REVIEW

Role for Drug Transporters in Chemotherapy-Induced Peripheral Neuropathy

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Chemotherapy-induced peripheral neuropathy (CIPN) is a common and dose-limiting toxicity to widely used chemotherapeutics. Although the exact molecular mechanism of chemotherapy-induced peripheral neuropathy remains elusive, there is consensus that it is caused by damage to the peripheral nervous system leading to sensory symptoms. Recently developed methodologies have provided evidence of expression of drug transporters in the peripheral nervous system. In this literature review, we explore the role for drug transporters in CIPN. First, we assessed the transport of chemotherapeutics that cause CIPN (taxanes, platins, vincristine, bortezomib, epothilones, and thalidomide). Second, we cross-referenced the transporters implicated in genetic or functional studies with CIPN with their expression in the peripheral nervous system. Several drug transporters are involved in the transport of chemotherapeutics that cause peripheral neuropathy and particularly efflux transporters, such as ABCB1 and ABCC1, are expressed in the peripheral nervous system. Previous literature has linked genetic variants in efflux transporters to higher risk of peripheral neuropathy with the taxanes paclitaxel and docetaxel and the vinca alkaloid vincristine. We propose that this might be due to accumulation of the chemotherapeutics in the peripheral nervous system due to reduced neuronal efflux capacity. Thus, concomitant administration of efflux transporter inhibitors may lead to higher risk of adverse events of drugs that cause CIPN. This might prove valuable in drug development where screening new drugs for neurotoxicity might also require drug transporter consideration. There are ongoing efforts targeting drug transporters in the peripheral nervous system to reduce intraneuronal concentrations of chemotherapeutics that cause CIPN, which might ultimately protect against this dose-limiting adverse event.

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting toxicity that is correlated with a number of widely used chemotherapeutic drugs. CIPN presents predominantly as a sensory polyneuropathy with paresthesia sometimes accompanied by pain, and patients often describe the symptoms as "walking on needles." These symptoms follow a symmetric, distal, stocking and glove distribution. CIPN can be very serious, but even mild to moderate symptoms commonly persist for up to 2 years after treatment cessation, significantly impairing quality of life.[1,2] With more patients surviving cancers due to improved pharmacological treatment, this severe and long-lasting adverse reaction is particularly concerning and of public health interest. The risk and incidence of CIPN depends on chemotherapeutic agent, cumulative dose, chemotherapy regimen, duration of exposure, and a number of both genetic and nongenetic factors. Clinical strategies for reducing these debilitating symptoms include dose reduction/delay, alternative chemotherapy when feasible, increasing duration of infusion, and experimental approaches, such as cryotherapy.[3] A number of pharmacological agents have been tested to treat or prevent CIPN, but results have been disappointing, leaving this clinical challenge unresolved.

Numerous effective chemotherapeutic drugs can cause CIPN. The incidence of CIPN varies between chemotherapeutics and depends on the specific drug and indication for treatment. Recent evidence indicates that cancer itself may exacerbate CIPN.[4] In this review, we have focused on the most widely used chemotherapeutics that produce substantial risk of developing CIPN. The taxanes paclitaxel and docetaxel both cause CIPN, with paclitaxel being slightly more neurotoxic than docetaxel.[4] Taxane-induced peripheral neuropathy will normally improve 4–6 months after treatment cessation, but some patients may experience varying degrees of peripheral neuropathy up to 2 years later.[1] Platinum-based chemotherapeutics (cisplatin, oxaliplatin, and carboplatin) also cause CIPN. Symptoms of cisplatin-induced and oxaliplatin-induced peripheral neuropathy may continue to worsen after cessation of treatment and some patients may experience initial symptoms after concluding treatment. The widely used vinca alkaloid vincristine causes peripheral neuropathy in nearly all patients, and, in contrast to the abovementioned chemotherapeutics, may cause motor neuropathy and autonomic neuropathy with symptoms such as constipation and abdominal pain. The proteasome inhibitor bortezomib, the microtubule-stabilizing epothilone ixabepilone and the angiogenesis inhibitor thalidomide also cause CIPN.[5]

The pathogenesis of CIPN differs between chemotherapeutics. Primary axonopathy of peripheral neurons have been described along with demyelination of large myelinated sensory fibers during taxane treatment.[6] Mechanisms,

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such as mitochondrial dysfunction and production of oxidative stress and immune-mediated toxicity, have also been linked to CIPN.[7] Exposure of the peripheral neurons to chemotherapeutic agents is also considered a critical determinant of the risk of CIPN, and variation in both drug metabolizing enzymes and transporters have been investigated as potential mechanisms underlying this dose-limiting toxicity.

