Review Article

Role of membrane transporters in cisplatin induced nephrotoxicity

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ABSTRACT

Transporters are important mediators of specific cellular uptake and thus, not only for effects, but also for side effects, metabolism, and excretion of many drugs such as cisplatin. Cisplatin is a potent cytostatic drug, whose use is limited by its severe acute and chronic nephro-, oto-, and peripheral neurotoxicity. For this reason, other platinum derivatives, such as carboplatin and oxaliplatin, with less toxicity but still with antitumoral action have been developed. Several transporters, which are expressed on the cell membranes, have been associated with cisplatin transport across the plasma membrane and across the cell: the copper transporter 1 (Ctr1), the Ctr2, the P-type copper-transporting ATPases ATP7A and ATP7B, the organic cation transporter 2 (OCT2), and the multidrug and toxin extrusion protein 1. Some of these transporters are also able to accept other platinum derivatives as substrate. Since membrane transporters display a specific tissue distribution, they can be important molecules that mediate the entry of platinum derivatives in target and also non-target cells possibly mediating specific effects and side effects of the chemotherapeutic drug. This paper summarizes the literature on toxicities of cisplatin compared to that of carboplatin and oxaliplatin and the interaction of these platinum derivatives with membrane transporters.

Keywords: Nephrotoxicity, ototoxicity, neurotoxicity, multidrug extrusion transporter 1, Organic cation transporter 2, copper transporter 2

INTRODUCTION

In the last several decades, novel cancer drugs have been developed and used in clinical practice, being more specific against cancer cells and extremely effective against several previously untreatable malignancies, the so-called molecularly targeted agents, but also suffer from nephrotoxicity which limits the efficacy of the treatment and impact their quality of life and overall survival.[1]

Most of the chemotherapeutic agents developed so far exert their action in the cell and therefore have to cross the cell membrane to reach their targets.[2] However, they are often poorly lipophilic compounds, which cannot easily pass the cell membrane and thus need to be transported into the cell by specific systems of protein nature called transporters.[3] General concept of drug movement across biological membranes is that they can pass cell membranes through passive diffusion at a rate related to their lipophilicity. However, it is becoming evident that membrane transporters are also important determinants of *in vivo* drug disposition, therapeutic efficacy, and adverse drug reactions.[3] In epithelial tissues, which are constituted by polarized cells, transporters are even specifically expressed on the apical or basolateral cell membrane.[4] In this way, a specific drug-transporter interaction can be exploited to target drugs to selected cells and tissues, but of course can also explain specific undesired adverse effects.[5] Membrane transporters such as the copper transporter-1 (ctr1), the ctr2, the p-type copper transporting atpases atp7a and atp7b, the organic cation transporter-2 (oct2), and the multidrug and toxin extrusion protein-1 (MATE 1) mediate cellular transport of cisplatin.[5]Transporter mediated uptake has been shown to be an important process mediating cellular accumulation of cisplatin. Cisplatin is one of the most widely utilized antitumor drugs in the world.[6]

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Cisplatin was the first platinum-based drug that revolutionized the treatment of neoplastic diseases. For example, before the introduction of cisplatin as chemotherapeutic agent, testicular cancer was associated with a survival rate of only 5%.[7] Today, the treatment of this cancer with a combination of new surgical techniques and cisplatin chemotherapy allows to achieve a cure rate of over 90%. Currently, cisplatin is widely used for the therapy of solid tumors.[8] However, its use is limited by severe side effects such as nephro- and ototoxicity and peripheral neurotoxicity. Therefore, there is a need to put an effort in developing less toxic platinum derivatives.[9]

Action of cisplatin on cell growth was unexpectedly discovered by Rosenberg in 1965 by investigating the effects of an electric field on the growth of *Escherichia coli* bacteria.[10] When placed in an electric field using platinum-conducting plates, bacteria ceased to divide. Rosenberg hypothesized that if cisplatin could inhibit bacterial cell division, it could also suppress tumor cell growth. Cisplatin was approved by the FDA in 1978 for the treatment of metastatic testicular or ovarian cancer and is also administered for many other types of solid tumors.[11]

