoter sequences of certain cancer-specific OATP1B3 variants and regulate their mRNA expression (Han et al., 2013). Consistently, HIF1α was found to regulate the transcription of \textit{SLCO1B3} via two HIF response elements in intron 1 of \textit{SLCO1B3} gene (Ramachandran et al., 2013). In addition, the mRNA expression of \textit{SLCO1B3} and \textit{SLCO2B1} has been found to be induced by HIF-1α stabilizers but reduced by HIF-1α knockdown (Shi et al., 2014).

HNFs are a group of phylogenetically unrelated transcription factors that regulate the transcription of a wide range of genes (Lau et al., 2018). Functional HNF1α response elements have been identified in the proximal promoter of \textit{SLCO1B1} (Jung et al., 2001; Maher et al., 2006). The regulation of \textit{SLCO} transcription by HNFs seems to be related to disease conditions. Lipopolysaccharide (LPS) could down-regulate the mRNA expression of \textit{Slco1b2}, which was attributed to a reduced binding of HNF1α, HNF3, and RXR:RAR to \textit{Slco1b2} promoter (Li and Klaassen, 2004). The increased expression of the cytokine tumor necrosis factor alpha (TNF-α) was reported to be a mechanism underlying the reduced expression of \textit{Slco1a1} and \textit{Slco1a4} in the mice with liver injury, which was probably through a HNF1-dependent signaling (Geier et al., 2003). In HNF1α-null mice, the mRNA expression

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of Slco1a1, Slco1a4, Slco1a5, Slco1b2, Slco2b1, Slco3a1, Slco4c1 in the liver, Slco1a1, Slco1a6, Slco2b1, Slco3a1, Slco4c1 in the kidney, and Slco2a1 in the duodenum were altered (Maher et al., 2006). There is also in vivo evidence in human subjects suggesting the regulation of SLCO1B1 expression by HNF1α (He et al., 2008). Ursodeoxycholic acid (UDCA) is an inhibitor of HNF1α. In healthy subjects, treatment with UDCA could cause significant alteration in the pharmacokinetics of rosuvastatin that is a well characterized OATP1B1 substrate. The regulation of SLCO transcription by HNFs could involve other NRs. For example, HNF1α and HNF3 could partner with RXR:RAR at the Slco1b2 promoter (Li and Klaassen, 2004). The down-regulation of SLCO1B3 expression in hepatocellular carcinoma (HCC) has been related to the high expression of HNF3β (Vavricka et al., 2004). Later, it was found that FXR, HNF1α and HNF3β simultaneously regulated the transcription of SLCO1B3 (Ohtsuka et al., 2006). In addition, HNF4α has also been found to promote SLCO1B3 transcription through the co-activation of β-catenin in HCC (Kitao et al., 2018).

Nrf2 is a nuclear transcription factor that regulates about 250 genes involved in cell homeostasis, including antioxidant proteins, detoxifying enzymes, drug transporters, and many cell protective proteins (Tonelli et al., 2018). In rodents, the activation of Nrf2 could down-regulate the transcriptional expression of Slco1a1 but up-regulate those of Slco2b1 and Slco1b2 (Cheng et al., 2005; Cheng et al., 2011; Aleksunes and Klaassen, 2012; Wu et al., 2012). In the liver of Nrf2 knockout mice, the mRNA expression of Slco1a6, Slco2b1 (Anwar-Mohamed et al., 2011) and Slco1b2 (Tanaka et al., 2009) were significantly decreased.

There are additional NRs which role in the transcription of SLCOs has been explored. In
human hepatocytes, all-trans retinoic acid (atRA) could activate the formation of RXR:RAR heterodimers which could down-regulate the mRNA and protein expression of OATP1B1 and OATP2B1 (Le Vee et al., 2013). The effects of atRA treatment on SLCO expression could be counteracted by knockdown of RXR and RAR. VDR, an NR that in complex with hormonally active vitamin D, 1,25(OH)2D3, regulates the expression of a wide array of physiologically important genes. In small intestinal epithelial cells, VDR has been shown to be involved in the transcriptional activation of SLCO1A2 (Eloranta et al., 2012). In addition, PPARα has also been reported to play a vital role in the down-regulation of Slco1a1, Slco1a4, Slco1b2 in mouse livers by the environmental toxic chemicals perfluorooctanoic acid and perfluorodecanoic acid (Cheng and Klaassen, 2008). In wild-type mice, treatment with PPARα ligands, including clofibrate, ciprofibrate, and diethylhexylphthalate, could significantly decrease the mRNA levels of Slco1a1, Slco1b2, Slco2a1, and Slco2b1 in the liver (Cheng et al., 2005). As recently reviewed elsewhere (Rodrigues et al., 2020; Zamek-Gliszczynski et al., 2021), however, we would like to point out that the direct clinical evidence remains very limited to support an importance of alteration in OATP transcriptional regulation in determining drug disposition and response. Further clinical studies are therefore needed to characterize the clinical relevance for these various regulatory mechanisms of OATP transcription.

2.2 Transcriptional regulation of OATs

Epigenetic mechanisms are involved in the transcriptional regulation of OATs. Both DNA methylation and histone modification may play a vital role. By identifying the TSS of
SLC22A8 gene, the Sugiyama group found that the promoter region of SLC22A8 has multiple CpG dinucleotides as the targets of DNA methylation (Kikuchi et al., 2006). In their follow-up studies, DNA methylation was found to repress the activity of the SLC22A8 promoter and decrease the expression of SLC22A8, whereas the transcription could be resumed when using methyltransferase inhibitors (Kikuchi et al., 2006). DNA methylation is also highly related to the tissue specific expression of OAT1 and OAT3 (Jin et al., 2012). Compared to the renal cortex, most of the CpG dinucleotides around the TSSs of hepatic Slc22a6 and Slc22a8 were highly methylated, which consistent with their high expression levels in the kidney but low levels in the liver. Recently, another study showed that histone hypoacetylation rather than DNA hypermethylation was involved in the transcriptional suppression of SLC22A7 in HCC cell lines (Wang et al., 2021b). When histone hypoacetylation was mitigated with a histone deacetylase inhibitor, the expression of SLC22A7 was increased.

