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REVIEW

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Platinum accumulation in oxaliplatin-induced peripheral neuropathy

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Abstract

Oxaliplatin-induced peripheral neuropathy (OIPN) is a common and dose-limiting toxic effect that markedly limits the use of oxaliplatin and affects the quality of life. Although it is common, the underlying mechanisms of OIPN remain ambiguous. Recent studies have shown that the platinum accumulation in peripheral nervous system, especially in dorsal root ganglion, is a significant mechanism of OIPN. Several specific transporters, including organic cation transporters, high-affinity copper uptake protein1 (CTR1), ATPase copper transporting alpha (ATP7A) and multidrug and toxin extrusion protein 1 (MATE1), could be associated with this mechanism. This review summarizes the current research progress about the relationship between platinum accumulation and OIPN, as well as suggests trend for the future research.

KEYWORDS
chemotherapy, oxaliplatin, peripheral neuropathy, platinum accumulation

1 | INTRODUCTION

Oxaliplatin is widely used in the treatment of various malignant tumors and is the standard drug for adjuvant chemotherapy for colorectal cancer.[1] However, oxaliplatin can cause peripheral neuropathy during administration, including acute and chronic peripheral neuropathy. Acute peripheral neuropathy is mainly sensory abnormalities related to cold stimuli, usually occurring in the distal extremities. Some patients will have discomfort in the oral cavity, throat, jaw, and muscle spasm, with an incidence of 85% to 95%. It can occur within hours to days after the treatment, with the peak value 3 days and generally recovering within 1 week. It is a well-established risk factor of chronic oxaliplatin-induced peripheral neuropathy (OIPN).[2,3] Chronic peripheral neuropathy is characterized by bilateral symmetric

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paresthesia, dysesthesia and pain, mainly on both feet and/or at the ends of both hands (in a "glove-sock" distribution). Which significantly reduces the quality of life of cancer survivor. Due to its dose-dependent characteristic, symptoms of the chronic OIPN may appear in 42.1% to 69% of patients after 4 to 6 cycles after chemotherapy.[4-8] Despite intense preclinical and clinical work, no drug gets recognition to prevent OIPN, and duloxetine is recommended for the treatment of OIPN by the American Society of Clinical Oncology (ASCO), but adverse drug reactions make it controversial.[9]

For seeking truly effective treatment of OIPN, studies have been committed to explore the potential mechanisms for years. Oxaliplatin accumulation in the peripheral nervous system (PNS) is considered a key step in neurotoxicity development, but the exact mechanisms are unclear.[10] The aim of this review is to summarize the current the current research progress and describe how platinum accumulation is responsible for neuropathy onset and progression.

2 | PLATINUM ACCUMULATION AND OIPN

2.1 | Where does platinum accumulate in the PNS

Once entering systemic circulation, oxaliplatin rapidly hydrolyzed to oxalate ligand and Pt-diaminocyclohexane (Dach).[11,12] As the major platinum complex in circulation, Pt-(dach) reaches the organs and tissues by binding to endogenous low-molecular-weight species like cysteine, methionine, and glutathione (GSH) and high-molecular-weight compounds like albumin, globulin, and hemoglobin.[13] Dorsal root ganglion is composed of centripetal sensory fibroblasts, which transduce somatosensory and visceral sensations into to the spinal cord.[14] Unlike the central nervous system (CNS), dorsal root ganglion (DRG) lacks the protection of the blood-brain barrier, so chemotherapy drugs and other toxic drugs can easily enter the sensory neuron cell body of DRG. Accumulation of these drugs in DRG results in neurological damage.[15-18] Recent studies have indicated that platinum concentration dose-dependently increased in the rat DRG and correlated with the degree of neurotoxicity after repeated oxaliplatin administration.[19-23] Therefore, platinum accumulation in the PNS, especially in DRG, is one of the important mechanisms of OIPN (Figure 1).