Over the last decade, a number of clinical pharmacogenetic studies have associated polymorphisms in transporter genes with risk of CIPN (**Table 1**), although these associations are not consistent and are rarely validated. This effect was assumed to be caused by altered pharmacokinetics, but polymorphisms in transporter proteins only cause minor pharmacokinetic differences.[8] Consistent with the findings in humans, *Mdr1a/Mdr1b* knockout mice only exhibit 30% higher area under the paclitaxel concentration-time curve after intravenous administration.[9] The peripheral nervous system is not protected by the blood-brain barrier,[10] which protects the central nervous system from xenobiotics. This may explain why chemotherapeutics cause peripheral- and not central nerve damage. Although it is well-known that drug transporters play a key role in regulating tumor toxicity of chemotherapeutics, their role in regulating tissue-specific toxicity has only recently been elucidated. A number of studies have highlighted the role of drug transporters in chemotherapy-induced ototoxicity, nephrotoxicity, and cardiotoxicity.[11–13] Due to the high number of studies linking CIPN to transporter polymorphisms, we reviewed the literature to find plausible mechanisms underlying these associations.

TRANSPORTER-MEDIATED DISTRIBUTION OF CHEMOTHERAPEUTICS THAT CAUSE PERIPHERAL NEUROPATHY

Below, we have assessed the role for membrane transporters in the uptake and efflux of chemotherapeutic agents that lead to substantial risk of CIPN. Direct evidence for transport (i.e., genetic overexpression or knockdown of transporters) is summarized in **Table 2**. Although thalidomide treatment is associated with CIPN,[14] there is no evidence for its transport by SLC or ABC transporters and this chemotherapeutic was not considered further.

Table 1 Clinical pharmacogenetic studies correlating risk of chemotherapy-induced peripheral neuropathy to genetic variants in genes encoding drug transporters

Class	Drug	Transporter (gene)	dbSNP	Outcome	Odds ratio [95% confidence interval]	Ref.
Taxanes	Paclitaxel	P-gp (*ABCB1*)	rs3213619	NCI CTCAE version 2. Grade ≥ 2 neurotoxicity.	0.5 [0.3–0.8]	71
			rs1045642	NCI CTCAE version 4. Grade ≥ 2 neurotoxicity.	2.8 [1.2–6.5]	72
			rs1128503	NCI CTCAE version 4. Grade ≥ 2 neurotoxicity.	2.4 [1.1–5.4]	73
		MRP2 (*ABCC2*)	rs17222723	NCI CTCAE version 2 Grade ≥ 2 neurotoxicity.	0.6 [0.4–0.9]	71
	Docetaxel	P-gp (*ABCB1*)	rs2032582	NCI CTCAE version 2. Time to onset of peripheral neuropathy.	1.9 months for reference genotypes vs. 0.7 months for carriers of variant	27
Platinum-based	Oxaliplatin	BCRP (*ABCG2*)	rs3114018	NCI CTCAE version 2. Grade ≥ 2 neurotoxicity when combined with *CCNH* rs2230641.	2.5 [1.2–5.1]	74
Vinca alkaloids	Vincristine	MRP1 (*ABCC1*)	rs3887412	NCI CTCAE version 3. Grade 2-3 peripheral neuropathy vs. no peripheral neuropathy after two-three cycles of vincristine.	3.4 [1.5–7.7]	75
			rs2644983		4.2 [1.7–10.5]	
			rs11864374	Obtained from medical records. Grade 1-4 peripheral neuropathy vs. no peripheral neuropathy.	0.4 [0.2–0.8]	76
			rs3743527		0.3 [0.1–0.8]	
			rs1967120		0.4 [0.2–0.8]	
			rs17501331		2.5 [1.1–5.7]	
			rs12923345		2.4 [1.1–5.3]	
			rs11642957		0.4 [0.2–1.0]	
			rs3784867	NCI CTCAE version 4. Grade ≥ 2 peripheral neuropathy.	4.9 [2.0–12.1]	77
		MRP2 (*ABCC2*)	rs3740066	Obtained from medical records. Grade 1-4 peripheral neuropathy vs. no peripheral neuropathy.	0.2 [0.1–0.5]	76
			rs12826		0.2 [0.1–0.5]	
		P-gp (*ABCB1*)	rs4728709	NCI CTCAE version 3. Grade 1-2 peripheral neuropathy vs. no peripheral neuropathy.	0.3 [0.1–0.9]	78