Earlier findings have revealed the transcriptional regulation of OATs by transcriptional factors and particularly various NRs. As early as in 2003, studies have found that the promoter regions of SLC22A6 and SLC22A8 have the binding sites for several transcription factors including PAX1, PBX, WT1 and HNF1 (Eraly et al., 2003). There is considerable evidence supporting that transcription factors function in transcription of OATs. For example, in reporter gene assays, expression of the transcription factor B-cell CLL/lymphoma 6 (BCL6) led to increased activities of the reporter luciferase that was driven by the promoters of Slc22a6 and Slc22a8 (Wegner et al., 2012). However, BCL6 seemed to not directly activate the promoter of SLC22A6. It indirectly enhanced the transcription by increasing the protein expression of HNF1α (Wegner et al., 2014). In addition, ERα can indirectly regulate
the transcription of SLC22A6 as well (Euteneuer et al., 2019). There was no direct binding of ERα to the SLC22A6 promoter. Instead, the ligand-activated ERα could activate the CCAAT-box-binding transcription factor (CBF) and heterogeneous nuclear ribonucleic protein K (HNRNPK), both of which could bind to the promoter of SLC22A6 and enhance its transcription. On the other hand, the ligand-activated LXRα could reduce SLC22A6 expression in the renal S2 cells, which in turn resulted in a decreased transport of OAT1 substrates in these cells (Kittayaruksakul et al., 2012). However, LXRα may have a cell-specific effect on the expression of different OATs. In the hepatocytes isolated from the rats with hypercholesterolemia, the expression of both LXRα and Oat2 were found to be reduced. In follow-up experiments with HepG2 cells treated with hypercholesterolemic serum, LXRα activation could rescue the reduced expression of SLC22A7 (Liu et al., 2016a).

Studies have also shown the regulation of OAT transcription by xenobiotic responsive NRs. Ligand-activated CAR and AhR could down-regulate SLC22A7 expression (Jigorel et al., 2006; Le Vee et al., 2015). The indoxyl sulfate was reported to induce the expression of SLC22A6 via AhR-EGFR signaling in the kidney, which could be suppressed by AhR antagonism (Jansen et al., 2019). Methotrexate is a well characterized substrate of OATs. Interestingly, treatment with methotrexate could decrease the expression of Slc22a6 and Slc22a8 in rat kidneys (Shibayama et al., 2006). As the decrease was accompanied with downregulation of CAR and PXR expression, it is likely that these two NRs was involved in the reduction of Slc22a6 and Slc22a8 expression. Moreover, the activation of Nrf2 was reported to cause a significant decrease in Slc22a7 mRNA expression (Wu et al., 2012). In addition, FXR could regulate the transcription of SLC22A7 either directly or indirectly.
(Popowski et al., 2005). FXR could directly bind to and inhibit the transactivation of \textit{SLC22A7} promoter. FXR activation could also lead to an increased expression of the gene encoding the SHP protein (Lee et al., 2000), which is a corepressor of HNF4α. The increased SHP would therefore decrease the nuclear binding activity of HNF4α, ultimately leading to a decrease in the expression of \textit{SLC22A7} (Popowski et al., 2005).

The role of cellular signaling with HNFs in regulation of \textit{OAT} transcription has been widely studied. HNF1α and HNF4α may regulate the transcription of many \textit{OAT} genes in developing kidneys because there exist a number of HNF1α/HNF4α binding elements at the proximal promoter regions of \textit{OAT} genes (Gallegos et al., 2012; Martovetsky et al., 2013; Nigam et al., 2015). Motif analysis of \textit{cis}-regulatory enhancers in the developing proximal tubules of rodents has suggested that Hnf4a and Hnf1a were the main transcriptional regulators of multiple SLC drug transporters, which include \textit{Slc22a6}, \textit{Slc22a8}, \textit{Slc22a1}, \textit{Slc22a2} and \textit{Slc47a1} (Martovetsky et al., 2013). Human HNF1α/β was also found to bind with the HNF1-motif that was located near the TSS of \textit{SLC22A6}, \textit{SLC22A8}, \textit{SLC22A11}, and \textit{SLC22A12} genes, thereby enhancing the promoter activity and activating the transcription of these transporter genes (Kikuchi et al., 2006; Kikuchi et al., 2007; Saji et al., 2008; Jin et al., 2012). Of note, mutations in the HNF1-motif could fully abolish the enhanced promoter activity that was associated with HNF1α/β binding. Besides HNF1α/β, HNF4α also regulates the transcription of \textit{OAT} genes in a similar manner (Ogasawara et al., 2007; Thiagarajan et al., 2011). The involvement of HNF1α in \textit{OAT} gene transcription has also been evidenced in genetic mouse models (Maher et al., 2006; Kikuchi et al., 2007). In HNF1α-null mice, the mRNA expression of \textit{Slc22a6}, \textit{Slc22a8} and \textit{Slc22a12} was significantly decreased in the
kidney and that of Slc22a7 was reduced in both liver and kidney. However, the expression of Slc22a8 was increased in the duodenum. OAT2, OAT5, and OAT7 are three OATs in human liver. Whereas SLC22A7 gene is subject to the transactivation by HNF4α (Popowski et al., 2005), the experimental evidence from genetic manipulation and reporter gene assays, together with expression analysis in surgical liver tissues, has indicated that HNF1α is a critical transcriptional factor in regulation of SLC22A10 and SLC22A9 expression (Klein et al., 2010).