A common event happening when platinating agents enter a cell is their aquation that is losing of chloride or oxalate ions and gaining two water molecules to form aquaions. The low intracellular concentration of chloride ions facilitates this process.[12] Positively charged aquated form is more reactive to the cellular targets, such as nucleophilic molecules within the cell, including DNA, RNA, and proteins.[13] It is generally accepted that DNA is the preferential cytotoxic target for cisplatin and other platinating agents: these substances bind preferentially the imidazole ring of the purines guanine and adenosine forming monoadducts, intrastrand crosslinks, and interstrand crosslinks.[14] All crosslinks distort the structure of the DNA duplex and begin the DNA damage response signaling, resulting in cell cycle arrest and apoptosis.[15]

CISPLATIN TOXICITY

Cisplatin treatment, even though effective against tumors, has severe side-effects such as nephrotoxicity, which is often dose-limiting, ototoxicity, and peripheral neurotoxicity.[5]

Nephrotoxicity

In patients cisplatin-induced nephrotoxicity manifests acutely and/or chronically. Clinically, cisplatin nephrotoxicity develops after 10 days of cisplatin administration and is manifested as lower glomerular filtration rate, higher serum creatinine, and reduced serum magnesium and potassium levels. Interestingly, striking differences between patients in susceptibility to progressive nephrotoxicity are even though nephrotoxicity can be controlled by diuretics and prehydration of patients.[16] It is recognized that the prevalence of cisplatin nephrotoxicity is high, occurring in about one third of patients undergoing cisplatin treatment In animal studies it has been shown that the kidney accumulates more cisplatin than other organs and that the proximal tubules are principally damaged by cisplatin.[17]

Ototoxicity

Ototoxicity is an untypical side effect for a chemotherapeutic drug. Cisplatin treatment causes a hearing loss, which can also lead to deafness.[18] Ototoxicity remains an unresolved clinical problem especially in infants and younger children, where it leads to a considerable risk of delayed language development due to impaired perception of higher frequency consonant sounds that is of great importance in the presence of background noise.[19] The incidence of ototoxicity is reported to be between 23% and 50% in adults and greater than 50% in children, clinical symptoms of toxicity consist of bilateral symmetrical high-frequency sensorineural hearing loss, ear pain, or tinnitus.[20] Damage induced by cisplatin begins at the cochlea base, where high-frequency sounds are processed, and proceeds toward the apex, affecting also hearing at lower frequencies as the cumulative dose increases.[20] In the cochlea, cisplatin seems to induce the generation of reactive oxygen species and/or the depletion of scavenging enzymes causing cell apoptosis.[21]

Neurotoxicity

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.[5] Symptoms include unpleasant distal paresthesia (tingling in the extremities) and numbness, associated with large fiber sensory -loss (reduced vibration and joint position sensations) and diminished or absent muscle stretch reflexes.[22] Sensory ataxia (incoordination) may be disabling in those patients who have severe neuropathy. These symptoms may appear as soon as 1 month after initiating treatment.[23] The neuropathy may only partially recover or not recover at all. In rodents, cisplatin affects sensory nerve structure and function, showing preferential toxicity to large diameter neurons and proprioceptive sensory modalities, while motor nerves are spared from toxicity. The mechanism of platinum neurotoxicity remains in completely understood although it may involve platinum accumulation within the DRG leading to atrophy or loss of peripheral sensory neurons.[24]

CELLULAR TRANSPORT OF CISPLATIN

Several different transporters seem to be involved in the cellular transport of cisplatin: the Ctr1, the Ctr2, the P-type copper-transporting ATPases ATP7A and ATP7B, the OCT2, and the MATE1.[5]

