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Solute Carrier Transportome in Chemotherapy-Induced Adverse Drug Reactions

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Abstract

Members of the solute carrier (SLC) family of transporters are responsible for the cellular influx of a broad range of endogenous compounds and xenobiotics. These proteins are highly expressed in the gastrointestinal tract and eliminating organs such as the liver and kidney, and are considered to be of particular importance in governing drug absorption and elimination. Many of the same transporters are also expressed in a wide variety of organs targeted by clinically important anticancer drugs, directly affect cellular sensitivity to these agents, and indirectly influence treatment-related side effects. Furthermore, targeted intervention strategies involving the use of transport inhibitors have been recently developed, and have provided promising lead candidates for combinatorial therapies associated with decreased toxicity. Gaining a better understanding of the complex interplay between transporter-mediated on-target and off-target drug disposition will help guide the further development of these novel treatment strategies to prevent drug accumulation in toxicity-associated organs, and improve the safety of currently available treatment modalities. In this report, we provide an update on this rapidly emerging field with particular emphasis on anticancer drugs belonging to the classes of taxanes, platinum derivatives, nucleoside analogs, and anthracyclines.

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Keywords

Adverse drug reactions; Anticancer; Solute carrier; Toxicity

1. Introduction

The expression and localization of transporters within specific tissues contributes to a dynamic interplay between intracellular substrate concentrations and the extracellular environment of various cell types. Disruption of this sensitive balance has the potential to modify intracellular accumulation of xenobiotics and may contribute to increases in the incidence and severity of tissue-specific organ damage. In this article, we will focus on the contribution of solute carrier (SLC) family members to the initial cellular influx of substrates and how these proteins can directly contribute to toxicities associated with small-molecule oncology drugs. Of note, transporters involved in cellular efflux, such as members of the ATP-binding cassette (ABC) family, might also play a role in toxicities associated with the same drugs. However, these proteins are predicted to mitigate the risk of toxicity rather than precipitating toxicity, and this area is beyond the scope of the present review. Rather than presenting a comprehensive overview of the field, we aimed in this article to highlight examples of well-established toxicities associated with commonly used anticancer drugs that are dependent on specific solute carriers in order to stimulate discussion within the transporter community and further advance the field.

1.1 Transporter Function

A selectively permeable plasma membrane is a ubiquitous feature of all life forms (Grecco et al. 2011; Singer and Nicolson 1972), and membrane transporters are the key regulators of this selective cellular permeability (Kaback et al. 2001). These proteins mediate the uptake and efflux of many endogenous metabolites such as amino acids, nucleosides, sugars, as well as many dietary compounds and therapeutic agents (Borst and Elferink 2002). Therefore, along with their essential contribution to normal physiology and pathophysiology, membrane transporters are also key determinants of therapeutic responses to drugs, including unwanted adverse events.

The human genome encodes more than 400 membrane-transporter genes belonging to two major super-families: ABC transporters and SLC transporters, which are involved in most essential biological processes (Borst and Elferink 2002; He et al. 2009; Hediger et al. 2013; Nigam 2015). Among these, about 20 “multi-specific” transporters belonging to either super-family have been widely implicated in drug transport (DeGorter et al. 2012; Giacomini et al. 2012; Nigam 2015). Tissue types that are involved in the absorption, distribution, metabolism, and excretion (ADME), such as the kidney, liver, intestine, and endothelial barriers, have high expression of transporters that accumulate substrates within these organ types (International Transporter Consortium et al. 2010). At the cellular level, transporter-mediated uptake or efflux can involve drug sensitive or resistant (Borst et al. 2000) phenotypes in target cells, thereby affecting therapeutic efficacy. Conversely, transporter-mediated drug accumulation in non-target cells can contribute to drug toxicity profiles (Sprowl and Sparreboom 2014). Consequently, drug transporters, in addition to

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drug-metabolizing enzymes, have emerged in recent years to be critical determinants of drug disposition, therapeutic efficacy, toxicity profiles, and drug–drug.

1.2 Role of SLCs in Toxicity

Increasing evidence has confirmed that SLC expression and localization at non-target tissues can play an important role in drug distribution and subsequent toxicity profiles (Sprowl and Sparreboom 2014; Yang and Han 2019). In addition, the ability of drugs to compete for the natural substrates of these transporters can potentially lead to altered cellular function and trigger unwanted adverse reactions. Since virtually all currently used oncology drugs can cause severe dose-limiting toxic side effects and, in some cases, cause life-threatening toxicities associated with organ damage, knowledge of specific SLCs that recognize such drugs can theoretically contribute to the development of improved and safer treatment strategies. Furthermore, the contribution of SLCs to observed differences in chemotherapeutic clinical response rates and toxicity profiles between genders remains poorly understood. The identification of pharmacodynamic biomarkers of SLC function that can potentially guide treatment decisions has led to the design of strategies involving the administration of concurrent medications that ameliorate the incidence and/or severity of these side effects. Besides a direct contribution of SLCs to the tissue-specific uptake of anticancer drugs, these proteins can also indirectly contribute to altered drug distribution patterns due to their involvement in clearance mechanisms in organs of elimination such as the liver and kidney. In the last few decades, technological advances in cloning have resulted in the identification of several important SLC families mediating the transport of organic cations and organic anions, the so-called organic cation transporters (OCTs), organic anion transporters (OATs), and organic anion transporting polypeptides (OATPs).

1.2.1 Organic Cation Transport—About 40% of approved prescription drugs are positively charged at neutral pH (“organic cations”), and the membrane transport of these agents depends on facilitated carriers. In recent years, considerable progress has been made in the study of transporters belonging to the OCT family. Subsequent studies in heterologous expression models have confirmed that members of this transporter family mediate the cellular uptake of many structurally diverse endogenous compounds and an increasingly large number of cationic anticancer drugs. The organic cation transporters OCT1 (*SLC22A1*) and OCT2 (*SLC22A2*) have particular relevance in this connection, since they are highly expressed at the basolateral membranes of hepatocytes and renal tubular cells, respectively, and these proteins are considered major transporters in the secretion of organic cations from the circulation into the liver and kidney. Consequently, OCT1 and OCT2 facilitate the hepatocellular and renal excretion of organic cationic compounds and play an important role in governing systemic elimination of many drugs. The contribution of OCTs to hepatic and renal organic cation secretion was first conclusively demonstrated from the clearance of the prototypic organic cation, tetraethylammonium (TEA), in mice from which Oct1, Oct2, or both were eliminated (Jonker et al. 2001, 2003). These studies demonstrated that the renal TEA clearance in the Oct1-null mouse [Oct1(−/−)] was actually increased, reflecting (1) reduced hepatic clearance, (2) elevated plasma concentrations of TEA, and (3) sufficient expression of Oct2 in the kidney to handle the increased plasma load. Renal TEA clearance in the Oct2-null mouse [Oct2(−/−)] was unchanged compared

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to control, reflecting sufficient expression of Oct1 in the murine kidney to efficiently clear TEA, even in the absence of Oct2. Most importantly, the elimination of both Oct1 and Oct2 in mice [Oct1/2(−/−)] completely eliminated active secretion of TEA. Although mice express substantial levels of both Oct1 and Oct2 in the kidney, in humans there is strong agreement that OCT2 dominates renal organic cation transport, whereas OCT1 dominates hepatic organic cation transport.

In the liver, a transporter belonging to the class of multidrug and toxin extrusion (MATE) proteins called MATE1 (*SLC47A1*) is localized at the bile-canalicular membrane of hepatocytes, and forms a functional unit with the basolaterally expressed OCT1 to mediate the secretion of many cationic drugs from the circulation across the hepatocyte into the bile (Fig. 1). In the luminal membrane of the proximal tubular epithelium, MATE1 cooperates with the basolaterally expressed OCT2 in the vectorial renal secretion of organic cations (Fig. 1). Previously reported experimental data indicate that the tubular secretion of several dual OCT2/MATE1 substrates, including cisplatin (Franke et al. 2010b) and oxaliplatin (Sprowl et al. 2013a), is decreased in Oct1/2(−/−) mice, but not in Oct1(−/−) and Oct2(−/−) mice (Filipski et al. 2009), as well as in Mate1 knockout [Mate1(−/−)] mice (Li et al. 2013; Nakamura et al. 2010). The contribution of these transporters to the hepatic and renal handling of xenobiotics in mammals has been most extensively studied for the biguanide analog metformin, a first-line medication for the treatment of type 2 diabetes that has intrinsic anticancer and chemo-preventative properties as well (Chae et al. 2016; Heckman-Stoddard et al. 2016). These studies have demonstrated that OCT1 mediates >75% of metformin uptake into hepatocytes, and that OCT2 (Oct1/2 in mice) mediates >60% of metformin uptake into renal tubular cells (Higgins et al. 2012). Consequently, the hepatic exposure of metformin is decreased ~4–8 fold in Oct1(−/−) mice (Shu et al. 2007; Wang et al. 2002), decreased 4.2-fold in Oct1/2 (−/−) mice (Higgins et al. 2012), and increased 8.4-fold in Mate1(−/−) mice (Li et al. 2013). In the case of Oct1/2- or Mate1-deficiency, this resulted in significantly altered systemic exposure to metformin (Higgins et al. 2012; Tsuda et al. 2009).