2.3 Transcriptional regulation of OCTs

The impact of genetic variants and epigenetic regulation of OCTs in general has been briefly summarized recently (Kolz et al., 2021). Herein we select to review the findings related to transcriptional regulation. Among epigenetic mechanisms, DNA methylation is likely the most extensively investigated for the transcriptional regulation of OCT genes. OCT1 is highly expressed in human livers. Based on microarray analyses with patient liver tissues, Schaeffeler et al found that SLC22A1 expression was lower in hepatocellular carcinoma as compared with normal liver tissues, which was accompanied with DNA hypermethylation at the promoter of SLC22A1 (Schaeffeler et al., 2011). In addition, the level of SLC22A1 mRNA in cisplatin-resistant human esophageal cancer cells was found to be markedly reduced as compared to that in the sensitive cells (Lin et al., 2013). Consistently, the promoter of SLC22A1 was highly methylated in the cisplatin-resistant cells. As cisplatin is a moderate substrate of OCT1, DNA methylation could be a mechanism accounting for cisplatin chemo-resistance in some cancer patients.
Human OCT2 is a rather kidney-specific transporter. DNA methylation was found to be associated with the tissue specificity of human OCT2. The CpG sites in the proximal promoter of SLC22A2 gene were reported to be hypermethylated in the liver while hypomethylated in the kidney, which is consistent with a relatively low hepatic expression but a much high renal expression of SLC22A2 (Aoki et al., 2008). The hypomethylation of SLC22A2 promoter occurred particularly at the CpG site in the E-box that is the binding site of the basal transcription factor called upstream stimulating factor (USF) 1. Increased methylation of SLC22A2 proximal promoter could dramatically reduce the binding of USF1 to the E-box, leading to a reduced SLC22A2 transcription. Renal cell carcinoma (RCC) is characterized by multi-drug resistance. The Zeng group has identified the repressed expression of SLC22A2 as a mechanism for oxaliplatin resistance in RCC (Liu et al., 2016b). They revealed that the repressed SLC22A2 expression was characterized by hypermethylation in SLC22A2 promoter which blocked the interaction between the transcription factor MYC and the E-Box motif and prevented MYC from recruiting the histone methylase mixed-lineage-leukemia 1 (MLL1) to catalyze the trimethylation of lysine 4 on histone 3 (H3K4me3), eventually leading to the repressed SLC22A2 transcription. Importantly, the epigenetic activation of SLC22A2 by the DNA methylation inhibitor decitabine could sensitize RCC cells to oxaliplatin treatment in the animal model. They further found that histone acetylation also regulates SLC22A2 expression in RCC (Zhu et al., 2019). In normal kidney tissues, a dynamic balance of histone acetylation is maintained by histone acetyltransferases (HATs) and histone deacetylases (HDACs). In RCC cells, the interaction between HDAC7 and MYC was disrupted, leading to high abundance of HDAC7 and low
levels of histone acetylation at H3K18ac and H3K27ac around SLC22A2 promoter that contributed to the repression of SLC22A2 transcription. In addition, Saito et al reported that the placental expression of SLC22A2 was likely subject to epigenetic regulation as well (Saito et al., 2011). The mRNA expression of SLC22A2 was higher in the biallelic placental samples than that in monoallelic samples, which was associated with an increased H3 acetylation but decreased trimethylation of lysine-9 on histone H3 (H3K9me3) around SLC22A2 promoter.

For the widely expressed human OCT3, the proximal promoter has been reported to be located within a large CpG island extending into exon one of which hypermethylation might cause a reduced expression of SLC22A3 gene (Chen et al., 2013). Compared with normal tissues, the hypermethylation of SLC22A3 promoter was associated with reduced SLC22A3 transcript levels in prostate tumors. However, the hypermethylation of SLC22A3 promoter appeared to be prostate tumor-specific as it was not detected in other tumor tissues (Chen et al., 2013). In addition, metformin, which is a first-line therapy for type 2 diabetes, has been reported to reduce DNA methylation at the genes encoding metformin transporters including SLC22A3 (Garcia-Calzon et al., 2017). While the exact mechanism has not been revealed, these epigenetic changes seem to be associated with metformin anti-diabetic efficacy.

The role of NRs in regulation of OCT gene transcription has also been explored. At present, the regulatory role of PXR in SLC22A1 expression remains controversial. It has been suggested that doxorubicin treatment could suppress SLC22A1 expression by increasing the expression of PXR in renal tubular epithelial cells (Nagai et al., 2019). The transcriptional activity of SLC22A1 promoter and consequently the mRNA expression of SLC22A1 were reported to be subject to the suppression by ligand-activated PXR in human hepatocytes.
The effect by a PXR agonist has been ascribed to its competitively sequestrating the coactivator steroid receptor coactivator 1 (SRC-1) from the HNF4α response element and E-box in the SLC22A1 promoter, reducing the transactivation of SLC22A1 gene by HNF4α and USF transcription factors. However, in chronic myeloid leukemia (CML) cell lines and primary CML cells, the expression of SLC22A1 was upregulated by the agonists of PXR, RAR and RXR (Austin et al., 2015). The PXR agonist rifampin was reported to increase the mRNA expression of SLC22A1 in peripheral blood cells and enhance the glucose-lowering effect of metformin in healthy human subjects (Cho et al., 2011). In addition, overexpression of PXR was found to increase the mRNA expression of Slc22a1 in rat hepatocytes, while treatment with the PXR agonist PCN induced the expression of Slc22a1 in the liver and that of Slc22a2 in the kidney in rats (Maeda et al., 2007). Further studies are needed to clarify the role of PXR in OCT gene transcription in different cells and tissues and the in vivo effects.

It has been reported that an increased level of CDCA, which could be induced by cholestasis, down-regulates the mRNA expression of SLC22A1 and SLC22A3 in the liver (Saborowski et al., 2006; Nies et al., 2009). As CDCA is a ligand of FXR, the down-regulation has been attributed to the inhibition of HNF4α-mediated transactivation that results from CDCA-induced expression of the transcriptional repressor SHP via FXR signaling. In agreement with this, the expression of Slc22a1 was significantly downregulated in rats with obstructive cholestasis (Denk et al., 2004). In addition, by treating human renal proximal tubular cells (RPTEC/TERT1 cells) and OCT2-CHO-K1 cells with CDCA and an FXR antagonist, Z-guggulsterone, a recent study have suggested that FXR also plays a role in...
regulation of renal SLC22A2 expression (Wongwan et al., 2020).