2.2 | How does platinum accumulation lead to OIPN

After oxaliplatin enters DRG, it can interact with the DNA of organelles such as the nucleus and mitochondria of neuron cells and form DNA adducts. These changes can affect DNA replication, block cell cycle, inhibit DNA repair, and induce neuronal apoptosis.[24] Platinum accumulation in DRG is considered as a key step in OIPN.[17,25] Several hypotheses regarding how platinum accumulation leads to OIPN have been proposed, including nucleolar damage, mitochondrial dysfunction, and oxidative stress (Figure 1).

2.2.1 | Nucleolar damage

Once oxaliplatin accumulates in DRG neurons, it interacts with the nuclear DNA to form DNA-platinum adducts.[15] DRG neurons require a high level of active transcription to maintain their normal structure and function. However, oxaliplatin-induced nucleolar DNA damage leads to global transcriptional arrest of neuronal cells, which may activate apoptosis pathways, leading to neuronal atrophy.[26-29] Several preclinical studies in mice models have shown increased numbers of DRG neurons with atypical morphological nuclear features (eg, nucleolar eccentricity, multinucleolation) are smaller nucleolar size after repeated oxaliplatin administration, and these are associated with OIPN severity.[15,30-33]

2.2.2 | Mitochondrial dysfunction

Mitochondria have its own round mitochondrial DNA (mtDNA), encoding 13 proteins that are involved in the synthesis of

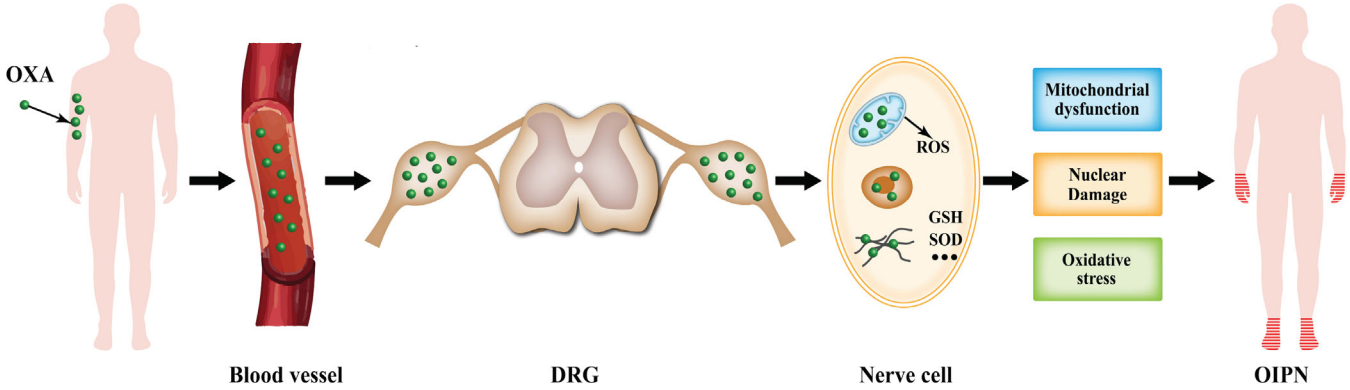

FIGURE 1 Once oxaliplatin (OXA) enters systemic circulation, it will accumulate in DRG which lacks the protection of the blood-brain barrier. Platinum accumulation will lead to oxaliplatin-induced peripheral neuropathy (OIPN) by nucleolar damage, mitochondrial dysfunction and oxidative stress

mitochondrial electron transport chain subunits and the production of cellular energy.[34-36] Mitochondrial dysfunction plays a key role in the pathophysiology of platinum-induced peripheral neuropathy.[37,38] After entering neuronal cells, platinum combine with mitochondrial DNA to form DNA-platinum adducts. The combination could modify the permeability of mitochondrial membrane through affecting proteins such as voltage-dependent anion-selective channels,[39,40] and also inhibit the transcription and replication of mitochondrial DNA that induce the mitochondrial morphological changes, dysfunction, and final apoptosis.[41] In the PNS, 95% mitochondria are located in axons, mitochondrial dysfunction would lead to chronic energy deficiency of neurons, further result in abnormal spontaneous discharge and compartmental degeneration of DRG primary afferent neurons.[25,42,43] In recent years, several in vitro and in vivo OIPN models focused attention on the "mitochondrial toxicity hypothesis" which suggests that impaired mitochondrial function leads to afferent sensory neuron damage.[37,39-42] Mitochondrial dysfunction is a major promoter of OIPN and may be a potential therapeutic target.[44-46]