dbSNP, single nucleotide polymorphism database identifier; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 2 Summary of direct *in vitro* evidence (i.e., genetic overexpression or knockdown) of drug transport of chemotherapeutics that cause peripheral neuropathy

Transporter	Gene	Paclitaxel	Docetaxel	Oxaliplatin	Cisplatin	Carboplatin	Vincristine	Bortezomib	Ixabepilone
MRP1	ABCC1	✓	-	-	-	-	-	*	-
MRP2	ABCC2	✓	✓	-	-	-	✓	*	-
MRP7	ABCC10	✓	-	-	-	-	-	-	-
BCRP	ABCG2	-	-	-	-	-	-	*	*
P-gp	ABCB1	✓	✓	-	-	-	✓	✓	✓
OCT2	SLC22A2	-	-	✓	✓	*	-	-	-
OCTN1	SLC22A4	-	-	✓/*	-	-	-	-	-
OCTN2	SLC22A5	-	-	✓/*	-	-	-	-	-
OAT2	SLC22A7	✓	-	✓	-	-	-	-	-
MATE1	SLC47A1	-	-	✓	-	-	-	-	-
OATP1B1	SLCO1B1	✓	✓	-	-	-	✓	✓	-
OATP1B3	SLCO1B3	✓	✓	✓	✓	✓	✓	-	-
CTR1	SLC31A1	-	-	✓	✓	✓	-	-	-
References		17,19–23,26	22,28,29	35,39–41,43,45	34,35,43,45	34,35,43,45	17,46,47,49–52	53,56	57

✓ Direct evidence of transport (i.e., genetic overexpression or knockdown).
- Literature not available.
*Evidence against transport.

Taxanes

Both the uptake and efflux of taxanes have been characterized *in vitro* and their contribution to pharmacokinetics and peripheral neuropathy studied in rodents. Paclitaxel is a well-known substrate for P-gp (MDR1, *ABCB1*)[9,15–17] and P-gp inhibition enhances oral absorption of the drug.[18] Multidrug resistance associated protein 2 (MRP2; *ABCC2*)[9,19] and MRP7 (*ABCC10*)[20,21] have been shown to efflux paclitaxel *in vitro* but their contribution to paclitaxel distribution outside the tumor cell is not well-characterized. Paclitaxel uptake by organic anion transporting polypeptide 1B3 (OATP1B3; *SLCO1B3*) and OATP1B1 (*SLCO1B1*) was highly dependent on the taxane solubilizer.[22,23] Additionally, paclitaxel is an OATP1B1 and OATP1B3 inhibitor at clinically relevant concentrations.[24,25] Human OAT2 transports paclitaxel but OAT2-mediated paclitaxel transport is saturated at nM concentrations, which might limit its role at pharmacological concentrations.[26] Another widely used taxane, docetaxel, is also a substrate for P-gp.[27,28] Similar to paclitaxel, docetaxel is also a substrate for MRP2.[29] Docetaxel is transported by OATP1B1 and OATP1B3,[22,29–31] and *in vivo* evidence suggests that these uptake transporters play a more central role for the pharmacokinetics of docetaxel compared with paclitaxel. In *Slco1b2*(-/-) mice, the clearance of docetaxel is 66–83% lower[30,32] compared with only 30% lower clearance for paclitaxel.[33] Interestingly, despite minor changes in paclitaxel pharmacokinetics, *Slco1b2*(-/-) mice are protected against paclitaxel-induced neurotoxicity.[33] Whether this translates to humans is unknown.