Other NRs are also involved in transcriptional regulation of OCT genes. By measuring the promoter activity in rat renal epithelial cell line LLC-PK1, Asaka et al have demonstrated that testosterone treatment could stimulate the promoter activity of rat Slc22a2 via the androgen receptor-mediated signaling pathway (Asaka et al., 2006). In the kidney of PPARα-null mice, the expression of Slc22a2 was decreased, suggesting that PPARα, which is highly expressed in the liver and kidney, may regulate the expression of Slc22a2 (Freitas-Lima et al., 2020). As the uptake of cisplatin into the proximal tubules is significantly mediated by OCTs, deletion of PPARα was protective of cisplatin-induced nephrotoxicity in mice (Freitas-Lima et al., 2020). PPARα was also found to mediate the circadian expression of Slc22a2 in mice (Oda et al., 2014). There are two HNF4α response elements in human SLC22A1 promoter which were involved in HNF4α-mediated transactivation of SLC22A1 transcription (Saborowski et al., 2006). HNF4α could enhance SLC22A1 promoter activity by synergistic interaction with the transcription factor USF1 or USF2 (Kajiwara et al., 2008). Lastly but not least, the activation of glucocorticoid receptor could indirectly increase the expression of SLC22A1 by upregulating HNF4α expression in human primary hepatocytes (Rulcova et al., 2013).

2.4 Transcriptional regulation of OCTNs

There is evidence supporting a role of DNA methylation in regulation of OCTN gene transcription. Qu et al identified a region (from -354 to +85) in SLC22A5 promoter that was critical to the transcription of SLC22A5 gene (Qu et al., 2013). The methylation of CpG sites
in this region was found to be negatively correlated with the expression of SLC22A5 in cancer cells. Treatment with the demethylating agent decitabine could significantly reduce the hypermethylation at the SLC22A5 promoter, which enhanced the expression of SLC22A5 and consequently the transporter activities in HepG2 and LS174T cancer cells. Scalise et al. have also indicated that DNA methylation is an important mechanism underlying the down-regulation of SLC22A5 expression in epithelial cancer cells (Scalise et al., 2012). After treatment with 5-aza-cytidine, which is a demethylating agent, the mRNA expression of SLC22A5 could increase for 10 times in these cancer cells. Future studies are needed to determine the details of epigenetic regulation on OCTN transcription.

PPARs are among the major transcriptional factors characterized in the transcriptional regulation of OCTNs. The regulation of OCTNs by PPAR has been found to widely exist in humans, rodents, cattle, pigs and other animals. With multiple approaches to activation of PPARα, including treatment with PPARα agonists such as clofibrate and WY-14,643, oxidized fat diet feeding, and food restriction, the Eder group have demonstrated that PPARα activation can lead to the upregulation of Slc22a5 in mice, rats, and pigs (Luci et al., 2006; Koch et al., 2007; Luci et al., 2007; Ringseis et al., 2007a; Ringseis et al., 2007b; Ringseis et al., 2007c; Koch et al., 2008; Luci et al., 2008; Ringseis et al., 2008a; Ringseis et al., 2008b; Ringseis et al., 2009). In line with this, the expression of Slc22a5 is significantly reduced in PPARα-null mice (van Vlies et al., 2007; Koch et al., 2008). Moreover, Maeda et al. have analyzed the 5'-flanking promoter region of rat Slc22a5 and identified several putative peroxisome proliferator response elements (PPREs) (Maeda et al., 2008). After treatment with the PPARα agonist fenofibrate, there was an enhanced binding of PPARα to the
proximal PPREs of $\text{Slc22a5}$. However, the increase of $\text{Slc22a5}$ promoter activity after PPARα activation was less than what was expected from that of $\text{Slc22a5}$ mRNA levels, suggesting existence of additional PPREs which might be located outside the proximal promoter region of $\text{Slc22a5}$ gene. In fact, a subsequent study by Eder group revealed that there were functional PPREs in the first intron of $\text{Slc22a5}$, which were highly responsive to both exogenous PPARα/RXR expression and agonists (Wen et al., 2010). The sequence of intron 1 containing the PPREs showed a high degree of similarity between mice and rats. Functional PPREs have also been identified in the intron 1 of porcine, bovine, and human $\text{SLC22A5}$ genes (Luo et al., 2014), suggesting that the regulation of $\text{SLC22A5}$ by PPARα is highly conserved across species. Besides $\text{OCTN2}$, the transcription of $\text{OCTN3}$ seems to be also subject to PPARα regulation. The expression of $\text{Octn3}$ gene was lower in the kidney and small intestine of PPARα-null mice as compared to wild-type mice (van Vlies et al., 2007; Koch et al., 2008). PPARα activation increased the expression of $\text{Octn3}$ and its transport function in rat astrocytes as well (Januszewicz et al., 2009).

By using different PPAR-null models and specific PPAR inhibitors, D'Argenio et al. have demonstrated that PPARγ could also regulate the expression of $\text{Slc22a5}$ gene in colon via binding to the PPRE at the first intron as a heterodimer with RXRα (D'Argenio et al., 2010). The expression of $\text{SLC22A5}$ and the corresponding transport function could be increased by the PPARγ agonists thiazolidinediones and luteolin in mice and colon cells (D'Argenio et al., 2010; Qu et al., 2014). Notably, the colon $\text{Slc22a5}$ expression in PPARα-null mice was significantly upregulated by overexpression of a constitutively active PPARγ mutant, indicating an independent regulation by PPARγ (D'Argenio et al., 2010). Additional
transcriptional factors may be involved in regulation of OCTN expression. For example, SLC22A5 has been reported to be an estrogen-dependent gene via an intronic estrogen-responsive element (ERE) in breast cancer cells (Wang et al., 2012a). In addition, as a line of clinical evidence, the mRNA level of SLC22A5 has been reported to be decreased in liver biopsies of those patients received the PXR agonist carbamazepine (Oscarson et al., 2006). However, the number of transcriptional factors in understanding of OCTN transcription are still limited.