2.2.3 | Oxidative stress

Excessive production of reactive oxygen species (ROS) leads to an imbalance between oxidation and antioxidant systems. It is a key pathogenic mechanism involved in OIPN.[47] Mitochondria and peroxisomes help maintain the redox cellular state in that they produce and scavenge ROS, respectively.[42] The mitochondrial structure and function impairment caused by oxaliplatin increases the production of free radicals and bioenergy depletion, antioxidant depletion, biomolecular damage, demyelination, neuroinflammation, mitophagy impairment, and alterations of cellular protein, lipid, and DNA that ultimately lead to apoptosis.[42,46,48-51] It is demonstrated that oxaliplatin treatment in rats results in a decrease in antioxidant enzymes (eg, malondialdehyde, glutathione, and superoxide dismutase), inhibition of mitochondrial enzymes (eg, citrate synthase and ATP synthase), and an increase in superoxide anion production, lipid peroxidation, protein and DNA oxidation in DRG neurons.[52-59] Several studies confirmed that the co-treatment with oxaliplatin and antioxidant compounds can prevent oxidative phenomena and decrease OIPN in rats.[55-59]

3 | MECHANISMS OF PLATINUM ACCUMULATION

It is crucial to understand the mechanism of oxaliplatin accumulation in DRG to elucidate the etiology of OIPN and to develop new therapeutic interventions. Several proteins have been implicated in oxaliplatin influx or efflux in the DRG. We summarize the current research progress of the various transporters that have been correlated with facilitating oxaliplatin movement across cell membranes (Figure 2).

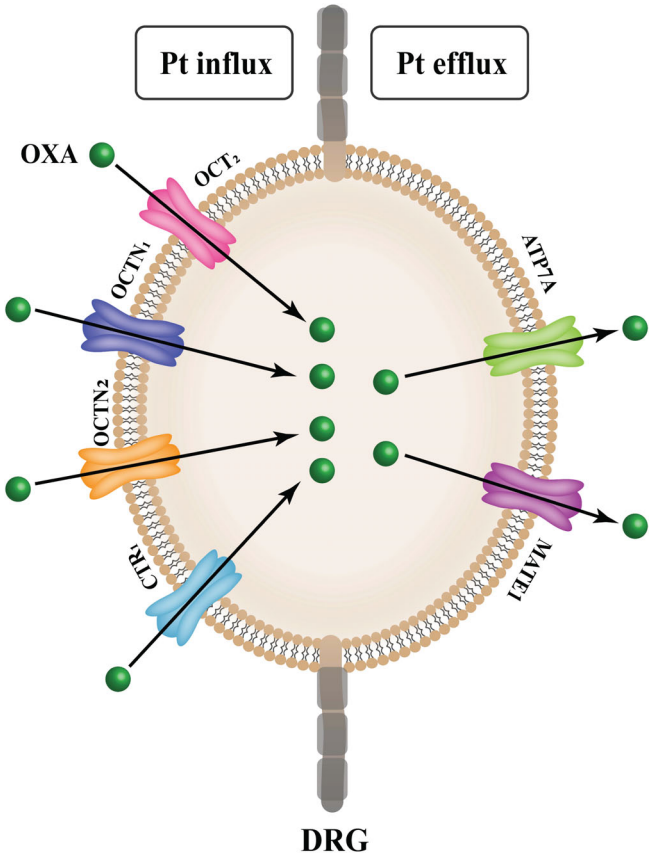

FIGURE 2 Several proteins have been implicated in oxaliplatin influx or efflux in the DRG. OCT2, OCTN1/2, CTR1 may participate in the oxaliplatin influx. ATP7A and MATE1 may participate in the oxaliplatin efflux. Multiple proteins working together lead to the accumulation of platinum