Because hepatic uptake is required for inhibition of gluconeogenesis, the pharmacodynamic properties of metformin are markedly attenuated in Oct1(−/−) mice resulting in higher fasting plasma glucose levels (Shu et al. 2007). This is consistent with prior findings that several well-documented, relatively common loss-of-function variants in OCT1 are associated with a decreased glycemic response resulting in higher blood glucose levels in patients with type 2 diabetes (McCreight et al. 2016), and with altered efficacy in patients with cancer (Joerger et al. 2015), but not with the steady-state pharmacokinetics of metformin (Christensen et al. 2015; Stage et al. 2015a). Studies in dizygotic and monozygotic twin pairs have confirmed that the impact of reduced-function alleles in OCT1 on the pharmacokinetics of metformin in humans is of minor clinical importance (Stage et al. 2015b). In contrast, genetic variations in OCT2, MATE1, and MATE2-K, a related transporter expressed in human but not rodent kidney, have been shown to significantly affect the pharmacokinetics of metformin (Pawlyk et al. 2014; Wang and Weinshilboum 2014). These studies are consistent with the known physicochemical properties of metformin dictating that its elimination is predominantly by renal excretion (up to 90% of the dose), with a negligible contribution from liver metabolism or biliary secretion, despite

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the expression of MATE1 on the canalicular membrane of hepatocytes (Jensen et al. 2016). Moreover, both human and rodent OCT2 have about a 10- and 100-fold greater capacity to transport metformin as compared with OCT1 (Kimura et al. 2005). On this basis, metformin is recommended by regulatory agencies such as the FDA as a probe for determining OCT2-mediated transport when investigating possible drug interactions with new chemical entities, including anticancer drugs. As such, a sound mechanistic understanding of pharmacokinetic interactions with metformin is considered of high clinical importance. It should be pointed out that interactions involving altered levels within the kidney are not necessarily reflected in an equivalent change in systemic exposure (Sprowl and Sparreboom 2014). Nonetheless, published studies have demonstrated that many known OCT2 inhibitors, including cimetidine, dolutegravir (Song et al. 2016; Zong et al. 2014), ranitidine (Cho et al. 2014), and verapamil (Cho and Chung 2016) can significantly increase the area under the curve (AUC) of metformin (Koepsell 2015). Furthermore, it has been recommended that dose adjustments of metformin be considered to maintain optimal glycemic control when patients are starting/stopping these agents while taking metformin (Song et al. 2016). The clinical impact of these interactions is further supported by the recent finding in a population of >400,000 incidental metformin users that the risk of early therapy discontinuation, as a proxy for intolerance, is associated with the concomitant use of drugs that are known to inhibit OCT2 and/or MATE1 (Stage et al. 2016).

1.2.2 Organic Anion Transport—In the liver, two transporters belonging to the class of OATPs called OATP1B1 (*SLCO1B1*) and OATP1B3 (*SLCO1B3*; Fig. 2) are localized at basolateral membrane of hepatocytes and mediate the uptake of a remarkably broad range of substrates from the circulation across the outer membrane of hepatocytes. These agents include charged organic anions (e.g., methotrexate and statins), endogenous and xenobiotic glucuronides (e.g., of bilirubin and sorafenib), charged organic cations (e.g., tyrosine kinase inhibitors such as imatinib), polar zwitterions (e.g., fexofenadine), uncharged hydrophobic agents (e.g., taxanes such as paclitaxel), as well as chemically diverse platinum-based therapeutics (e.g., cisplatin) (Lancaster et al. 2013). The in vivo pharmacological characterization of this transport mechanism was first performed in mice knockout for the orthologue transporter Oatp1b2 [Oatp1b2(−/−)] (Zaher et al. 2008) with the prototypical substrate pravastatin, a member of the class of statins used for the treatment of dyslipidemia and the prevention of cardiovascular disease. This initial work demonstrated that the liver-to-plasma ratios of pravastatin were reduced by four to fivefold in Oatp1b2(−/−) mice, which was independently verified in another Oatp1b2-deficient mouse strain (Salphati et al. 2014). Subsequent investigation demonstrated that 95–99% of pravastatin uptake into the liver is mediated by OATP1B1 (Izumi et al. 2018), and that the altered liver-to-plasma ratios of pravastatin, as well as other substrates (Zimmerman et al. 2013), observed in Oatp1b2(−/−) mice can be at least partially restored in humanized transgenic animals with liver-specific expression of OATP1B1 (Salphati et al. 2014).

Historically, the two major transport families contributing the renal secretion of organic compounds were divided into two different groups named “organic cation system” and “organic anion system”; classical substrate for the former included TEA, which was inhibited by cimetidine, while the latter was shown to efficiently transport p-aminohippurate

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(PAH) and inhibited by probenecid (Hagenbuch 2010). It was not until the late 1990s that the transport systems responsible for the organic anion systems in the kidney were identified as OAT1 (SLC22A3) and OAT3 (SLC22A5) (VanWert et al. 2010). Even though early studies showed that organic anions such as pyrazionate and PAH did not impact the accumulation of organic cations such as cisplatin in renal cortex slices (Safirstein et al. 1984), recent in vivo investigation suggested an correlation between the organic anion system disruption and the development of cisplatin nephrotoxicity. Of note, a number of studies have reported that the classical organic anion inhibitor, probenecid, can reduce the tubular secretion of total platinum after cisplatin administration in rats (Osman and Litterst 1983), rabbits (Caterson et al. 1983), dogs (Klein et al. 1991), and humans (Jacobs et al. 1984), and can partially protect against cisplatin nephrotoxicity in mice (Ban et al. 1994; Ross and Gale 1979). Similar findings have been reported for furosemide (Daley-Yates and McBrien 1985), an agent now known, like probenecid, to be an inhibitor of OAT1/OAT3 (Hosoyamada et al. 1999; Kusuhara et al. 1999; Lu et al. 1999; Vallon et al. 2008).

2 Toxicity Induced by Chemotherapeutics

2.1 OATPs and Paclitaxel-Induced Peripheral Neuropathy

Paclitaxel is a taxane antineoplastic agent that elicits its antitumor effects by disrupting the microtubule dynamics and causing mitotic arrest and cell death in a variety of tumor types. Paclitaxel remains among the most widely used drugs in the treatment of a variety of solid tumors, including early-stage breast cancer, but its clinical use is associated with debilitating damage to peripheral nerves (neuropathy). This damage is a tremendous health problem worldwide and remains one of the most important complications of contemporary oncology regimens as it may limit further use of curative-intent treatment and/or may cause long-term quality of life concerns. Since the majority of patients with cancer receiving paclitaxel-based chemotherapy are at high risk of experiencing peripheral neuropathy, a large community of cancer survivors could potentially benefit from the SLC contributing to this chemotherapy-induced toxicity.

Several tubulin poisons, including paclitaxel, induce a chronic, dose-dependent sensory peripheral neuropathy that is characterized by tingling, numbness, increased sensitivity to cold and touch, and burning pain of the distal extremities. The incidence of this side effect is particularly high in the case of paclitaxel, as it occurs in up to 70–80% in patients with breast cancer (De Iuliis et al. 2015). With continued dosing, the painful symptoms increase in severity and can persist for years (Peters et al. 2007), or even cause a lifelong functional impairment that impacts quality of life (Mielke et al. 2006). The mechanistic basis of this side effect has remained uncertain until relatively recently (Carozzi et al. 2015). Previously, studies have reported that paclitaxel is able to induce injury to sensory neurons resulting in morphological and biochemical changes in the dorsal root ganglion (DRG) satellite glial cells, proliferation of macrophages within the peripheral nervous system, activation and increases within the microglial and astrocyte populations within the spinal cord (Brewer et al. 2016; Marmiroli and Cavaletti 2016). Additionally, paclitaxel also causes acute pain syndrome in patients that precipitates within 1–3 days of paclitaxel administration and resides within 1 week. This acute pain syndrome has been postulated to be caused by the

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activation of toll-like receptor 4 (TLR4) in the DRG and spinal dorsal horn (Yan et al. 2015), which has been shown to be the main site of paclitaxel accumulation within the nervous system (Cavaletti et al. 2000).