2.5 Transcriptional regulation of PEPTs

The evidence on the transcriptional regulation of PEPT transporters is not as much as that for the SLC drug transporters described above. Most related studies have been focused on PETPT1. There is little understanding of epigenetic regulation of PEPTs until very recently. Wang et al reported a suppressed expression of SLC15A1 (PEPT1) in colon cancer due to DNA methylation and histone deacetylation (Wang et al., 2021a). DNA methyltransferase 1 was characterized as the primary determinant of the hypermethylation of SLC15A1 proximal promoter. In addition, the absence of CBP/P300-mediated H3K18/27Ac combined with the histone deacetylases-mediated histone hypoacetylation around the SLC15A1 promoter also accounted for the repressed expression of SLC15A1.

The transcriptional regulation of PEPTs by NRs has not been well investigated either. Among a few studies, cholate-induced FXR/PPARα activation/inhibition has been reported to play a role in SLC15A1 transcription (Okamura et al., 2014; Liang et al., 2020). In the intestine of diabetic rats, the level of CDCA was significantly increased. As a natural ligand
of FXR, CDCA could down-regulate the expression of rat Slc15a1, which could be reversed by treatment with the FXR inhibitor glycine-β-muricholic acid or by FXR knockdown (Liang et al., 2020). On the other hand, treatment with the PPARα agonist WY-14643 increased the mRNA level of SLC15A1 and its transport function in rat intestine and human intestinal Caco-2 cells (Shimakura et al., 2006a). The increase in free fatty acids, which are endogenous ligands for PPARα, could also significantly increase the expression of Slc15a1 mRNA in rodents (Shimakura et al., 2006a). Two nucleotide sequences homologous to PPRE have been identified within 2.0 kb upstream to the TSS of the mouse and human SLC15A1 gene (Okamura et al., 2014). The bile acids accumulated in intestinal epithelial cells after eating could interfere with the recruitment of the co-transcriptional activator CBP/p300 to the promoter region of SLC15A1 gene, thereby inhibiting PPARα-mediated transactivation of SLC15A1. However, the regulatory effects of PPARα on SLC15A1 expression has not been fully confirmed in other studies (Hirai et al., 2007; Saito et al., 2008).

A few other transcription factors, including Sp1, Cdx2 and Nrf2, have also been shown to regulate the transcriptional activity of SLC15A1 promoter (Shimakura et al., 2005; Shimakura et al., 2006b; Geillinger et al., 2014). The -172 ~ -35 bp region of SLC15A1 promoter lacks TATA-box; however, it contains GC-rich sites which can bind with the transcription factor Sp1 to recruit the TATA-binding protein and initiate transcription (Shimakura et al., 2005). The mutation of the Sp1 sites resulted in a reduced transcriptional activity of human SLC15A1 promoter. Moreover, while co-expression of Cdx2 and Sp1 has been found to synergistically activate the SLC15A1 promoter, the mutation of Sp1 sites reduced the effect of Cdx2 (Shimakura et al., 2006b). In addition, an increased Nrf2 activity
was found to upregulate the expression of \textit{SLC15A1} via binding with the antioxidant response elements (AREs) which are close to the start codon in human \textit{SLC15A1} gene (Geillinger et al., 2014).

### 2.6 Transcriptional regulation of MATEs

Only limited findings are available regarding transcriptional regulation on MATE transporters. A CpG island located in the 27 kb upstream of \textit{SLC47A1} gene has been identified as an enhancer (Tanaka et al., 2018). The methylation levels of this CpG island were negatively correlated with the mRNA expression of \textit{SLC47A1} in the liver (Tanaka et al., 2018). However, the detail regulation of \textit{SLC47A1} expression through DNA methylation is currently unclear. As for OCT2 described above, the expression of another MATE transporter, MATE2, has been reported to be suppressed in RCC (Yu et al., 2017). The suppression was related to histone modification. Specifically, the protein scaffold adjacent to the \textit{SLC47A2} gene was found to be enriched with histone H3K4me3 and lysine 27 trimethylation (H3K27me3) in normal renal tissues. In RCC, the binding between the histone methylase MLL1 and the promoter region was lost, reducing H3K4me3 enrichment and the transcriptional activity of \textit{SLC47A2} promoter. In addition, there was deacetylation of H3K27 in RCC which prevented the enrichment of H3K4me3 as well.

Several studies have explored the role of transcriptional factors in transcription of \textit{MATEs}. The Giacomini group has characterized the transcriptional activity of the basal promoter of human \textit{SLC47A1} gene. They identified polymorphic sequences in the promoter region which could bind to two transcriptional factors, activating protein-1 (AP-1) and...
activating protein-2 repressor (AP-2rep), in regulation of the transcription of SLC47A1 gene (Ha Choi et al., 2009). By using different NR pharmacological activators, a study by Lickteig et al have suggested that AhR, CAR, PXR, Nrf2 and PPARα do not play a critical role in the transcription of Slc47a1 and Slc47a2 in mouse livers (Lickteig et al., 2008). However, the mRNA expression of Slc47a1 in the kidney of PPARα-null mice was increased (Freitas-Lima et al., 2020) and dramatically decreased in the liver of HNF4α-null mice (Lu et al., 2010), suggesting a role of these two NRs in tissue-specific MATE transcription. In addition, the mRNA expression of Slc47a1 was significantly increased in the liver of NADPH-cytochrome P450 oxidoreductase (Cpr)-null mice where Nrf2 was activated (Cheng et al., 2014). Moreover, treatment with the Nrf2 activator bardoxolone methyl was found to significantly increase the mRNA expression of SLC47A1 in human renal proximal tubular epithelial cells (Atilano-Roque et al., 2016). Interestingly, by using microfluidic culture of human proximal tubules, Fukuda et al have demonstrated that fluid shear stress stimulates MATE2-K expression via Nrf2 pathway activation (Fukuda et al., 2017). Lastly but not least, FXR may be involved in the transcriptional regulation of human MATEs because treatment with its ligand CDCA could significantly increase the mRNA expression of SLC47A1 and SLC47A2 in human renal proximal tubular cells (Wongwan et al., 2020). Further mechanistic studies are needed to clarify the regulatory role of these NRs in transcription of MATE genes.