Platins

The DNA-binding platinum-based chemotherapeutics cisplatin, carboplatin, and oxaliplatin were shown to be substrates of copper carriers, such as copper uptake protein 1 (CTR1),[34,35] although a role for CTR1-mediated platinum cellular uptake appears limited.[36] In mouse models, CTR1 contributes to the basolateral uptake of cisplatin in the kidneys and regulates cisplatin-induced nephrotoxicity.[37] In rat dorsal root ganglion (DRG), oxaliplatin appears to damage primarily CTR1-expressing neurons,[38] consistent with its importance in regulating oxaliplatin distribution to these cells. Although there are conflicting reports for transport of oxaliplatin by the organic anion transporters novel 1 and 2 (OCTN1/2), a careful analysis in a tightly regulated expression system suggests that OCTN1 does not transport this platinum agent to any significant extent.[39,40] This lack of transport of oxaliplatin by OCTN1 limits the interpretation of findings from oxaliplatin-induced peripheral neuropathy studies under conditions of OCTN1 inhibition in rats and highlights the sensitivity of both *in vitro* transport assays and *in vivo* neuropathy studies to experimental systems and species differences.[41,42] Additionally, oxaliplatin and cisplatin are substrates for OCT2,[43] which was shown to regulate the neurotoxicity of oxaliplatin in mice.[44] Multidrug and toxin extrusion 1 (MATE1; *SLC47A1*) may play a role in the efflux of oxaliplatin.[41] Knockdown of MATE1 using siRNA leads to increased oxaliplatin-mediated neuropathy in rats.[41] Transport of carboplatin is not well-characterized; carboplatin is not transported by OCT2,[43] although its uptake

might be mediated by CTR1.[35] All three platinum-based chemotherapeutics are substrates for OATP1B3 and cis-platin is a substrate for OATP1B1.[45]

Vincristine

Among the antimitotic vinca alkaloids, vincristine is the most widely used chemotherapeutic. Vincristine is a substrate for P-gp[46] and high expression of P-gp results in increased resistance to vincristine in cancer cells.[47] Concomitant treatment of patients with vincristine and the known P-gp/CYP3A4 inhibitor cyclosporin A leads to exacerbated CNS toxicity, suggesting potent inhibition of P-gp at the blood-brain barrier.[48] In addition to P-gp, vincristine is a substrate for MRP1[17] and knockout of this gene in mice reduces the maximum tolerated dose of vincristine, particularly when combined with genetic deletion of P-gp.[49] MRP2 can also transport vincristine in cells but the significance of this transport *in vivo* is not known.[50] Similarly, vincristine has been shown to be transported by OATP1B1 and OATP1B3 *in vitro*,[51,52] although their contribution to vincristine disposition or neurotoxicity are not characterized.

Bortezomib

There is limited information on the transport of the proteasome inhibitor bortezomib. Bortezomib cytotoxicity is influenced by the level of P-gp, but not BCRP or MRP1[53] expression in cancer cell lines but direct evidence of transport by P-gp is lacking. Polymorphisms in *ABCB1* and *ABCC1* were linked to treatment response,[54] although the significance of these associations require validation. Interestingly, bortezomib appears to inhibit proteasome-mediated internalization of CTR1 caused by platinum-based chemotherapy in tumor cells, enhancing cisplatin uptake and cell killing both *in vitro* and *in vivo*.[55] Transporter-mediated uptake of bortezomib by OATP1B1 was measurable but contributed insignificantly to intracellular levels of the drug.[56]

Epothilones

In vitro studies showed that the epothilone ixabepilone is a P-gp substrate, but not a BCRP substrate.[57] Thus, P-gp inhibitors reverse MDR1-mediated drug resistance to ixabepilone in MDCK cells. Additionally, P-gp inhibition leads to reduced efflux of ixabepilone in LLC-MDR1 cells.[57]

EXPRESSION OF DRUG TRANSPORTERS IN HUMAN DORSAL ROOT GANGLION

The expression of drug transporters in the peripheral nervous system was reported in several recent studies. Two studies utilized RNA sequencing of human DRG (hDRG),[58,59] whereas another study reported a proteomic analysis of hDRG lysate.[60] To assess transporter expression, we cross-referenced these datasets for expression of drug transporters that transport chemotherapeutics with significant CIPN, as outlined in the previous section. The expression of key transporters in hDRG that are relevant for chemotherapeutics that cause CIPN are summarized in **Table 3**. Expression of drug transporters was confirmed if FPKM was > 1 for RNA sequencing datasets. At the protein level, expression of drug transporters was defined as

detectable protein expression in at least two samples from the proteomic dataset (table S1 from Schwaid *et al.*[60]).