The notion that the DRG neurons play a central role in the elicit side effects associated with paclitaxel chemotherapy is supported by the rationale that paclitaxel has easy accessibility to the DRG and subsequent accumulation which is supported by reports of detectable levels of paclitaxel in the spinal cord and sciatic nerve, presumably mediated by the transport along the centripetal and centrifugal branches of the axon in DRGs (Cavaletti et al. 2000). Furthermore, previous cellular uptake studies have demonstrated that paclitaxel, along with other structurally related taxanes such as docetaxel, accumulates via a facilitated transport mechanism (Smith et al. 2005). Consequently, after administration of paclitaxel, tissue disposition patterns and resulting pathological changes are restricted to cell types that are capable of transporting the movement of paclitaxel from the extracellular environment. This is consistent with accumulating evidence that the transmembrane transport of paclitaxel is mediated by specific OATPs. In particular, it has been reported that both paclitaxel and docetaxel are transported substrates of human OATP1B1 and OATP1B3 (Baker et al. 2009; de Graan et al. 2012; Smith et al. 2005, 2007), as well as the single functional homologue Oatp1b2 in mice (Nieuweboer et al. 2014) and rats (Franke et al. 2010a; Nieuweboer et al. 2014). These findings have been independently verified (Iusuf et al. 2015; Marada et al. 2015; Sun et al. 2016; van de Steeg et al. 2011, 2013), and are consistent with in vitro studies that have identified paclitaxel as a potent inhibitor of OATP1B1- (Gui et al. 2008, 2009) and OATP1B3-mediated transport (Gui et al. 2008; Letschert et al. 2006; Yamaguchi et al. 2008). However, none of the other known nine human OATPs are capable of transporting paclitaxel (Svoboda et al. 2011), and similar results have been obtained with docetaxel (Lee et al. 2015). Thus, the reported differing affinities highlight the notion that OATPs capable of transporting paclitaxel need to be expressed in tissues such that the drug can cross the plasma membrane and then exert cellular injury. In this context, it is noteworthy that the Oatp1b2 protein is expressed in mouse DRG (Sprowl et al. 2013a), and an independent study evaluating all 15 mouse OATPs confirmed expression of Oatp1b2 in murine neurons (Feurstein et al. 2010).

Comparative pharmacokinetic analysis after a clinically relevant dose of paclitaxel in wild-type mice and Oatp1b2(−/−) produced a modest increase in systemic exposure (Durmus et al. 2015). The minor change in systemic exposure of Oatp1b2-deficient animals to paclitaxel suggests rodents recapitulate pharmacokinetic observations in human patients and serves as an appropriate preclinical model (Nieuweboer et al. 2014). The absence of significant changes in systemic exposure also demonstrates that the genotype-dependent differences are unlikely to influence the extent of paclitaxel-induced peripheral neuropathy. In line with docetaxel studies (de Graan et al. 2012), the genetic deficiency of Oatp1b2 contributed to significant decreases in liver and DRG uptake of paclitaxel (Nieuweboer et al. 2014). The diminished accumulation of paclitaxel in DRGs from Oatp1b2-deficient mice demonstrates the preclinical utility of evaluating peripheral neuropathy, namely the Von Frey Hairs test, to assess mechanical allodynia (Boehmerle et al. 2014; Peters et al. 2007; Yan et al. 2015). After paclitaxel treatment, wild-type mice experience a 50% decrease in sensitivity to mechanical stimulation. Although several reports have suggested that metabolites of

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paclitaxel may also contribute to peripheral neuropathy (Sparreboom et al. 1995), this phenotype is casually related to paclitaxel itself as direct administration of clinically relevant concentrations of three major paclitaxel liver metabolites: 6α-hydroxy-paclitaxel, 3′-p-hydroxy-paclitaxel, and 6α,3′-p-dihydroxy-paclitaxel did not produce neuropathic pain, when compared to the parent drug. In contrast to wild-type mice, Oatp1b2 deficiency recapitulated mechanical sensitivity that resembled baseline values or vehicle-treated group, and is protected from acute paclitaxel-induced peripheral neuropathy (Leblanc et al. 2018). Thermal sensitivity and electrical nerve conductance were also preserved in Oatp1b2(−/−) after chronic treatment. In support of Oatp1b2's functional involvement in accumulation of paclitaxel in DRGs, cabazitaxel, a taxane derivative approved for the treatment of prostate cancer, rarely causes peripheral neuropathy (Omlin et al. 2015) and is not transported by OATP1B-type transporters (Nieuweboer et al. 2014).

Various approaches have been proposed to predict, prevent, and/or treat paclitaxel-induced peripheral neuropathy (Scripture et al. 2006). The predictive strategies have predominantly focused on the search for hereditary biomarkers that could identify patients at increased risk of toxicity through candidate gene (Boora et al. 2016; Green et al. 2009; Hertz et al. 2012, 2013; Leskela et al. 2011; Sissung et al. 2006; Tanabe et al. 2017; Abraham et al. 2014; de Graan et al. 2013) or genome-wide association studies (Baldwin et al. 2012; Bergmann et al. 2013; Lam et al. 2016; Sucheston et al. 2011). However, the findings from these studies done to date have identified non-overlapping single or pathway biomarker associations that preclude immediate clinical implementation (Brewer et al. 2016; Schneider et al. 2015a, b; Frederiks et al. 2015; Hertz 2013). In addition, the decision to act on a toxicity biomarker is hampered in many diseases by the lack of available alternative treatments to replace paclitaxel and/or the need for a patient-tailored reduction in the paclitaxel dose to prevent toxicity, which will have negative effects on the disease management.

To date there have been more than 40 randomized controlled clinical trials of agents to prevent or treat peripheral neuropathy associated with paclitaxel, and these trials have not provided convincing evidence for a clinically beneficial agent (Hershman et al. 2014). One area of research currently being pursued is based on the hypothesis that agents with inhibitory properties toward OATP1B-type transporters could be exploited as neuro-protectants in conjunction with paclitaxel-based chemotherapy (Fig. 3). One of the candidate inhibitors is nilotinib, an inhibitor of the Bcr-Abl kinase used in the treatment of certain leukemias. Pretreatment with this agent protected against acute and chronic forms of paclitaxel-induced peripheral neuropathy in mice, without affecting the disposition properties of paclitaxel or its antitumor properties (Leblanc et al. 2018). The optimal pharmaceutical and pharmacological properties of nilotinib provide rationale for an excellent modulator of the off-target cellular disposition of paclitaxel and subsequent toxicities. Nilotinib is orally bioavailable and has a long half-life resulting from its relatively slow systemic clearance (Xia et al. 2012); this slow clearance will ensure sufficient nilotinib levels to modulate the cellular disposition of paclitaxel. Interestingly, high-dose TKI pulse-exposure, in contrast to a chronic low-dose daily exposure, is becoming a more well-received concept in the treatment of various cancer (Lipka et al. 2012). The increase of familiarity of clinicians with this high-dose pulse strategy of nilotinib will ultimately help facilitate the translation of our propose concept of utilizing nilotinib, as

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a transporter inhibitor, as adjunct therapy in paclitaxel-based chemotherapies to reduce toxicities. Interestingly, recent preclinical study of nilotinib-paclitaxel combination showed exquisite activity (Holbeck et al. 2017), resulting in tumor regressions in models of breast cancer xenografts with no tumor regrowth observed for more than 80 days following the end of therapy. Although confirmation of these initial findings is required, in patient-derived tumor models that more faithfully represent the characteristics of primary human breast cancer compared with xenografted cell lines (Hidalgo et al. 2014), these combined initial observations indicate that combining paclitaxel with inhibitors of OATP1B-type transporters such as nilotinib has the potential to simultaneously reduce toxicities and increase anticancer effects.

2.2 OCT2 and Oxaliplatin-Induced Peripheral Neurotoxicity

Oxaliplatin is a platinum-based chemotherapeutic that is widely used in the treatment of colorectal and gastric cancers, but its clinical use is associated with debilitating damage to peripheral nerves. This side effect remains one of the most important complications of contemporary oncology regimens as it may limit further treatment and/or may cause long-term quality of life concerns. The characteristic pattern of peripheral neurotoxicity associated with oxaliplatin affects up to 92% of patients (Argyriou et al. 2008), occurs immediately after infusion, and is characterized by cold-exacerbated paresthesia, muscle spasms, and fasciculations. Another distinctive feature of oxaliplatin-induced neurotoxicity is pharyngolaryngeal dysesthesia, an acute sensation of respiratory discomfort without any objective evidence of respiratory distress. Although these acute symptoms typically resolve within 1 week, at higher cumulative doses, oxaliplatin induces a dose-limiting sensory neurotoxicity that leads to functional impairment, which could last several months to even years following discontinuation of treatment or in more severe cases may display permanent, incomplete recovery (McWhinney et al. 2009).