3. Closing remarks

SLC drug transporters are present in tissues with varying abundance. It would be a prerequisite to clarify the accurate localization and abundance of these transporters, before
elucidating their role in the absorption, distribution, metabolism, excretion, and consequently the pharmacological and toxicological effects of clinical drugs. The transcriptional regulation is the major determinant of tissue distribution and abundance for these drug transporters. We have provided an overview and collected information on transcriptional regulation of major SLC drug transporters in this review. In consideration of space limit, however, we are unable to discuss the molecular mechanisms in detail for the transcriptional regulation of these transporters. Neither did we include all SLC families whose members sometimes facilitate the movement of clinical used drugs across the membrane. In addition, there are progresses in terms of preclinical evidence and clinical implication which deserve a specific review under individual topics. These limitations have inevitably compromised the comprehensiveness of this review.

Whereas the importance of SLC transporters in drug disposition and response is widely appreciated, understanding the role of epigenetic and NR-mediated transcriptional regulation has just begun. There are progresses suggesting clinical implication of such regulation for SLC drug transporter genes. For example, by targeting the epigenetic mechanism of OCT2 transcription, a sequential combination therapy using the DNA methylation inhibitor decitabine has been proposed to overcome the resistance of RCC to oxaliplatin chemotherapy (Liu et al., 2016b). However, overall, the clinical evidence remains very limited. It is challenging to ascertain the effects by an alteration in transporter transcription on drug disposition and response in animal models and particularly in human subjects in vivo. While one mechanism or one NR may govern the transcription of multiple SLC drug transporter genes, an individual transporter can be regulated via multiple mechanisms as well. The lack
of selective probe substrates, inhibitors, and regulatory molecules for specific drug transporters has been bringing another layer of complexity in interpretation of in vivo data. Current effort in characterizing drug-drug interactions (DDIs) for an increasing number of compounds will bring us much-needed probe drugs to assess the function of SLC drug transporters and their regulation. Moreover, investigating the impact of SLC transcriptional changes on drug disposition and response with appropriate probe compounds in genetic animal models and genetically polymorphic human populations may yield invaluable preclinical and clinical evidence soon. Of note, there are also different levels of regulation on transporter function. For example, post-translational modification on transporter proteins have been widely reported to affect SLC drug transporter function (Murray and Zhou, 2017; Xu and You, 2017; Czuba et al., 2018; Lee et al., 2020). A novel kinase-dependent posttranslational regulation of OATP1B1 activity has been recently characterized as a mechanism underlying DDIs between broad OATP1B1 substrates and the commonly prescribed tyrosine kinase inhibitors (TKI) (Hayden et al., 2021). We have also identified a mechanism regulating the membrane translocation of OCT2 and consequently the nephrotoxicity of cisplatin, a widely prescribed anticancer drug (Yang et al., 2020). Our understanding of a full range of regulatory mechanisms for drug transporters will eventually have an impact on optimization of pharmacotherapy regimens in order to improve drug efficacy and avoid unnecessary toxicity.

AUTHORSHIP CONTRIBUTIONS

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FOOTNOTES

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Figure Legends

Fig 1. Location of major SLC drug transporters in human liver, intestine, blood-brain barrier (BBB), and kidney. OATPs: Organic anion-transporting polypeptides; OATs: Organic anion transporters; OCTs: Organic cation transporters; OCTNs: Organic cation/carnitine transporters; PEPTs: Peptide transporters; MATEs: Multidrug and toxin extrusion proteins.

Fig 2. Epigenetic regulation of gene expression by DNA methylation and histone acetylation. As shown, the degree of methylated CpG islands in a promoter is usually negatively correlated with the level of gene expression. Histone acetylation is also an important epigenetic mechanism for gene expression regulation. The histone acetylases (HATs) may catalyze the transfer of acetyl groups to the lysine residues on the histone tail and activate gene transcription, whereas histone deacetylases (HDACs) can deacetylate histone and inhibit gene transcription instead.
### Table 1. Major solute carrier (SLC) drug transporters.\(^a\)

