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Review

Saving Ears and Kidneys from Cisplatin

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Abstract. *Cisplatin is a potent cytostatic drug, whose use is limited by its severe acute and chronic nephro-, oto-, and also peripheral neuro-toxicity. Since transporters are important mediators of specific cellular uptake of many drugs such as cisplatin, their role as possible targets of specific organ protection against undesired cisplatin toxicities is under investigation. Several transporters are able to mediate the movement of cisplatin across the plasma membranes: Copper transporter-1 (Ctr1), copper transporter-2 (Ctr2), P-type copper-transporting ATPases ATP7A and ATP7B, organic cation transporter-2 (OCT2), and multidrug extrusion transporter-1 (MATE1). Some of these transporters are also able to accept other platinum derivatives as substrates. In the present review article, we focus on the role of Ctr1 and OCT2 for cellular uptake of cisplatin and on the possibilities to reduce cisplatin-associated toxicities decreasing cisplatin uptake mediated by these transporters. The ubiquitously expressed Ctr1 seems to be involved in general cisplatin uptake in tumor and normal cells. Conversely, OCT2 expression is restricted to few cells such as renal, cochlear, and nervous cells, while its expression in some tumors seems to be epigenetically down-regulated. For this reason, specific inhibition of OCT2 may be effective in decreasing cisplatin uptake in non-target cells, without compromising its anti-tumoral efficacy, and therefore OCT2 may be the target for a suitable protective therapy.*

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Transporters are plasma membrane proteins, which can mediate specific cellular uptake, metabolism, and excretion of many drugs such as cisplatin; thereby they can mediate effects, but also side effects of drugs. The clinical use of the potent cytostatic drug cisplatin is limited by its severe acute and chronic nephro-, oto- and peripheral neuro-toxicity. These serious side-effects prompted the development of other platinum derivatives such as carboplatin and oxaliplatin, which maintain anti-tumoral efficacy while producing less nephrotoxicity but stronger myelosuppression and neurotoxicity than cisplatin (1). The cellular influx and efflux of cisplatin seems to be mediated by several different transporters such as copper transporter-1 (Ctr1) (2), the copper transporter-2 (Ctr2) (3), P-type copper-transporting ATPases ATP7A and ATP7B (4), organic cation transporter-2 (OCT2) (5, 6), and the multidrug and toxin extrusion transporter 1 (MATE1) (7, 8). At least some of these transporters also accept other platinum derivatives as substrates (7). An important aspect to consider when investigating specific cisplatin toxicities is the tissue distribution of membrane transporters. In this optic, these proteins can mediate the specific uptake of cisplatin or of other platinum derivatives in target but also in non-target cells, mediating not only its specific anti-tumoral effects but also unwanted side-effects. In the present review article, we summarize current literature data as well as our own presented at the XIth International Symposium on Platin Coordination Compound in Cancer, on the role of transporters in mediating cisplatin uptake and toxicities and the thereby possible implications for protective therapies with a focus on the Ctr1 and the OCT2.

Cisplatin Toxicities

The main side-effects of cisplatin treatment are nephrotoxicity, which is often dose-limiting, ototoxicity, and neurotoxicity. In patients, cisplatin-induced nephrotoxicity manifests acutely and/or chronically as a decrease in renal plasma flow and in glomerular filtration rate (9, 10), higher serum creatinine, and reduced serum magnesium and potassium levels (11). Even though nephrotoxicity can be

controlled by diuretics and pre-hydration of patients, its prevalence is still high, occurring in about one-third of patients undergoing cisplatin treatment (11). Animal studies showed that the kidney accumulates more cisplatin than other organs and that the main damage induced by cisplatin occurs in the proximal tubules (12, 13). Ototoxicity is an untypical side-effect for a chemotherapeutic drug. Cisplatin treatment causes hearing loss, possibly leading to deafness, which is still an unresolved clinical problem. This is especially dramatic in infants and younger children, where ototoxicity can lead to delayed language development which in turn might have devastating consequences for a young child's social and educational development (14). The incidence of ototoxicity is reported to be between 23-50% in adults and greater than 50% in children (1). Cisplatin-induced damage first occurs at the cochlea base, where high-frequency sounds are processed, and with increasing cumulative dose proceeds towards the apex, affecting also hearing at lower frequencies (15). Most patients treated with cisplatin develop a symptomatic and clinically-detectable sensory neuropathy, caused by its preferential uptake in the dorsal root ganglia (DRG), which produces a dose-related large fiber sensory neuropathy (16, 17). Interestingly, oxaliplatin treatment is also associated with the development of significant neurological dysfunction (18, 19). Followingly, we will focus on Ctr1 and OCT2 as cisplatin uptake transporters.