The efflux transporters P-gp (*ABCB1*), BCRP (*ABCG2*), MRP1 (*ABCC1*), and MATE1 (*SLC47A1*) are expressed in hDRG, whereas MRP2 (*ABCC2*) is not. High expression of efflux transporters in the peripheral nervous system makes sense from an evolutionary standpoint. The peripheral nervous system is not protected by the blood-brain-barrier and thus expression of efflux transporters is crucial to confer protection against neurotoxic agents. The uptake transporters OCTN1/OCTN2 (*SLC22A4/SLC22A5*) and CTR1 (*SLC31A1*) are expressed in hDRG. These transporters mediate cellular uptake of endogenous substances, such as OCTN1/OCTN2-mediated uptake of ergothioneine or CTR1-mediated copper transport. The transcriptomic and proteomic data did not support expression of other SLC uptake transporters, such as OATP1B1 and OATP1B3, OAT2, or OCT2. This is in contrast to a previous report showing expression of OCT2 mRNA in human DRG.[44] We were unable to find an exhaustive source for protein expression data in hDRG as the published datasets did not contain comprehensive evaluation of drug transporters (**Table 3**). Finally, these data highlight expression of drug transporters in the hDRG but do not provide evidence for localization or function. Further evaluation of these properties will be critical for the field.

DISCUSSION AND FUTURE PERSPECTIVES

This review highlights a number of important features of chemotherapy transport in sensory neurons. Although there is very little direct human evidence of the importance of chemotherapy transport in the peripheral nervous system, the number of clinical associations between polymorphisms in transporter genes with CIPN and expression of key transporters in the dorsal root ganglion supports their role in the disposition of chemotherapeutics to the peripheral nervous system (**Figure 1**).

P-gp overexpression is a well-established cause of tumor resistance to chemotherapeutics and intestinal P-gp limits the oral absorption of drugs, such as paclitaxel.[61] Inhibition of this efflux transporter has been investigated as an approach to counter both intestinal and tumor efflux of chemotherapeutics.[62–64] Although organ or tumor level inhibition of P-gp could improve the bioavailability and tumor distribution of chemotherapeutics, inhibition of efflux transporters may cause increased accumulation of chemotherapeutics in the peripheral nervous system. Several pharmacogenetic studies have correlated polymorphisms in efflux transporters with risk of CIPN (**Table 1**). Additionally, a recent clinical study among patients with breast cancer showed that miR-451a regulates P-gp expression and may be a risk factor for paclitaxel-induced peripheral neuropathy.[65] We recently showed that inhibition of P-gp leads to increased neuronal accumulation of paclitaxel in cultured neurons and in patients with breast cancer and ovarian cancer.[66] Interestingly, several widely prescribed drugs that inhibit P-gp, including the prominent cholesterol-lowering drug atorvastatin, led to substantially increased risk of paclitaxel-induced peripheral neuropathy when used in combination with paclitaxel. Collectively,

Table 3 Data from RNA sequencing and proteomic studies show expression of drug transporters involved in transport of chemotherapeutics that cause peripheral neuropathy

Transporter (gene/transporter)	RNAseq hDRG (> 1 FPKM cutoff)		Proteomics hDRG	
	Flegel *et al.* (2015)	Ray *et al.* (2018)	Schwaid *et al.* (2018)	Stage *et al.* (2020)
ABCC1/MRP1	+	+	+	+
ABCC2/MRP2	–	–	n.d.	–
ABCC10/MRP7	+	+	n.d.	n.d.
ABCG2/BCRP	+	+	n.d.	n.d.
ABCB1/P-gp	+	+	+	+
SLC22A2/OCT2	–	–	n.d.	n.d.
SLC22A4/OCTN1	+	+	n.d.	n.d.
SLC22A5/OCTN2	+	+	n.d.	n.d.
SLC22A7/OAT2	–	–	n.d.	n.d.
SLC47A1/MATE1	+	+	n.d.	n.d.
SLCO1B1/OATP1B1	–	–	n.d.	n.d.
SLCO1B3/OATP1B3	–	–	n.d.	n.d.
SLC31A1/CTR1	+	+	n.d.	n.d.