<table>
<thead>
<tr>
<th>SLC Subfamily(^b)</th>
<th>Species</th>
<th>Transporter Gene Name (Protein Name)</th>
<th>Organ with highest expression(^c)</th>
<th>Common substrates(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OATPs</td>
<td>Humans</td>
<td><em>SLCO1A2</em> or <em>SLCO1A3</em> (OATP-A or OATP1A2)</td>
<td>Brain</td>
<td>Bromsulphthalein (BSP), Methotrexate, Enalapril, Levofloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>SLCO1B1</em> (OATP1B1)</td>
<td>Liver</td>
<td>Cobimetinib, Lovastatin, Clotrimazole, Valsartan, Cyclosporine, Rifampicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>SLCO1B3</em> (OATP1B3)</td>
<td>Liver</td>
<td>Rifampicin, Olmesartan, Methotrexate, Digoxin, Pioglitazone</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>SLCO1B3</em>- <em>SLCO1B7</em> or <em>LST-3TM12</em> (OATP1B3-1B7)</td>
<td>Liver and Breast</td>
<td>Taurocholic acid, Lithocholic acid, Ezetimibe</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>SLCO2A1</em> (OATP2A1)</td>
<td>Lung</td>
<td>Alprostadil, Latanoprost, Iloprost</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>SLCO2B1</em> (OATP2B1)</td>
<td>Liver</td>
<td>Azilsartan, Balsalzide, Gavestinel, Valsartan</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>SLCO3A1</em> (OATP3A1)</td>
<td>Brain</td>
<td>Benzylpenicillin, Safinamide, Iloprost</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>SLCO4A1</em> (OATP4A1)</td>
<td>Lung</td>
<td>Liothyronine, Levothyroxine, Benzylpenicillin,</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>SLCO4C1</em> (OATP4C1)</td>
<td>Kidney</td>
<td>Liothyronine, Digoxin, Saxagliptin, Ouabain</td>
</tr>
<tr>
<td>Rodents</td>
<td><em>Slco1a1</em> (Oatp1a1 or Oatp1)</td>
<td>Liver and Kidney</td>
<td>Estradiol 17beta-d-glucuronide</td>
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<tr>
<td></td>
<td><em>Slco1a4</em> (Oatp1a4 or Oatp2)</td>
<td>Brain, Liver and Kidney</td>
<td>Sulfhorhodamine-101 (SR-101)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Slco1a5</em> (Oatp1a5)</td>
<td>Kidney</td>
<td>Fexofenadine, Celiprolol</td>
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<tr>
<td></td>
<td><em>Slco1a6</em> (Oatp1a6)</td>
<td>Kidney</td>
<td>Taurocholic acid (TCA)</td>
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</tr>
<tr>
<td></td>
<td><em>Slco1b2</em> (Oatp1b2)</td>
<td>Liver</td>
<td>Pitavastatin</td>
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<tr>
<td></td>
<td><em>Slc16a2</em> (Oatp1c1)</td>
<td>Liver and Kidney</td>
<td>Sulfhorhodamine-101 (SR-101), Thyroxine (T4)</td>
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<tr>
<td></td>
<td><em>Slco2a1</em> (Oatp2a1)</td>
<td>Lung and Liver</td>
<td>Phenolsulfonphthalein</td>
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<tr>
<td></td>
<td><em>Slco2b1</em> (Oatp2b1)</td>
<td>Ubiquitous</td>
<td>Fexofenadine Rosuvastatin</td>
<td></td>
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</table>

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<table>
<thead>
<tr>
<th>Protein</th>
<th>Species</th>
<th>Tissue</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slco3a1 (Oatp3a1)</td>
<td>Humans</td>
<td>Brain</td>
<td>Sodium fluorescein</td>
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<tr>
<td>Slco4c1 (Oatp4c1)</td>
<td>Humans</td>
<td>Kidney and Lung</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Slco4c1 (Oatp4c1)</td>
<td>Rodents</td>
<td>Kidney</td>
<td>same as Slco3a1</td>
</tr>
<tr>
<td>Slco4c1 (Oatp4c1)</td>
<td>Rodents</td>
<td>Liver</td>
<td>same as Slco3a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Humans</td>
<td>Kidney</td>
<td>Cimetidine, Methotrexate, Indomethacin, Probenecid, Oxytetracycline, Hydrochlorothiazide</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Kidney</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Liver</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Kidney</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Liver</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Kidney</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Liver</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Kidney</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Liver</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Kidney</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Liver</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Kidney</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Liver</td>
<td>same as SLC22a1</td>
</tr>
<tr>
<td>SLC22a1 (OAT1)</td>
<td>Rodents</td>
<td>Kidney</td>
<td>same as SLC22a1</td>
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<tr>
<td>OCTNs</td>
<td>Humans</td>
<td>Skeletal muscle, Kidney, Heart and Placenta</td>
<td>Amphetamine, Nicotine, Formoterol, Formoterol, Colistin, Oxaliplatin</td>
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<tr>
<td>OCTNs</td>
<td>Rodents</td>
<td>Kidney, Liver and Testis</td>
<td>same as SLC22a5</td>
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<tr>
<td>LOC303140 (Octn3)</td>
<td>Testes</td>
<td>Acetylcarnitine</td>
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<tr>
<td>PEPTs</td>
<td>Humans</td>
<td>Intestine</td>
<td>Cephalexin, Enalapril</td>
</tr>
<tr>
<td>SLC Drug Transporter</td>
<td>Species</td>
<td>Location</td>
<td>Substrates</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>(PEPT1)</td>
<td>Rodents</td>
<td>Slc15a1 (Pept1)</td>
<td>Intestine</td>
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<tr>
<td>MATEs</td>
<td>Humans</td>
<td>SLC47A1 (MATE1)</td>
<td>Adrenal gland</td>
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<td></td>
<td></td>
<td>SLC47A2 (MATE2 or MATE2-K)</td>
<td>Kidney</td>
</tr>
<tr>
<td>Rodents</td>
<td>Slc47a1 (Mate1)</td>
<td>Kidney and Liver</td>
<td>same as SLC47A1</td>
</tr>
<tr>
<td></td>
<td>Slc47a2 (Mate2)</td>
<td>Testis</td>
<td>same as SLC47A2</td>
</tr>
</tbody>
</table>

Note: *Only those SLC drug transporters reviewed in the text are presented. OATPs: organic anion-transporting polypeptides; OATs: organic anion transporters; OCTs: organic cation transporters; OCTNs: organic cation/carnitine transporters; PEPTs: peptide transporters; MATEs: multidrug and toxin extrusion proteins. The information is extracted from The Human Protein Atlas (www.proteinatlas.org) and UniProt (www.uniprot.org). Only selected compounds are presented; Please refer to the literatures for a more comprehensive list of the substrates (Roth et al., 2012; Cesar-Razquin et al., 2015; Lin et al., 2015; Bhutia et al., 2016; Murray and Zhou, 2017; Rives et al., 2017; Nigam, 2018; Schlessinger et al., 2018; Liu, 2019; Ayka and Sehirli, 2020; Bednarczyk and Sanghvi, 2020; Huang et al., 2020; Koepsell, 2020; Pacha et al., 2021; Pizzagalli et al., 2021; Yang and Shu, 2021).
Table 2. Regulatory mechanisms and protein factors involved in transcription of solute carrier (SLC) drug transporter genes.

