

Role of copper transporters in platinum resistance

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Abstract

Platinum (Pt)-based antitumor agents are effective in the treatment of many solid malignancies. However, their efficacy is limited by toxicity and drug resistance. Reduced intracellular Pt accumulation has been consistently shown to correlate with resistance in tumors. Proteins involved in copper homeostasis have been identified as

Pt transporters. In particular, copper transporter receptor 1 (CTR1), the major copper influx transporter, has been shown to play a significant role in Pt resistance. Clinical studies demonstrated that expression of CTR1 correlated with intratumoral Pt concentration and outcomes following Pt-based therapy. Other CTRs such as CTR2, ATP7A and ATP7B, may also play a role in Pt resistance. Recent clinical studies attempting to modulate CTR1 to overcome Pt resistance may provide novel strategies. This review discusses the role of CTR1 as a potential predictive biomarker of Pt sensitivity and a therapeutic target for overcoming Pt resistance.

Key words: Resistance; Cisplatin; Copper transporter receptor 1; Copper transporter; Copper transporter receptor 2; ATP7A; ATP7B

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Core tip: Platinum (Pt)-based chemotherapy is the backbone of treatment for various solid malignancies in both curative and palliative settings. However, the efficacy of Pt is limited by toxicity and inevitable resistance. Hence, it is important to understand the mechanisms of Pt resistance to not only identify treatment non-responders, but more importantly to help develop strategies to overcome resistance and improve efficacy. We herein discuss our current understanding of the mechanisms of Pt resistance, with a particular emphasis on the role of copper transporter receptor 1 in Pt resistance.

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INTRODUCTION

Role of platinum chemotherapeutics in cancer

Cisplatin, also called the "penicillin of cancer", has

remained the mainstay of treatment for a variety of solid tumors over the last four decades and is an essential component of both curative-intent and palliative chemotherapy regimens^[1,2]. First described in 1845 as Peyrone's salt and subsequently noted to inhibit binary fission in *Escherichia coli* bacteria, cisplatin is platinum (Pt)-based alkylating agent that binds to DNA and causes intra/inter strand crosslinking which interferes with cell division and causes apoptosis. Carboplatin and oxaliplatin are newer members of the Pt family of compounds with similar mechanisms of action as cisplatin but with different toxicity profiles.

Pt agents have a number of toxicities that limit their clinical use. The most common adverse effects from cisplatin include nephrotoxicity, ototoxicity, neurotoxicity and myelosuppression. Cisplatin is also highly emetogenic. Carboplatin is less emetogenic and has a lower risk of nephrotoxicity and ototoxicity; however, it is more myelosuppressive than other Pt compounds. Oxaliplatin which is significantly neurotoxic has the lowest risk of nephrotoxicity and ototoxicity amongst Pt compounds.

Despite the same class, each Pt drug has a unique role in the management of individual cancers, and in most circumstances these agents are not interchangeable. Cisplatin is the most active Pt agent against testicular, lung, ovarian and bladder cancers, and is the only Pt drug recommended in curative-intent treatment for these malignancies. In contrast, carboplatin may be substituted for cisplatin in the palliative setting for advanced solid tumors where cisplatin may not be tolerated due to adverse effects. In general, oxaliplatin is the Pt of choice for colon cancer.

Pt resistance is an inevitable occurrence with rare exception. Aside from germ cell tumors, metastatic solid tumors are generally thought to be incurable with cytotoxic chemotherapy due to the development of resistance and subsequent disease progression. While advances in molecular biology and genomic (personalized) medicine have driven an exponential increase in therapeutic options and improved outcome in various malignancies, Pt-based chemotherapy remains the backbone of treatment for a variety of solid tumors. Therefore, it is crucial to understand mechanisms of Pt resistance in order to develop strategies to overcome this nearly universal phenomenon.

Mechanisms of Pt resistance

The clinical utility of Pt agents is limited by both intrinsic and acquired resistance. For example, cisplatin-based treatment is associated with up to 80% response rates in patients with limited stage small cell lung cancer; however, the median overall survival is less than a year due to lack of durable response^[3]. Understanding the mechanisms of Pt resistance may improve clinical outcomes. Pt resistance is complex and is regulated by a cascade of events that interfere with any of the multiple steps involved in its cytotoxic actions, from initial drug entry into the cell to the final stages of apoptosis.