The cellular and molecular mechanisms underlying oxaliplatin-induced neurotoxicity remain incompletely understood to this day. However, studies performed during the last decade have provided crucial insights into the pathophysiological events that contribute to the development of oxaliplatin-induced neurotoxicity. Unlike the central nervous system, the peripheral nervous system, consisting of nerves and ganglia outside of the brain and spinal cord, is not protected by the blood–brain barrier, and is particularly sensitive to oxaliplatin-induced injury. Within the peripheral nervous system, oxaliplatin accumulates and causes toxicity only in the sensory neurons, while the motor neurons are spared (Thompson et al. 1984). As with paclitaxel, the DRG has emerged as the major target of oxaliplatin-induced neurotoxicity (Cavaletti et al. 2001; McKeage et al. 2001), and both structural and functional alterations in the DRG are thought to be the major reason for the development of the observed toxicity (Jamieson et al. 2005). Morphological and anatomical examinations have determined key structural changes in the DRG during oxaliplatin treatment, including alterations in the nuclear/nucleolar morphology, selective atrophy of a subpopulation of cells, platinum-DNA adduct formation, and apoptosis (Cavaletti et al. 2001). The functional changes include sodium channel dysfunction, leading to altered peripheral-nerve excitability, as well as oxaliplatin-dependent changes in the function and expression of several ion channels in the DRG leading to increased nociception (Trevisan et al. 2013; Zhao et

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al. 2012). The ion channels are activated by mechanical, thermal, chemical, and noxious stimuli, and oxaliplatin-induced changes in their function and expression contribute to the sensory neuropathic symptoms observed in patients treated with oxaliplatin. Notably, oxaliplatin-induced neurotoxicity is not associated with axonal degeneration as observed in diabetic neuropathy, and damage to the DRG is believed to be causative in the development of neurotoxicity (Gregg et al. 1992).

The key event that triggers the development of pathological changes in the structure and function of DRG is the initial accumulation of oxaliplatin. Multiple studies have shown that oxaliplatin preferentially accumulates in DRG (McKeage et al. 2001), accounting for its selective toxicity to the peripheral sensory system. Unlike sensory neurons, the motor neurons are spared due to lack of oxaliplatin accumulation, highlighting the role of oxaliplatin uptake in the development of neuropathic symptoms. Importantly, in patients, the severity of neuropathy correlates with the platinum concentration in peripheral nerves (Gregg et al. 1992), confirming that oxaliplatin uptake is the major determinant of neurotoxicity. Interestingly, oxaliplatin levels in DRG remain high for prolonged time periods, even after discontinuation of treatment (Holmes et al. 1998). Although efflux transporters (or lack thereof) may be playing a role in the highly prolonged levels of oxaliplatin in DRGs, the transporter-mediated initial influx of oxaliplatin is one of the earliest steps driving cellular accumulation and believed to be the major determinant for subsequent neurotoxicity.

Identification of the biological processes involved in oxaliplatin accumulation in DRG is critical to understanding the mechanisms responsible for oxaliplatin-induced neurotoxicity. Several recent studies have proposed candidate transporters of oxaliplatin and related platinum complexes in heterologous cell culture models. In particular, OCTs belonging to the *SLC22A* family that includes OCT2 (*SLC22A2*) have been implicated in the transport of oxaliplatin and other platinum-based drugs (Sprowl et al. 2013c). Using genetic and pharmacological strategies, in vivo evidence has been accumulating for the direct role of OCT2 in the development of oxaliplatin associated neurotoxicity (Sprowl et al. 2013a). More specifically, recent studies involving genetically engineered mouse models have documented that the acute and chronic forms of oxaliplatin-induced peripheral neurotoxicity are dependent on OCT2, a transporter that regulates the transfer of drug from the circulation into satellite glial cells (SGC) in the DRG. These studies also demonstrate that tyrosine phosphorylation of OCT2 by the protein kinase YES1 is essential for function and targeting this post-translational modification can be exploited to modulate transport activity (Hu and Sprowl 2018; Sprowl et al. 2013a, c, 2016).

In addition to OCT2, several other uptake transporters in rodents have been postulated to be of potential relevance to the pharmacokinetics and toxicity of oxaliplatin, including Oct1 (Li et al. 2011), Oct3 (Yokoo et al. 2008), Octn1 (Nishida et al. 2018), Mate1 (Jong et al. 2011), Ctr1 (Ip et al. 2013), and Oatp1b2 (Lancaster et al. 2013). Although these transporters are all expressed in isolated DRGs from wild-type mice, uptake studies in engineered HEK293 cells overexpressing individual transporters have suggested that oxaliplatin may not be a transported substrate of these OCTs and OATPs, and that transport by OCT2 was more efficient than that observed for MATE1 and OCT3 (Sprowl et al. 2013a; Zhang et al. 2006).

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Additional studies are required to define the individual and collective contributions of these alternative neuronal uptake mechanisms for oxaliplatin. Preliminary studies performed to resolve this question experimentally with the use of primary SGCs cultures from mouse DRGs have indicated that about 80% of oxaliplatin uptake in these cells is mediated by OCT2, suggesting that the collective contribution of alternative mechanisms, including passive diffusion, may be minimal.

Targeting OCT2 is particularly appealing as an approach in ameliorating oxaliplatin-induced toxicities because potent and specific inhibitors are unlikely to sacrifice treatment efficacy in view of the general lack of OCT2 expression in tumor cells (Franke et al. 2010b), including colorectal cancers (Sprowl et al. 2013a). Importantly, since OCT2 inhibition may reduce the initial accumulation of platinum-based agents, the neuroprotective effects of OCT2 inhibition observed in the acute toxicity models may also lead to reduction in chronic pain and neuropathic symptoms frequently observed in patients. This possibility is strongly supported by the recent finding that patients receiving oxaliplatin-based chemotherapy who manifest symptoms of the acute neurotoxicity syndrome are those who will also eventually develop the chronic toxicity (Argyriou et al. 2013).

2.3 OCT2 and Cisplatin-Induced Nephrotoxicity

Cisplatin is another DNA-crosslinking, platinum-based chemotherapeutic agent that is among the most widely used anticancer drugs in both adult and pediatric populations (Dasari and Bernard Tchounwou 2014). In the conventional treatment regimens in which the drug is administered once every 3 weeks, dose-limiting side effects include renal tubular dysfunction (nephrotoxicity), and to a lesser extent, hearing loss (ototoxicity) and damage to peripheral nerves. Severe and irreversible damage to the kidney remains the single most important complication of cisplatin treatment as it may limit further treatment or even threaten life. This side effect primarily affects the S3 segment of the renal proximal tubules and occurs in up to 40% of patients despite intensive prophylactic measures, including extensive pre- and post-hydration regimens with hypertonic saline (Arany and Safirstein 2003; de Jongh et al. 2003). Furthermore, about 20% of all acute renal failure cases among hospitalized patients are due to cisplatin-containing chemotherapy (Berns and Ford 1997). As previously observed with toxicities associated with paclitaxel and oxaliplatin, the exact pathogenesis of cisplatin-related chronic toxicities and identity of SLCs involved in these processes, in which quiescent cells are selectively damaged, has remained unclear until relatively recently (Waissbluth and Daniel 2013; Yao et al. 2007).

Using transfected HEK293 cells, it was previously reported that cisplatin is a substrate for OCT2, as indicated by saturable uptake with an estimated Michaelis-Menten constant of 11 μM (Filipski et al. 2008). The localization of OCT2 in the S3 segment of the renal proximal tubules (Leibbrandt et al. 1995) suggests that OCT2 may be a key regulator in the renal elimination of cisplatin and may indirectly regulate the extent to which the drug causes kidney damage. This hypothesis has been verified in several studies with the use of Oct1/2(−/−) mice (Filipski et al. 2009), which are partially protected against cisplatin nephrotoxicity (Ciarimboli et al. 2010). Additionally, higher expression of OCT2 in male rodents correlated with a greater propensity and susceptibility to proximal tubular injury

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compared to female rodents. Subsequent investigation demonstrated that OCT2 is also highly expressed in the cochlea, and that Oct1/2(−/−) mice are completely protected from platinum-induced ototoxicity (Ciarimboli et al. 2010; Lanvers-Kaminsky et al. 2015) as well as from cisplatin-mediated peripheral neurotoxicity (Sprowl et al. 2013 a; Hucke et al. 2019).