<table>
<thead>
<tr>
<th>Regulatory mechanisms/protein factors</th>
<th>Transporters</th>
<th>Representative Agonist/Activator</th>
<th>Representative Antagonist/Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA methylation</td>
<td>OATP1B1, OATP1B3, OATP3A1, OATP4A1, OATP4C1, OATP2A1, Oatp1b2, Oatp1a1, Oatp1a6, Oatp1c1, Oatp1a4, OAT1, OAT3, Oat1, Oat3, OCT1, OCT2, OCT3, OCTN2, PETPT1, MATE1</td>
<td>5-Aza-2'-deoxy Cytidine (5azadC), Decitabine, Metformin</td>
<td></td>
</tr>
<tr>
<td>Histone modification</td>
<td>OATP2A1, OATP2A1, OATP1B1, OATP1B3, Oatp1b2, Oatp1a1, Oatp1a6, Oatp1c1, Oatp1a4, OAT2, OCT2, PETPT1, MATE2</td>
<td>Histone deacetylase inhibitor: Trichostatin, Vorinostat (SAHA)</td>
<td></td>
</tr>
<tr>
<td>Pregnane X receptor (PXR)</td>
<td>Oatp2, OATP1B1, OATP1B3, OATP2B1, OATP2A1, OATP-A, OATP1A2, Oat1, Oat3, OCT1</td>
<td>Pregnenolone 16α-carbonitride (PCN), Rifampicin, Phenobarbital Doxorubicin, Spiironolactone</td>
<td></td>
</tr>
<tr>
<td>Aryl hydrocarbon receptor (AhR)</td>
<td>Oatp2b1, Oatp3a1, OATP4C1, OATP1B1, OATP2B1, Oatp1a1, Oatp2, OAT1, OAT2</td>
<td>2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), Polychlorinated biphenyl 126, Beta-naphthoflavone, Diesel exhaust particles (DEPs), Indoxyl sulfate, 3-methylcholanthrene</td>
<td></td>
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<tr>
<td>Constitutive androgen receptor (CAR)</td>
<td>OATP1A2, OATP1B3, OATP2B1, OATP1B3, Oatp1a1, Oatp1a4, Oatp2, OAT2, Oat1, Oat3</td>
<td>Diallyl sulfide, Phenobarbital, 6-(4-chlorophenyl)-imidazo [2,1-b] thiazole-5-Carbaldehyde-O-(3,4-dichlorobenzyl)oxime (CITCO)</td>
<td></td>
</tr>
<tr>
<td>Farnesoid X receptor (FXR)</td>
<td>OATP1B1, OATP1B3, OAT2, PETPT1, Pept1, MATE1, MATE2-K</td>
<td>Vitamin A, Bile acids, Chenodeoxycholic</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Pathway</th>
<th>Transporters</th>
<th>Lipids/Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver X receptor (LXR)</td>
<td>OATP1B1, Oatp1b2, OAT1, OAT2</td>
<td>Oxysterols, Berberine, TO-901317, GW3965, 22(R)-hydroxycholesterol, 22(S)-hydroxycholesterol, 9-cis retinoic acid (9cRA), 25-hydroxycholesterol (HC)</td>
</tr>
<tr>
<td>Hypoxia-inducible factor 1 alpha (HIF-1α)</td>
<td>OATP1B3, OATP1B3, OATP2B1</td>
<td>Lipopolysaccharide, Ursodeoxycholic acid (UDCA)</td>
</tr>
<tr>
<td>Hepatocyte nuclear factors (HNFs)</td>
<td>OATP1B1, OATP1B3, Oatp1b2, Oatp1, Oatp2, Oatp1a1, Oatp1a4, Oatp1a5, Oatp1b2, Oatp2b1, Oatp1a1, Oatp1a6, Oatp2b1, Oatp3a1, Oatp4c1, Oatp2a1, OAT1, OAT2, OAT3, Oat1, Oat3, OCT1, Mate1</td>
<td></td>
</tr>
<tr>
<td>Nuclear factor erythroid 2-related factor 2 (Nrf2)</td>
<td>Oatp1a1, Oatp2b1, Oatp1b2, Oatp1a6, OAT2, Oat2, PEPT1, MATE1, MATE2-K</td>
<td>Sulforaphane, Retinoic acid, Oltipraz</td>
</tr>
<tr>
<td>Retinoid X receptor (RXR)</td>
<td>OATP1B1, OATP2B1, OCT1, OCTN2</td>
<td>all-trans retinoic acid (atRA), 9-cis retinoic acid (CRA)</td>
</tr>
<tr>
<td>Retinoic acid receptor (RAR)</td>
<td>OATP1B1, OATP2B1, OCT1,</td>
<td>all-trans retinoic acid (atRA), 9-cis retinoic acid (CRA)</td>
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<tr>
<td>Vitamin D receptor (VDR)</td>
<td>OATP1A2,</td>
<td>1α25-dihydroxy-vitamin D3 (D3)</td>
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<tr>
<td>Peroxisome proliferator-activated receptor alpha (PPARα)</td>
<td>Oatp1a1, Oatp1a4, Oatp1b2, Oatp2a1, Oatp2b1, OCT1, OCT2, Oct2, OCTN2, Ocn2, OCTN3, PETPT1, PepT1, Mate1</td>
<td>Perfluorooctanoic acid, Perfluorodecanoic acid, Clofibrate, Ciprofibrate, Diethylhexylphthalate, Fenofibrate</td>
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<tr>
<td>PPARγ</td>
<td>OCTN2</td>
<td>Thiazolidinediones (troglitazone and rosiglitazone), Luteolin,</td>
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<tr>
<td>Androgen receptor (AR)</td>
<td>Oct2</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Estrogen receptor (ER)</td>
<td>OAT1, OCTN2</td>
<td>Estrogen</td>
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</table>

Note: a Only those regulatory mechanisms/protein factors reviewed in the text are presented.

b OATPs: organic anion-transporting polypeptides; OATs: organic anion transporters; OCTs: organic cation transporters; OCTNs: organic cation/carnitine transporters; PEPTs: peptide transporters; MATEs: multidrug and toxin extrusion proteins. The upper case letters represent human proteins, while the others are rodent proteins.
Fig 1