Ctr1

Ctr1, Solute Carrier 31A1-SLC31A1 is a membrane protein that plays a significant role in the cellular cisplatin uptake. Down-regulation of Ctr1 extensively reduced cisplatin uptake in yeast and in mouse embryonic fibroblasts.[9] The natural substrate of Ctr1 is monovalent copper (Cu+). Cu+ uptake by Ctr1 triggers transporter internalization.[25] However, whether this phenomenon also happens upon cisplatin transport is debated. As observed for Cu+, cisplatin binds to Methionine-rich motifs of the extracellular domain of Ctr1. Ctr1 carries out vital physiological function supplying the cell with

copper, which is an essential cellular nutrient used in a broad range of enzymatic reactions. Because of its important biological role, Ctr1 is almost ubiquitously expressed and perhaps may not be the decisive transporter for specific cisplatin toxicities. Since several cell lines from human tumor samples express Ctr1- mRNA, this transporter could represent the uptake route of cisplatin in cancer cells. Indeed, high expression levels of Ctr1 have been associated with cisplatin therapeutic success whereas Ctr1 mutations are associated with cisplatin resistance. Ctr1 has been also associated with the cellular transport of carboplatin and oxaliplatin.[26]

Ctr 2

Ctr2, SLC31A2 is a copper transport protein with substantial structural homology to Ctr1. Ctr2 is mainly expressed in late endosomes and lysosomes, where it probably mediates the efflux of copper under conditions of low environmental copper concentration.[11] A similar function of Ctr2 was proposed for cisplatin. Studies in Ctr2-deficientmice suggested that Ctr2 functions as an indirect regulator of Cu+-uptake and intracellular flux by stabilizing the biosynthesis of cleaved Ctr1. The cleaved Ctr1 is a transporter form which lacks metal binding Methionine- and Histidine-rich motifs and of consequence has decreased Cu+ and also cisplatin uptake function.[27] Therefore, high expression of Ctr2 seems to be associated with resistance to the cytotoxic effect of cisplatin and knockdown of Ctr2 was associated with an increased cisplatin accumulation and cytotoxicity.[28]

Copper-transporting (ATP7A and ATP7B)

The P-type copper-transporting ATPases ATP7A and ATP7B are also involved in cellular cisplatin handling.[29] These transporters play an important role in regulating the cellular copper levels, because too high intracellular copper concentrations are toxic for the cell.[30] Inactivation of these transporters, as present, for example, in Menkes' disease (inactivation of ATP7A) and in Wilson's disease (inactivation of ATP7B), is associated with copper deficiency because of impaired copper efflux from enterocytes into the blood or massive cellular copper overload, respectively.[9] While ATP7A is mainly expressed in intestine, choroid plexus, vascular smooth muscle and endothelial cells, as well as in cerebrovascular endothelial cells, ATP7B is principally expressed in the liver and the brain.[31] Regarding the transport of cisplatin, ATP7A and ATP7B mediate its efflux from the cell or its distribution to specific subcellular compartments.[32] For this reason, the expression of these transporters is correlated with cisplatin cellular sensitivity and resistance ATP7B is stronger associated with the acquisition of resistance than Ctr1 or ATP7A. Besides cisplatin, ATP7A and B transporters also interact with carboplatin and oxaliplatin.[33] Even though the effects of ATP7A and B transporters on cisplatin cellular distribution are very similar to those observed for copper, platinum drugs are not readily exported after vesicular sequestration.[33] Interestingly, copper transport systems are expressed and active in DRG, which are sensitive to toxicity from platinum derivatives. Here, Ctr1 is expressed in large-sized neurons and ATP7A in small DRG neurons, suggesting that large neurons are especially sensitive and small neurons are protected from toxic effects of platinum derivatives.[34]