+ Expression confirmed.
– No expression
hDRG, human dorsal root ganglion; n.d., not determined.

this supports the proposal that inhibition of efflux transport might cause increased accumulation and toxicity of paclitaxel in sensory neurons. This is further supported by a study showing that concomitant administration of paclitaxel with the well-established P-gp inhibitor valspodar causes a minor shift in paclitaxel plasma pharmacokinetics.[63] Despite apparently unaltered plasma concentrations, this combination leads to higher risk of paresthesia and pain,[62] supporting a protective role of P-gp in the peripheral nervous system. These interesting clinical findings warrant further evaluation. Additional investigation is also needed to understand why P-gp activity in the peripheral nervous system is more sensitive to changes in transport expression and function than P-gp at the blood-brain-barrier. The relative expression levels of P-gp at peripheral and central nerve barriers and the contribution of other uptake and efflux transporters at these sites should also be evaluated.

CTR1 might play a key role for disposition of platinum-based chemotherapy. This transporter is highly
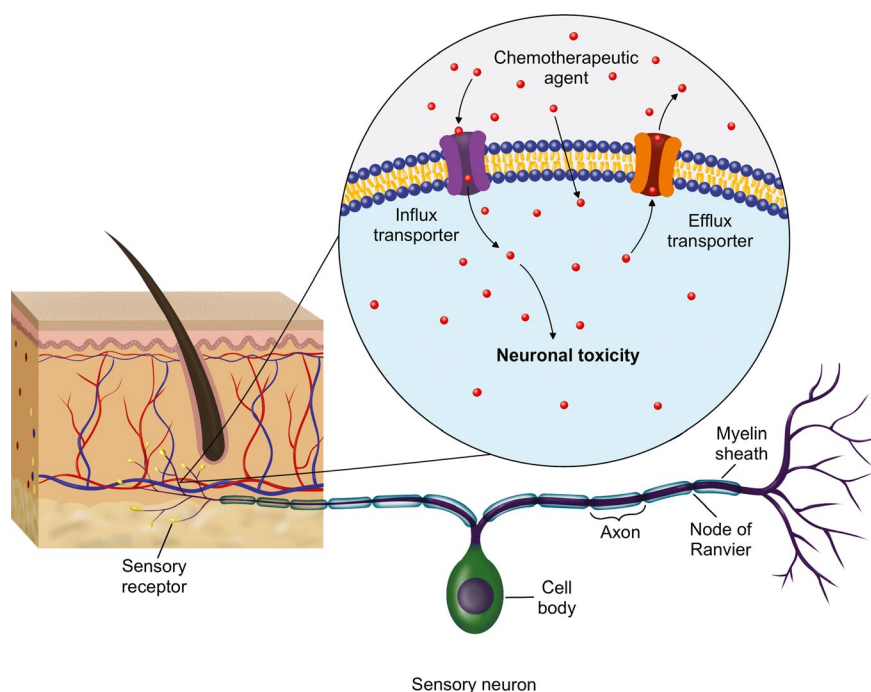
Figure 1 Drug transporters regulate influx and efflux of chemotherapeutics in the peripheral nervous system likely modulating toxicity and peripheral neuropathy.

expressed in many tissues, including peripheral neurons and tumor tissue and expression of CTR1 in tumor cells correlates with response to platinum-based chemotherapy.[67] Although the attempt to increase CTR1 activity to increase platinum uptake in tumor tissue could improve chemotherapy response, the wide tissue distribution of CTR1 might also lead to increased risk of off-target toxicity due to increased permeability of platins. An additional concern to targeting CTR1 includes interfering with cell copper balance, which may result in unwanted toxicity. Clinical attempts to target CTR1 to increase tumor uptake of platinum-based chemotherapy should only be done with significant consideration to adverse effects and toxicity.