3.1 | Organic cation transporter2 (OCT2)

OCT2 is a member of the SLC22 transporter family, encoded by the SLC22A2 gene, which mediates the uptake of a variety of organic cations in cells.[60] It is a key factor of platinum drug uptake and cytotoxicity, and contributes to platinum accumulation in the kidneys, inner ear and PNS, leading to nephrotoxicity, ototoxicity, and peripheral neuropathy.[61-64] The highest expression of human OCT2 (hOCT2) mRNA is reported in the kidney, whereas less in other organs (eg, lungs, bladder, brain, spinal cord, placenta, testis, nasal mucosa, etc.).[60,65] It has been confirmed that OCT2 is expressed in 20% DRG neurons, small to medium size neurons, belonging to the myelin free hurtful neurons (substance P or calcitonin gene-related peptide positive) and myelin neuron subgroup (TrkC or TrkB positive).[66-68]

Oxaliplatin is an excellent substrate of OCT2 and can be effectively transported by OCT2 from the extracellular space into the DRG neuron cell bodies.[69] Researches reported that OCT2 significantly increased oxaliplatin accumulation and cytotoxicity, and OCT2-mediated oxaliplatin accumulation was related to time and concentration, but not saturated.[70] Oxaliplatin uptake, DNA-platinum adduct formation, and HEK293 drug sensitivity were significantly increased in HEK293/hOCT2

overexpressed cells compared with HEK293/Neo control cells. Additionally, cimetidine, a competitive inhibitor of OCT2, is known to significantly reduce platinum uptake in neuronal cells.[71] Notably, thermal sensitivity or mechanical allodynia induced by oxaliplatin can be eliminated by knockout of OCT1/2 and concurrent administration of cimetidine in animal models.[64] Several proteins can affect the functional activity and expression of OCT2. hOCT2 can be inhibited by phosphoinositide 3-kinase, protein kinase C, and protein kinase and activated by calmodulin (CaM) or calcium/CaM-dependent kinase II by changing substrate affinity.[72-74] However, it is not clear whether these signaling pathways are related to OCT2-mediated oxaliplatin accumulation.[53,75-78] Lysosomal-associated transmembrane protein 4A (LAPTM4A) regulates the function of hOCT2 by influencing hOCT2 transport on the cell membrane and processing it through an intracellular sorting mechanism.[79] The regulatory protein RS1 and the ischemia/reperfusion inducible protein (IRIP) are also involved in hOCT2 intracellular transport.[80] To date, there has been no study on OIPN and LAPTM4A, RS1, or IRIP. Recently, it has been reported that the phosphorylation of SRC family kinase Yes1 tyrosine can increase the functional activity of hOCT2 in the plasma membrane. In mouse models, inhibition of Yes1 can reduce OCT2 transport oxaliplatin in DRG cells and reduce acute OIPN without affecting oxaliplatin's antitumor activity.[81]

Interestingly, OCT2 expression was reported to be low or unexpressed in tumor cell lines and patient tumor samples, and it was then not associated with oxaliplatin antitumor efficacy in cell lines or patients.[64,71,81,82] Thus, OCT2 plays an important role in the oxaliplatin accumulation in DRG neurons and may be the optimal therapeutic target for OIPN without altering oxaliplatin antitumor efficacy.

3.2 | Organic cation transporter, novel type 1 (OCTN1), and OCTN2

OCTN1 (encoded by SLC22A4) and OCTN2 (encoded by SLC22A5), located on chromosome 5q31, are also belong to the SLC22 transporter family.[83,84] Their expression can be detected in multiple organs and tissues (eg, kidney, ileum, colon, spleen, brain, heart, skeletal muscle, etc).[85] They are polyspecific transporters that can transport a variety of organic cations, zwitterions, and uncharged compounds.[86,87] Human OCTN1 and OCTN2 (hOCTN1 and hOCTN2) are localized in both plasma membranes and mitochondria.[88] OCTN1 and OCTN2 are expressed in all types of DRG neurons, especially small and medium-sized DRG neurons (about 10% of small and medium-sized neurons).[23]