While not fully understood, identified mechanisms of resistance include: Increased glutathione and metallothionein, which inactivates the reactive forms of Pt^[4-6], activation of nucleotide excision repair pathway and other pathways associated with DNA repair^[7,8], and dysregulation of the tumor suppressor *p53* gene that is required for apoptosis^[9-12]. Dysregulation of the Ras and MAPK pathway^[13,14] and the heat-shock proteins^[15] have also been implicated in Pt resistance.

Despite the multifactorial nature of Pt resistance, reduced intracellular drug accumulation is one of the most consistently identified features of cisplatin-resistant cell lines^[4,16]. Reduced influx or increased efflux of the drug is associated with decreased intracellular accumulation. Pt drug influx has been attributed to both non-saturable as well as energy-dependent active transport processes^[17,18]. Currently identified Pt influx transporters include copper transporter receptor 1 (CTR1) and organic cation transporters belonging to the soluble carrier (SLC) SLC22A2 family. On the contrary increased levels of the multidrug resistance associated transporter protein MRP2 (cMOAT), adenosine triphosphate (ATP) binding cassette (ABC) multidrug transporters, CTR2 and copper-transporting P-type adenosine triphosphates (ATPase's) have been observed to confer resistance^[19,20]. In this review we will focus on the importance of intratumoral Pt levels in promoting chemosensitivity and the role of CTRs, specifically CTR1, in contributing to Pt resistance.

INTRACELLULAR PT AND TUMOR PT-SENSITIVITY

It has been hypothesized that reduced intracellular Pt concentration may confer resistance to Pt-based chemotherapy. Both *in vitro* and *in vivo* studies provide data to support this hypothesis.

***In vitro* studies**

Lanzi *et al*^[21], demonstrated that a reduction of drug accumulation in cisplatin-resistant (A431/Pt) human cervix squamous cell carcinoma compared to Pt-sensitive squamous cancer cells directly correlated with the extent of cisplatin-induced DNA damage. Mann *et al*^[22], noted that, in human ovarian cancer cell lines, decreased Pt drug accumulation is associated with resistance. Several other investigators observed similar positive correlations between accumulation of Pt and cytotoxicity in cancer cell lines derived from ovarian, leukemia and lung cancer tissues^[23-26]. All these studies support drug accumulation as a contributing factor to Pt resistance. However, cell line studies represent only a single phenotype and do not take into account complex tumor- host interaction that may allow for other mechanisms of chemoresistance.

***In vivo* studies**

It has been demonstrated that the elimination of Pt compounds is triphasic in nature, with a terminal

plasma half-life of 5.4 d for cisplatin. In contrast, Pt has a long half-life in human tissue that is yet to be quantified^[27]. Pt and DNA adducts were detectable in autopsy tumor samples from patients who had received Pt up to 15 mo ante mortem^[28,29]. In a prospective study of two groups of advanced non-small cell lung cancer (NSCLC) patients receiving cisplatin at two different doses, plasma Pt concentration correlated with the dose of cisplatin administered, however tissue Pt concentration did not. In this study there was a weak correlation between simultaneous plasma and tumor tissue concentration^[30]. In 44 patients with NSCLC who had received neoadjuvant Pt-based therapy and subsequently underwent surgical resection, tissue Pt concentrations in resected tumor specimens significantly correlated with percent reduction in tumor ($P < 0.001$). The same correlations were seen irrespective of the Pt drug utilized, number of cycles and histologic subtype. Patients with higher intratumoral Pt concentrations also had longer time to recurrence ($P = 0.034$), progression-free survival ($P = 0.018$), and overall survival ($P = 0.005$). This was the first clinical study to establish a relationship between tissue Pt concentration and tumor response, and supports Pt accumulation as an important mechanism of resistance even in the clinical setting^[31]. In another study of 19 patients with muscle invasive bladder cancer who had received Pt-based neoadjuvant therapy, total Pt concentration in normal adjacent bladder tissue significantly differed by tumor pathologic response ($P = 0.011$). Specimens with pathologic complete responses had the highest Pt concentrations compared to those with a down-staging to non-muscle invasive disease ($P = 0.0095$) or no response/progression ($P = 0.0196$)^[32]. These findings suggest that intratumoral Pt accumulation may be an important determinant of Pt sensitivity and tumor responses across tumor types.