Copper transporter-1 (Ctr1). Ctr 1 is a member of the solute carrier SLC31A family, which is ubiquitously expressed due to the biological importance of copper as an essential nutrient (20, 21). Ctr1 is a 23-kDa channel-like transporter, which consists of three transmembrane domains, and oligomerizes in trimers to form a pore for the transport of copper (21-23). The transport of copper by Ctr1 is strongly inhibited by silver and not by divalent cations, suggesting that the reduced form of copper, Cu(I), is the substrate of the transporter (24). Global genetic deletion of Ctr1 is embryonically lethal (20, 23), probably due to insufficient copper supply to the body. Yonezawa and Inui recently underlined that Ctr1 is an equilibrative transporter (25). This fact could be important in the comparison with the OCT2, a concentrative transporter. Ctr1 has been shown to mediate the cellular uptake of cisplatin and other platinum drugs such as oxaliplatin (26-29). Ctr1 seems to control the cellular accumulation of platinum drugs at low concentrations, since the cellular accumulation of oxaliplatin at higher concentrations is not dependent on Ctr1 (28). Overexpression of Ctr1 in different cell lines causes a significant increase of cisplatin uptake (26), while its knock-out or knock-down using siRNA, significantly reduces cisplatin uptake in yeast and mouse embryonic fibroblasts and in human embryonic kidney (HEK293) cells (2, 28, 30, 31). However, cimetidine, a substrate of organic cation transporters (OCT), could further reduce cisplatin uptake and also toxicity in Ctr1 knock-down HEK293 cells (31), suggesting that other transport systems like the OCTs may also contribute to cellular transportation of cisplatin. However, it should also be considered that cimetidine may have off-target effects. Immunohistochemical analyses of mouse cochlea showed that Ctr1 is expressed in outer hair cells, inner hair cells, stria vascularis, spiral ganglia, and surrounding nerves of the mouse cochlea (32). In the same study, copper sulfate effectively protected hair cells against cisplatin toxicity through competition at the Ctr1. In another further study performed in postnatal day 3 rat cochlear organotypic cultures, Ctr1 expression was identified in the organ of Corti, in the epithelium of the stria vascularis, and in the spiral ganglion neurons (33), structures that are the major targets of cisplatin-induced cochlear damage (34). However, co-administration of cisplatin with copper sulfate had only a modest protective effect on hair cells (33). Furthermore, copper sulfate *per se* was toxic for these cells (33). In contrast, treatment of cochlear cultures with cisplatin together with cimetidine, a substrate of OCT, conferred a considerable protection against cisplatin-induced hair cell loss (33).

Ctr1 has also been identified in cell bodies and plasma membranes of larger-sized rat DRG neurons, suggesting that this transporter is implied in the development of neurotoxicities induced by platinum derivatives such as cisplatin and oxaliplatin (35). These large-sized DRG neurons are more vulnerable to damage from platinum drug treatment than small-sized DRG neurons (36, 37). *Ctr1* mRNA is also highly expressed in several cisplatin-sensitive cell lines derived from human tumor samples (6), suggesting that this transporter could represent the uptake route of cisplatin in cancer cells. Indeed, the analysis of a public gene expression dataset showed that outcome of treatment with platinum drugs was more favorable in ovarian cancer patients with elevated levels of hCtr1 in their tumors than in those expressing low hCtr1 levels (38). In 40 women with ovarian carcinoma, high and low *Ctr1* mRNA expression were significantly associated with sensitivity to platinum-based chemotherapy and progression-free survival, and with resistance to platinum-based chemotherapy and the shortest survival, respectively (39). Moreover, there are some clinical studies showing that mutations of the *Ctr1* are associated with resistance against cisplatin-based chemotherapy. The screening of 282 non-small cell lung carcinoma Chinese patients revealed a significant relationship between rs7851395 and rs12686377 polymorphisms of Ctr1 and platinum resistance, as well as clinical outcomes (40). The important biological role of the Ctr1 and its ubiquitous expression in healthy tissues as well as in tumors complicate the use of a protective therapy by competition of the uptake

of platinum drugs mediated by Ctr1. Such an approach could induce a general cellular toxicity or even protect tumor cells against chemotherapy. Furthermore, an additional transport system mediating the specific uptake of platinum drugs in non-target tissues, such as renal and cochlear tissue appears to be present. Moreover, a recent study put the role of Ctr1 for the cellular uptake of platinum derivatives once again up to discussion by showing that, in contrast to what was found in previous studies, the hCTR1 is not internalized in response to extracellular platinum drug exposure and is not the major entry route of platinum drugs into cells (41).