HEK293 cells overexpressed rats OCTN1, OCTN2, hOCTN1, and hOCTN2 showed higher oxaliplatin uptake than mock-transfected control cells, and the uptake and toxicity of oxaliplatin in primary cultured rat DRG neurons were mediated by OCTN1 more than OCTN2.[21] Recently, two studies have reported that both OCTN1 and OCTN2 affect platinum accumulation, cytotoxicity, and neurotoxicity in HEK293, PC12, and FLP-in-293 cells, whereas only OCTN1 knockdown or co-administration of ergothioneine (an OCTN1 inhibitor) can reduce platinum accumulation and OIPN in rat DRG neurons.[22,23] Despite these results, there is no existing evidence on whether OCTN1 inhibition will affect the antitumor efficacy of oxaliplatin because OCTN1 is also expressed by normal colon cells and tumor cell lines including colorectal SW480 cells.[83,89,90] The binding of runt-related transcription factor 1 (RUNX1) to SLC22A4 intron 1 is involved in the transcriptional regulation of hOCTN1, but whether RUNX1 is involved in OIPN has not been investigated.[91] Taken together, the evidence indicates that OCTN1 contributes to oxaliplatin influx and may be responsible for OIPN in the rat model. Future studies are required to assess this attractive molecule as a therapeutic target.

3.3 | High-affinity copper uptake protein 1 (CTR1)

Human CTR1 (hCTR1), encoded by the gene SLC31A1 located on 9q31, was first cloned in 1997.[92] It is a major mammalian transporter with a high affinity for copper uptake and contains three transmembrane domains with metal binding sites rich in methionine and histidine.[93] In humans and rodents, CTR1 is expressed in specific tissues and cells.[94-96] In the PNS, CTR1 was mainly expressed in the large DRG neuron subsets (13.6% ± 3.1%), and immunohistochemical staining showed that CTR1 was localized in the plasma membrane and vesicular cytoplasm of the large DRG neuron bodies.[97,98]

Evidence shows that CTR1 plays an important role in oxaliplatin uptake and toxicity and loss of CTR1 function in yeast affects oxaliplatin uptake.[99] Platinum drug therapy can lead to atrophy of CTR1-positive DRG neuron cell body of rats, oxaliplatin is the most toxic, followed by cisplatin and carboplatin. Oxaliplatin significantly reduced the mean cell volume and the percentage of CTR1-positive neurons.[97,98] Therefore, different affinities of CTR1-mediated uptake can also explain the different neurotoxicity characteristics of platinum drugs.[100] Compared with the isogenic vector-transfected control cells, the HEK293 cells with the overexpression of rat CTR1 ingested about four times of platinum accumulation and the sensitivity to growth inhibition was increased by about three times. On the other hand, platinum accumulation in HEK293 cells expressing CTR1 could be inhibited by hypothermia, copper, and copper histidine (a chelating formula for copper that is clinically used to treat disorders of copper metabolism), in HEK293 cells expressing CTR1, suggesting that CTR1 was involved in oxaliplatin transport. However, when used in combination with oxaliplatin, copper histidine did not alter platinum accumulation or oxaliplatin neurotoxicity in DRG tissues.[101,102] These findings suggest that CTR1 is associated with oxaliplatin uptake and neurotoxicity, but more studies are needed to elucidate its specific mechanism.

3.4 | ATPase copper transporting alpha (ATP7A)

ATP7A is a copper exocrine membrane transporter expressed in intestinal epithelium, endometrium, prostate, testis, kidneys, and other tissues than liver.[103-105] Studies have demonstrated that *ATP7A* was

expressed in smaller DRG neurons and co-located with phosphorylated heavy neurofilament subunit.[98,102]

ATP7A mediates the exudation of cisplatin, carboplatin and oxaliplatin in cells, thus reducing the platinum accumulation.[106-108] An in vivo study revealed that oxaliplatin treatment did not change the size of ATP7A-immunoreactive strong positive neurons, but significantly reduced the size of CTR1 strong positive neurons.[102] This may be related to the increase of oxaliplatin efflux mediated by ATP7A. However, ATP7A has been detected in several types of human malignancies, and high ATP7A expression is associated with poor tumor response in patients treated with platinum-based drugs.[105,108-111] In summary, ATP7A is a participant of OIPN but may not be an ideal drug target as it may dampen the antitumor effect of oxaliplatin.