The demonstration that this solute carrier plays an important role in all clinically relevant platinum-related toxicities provides a rationale for the development of therapeutic interventions for cisplatin-containing regimens in patients involving the use of specific inhibitors of OCT2. Targeting OCT2 is particularly appealing as an approach in ameliorating cisplatin-induced toxicities because potent and specific inhibitors are unlikely to compromise treatment efficacy in view of the general lack of OCT2 expression in tumor cells (Franke et al. 2010b). However, the incomplete protection against cisplatin-associated renal tubular damage in Oct1/2(−/−) mice suggests the existence of a secondary pathway that contributes, independently of Oct1/Oct2-mediated renal tubular drug uptake, to cisplatin-induced renal damage (Sprowl et al. 2014). Recent rodent studies have suggested that the OCT2-independent pathway is regulated by the transporters OAT1 and OAT3, which mediate the accumulation of a nephrotoxic, mercapturic acid metabolite of cisplatin formed in the γ-glutamyltranspeptidase pathway (Hu et al. 2017).

Over the last three decades, various approaches have been proposed to afford tissue protection during cisplatin treatment, although most of these interventions have not been evaluated in animal models or humans. Indeed, there is still no known preventative treatment for cisplatin-induced renal dysfunction (dos Santos et al. 2012), ototoxicity (Langer et al. 2013; Travis et al. 2014), or neurotoxicity (Albers et al. 2014). Agents that have advanced to clinical testing, such as amifostine, are associated with intrinsic toxicity and, more importantly, do not appear to have a major impact on ameliorating the risk of developing severe nephrotoxicity (Gallegos-Castorena et al. 2007; Sastry and Kellie 2005), ototoxicity (Duval and Daniel 2012), or neurotoxicity (Hensley et al. 2009). Furthermore, the clinical application of many alternate strategies has been hampered by the recognition that (1) cisplatin has multiple intracellular targets and hence blocking a single injurious event will only have partial protective effects and (2) the protective approach may diminish the antitumor effects of cisplatin given the overlap in cell death signaling pathways between normal cells and tumor cells. Therefore, an ideal approach is to simultaneously protect the kidneys and other afflicted tissues such as cochlea and peripheral nerves without affecting the therapeutic effects in tumors. The development of such an approach would rely on the identification of the critical differences between normal and malignant cells during cisplatin treatment.

One of these agents, cimetidine, has shown some promise in ameliorating cisplatin-induced nephrotoxicity (Franke et al. 2010b) and ototoxicity (Ciarimboli et al. 2010), as well as oxaliplatin-induced neurotoxicity in experimental mouse models (Sprowl et al. 2013a). To obtain preliminary evidence for the usefulness of adding cimetidine to cisplatin-based therapy in cancer patients, randomized cross-over trials (Sprowl et al. 2013b) have been performed and demonstrated that inhibition of OCT2 function by cimetidine did not affect the antitumor or disposition properties of cisplatin. However, cimetidine did not completely

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eradicate renal tubular damage, in line with another recent clinical trial indicating that the renoprotective effects associated with cimetidine are only partial (Zhang and Zhou 2012). This confirms in vitro studies suggesting that cimetidine is an inefficient and non-specific inhibitor of OCT2 (Ito et al. 2012; Motohashi et al. 2004), and that identification of alternate OCT2 inhibitors is urgently needed. Such agents would ideally have (1) high potency, (2) high specificity, (3) low drug–drug interaction potential, (4) intrinsic antitumor properties, (5) favorable pharmaceutical properties, (6) non-overlapping toxicity profiles, and (7) potentially other renoprotective features, including inhibition of OAT1 and OAT3. Among possible candidates for further exploration, palbociclib, an FDA-approved inhibitor of CDK4/6 used in the treatment of breast cancer, is of particular interest because it has been previously shown that other inhibitors of cyclin dependent kinase are able to afford protection against cisplatin-induced kidney injury in experimental models (Price et al. 2009). Preliminary studies performed in mice have suggested that cisplatin-induced nephrotoxicity can be mitigated by pretreatment with palbociclib through a mechanism that is partially dependent on OCT2 (Pabla et al. 2015). Due to significant overlap of OCT/MATE inhibitors, it is important that the design of these intervention strategies aimed at selectively targeting OCT2-mediated uptake does not increase the residence time in proximal tubular cells due to unintended inhibition of MATE1-mediated efflux.

2.4 ENT1/OCTN1 and Cytarabine-Related Toxicities

Cytarabine is a nucleoside analog belonging to the family of antimetabolites due to its similarity in chemical structure to that of endogenous nucleosides. Cytarabine is utilized in a variety of leukemia subtypes but is a mainstay in the treatment of acute myeloid leukemia (AML) where it is an integral component of first-line therapy. All of the endogenous and xenobiotic nucleoside analogs are polar hydrophilic compounds that are poorly membrane permeable and require functional nucleoside transporter proteins to enter cells.

Nucleoside transporters facilitate the accumulation of both endogenous nucleosides and nucleoside-derived drugs that are utilized as anticancer and antiviral agents (Baldwin et al. 1999). Some cell types, including brain, enterocytes, and bone marrow cells, rely heavily on the nucleoside salvage pathway due to their inability to synthesis nucleosides de novo and thus rely heavily on the extracellular milieu for their primary source of nucleosides for use in RNA and DNA synthesis (Murray 1971). Nucleoside transporters play an integral role in the maintenance of extracellular concentrations of nucleosides, which are available to bind to receptors and modulate a variety of physiological processes. Transporter-mediated transport of nucleosides is thus a critical determinant in the salvage and consequently, nucleoside-mediated toxicity in many cell types (Griffith and Jarvis 1996).

The two major classes of nucleoside transporters in mammalian cells and tissues consist of equilibrative nucleoside transporters (ENTs) and concentrative nucleoside transporters (CNTs). Two proteins of the former class, ENT1 (*SLC29A1*) and ENT2 (*SLC29A2*), are known to mediate the transport of purine and pyrimidine nucleosides across biological membranes down their concentration gradients. These transporters exhibit broad substrate selectivity and are subdivided based on their sensitivity (ENT1) or resistance (ENT2) to inhibition by nanomolar concentrations of nitrobenzylmercaptopurine ribonucleoside

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(NBMPR) (Damaraju et al. 2003). In addition to ENT1, several non-canonical putative nucleoside transporters, including OCTN1, can potentially transport nucleoside analogs in a manner that is sensitive to nanomolar concentrations of NBMPR (Drenberg et al. 2017).

The clinical use of cytarabine is associated with dose-limiting damage to normal bone marrow (myelosuppression), which occurs in the majority of patients, as well as with damage to the skin (toxic erythema), and these complications may require dose-modification, limit further treatment, or even threaten life (Hwang et al. 2012; Zhang et al. 2014). Interestingly, OCTN1 is highly expressed in several organs of particular relevance to cytarabine-based chemotherapy regimens, including myeloid progenitor cells in the bone marrow, proximal tubular cells in the kidney (Kobayashi et al. 2004), and epidermal keratinocytes in the skin (Wu et al. 2000). Preliminary evidence pointing to potential causality of this connection has come from population-based genetic studies indicating that patients with a functional polymorphic germline variant of OCTN1 (L503F; rs1050152) experience an increased frequency of febrile neutropenia (Drenberg et al. 2015). Furthermore, overexpression of this genetic variant (L503F) in HEK293 cells is associated with increased transport function (Urban et al. 2007) and increased formation of Ara-CTP, the active triphosphorylated form of cytarabine (Drenberg et al. 2017).

Consistent with the thesis that OCTN1 may be contributing to cytarabine-related toxicities, it has been reported that this transport system may also be operational for related cytotoxic nucleoside analogs such as gemcitabine, an agent used in the treatment of pancreatic cancer with activity in certain subtypes of AML (Drenberg et al. 2019), that causes dose-limiting anemia and neutropenia. Although this site of toxicity directly aligns with the expression profile of OCTN1, further study is warranted to determine the contribution of individual SLCs to gemcitabine-related side effects. In this context, it is worth pointing out that the intracellular accumulation of nucleoside analogs such as cytarabine was recently reported to occur independently of OCTN1 (Tschirka et al. 2018). In this work, the authors used an LC-MS/MS-based method to measure the intracellular levels of unchanged cytarabine, whereas prior studies involved the use of an analysis based on the measurement of total radioactivity [i.e., the total of parent drug and metabolite(s)]. This is a potentially important methodological difference as cytarabine can undergo rapid enzyme-mediated metabolism once inside cells to form mono-, di-, and tri-phosphorylated forms (Owens et al. 1992), which may easily escape detection and result in underestimating the actual extent of uptake. This possibility is supported by the finding that cytarabine is rapidly and extensively phosphorylated in HEK293 cells (Drenberg et al. 2017), and by the demonstration that in a comparative analysis intracellular levels of total radioactivity originating from cytarabine in cells overexpressing OCTN1 are high, while levels of the unchanged parent drug, as measured by LC-MS/MS, remain undetectable (Anderson et al. 2019).