CTRS

Pt chemotherapeutics cross the cell membranes by passive diffusion and transporters. Various ion pumps and transporters have been implicated in the transport of Pt agents, some of which are well-characterized^[33]. More recently, transporters involved in copper homeostasis have been identified as important in Pt influx and efflux. Copper is an essential micronutrient and a cofactor for many enzymes. However, its intracellular form is highly toxic, and hence, a complex network of proteins have evolved to chaperone copper to the copper-dependent proteins. Chaperone proteins include CTR1, CTR2, antioxidant protein (ATOX 1), ATP7A and ATP7B. All of the above discussed transporters possess a metal binding sequence that binds both copper and Pt^[34].

CTR1 is the most extensively studied Pt influx transporter and will be described in detail in the next section. CTR2, another copper uptake protein, has a substantial structural homology to CTR1 but functions as a Pt efflux transporter. Higher CTR2 levels correlated with

Pt resistance in ovarian cancer cell lines^[35]. It was also noted that in a human 2008 epithelial cancer cell model, higher expression of CTR2 was noted to be associated with increased intracellular copper and Pt resistance^[36]. Further studies are needed to better understand the role of CTR2 in cisplatin resistance in human cancers.

ATP7A and ATP7B are two copper transporting P-type ATPase that also maintain copper homeostasis and have been implicated in Pt efflux^[37,38]. ATP7A is thought to regulate Pt accumulation, primarily by sequestering Pt intracellularly, whereas ATP7B located in the Trans Golgi network mediates Pt drug efflux *via* a process that involves its transport into vesicles involved in the secretory pathway^[39]. In human epidermoid carcinoma KB-3-1 cell (a derivative of HELA-cervical cancer line), transfection with ATP7B conferred cisplatin resistance^[40]. Similarly in prostate cell lines, overexpression of ATP7B correlated with Pt resistance^[40]. The observation that human tumor cells transfected with ATP7B acquire resistance to cisplatin lends credence to the hypothesis that drug efflux plays a role in resistance^[41]. Several cell line studies, including one of fibroblasts derived from a patient with Menkes disease, which is characterized by copper deficiency, confirmed the role of efflux proteins in enhancing Pt resistance^[42,43]. ATP7B silencing resulted in enhanced cisplatin sensitivity and increased DNA adducts formation in cisplatin-resistant cells; however this was not observed with ATP7A silencing^[44]. In both NSCLC xenografts exposed to cisplatin and colorectal cancer patients treated with oxaliplatin, increased levels of ATP7B were associated with Pt resistance^[45,46]. In the only study to simultaneously assess influx and efflux transporters, expression of CRT1, ATP7A and ATP7B were measured in three pairs of parent cell lines and cisplatin-resistant cell lines derived from various types of invasive oral squamous cell carcinoma. ATP7B expression correlated with the acquisition of cisplatin resistance more closely than either CTR1 or ATP7A^[39].

PROFILE OF CTR1

Structure and localization

CTR1 is a 190 amino acid (aa) protein with three trans-membrane domains, a approximately 67 aa extracellular N-terminal (ecto) domain, and a approximately 15 aa C-terminal cytosolic tail^[47,48]. Crystallographic analysis of human CTR1 noted that the permeation conduit formed by the association of three CTR1 molecules involves a series of rings of methionines capable of chelating copper in a trimeric configuration^[48,49]. Two rings each containing three methionines are stacked on top of each other in the narrowest part of the pore, and a ring of three cysteines is located at the bottom of the pore. The aperture has a truncated cone shape measuring approximately equal 8 Å at the external entrance and approximately equal 22 Å at the intracellular end^[50]. The expression of CTR1 is ubiquitous and localizes to the plasma membrane in some cell lines and perinuclear vesicles in others^[51].

Role in copper transport

CTR1 is the primary influx transporter of copper in human cells. Transport of copper by CTR1 is energy-independent^[52] and results in conformational changes in CTR1^[53]. Knockout of both CTR1 alleles results in an embryonic lethal phenotype thought to be secondary to deficiency of copper^[54]. Organ-specific knockout of CTR1 in the intestine and liver confirms the role of CTR1 as an important copper transporter^[55,56]. The exact mechanism of copper transport across CTR1 is not yet completely understood and further studies are warranted.

ROLE OF CRT1 AS A PT TRANSPORTER

Despite the "narrowest opening" of trimetric CTR1 being smaller than the molecular size of cisplatin, studies suggest that prior to entering a cell, cisplatin is activated by interacting with the extracellular methionine clusters of CTR1, which results in the formation of an intermediate that is smaller than the radius of the narrowest opening CTR1^[57,58].