3.5 | Multidrug and toxin extrusion protein 1 (MATE1)

Human hMATE1 (hMATE1), encoded by SLC47A1 gene on chromosome 17P11.2, was first cloned in 2005.[112,113] The main functions of this solute carrier are the exportation of various organic cations, organic anions, uncharged compounds and zwitterions.[65,114] Expression of MATE1 can be detected in liver, kidney, skeletal muscle, adrenal gland and testis.[112] The expression of MATE1 in DRG neurons has been reported, but the distribution of MATE1 in DRG neurons has not been studied in detail.[22]

Oxaliplatin and cisplatin are relatively good substrates of hMATE1.[69,115-117] Previous studies have shown that the knockout of MATE1 increases platinum accumulation in mouse kidneys and leads to increased nephrotoxicity compared to wild-type controls.[118] Oxaliplatin uptake, platinum accumulation, cytotoxicity and neurotoxicity were reported to be regulated by MATE1 in transporter-expressing HEK293, PC12 and Flp-in-293 cells, and the MATE1 small interfering-RNA-injected rats developed more severe OIPN and DRG platinum accumulation than the control group.[22] Oxaliplatin is also considered as the substrate of MATE2-K, but no studies have confirmed that MATE2-K is related to OIPN.[117,119] Based on these findings, it is presumed that MATE1 is an efflux transporter that can induce OIPN. Further studies are needed to clarify the location of MATE1 in DRG and its role in OIPN.

4 | DRUG TREATMENT TARGETING PLATINUM ACCUMULATION

Cimetidine is a known OCT2 inhibitor that reduces oxaliplatin uptake in vitro and protects wild-type mice from oxaliplatin-induced mechanical allodynia and cold hypersensitivity.[64] However, there is no clinical evidence for cimetidine to date. Dasatinib, which has been regarded as a inhibitor the function of OCT2 transporter, may be an effective neuroprotective OIPN drug without affecting the antitumor effect of oxaliplatin in vitro and in vivo, and meanwhile it is currently undergoing phase Ib trials.[81,120] Ergothionine is a substrate/inhibitor of OCTN1, when administered in combination with oxaliplatin, OIPN can be improved by reducing the platinum accumulation in rat DRG neurons.[23] As a chelating formula of copper, copper histidine can inhibit CTR1-mediated oxaliplatin uptake in vitro, but when combined with oxaliplatin, it cannot reduce platinum accumulation in DRG neurons or prevent OIPN.[102] Although preclinical studies have suggested many potential therapeutic agents, none has been clinically recognized to treat or prevent OIPN.[9]

5 | CONCLUSIONS

OIPN is a dose-limiting side effect of oxaliplatin, and there are few preventive or treatment measures. Evidences have shown that platinum accumulation plays an important pathogenic role in OIPN and may be a valuable therapeutic target. Studies indicate that platinum accumulation in DRG neurons is mediated by multiple drug transporters including OCT2, OCTN1/2, CTR1, ATP7A, MATE1, and so on. There are two key issues that need to be addressed: one is identifying transporters that play key roles in the platinum accumulation, the other is whether up- or downregulation of these transporters will alter the antitumor effect of oxaliplatin. Future studies should focus on the specific mechanisms of platinum accumulation following oxaliplatin treatment and searching for therapies to prevent platinum accumulation or treat OIPN.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Guoli Wei, Zhancheng Gu: conception, organization, and execution of research project, write the first draft. Jialin Gu, Xiaofei Huang, Fengxia Qin: research project execution, review, and critique manuscripts. Rong Ding, Lingchang Li: conception and organization review of research projects and review of manuscripts. Jiege Huo: conception and organization of the research project, write the first draft and review, and comment on the draft.

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