2.5 OATPs and Irinotecan-Mediated Neutropenia and Diarrhea

Irinotecan is a prodrug of the topoisomerase I inhibitor, SN-38, and is utilized in a variety of chemotherapy containing regimens that are used to treat solid tumors such as colorectal cancers. Irinotecan is known to cause several debilitating adverse events such as myelosuppression and diarrhea. In contrast to the metabolism of irinotecan, which has been

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well documented and characterized (de Man et al. 2018), the pharmacokinetic processes of relevance to irinotecan disposition are less well characterized and are likely dependent on the interplay of drug transporters residing in organs such as the liver. In this context, the contribution of hepatocellular uptake transporters in the disposition of irinotecan remains poorly understood. Preclinical reports have shown that after irinotecan administration, the systemic exposure of SN-38, the active metabolite of irinotecan, is highly impacted by the deficiency of Oatp1a- and Oatp1b-type carriers in murine models and expression of human OATP1B1 or OATP1B3 (Iusuf et al. 2014). Furthermore, only a small fraction of the administered dose of irinotecan is excreted in the bile (0.9% for SN-38 and 3% for SN-38-glucuronide) (de Jong et al. 2006), which supports the notion that a large fraction of these metabolites formed within hepatocytes and being transported back into the system circulation, presumably by the hepatic efflux transporter ABCC3 (Kitamura et al. 2010). This increased SN-38 efflux can then be taken up again by adjacent hepatocytes in an OATP1B-mediated manner for further glucuronidation and/or biliary excretion termed “hepatocyte hopping” (Iusuf et al. 2012). This unusual mechanism is hypothesized as a physiological mechanism to overcome hepatocellular saturation and to efficiently facilitate detoxification through utilizing other elimination pathways such as Phase II conjugation and transporter-mediated excretion into the bile. This unusual mechanism for irinotecan elimination is supported by the observation of patients with functional variants of OATP1B1 that are associated with altered exposure to SN-38 and at risk for severe toxicity following irinotecan-based chemotherapies (Di Paolo et al. 2011).

Interestingly, in contrast to SN-38 and other known glucuronide metabolites (Ni et al. 2010; Zimmerman et al. 2013), SN-38-glucuronide accumulation is not mediated by OATP1B1 (Nozawa et al. 2005). Clinical observation of excessive SN-38-glucuronide buildup in the systemic circulation relative to unconjugated SN-38 could be explained by the lack of an efficient hepatocellular uptake mechanism for SN-38-glucuronide (Innocenti et al. 2014).

Since formation of SN-38 from irinotecan is essential to the therapy-related diarrhea (Fujita et al. 2016), recent studies have focused on connecting functional expression of intestinal transporters to the occurrence of this side effect. This work has resulted in the identification of OATP2B1 as a putative carrier of SN-38 on the basis of uptake studies performed in *Xenopus* oocytes (Fujita et al. 2016). This transporter is highly expressed in the small intestine (Tamai et al. 2000), and sensitive to inhibition by cyclosporine (Chen et al. 2020), an agent that has been exploited as a therapeutic to prevent the dose-limiting diarrhea associated with irinotecan treatment (Chester et al. 2003). The availability of a recently developed Oatp2b1-deficient mouse model will allow the unequivocal demonstration of a causal connection of OATP2B1-mediated transport of SN-38 with irinotecan-related diarrhea (Medwid et al. 2019).

2.6 SLCs and Doxorubicin-Related Cardiotoxicity

Doxorubicin, an anthracycline-derived DNA-intercalator, is widely used in the treatment of multiple tumor types, including breast cancers and soft tissue sarcomas. Common side effects associated with the use of doxorubicin include acute nausea and vomiting, mucositis, alopecia, and tissue extravasation. More serious, dose-limiting toxicities associated with

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doxorubicin include myelosuppression and cardiotoxicity, and these side effects are dependent on the cumulative dose administered. In particular, the risk for patients developing congestive heart failure is estimated at 5% (Von Hoff et al. 1979; Kremer et al. 2001), 18% (Kremer et al. 2001), and 36% (Swain et al. 2003) for cumulative doses of doxorubicin of <500 mg/m^2, 500–600 mg/m^2, and > 600 mg/m^2, respectively. Manifestation of acute cardiotoxicity presents as arrhythmias or ventricular dysfunction. However, since the myocardium has limited regenerative capacity (Lionetti and Ventura 2013; Yamada et al. 2015), chronic cardiotoxicity induced by anthracyclines culminates into dilated cardiomyopathy and congestive heart failure (Boucek Jr. et al. 1997; Lipshultz et al. 2013), which can occur months or even years after cessation of therapy. The risk of developing chronic cardiotoxicity is particularly high in young adult and adolescent cancer survivors (Lipshultz et al. 2013). Clinical risk factors associated with doxorubicin-induced cardiotoxicity also include pre-existing cardiac dysfunction and age (Doyle et al. 2005) as well as prior therapy involving radiation or chemotherapy (Singal and Iliskovic 1998).

The mechanisms by which anthracyclines such as doxorubicin accumulate into cardiomyocytes remain largely unknown. At physiological pH 7.4, the hydrophobic weak base doxorubicin is slightly cationic (Raghunand et al. 1999), and this recognition has resulted in recent efforts to connect uptake of anthracyclines to OCTs that can explain cell-type specific toxicity profiles. In particular, studies have demonstrated that overexpression of OCTN1 (Okabe et al. 2008), OCT1 (Andreev et al. 2016), or OCT6 (Okabe et al. 2005; Ota et al. 2007) is associated with significantly increased drug uptake and sensitivity of leukemic and ovarian cancer cells following exposure to doxorubicin. Furthermore, studies in *C. elegans* and *Danio rerio* corroborate involvement of OCT1 and possibly OCT2 (Brosseau et al. 2015) in the cellular uptake of doxorubicin. It is likely that cardiac expression of OCTs capable of transporting doxorubicin in the myocardium contributes as an initiating event that ultimately leads to treatment-related cardiotoxicity.

Among the class of OCTs, studies have confirmed the presence of several members at both the mRNA and protein levels in the human heart, with OCTN2 having the highest expression, followed by OCT3, OCTN1, and OCT1, while OCT2 is undetectable (Grube et al. 2011). In view of the predominant expression of OCT2 in the kidney, it is possible that this transport mechanism contributes to urinary excretion of anthracyclines and to doxorubicin-induced nephrotoxicity (Filipski et al. 2009; Ayla et al. 2011). Additional investigation has indicated that expression of these transporters is confined to either the vasculature (OCTN1, OCTN2, and OCT3) or to cardiomyocytes (OCTN1 and OCT1) (Grube et al. 2011; Iwata et al. 2008) of the myocardium, although other studies have demonstrated ubiquitous localization in the heart (Nishimura and Naito 2008). It has been suggested that OCTN2 is involved in the uptake of certain cardiovascular drugs, and is spatially regulated in a rat cardiomyopathy model (Iwata et al. 2008). Indeed, supplementation with the high-affinity OCTN2 substrate, L-carnitine, can reduce doxorubicin-induced upregulation of heart fatty acid binding protein (H-FABP) (Sayed-Ahmed et al. 2010), suggesting the potential for an OCTN2-mediated mechanism for doxorubicin uptake. In addition, expression of the structurally related transporter OCTN1 is correlated with augmenting the blockage of HERG potassium channels and potentiating *torsade de pointes* (McBride et al. 2009), which can lead to serious cardiac arrhythmias.

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OCT1 and OCT3 have also been linked to cardiovascular drug response, in particular to certain beta-blockers (Bachmakov et al. 2009; Kubo et al. 2013; Hassan et al. 2016), which are used principally as prophylactic treatment in managing cardiovascular function after anthracycline therapy. Additionally, OCT3 has been identified as an important regulator of neurological and cardiovascular response to endogenous substrates such as epinephrine and norepinephrine (Zwart et al. 2001; Hanafy et al. 2012; Ayala-Lopez et al. 2015; Zhu et al. 2012). Furthermore, case-control studies of the OCT3 gene locus have suggested its involvement in coronary vascular development, and multiples variants, including rs9381439, rs2048327, rs18190126, and rs9349379, were previously associated with decreased risk for coronary artery disease (Tregouet et al. 2009; Wang et al. 2016). Definitive demonstration of a direct contribution of any of the candidate transporters to doxorubicin-induced cardiotoxicity, for example, in mice with individual SLC deficiencies, remains warranted, and may provide opportunities for the future design of preventative intervention strategies with the use of selective transport inhibitors.