OCTs-3, SLC22A1-3

A specific interaction of cisplatin with OCTs has also been demonstrated. Since OCTs have a specific organ distribution, with high renal expression, the cisplatin-OCT interaction is of pecial interest to explain selective organ toxicity of cisplatin.[9] OCTs are highly expressed in excretory organs such as the liver and the kidneys, where they mediate the electrogenic uptake of heir substrates in hepatocytes and proximal tubule cells. OCTs are defined as polyspecific transporters, because they can transport several unrelated substances. The driving force for the cellular transport by OCTs is the electrochemical gradient of the substrate.[35] In excretory organs, OCTs mediate the first step of secretion process, consisting of substrate uptake through the basolateral plasma membrane (the blood-faced part of plasma membrane). The subsequent substrate efflux through the luminal membrane (the bile- or urine-faced part of plasma membrane) is the final secretion step, resulting in a vectorial substrate movement from the blood to the bile or urine in the liver or kidneys, respectively. In humans, the paralogs hOCT1 and hOCT2 are specifically expressed in the basolateral membrane of hepatocytes and renal proximal tubule cells, respectively.[36] Cisplatin seems to interact preferentially with hOCT2, suggesting that hOCT2 is the critical transporter for renal cisplatin uptake in humans. Also the second- and third generation platinum derivatives oxaliplatin are substrates of OCTs.[36] For the interpretation of translational studies, it is important to underline that the rodent OCT orthologs have a different organ distribution and kinetic properties compared with human OCTs: for example, in mice, OCT1 is expressed in renal proximal tubules at higher level than OCT2. Competition of OCT-mediated cisplatin transport is able to reduce cisplatin uptake and toxicity *in vitro* and *in vivo*. OCT2 has been demonstrated to be expressed in the mouse cochlea in hair cells of Corti organ and in the cells of the stria vascularis and in mouse and human DRG), structures that are especially sensitive to toxicity by platinum-derivatives. In animal models, it has been demonstrated that OCTs are critical mediators of cisplatin ototoxicity and oxaliplatin peripheral neurotoxicity.[5]

MATE1, SLC47A1

Several evidences indicate that MATE1 mediates secretion of cisplatin into the urine. Mice with genetic deletion of MATE1 are more sensitive to cisplatin nephrotoxicity.[37] Furthermore, cell transfected with MATE1 displayed a higher cisplatin uptake than control cells. Interestingly, MATE1 and MATE2-K, another member of MATE family which is solely expressed in human kidneys, seem to transport oxaliplatin with higher affinity than cisplatin, offering a possible explanation of the low oxaliplatin nephrotoxicity. As outlined above, the inhibition of OCT2 may be a protective strategy against cisplatin nephrotoxicity.[38] However, some inhibitors of OCT2 such as cimetidine and ondansetron interact with higher potency with MATE1, blocking cisplatin efflux from the cells and potentially increasing cisplatin renal toxicity.[39] Indeed, co-treatment of mice with cisplatin and cimetidine was effective in protecting the animals from ototoxicity but not from nephrotoxicity.[40] There are some investigations suggesting a role of novel OCTNs for oxaliplatin transport. These transporters are expressed on the apical membrane

of renal proximal tubule cells and in rat DRGs. When transfected in human embryonic kidney cells, rat and human OCTN1 and OCTN2 mediate significant oxaliplatin uptake suggesting that OCTNs are involved in oxaliplatin neurotoxicity.[9] Apart from these not directly ATP-dependent transporters, multidrug resistance-associated protein 2 transporter seems to be involved in the efflux of cisplatin and its conjugates from kidney cells, and for this reason to play an important role for control of cisplatin renal toxicity.[41]

CONCLUSION

Cellular transport of platinum derivatives is mediated by several transport systems. Some transporters, such as OCTs, are specifically expressed in organs, which are damaged by antitumor therapy with platinum derivatives. For this reason, they may be a target for protective intervention. However, an efficient protection can be only reached by specific inhibition of OCTs.

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