In vitro studies

Ishida *et al.*^[59], described CTR1 as a significant uptake transporter of cisplatin. They used a mutagenized wild type yeast cell library to select for mutants that grew in the presence of toxic doses of cisplatin. Cells with a CTR1 mutation that decreased CTR1 cell expression were noted to have profound Pt resistance compared to other mutants. In order to determine the mechanistic role of CTR1 in cisplatin resistance, cisplatin - DNA adducts were measured. They observed that decreased Pt uptake is responsible for lower Pt adduct levels and resistance. They also demonstrated that cisplatin, similar to copper, down-regulated CTR1 expression in yeast cell lines.

CTR1 knockout in intestinal epithelial mouse cell lines also led to a decrease in intracellular Pt levels and resistance^[60]. Similarly, overexpression of CTR1 was associated with cisplatin sensitivity in ovarian and colorectal cancer cell lines^[61,62]. In cisplatin-resistant small cell lung cancer cells, sensitivity was restored when CTR1 was introduced into these cells^[63]. Ivy *et al.*^[64] also noted that higher intracellular Pt correlated with higher CTR1 levels in human embryonic kidney cells and mouse embryonic fibroblasts. However contrary to other studies, the investigators noted that in ovarian tumor cells uptake of Pt was linear and non-saturable, suggesting that there could be other mechanisms besides CTR1 involved in Pt transport, including proteins involved in copper homeostasis^[64].

In vivo studies

In rat dorsal root ganglion, CTR1 expression by immunohistochemistry (IHC) and RT-PCR correlated with Pt uptake and treatment-induced cell body atrophy^[65]. Similarly, in a murine model utilizing mouse embryo fibroblasts, CTR1 knockout completely eliminated respon-

siveness of cells to Pt agents^[66]. In a mouse model of human cervical cancer (HPV16/E), the levels of cisplatin-induced DNA adducts correlated with CTR1 mRNA in most organs tested, including skin, lung, liver, pancreas, and uterus^[67].

CTR1 EXPRESSION AND CLINICAL OUTCOME

To date, several human studies have investigated the role of CTR1 in Pt sensitivity. In 15 patients with stage III/IV serous epithelial ovarian tumors who underwent optimal cytoreductive surgery (residual masses 1 cm or less) and subsequent Pt-based therapy, tumor CTR1 mRNA correlated with Pt sensitivity. Patients with no evidence of disease progression within 6 mo had higher CTR1 mRNA levels than in patients with refractory or resistant disease. Using clinical and array based expression data from the cancer genome atlas; the same investigators were able to independently validate the correlation of CTR1 mRNA levels with clinical outcomes in patients with advanced ovarian tumors who also underwent Pt-based therapy^[67]. Higher CTR1 expression by IHC in patients with stage III endometrial cancer who had received carboplatin also correlated with longer disease free and overall survival ($P = 0.009$)^[68].

In a study of 30 patients with NSCLC who had received neoadjuvant Pt-based chemotherapy, patients with undetectable CTR1 expression in their tumors had reduced intratumoral Pt concentrations and tumor response^[69]. In another study of 54 patients with stage III non-small lung cancer who received Pt-based combination chemotherapy, higher CTR1 expression correlated with longer progression free survival and overall survival ($P = 0.01$ and 0.047 , respectively)^[70]. More recently, we demonstrated that tumor CTR1 expression in cystectomy specimens of patients with muscle invasive bladder cancer correlated significantly with pathologic downstaging after Pt-based neoadjuvant chemotherapy^[71].

REGULATION OF CTR1

CTR1 expression has been shown to be regulated at both transcriptional and post-translational levels by various factors including transcription factor specificity protein 1 (Sp1) as well as copper and other heavy metals such as Cd, Zn and Ag^[72,73]. Sp1 is a zinc finger transcription factor that binds to GC-rich motifs in promoters and is involved in many cellular processes including cell differentiation, cell growth, apoptosis, immune responses and response to DNA damage. Song *et al.*^[74] demonstrated that three binding sites in the CTR1 promoter of Sp1 are involved in the basal and copper concentration-dependent regulation of CTR1 expression. The zinc-finger domain of Sp1 serves as a sensor of copper that regulates CTR1 expression in response to fluctuations in copper concentration^[74,75]. In addition,

modulation of Sp1 levels also affected the expression of CTR1. Cisplatin competes with copper for CTR1-mediated transport and trigger the rapid degradation of CTR1. It has been postulated that this mechanism serves to limit the toxic accumulation of the metal that it transports^[76,77]. The down-regulation of CTR1 expression after Pt exposure has been confirmed in various cell lines and is considered functionally significant as subsequent copper uptake, despite Pt absence, is noted to be decreased^[49,77].