Organic cation transporters. Organic cation transporters (OCTs) are transmembrane proteins, which mediate the movement of organic cations (OC) of endogenous (*e.g.* histamine, serotonin, dopamine) and exogenous (*e.g.* ifosfamide, cimetidine) origin across the plasma membrane (42, 43). These transporters are abundantly expressed in excretory organs such as the liver and the kidneys (43). The cells of these organs have a morphological and functional polarization in order to support the vectorial movement of substances, which is mediated by the concerted action of transporters specifically expressed on the basolateral and apical plasma cell membrane (43-46). The first step for OC secretion in these organs is their absorption from the basolateral side into the cells. In human kidney, this process is mainly mediated by OCT2, while in the liver it is supported by OCT1 (43). The second step is the secretion of OC from the tubular cell into the tubular lumen in the kidney or from the hepatocytes into the bile in the liver. This process is mediated by different transporters such as the H^+/organic cation antiporters OCTN1 and the MATE1 (47). OCTs have been assigned to the SLC22A family that includes among others also the electroneutral organic cation transporters (OCTNs, OCTN1-3) (48, 49). Transport of OC mediated by the three OCT subtypes (OCT1-3) is electrogenic, independent of Na^+, and reversible with respect to direction (49). The driving force is supplied by the electrochemical gradient of the transported OC. In this way, the uptake mediated by OCT is concentrative, in opposition to the transport mediated by Ctr1 that is equilibrative (25). Therefore, OCT can have a stronger activity than Ctr1 with respect to the transport of platinum derivatives (25). An interaction of cisplatin with renal transporter systems was already hypothesized before the molecular biology era, since cisplatin was found to be secreted in renal tubules (50). Later on, several *in vitro* studies using transfected and non-transfected cells (5, 51-55) and freshly-isolated rabbit or human proximal tubules (5, 56) demonstrated that OCT2 mediates the basolateral-to-apical transport of cisplatin and that competition at the transporter protects the cell against cisplatin toxicity (5, 55). Of special interest is the specific tissue distribution of the OCT subtypes. For example, human OCT1 (hOCT1) is highly expressed in the liver (57, 58) and in jejunium (mainly on the lateral membranes of the enterocytes) (59), while hOCT2 is preferentially expressed in the dopaminergic brain regions (60) and in human kidney (61). This specific tissue distribution of OCT can be of special importance for determining specific effects and side-effects of drugs such as cisplatin. Indeed, *in vitro* studies with HEK293 cells stably-transfected with hOCT showed that cisplatin interacts with hOCT2 but not with hOCT1 (5). In human proximal tubules cisplatin competed with basolateral OC transport, whereas it did not influence OC transport in hepatocytes (5). These findings suggest that a treatment with cisplatin in combination with other substrates that compete for hOCT2 may provide an effective option to decrease nephrotoxicity in the clinical setting. In animal studies, the renal uptake clearance of cisplatin and its renal toxicity were greater in male than in female rats, while the hepatic uptake clearance was similar between the sexes (54). These gender-dependent effects are due to stronger expression of rOCT2 in renal proximal tubules from male compared with female animals (54, 62). It is not known, whether the renal OCT2 expression in humans is under the control of sex hormones as well. However, the promoter region of human OCT2 does not contain the same androgen-responsive regions like rOCT2 (63). *In vivo* studies using mice in which OCT1 and OCT2 were genetically deleted demonstrated the importance of OCT transporters in mediating cisplatin toxicities. Deletion of OCT1 and OCT2 protected the mice from severe cisplatin-induced renal tubular damage and caused a significantly impaired urinary excretion of cisplatin without an apparent influence on its plasma levels (64). Another study confirmed the nephroprotection against cisplatin-induced nephrotoxicity in mice with genetic deletion of OCT1 and OCT2 (6). Additionally, this study demonstrated that OCT2 is expressed in the outer hair cells and also in cells of the stria vascularis in the cochlea and that OCT1/OCT2-deficient mice were resistant to cisplatin-induced ototoxicity. Interestingly, treatment of the wild-type animals with cisplatin together with cimetidine, a competitor for the transport by OCT, eliminated or lowered the ototoxic and nephrotoxic effects of cisplatin, respectively (6). A study in rats showed that such a protective strategy did not interfere with the anti-tumoral activity of cisplatin (65). Interestingly, OCT2 has been demonstrated to be expressed in DRG within the nervous system (66). Genetic or pharmacological knock-out of *OCT2* protected mice from hypersensitivity to cold or mechanical-induced allodynia induced by oxaliplatin treatment (64). Due to its specific tissue expression and to its interaction with cisplatin and oxaliplatin, OCT2 seems to be a suitable candidate target to establish protective therapies against unwanted toxicities of these drugs (67, 68). However, it remains to be established, whether the target cells of these

drugs also express this transporter. Interestingly, a reduced expression of OCT1, OCT2, and OCT3 due to epigenetic modifications such as DNA methylation was observed both in animal models and in tumor patients (69-71).

Collectively, these results indicate the critical importance of OCT2 in the handling of cisplatin in the kidney, in the inner ear and possibly also in DRG and provide a rationale for the development of new targeted approaches to mitigate these debilitating side effects of cisplatin chemotherapy.

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