Since hepatobiliary excretion is the main elimination pathway of doxorubicin (Legha et al. 1982; Bronchud et al. 1990; Robert et al. 1985, 1987; Maniez-Devos et al. 1986), recent studies have attempted to connect the function of hepatic OATPs with the disposition of doxorubicin (Gong and Kim 2013). These investigations have shown that deficiency of Oatp1a- and Oatp1b-type transporters in mice is associated with increases in systemic exposure to doxorubicin. In addition, introduction of the human transporters OATP1B1, OATP1B3, or OATP1A2 in the livers of these knockout mice can partially recapitulate the pharmacokinetic profile of doxorubicin observed in wild-type mice (Durmus et al. 2014). Drug uptake studies in cell-based models engineered to overexpress human OATP1A2 variants have corroborated the results in mice, and are consistent with previous reports involving other substrates (Lee et al. 2017). Although several related transporters, including OATP2B1, OATP3A1, and OATP4A1, are known to be expressed in the heart (Hanafy et al. 2012; Grube et al. 2006; Atilano-Roque and Joy 2017), there is currently an apparent lack of documentation that establishes a correlation of these OATPs with the cardiac uptake of anthracyclines, and thus their direct relevance to cardiovascular function after doxorubicin treatment remains uncertain.

3 Toxicity Induced by Targeted Therapeutics

In oncology, the last two decades have seen a dramatic transition from the use of traditional cytotoxic chemotherapy to the emergence of a new paradigm in rational drug design coupled with an uprising in the development of targeted agents, including the tyrosine kinase inhibitors (TKIs). To date, >45 different TKIs have received approval by the FDA for the treatment of a variety of diseases that were previously essentially resistant to standard chemotherapy, and many more can be expected to become available in the future (Drenberg et al. 2013). However, while TKIs offer possibly a number of important theoretical advantages over conventional cytotoxic chemotherapy, they are still afflicted by some of the same problems, including an extensive inter-individual pharmacokinetic variability, the existence of a rather narrow therapeutic window, and the occurrence of multiple, debilitating adverse events (Drenberg et al. 2013).

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Previous investigations on drug transporters and their contribution to pharmacological effects of TKIs have often exclusively focused on the effects on measures of systemic exposure, ignoring effects on local drug uptake and cellular retention in healthy tissues. Other investigations have tended to focus solely on the cellular target regulating pharmacological effects while ignoring the effects on systemic and/or local drug exposure. However, recently developed conceptual frameworks for an integrated approach have started to address questions related to the relevance of specific SLCs to the local tissue exposure of TKIs.

3.1 OAT6 and Sorafenib-Mediated Skin Toxicity

Sorafenib is a multi-kinase inhibitor (MKI) utilized in unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and thyroid carcinoma. Common debilitating adverse events of sorafenib include fatigue, infection, alopecia, hand-foot skin reaction, and rash. Of the listed adverse events, cutaneous adverse effects are among the most frequently observed toxicities with many TKIs, and their intensity can significantly affect both quality of life and health care economics (Macdonald et al. 2015). In one study, 40% of renal cell carcinoma patients taking sorafenib had a dermatologic reaction (Kane et al. 2006).

A particularly painful complication seen most frequently during the early weeks of use with MKIs such as sorafenib and regorafenib is known as hand-foot skin reaction (HFSR), in which hyperkeratotic plaques develop predominantly over sites of pressure or friction (Inaba et al. 2011; Lipworth et al. 2009). These plaques may have significant inflammation and xerotic hyperkeratosis, often in a bilateral symmetric distribution, causing pain and debilitation that interfere with activities of daily living (Macdonald et al. 2015). Sequential biopsy specimens from patients receiving MKIs have revealed progressive accumulation of hyperkeratosis with focal parakeratosis. The clinical incidence of HFSR varies among MKIs with a particularly high incidence being observed with sorafenib (>60%) (Zimmerman et al. 2016), and this appears to be unrelated to increased excretion of MKIs through sweat (Jain et al. 2010).

The hair follicle is a specialized mini-organ that is critically dependent on programmed keratinocyte differentiation (Botchkarev and Paus 2003; Cotsarelis 2006), and disruption of hair-follicle cycling or morphology is indicative of keratinocyte toxicity. Recent studies have indicated that sorafenib accumulates extensively in primary human epidermal keratinocytes compared to a panel of other TKIs, can decrease cell viability, and increase apoptosis (Zimmerman et al. 2016). The mechanism by which sorafenib is taken up into keratinocytes is concentration-, time-, and temperature-dependent. Since sorafenib is a poorly permeable compound, it is plausible that its uptake into keratinocytes is predominantly a transporter-mediated process. This hypothesis was verified by the recent demonstration that uptake of sorafenib in keratinocytes is dependent on OAT6, identified from a transportome-wide gene silencing screen (Tian et al. 2018), and that sorafenib-induced injury to keratinocytes in a mouse model of HFSR can be reversed by pretreatment with the OAT6 inhibitor, probenecid (Fig. 4) (Zimmerman et al. 2016). The translational significance of intervention strategies derived from the combinatorial use of probenecid and sorafenib or regorafenib (Belum et al. 2013) requires further investigation.

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4 Conclusions

In order to better understand the contribution of SLCs to debilitating side effects associated with anticancer drugs, there is an urgent need to further characterize the role of these proteins in the transport of drugs in both target and off-target tissues. This research would require the (1) expansion of the SLC proteomics field in various tissue types associated with toxicities of importance, (2) metabolomics approaches to further understand the trafficking of endogenous substrates of each transporter, and (3) the availability of agnostic screening platforms that allow for more rapid identification of drug-transporter and inhibitor-transporter pairs. Understanding the delicate balance of on-target and off-target tissue accumulation could then be exploited as a basis for the development of predictive tools as well as for the discovery of novel intervention strategies with application in the clinic in order to improve the safety of currently available treatment modalities.

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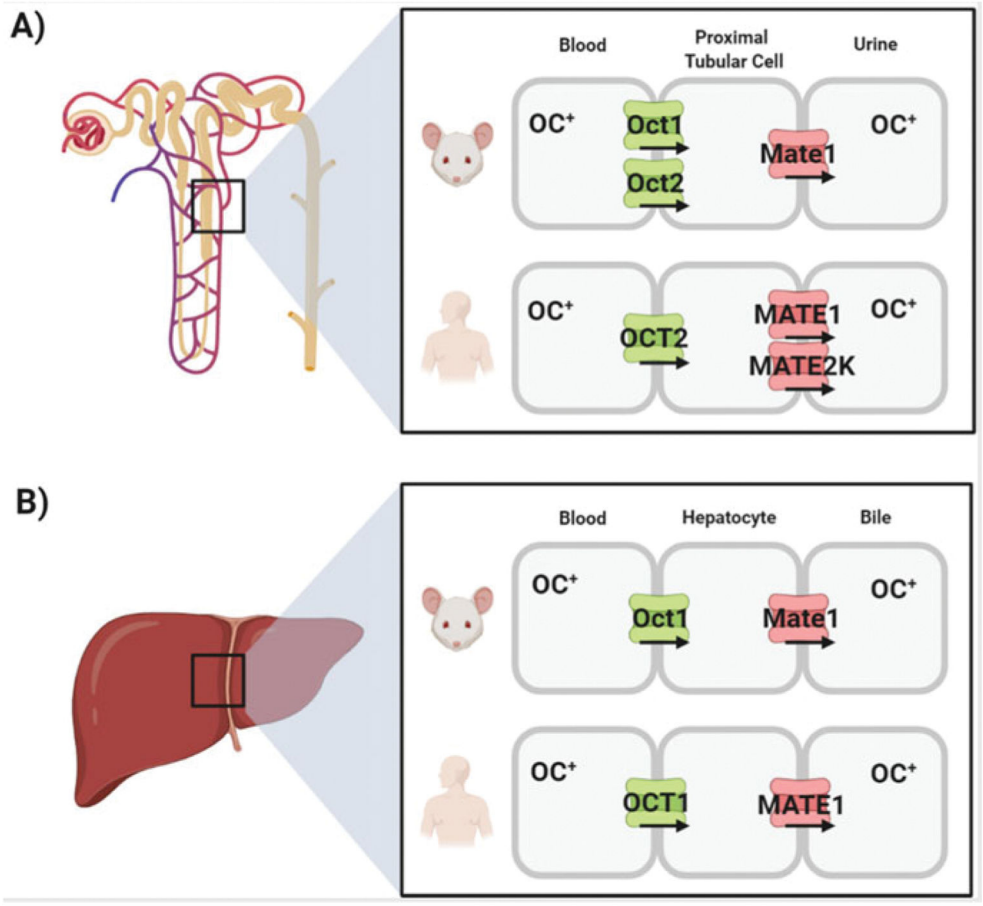

Fig. 1.