Both paclitaxel and ixabepilone were shown to activate the nuclear pregnane X receptor,[68] which is a known mechanism for induction of ABCB1 expression. Activation of this receptor by St. John's wort, rifampicin, or dicloxacillin causes upregulation of a number of important pharmacogenes, including CYP3A4 and ABCB1.[69] Increased expression of ABCB1 and corresponding increases in P-gp function could influence chemotherapeutic distribution to peripheral neurons. Induction of drug-metabolizing enzymes or drug transporters through pregnane X receptor typically requires prolonged exposure to the inducer and as both paclitaxel and ixabepilone treatment are given weekly or every third week, the clinical impact of potential induction of ABCB1 will require further investigation.

Published transcriptomic data do not support expression of OATP1B transporters in hDRG. This is in contrast to rodent studies that have shown both gene and protein expression of OATP1B2.[33,70] Additionally, RNAseq data does not support OCT2 expression, although Sprowl *et al*. showed that OCT2 is expressed in hDRG using quantitative polymerase chain reaction.[44] The expression of drug transporters in the peripheral nervous system should be supported by quantitative protein determination by liquid chromatography-tandem accurate mass spectrometry in hDRG before being dismissed. Species differences in transporter expression in the peripheral nervous system require consideration in the design and interpretation of drug transporter studies.

Very little is known about the role of membrane transporters in drug disposition to the human peripheral nervous system. Recent transcriptomic approaches and extensive rodent studies have shed important light on expression and activity of drug transporters in these tissues, although their function and impact in human models is unknown. There are two ongoing clinical studies (clinicaltrials.gov identifiers NCT04205903 and NCT04164069) aiming to inhibit uptake transporters of oxaliplatin and paclitaxel to reduce paclitaxel-induced and oxaliplatin-induced peripheral neuropathy in patients with cancer. These studies and continued laboratory efforts may lead to an increased understanding of the disposition of neurotoxic drugs that could also inform drug development. Cellular influx and efflux mechanisms are critical for drug distribution and should be considered when attempting to target drugs to the peripheral nervous system. For example, P-gp and MRP1 are highly expressed in sensory neurons and drugs that are substrates of these efflux transporters may not reach sufficient therapeutic concentrations in the peripheral nervous system. Expression and activity of transporters in supporting cells, such as Schwann cells or satellite cells, is currently unknown and should be assessed in the future.

As discussed previously, it seems tempting to try to upregulate efflux transporters to promote efflux of chemotherapy agents from sensory neurons. As this would also increase efflux of chemotherapeutics from tumor cells, this is not a compelling therapeutic strategy. However, using antibody-directed delivery of transport modulators to peripheral sensory neurons might prove a useful tool to modulate chemotherapy transport in the peripheral nervous system. This approach might be useful to inhibit uptake transporters or induce efflux transporters in the human DRG, ensuring low sensory neuron concentrations of chemotherapeutics, which are expected to limit CIPN. Future development is needed to test this approach in preclinical models and in humans.

It is important to note that CIPN is a complex phenotype. In this review, we have attempted to highlight the role of membrane transporters in the peripheral nervous system and their putative influence on CIPN. The evidence linking drug transporters to CIPN is primarily based on *in vitro* or animal studies and thus more work in human models is warranted. Although drug transporters may present a piece of the puzzle to help explain variability in CIPN, there are many other factors that should be taken into account. Predicting and understanding CIPN will require collaboration across research disciplines to build models to provide a deeper understanding of this dose-limiting toxicity.

In conclusion, drug transporters, particularly efflux transporters, are highly expressed in the human peripheral nervous system. Although there is limited direct evidence supporting a functional role of these transporters in sensory neurons in humans, an increasing body of evidence supports their involvement in regulating disposition of chemotherapeutics to the peripheral nervous system and thus drug transporters may play a role in CIPN.

Conflicts of Interest. A provisional patent application related to chemotherapy-induced peripheral neuropathy has been filed by University of Southern Denmark with Tore Bjerregaard Stage listed as inventor. All other authors declared no competing interest for this work.

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