Schematic depiction of the vectorial transport of organic cations (OC+) in the kidney (**a**) and liver (**b**) of rodents and humans

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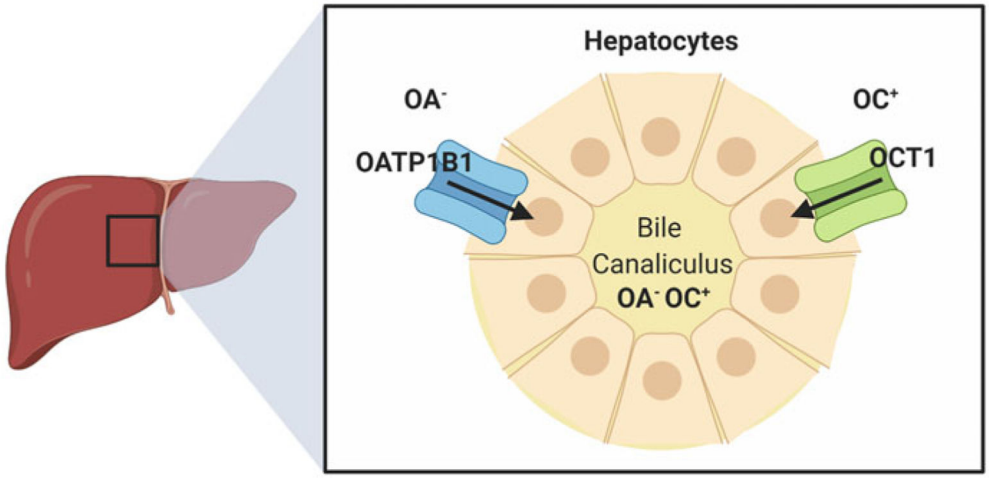

Fig. 2.

Schematic depiction of the transport of organic anions (OA−) and organic cations (OC+) in human hepatocytes by OCT1 and OATP1B1

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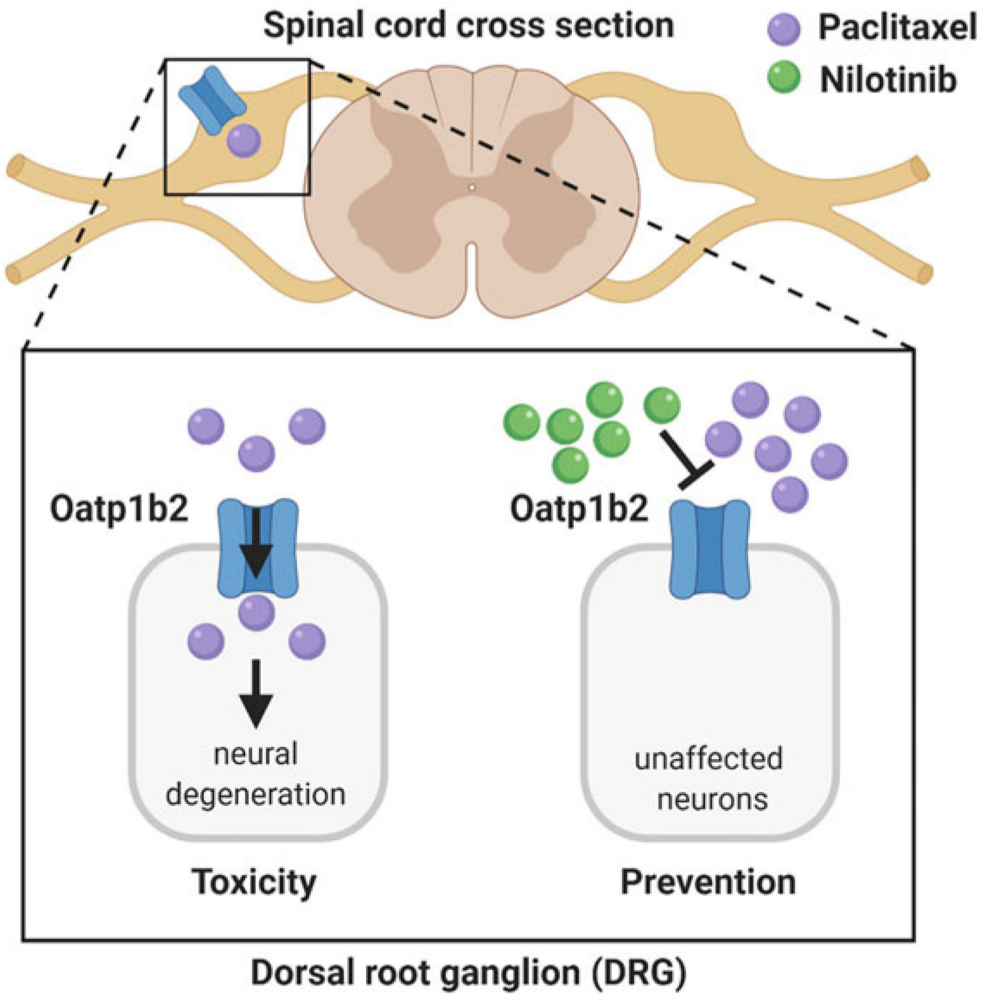

Fig. 3.

Proposed model of paclitaxel-induced injury to the peripheral nervous system. Murine Oatp1b2 mediates intracellular accumulation of paclitaxel, leading to peripheral neuropathy and neural degeneration (left). These effects can be blocked by the Oatp1b2 inhibitor nilotinib (right)

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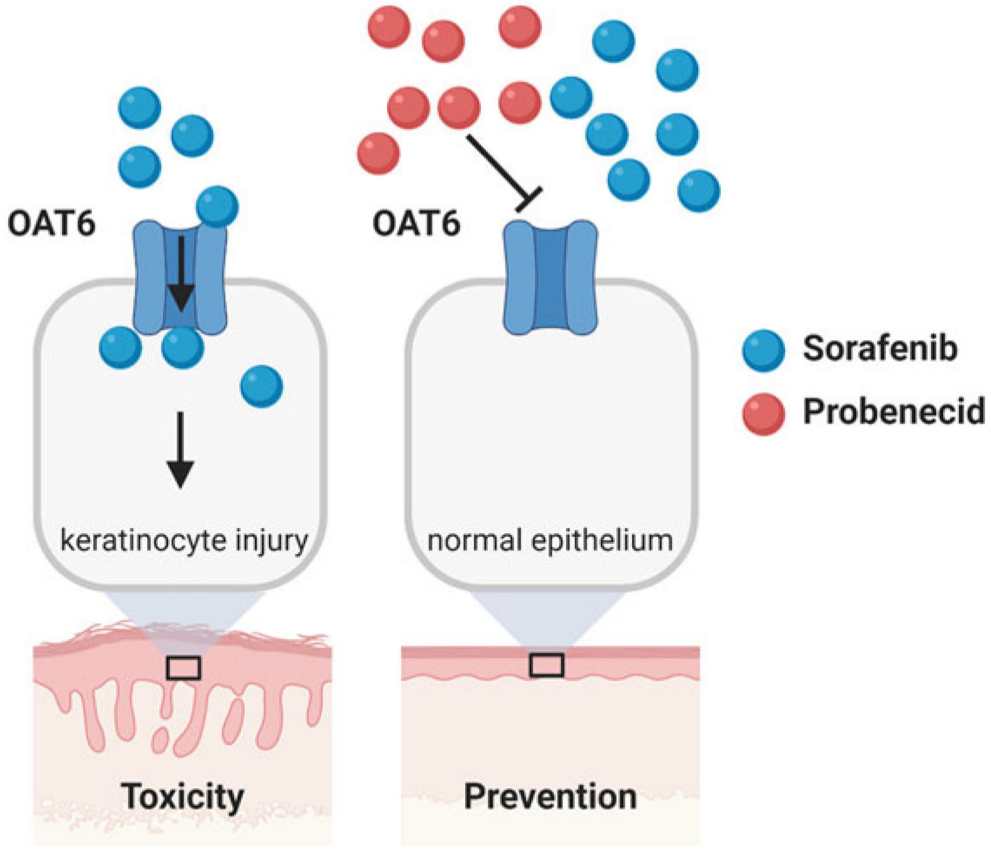

Fig. 4.

Proposed model of sorafenib-induced keratinocyte injury. Organic anionic transport 6 (OAT6) mediates intracellular concentrations of sorafenib, leading to cytotoxicity and keratinocyte injury (left). These effects can be blocked by the OAT6 inhibitor probenecid (right)