In a study of 282 Chinese patients with NSCLC who received Pt-based therapy, genetic polymorphisms of CTR1 at reference single nucleotide polymorphism (rs) rs7851395 and rs12686377 were associated with Pt resistance and poor clinical outcomes. Patients with a GT haplotype had increased susceptibility to Pt resistance, whereas AG haplotype conferred longer overall survival^[78]. In a second study of 204 Chinese patients, CTR1 polymorphism (rs10981694 A > C) correlated with Pt toxicity in patients with advanced stage NSCLC and could be potentially used for pretreatment evaluation of toxicity. However, the survival times of patients with different rs10981694 genetic polymorphisms were not significantly different^[72]. Functional implications of these polymorphisms are not clear.

CTR1 AS A THERAPEUTIC TARGET

Cisplatin-induced degradation of CTR1 was noted to be reversible with the proteasome inhibitor bortezomib in both mouse fibroblast and human ovarian carcinoma cell lines. This in turn correlated with increased cellular uptake and the cytotoxicity of cisplatin in a synergistic manner^[73]. Cells lacking CTR1 had no change in cisplatin uptake with bortezomib suggesting that bortezomib may act primarily through blocking CTR1 degradation. NCT01074411 is an ongoing phase 1 trial of intraperitoneal bortezomib and carboplatin that tests this hypothesis in patients with recurrent ovarian cancer.

Ag and zinc have been noted to induce CTR1 expression. In CTR1-transfected or nontransfected HEK293 cells Ag, Zn inhibited CTR1-mediated copper uptake^[52]. Also in IGROV1 and SKOV-3 cells treated with different concentrations of Zn, and Ag, there was a concentration-dependent increase in expression of CTR1 and Sp1^[79]. In a double-blind, placebo-controlled study of 34 patients with stage III/IV nasopharyngeal carcinoma receiving cisplatin-based chemotherapy, zinc supplement (75 mg/d) was associated with longer overall survival, local-free survival and disease-free survival compared with placebo ($P = 0.044$, $P = 0.007$, and $P = 0.033$, respectively)^[77]. More recently in ovarian cancer cells and xenograft mice, (-)-epigallocatechin-3-gallate (EGCG), a major polyphenol from green tea was noted to increase CTR1 mRNA and protein expression. These findings translated into EGCG enhancing the sensitivity of ovarian cancer SKOV3 and OVCAR3 cells to Pt through increased Pt accumulation and DNA-Pt adducts^[80]. Copper chelators are a class of compounds that preferentially bind either

cuprous or cupric forms of copper and potentially modulate copper redox-activity without removing copper from the system. They are characterized as either membrane-permeable or - impermeable and serve as an organ-selective copper delivery or deprivation system to manipulate the biological function of copper. Tetrathiomolybdate (TTM), a specific and effective copper chelator was initially developed as a therapeutic agent to treat Wilson's disease, which is characterized by excessive copper accumulation in liver and brain^[81]. TTM demonstrates antiangiogenic, antifibrogenic, and anti-inflammatory actions in preclinical studies. While TTM has a good safety index, most of its toxicity in animals is due to copper deficiency that is easily reversible with acute copper supplementation^[82]. Daily treatment with TTM has been shown to safely reduce bioavailable copper in 2-4 wk in humans and mice, likely through formation of a high-affinity tripartite complex with copper and proteins^[83]. Liang *et al.*^[76] demonstrated that in cisplatin-resistant ovarian cancer cell lines derived from patients, resistance associated with reduced expression of the CTR1 could be overcome by copper-lowering agents (TTM, D-penicillamine and trientine) which enhanced CTR1 expression. In a murine model of human cervical cancer, combined therapy with TTM and cisplatin enhanced therapeutic efficacy by increasing tumor-specific uptake of Pt^[67]. Similarly, in oxaliplatin-resistant cell lines derived from human cervical carcinoma, D-penicillamine in combination with cisplatin and oxaliplatin overcomes resistance through increased CTR1 expression by up regulation of Sp1^[84]. These studies provided the mechanistic rationale for using copper chelation to overcome Pt resistance in cancer patients. Trientine was combined with carboplatin in ovarian cancer patients^[85]. NCT01837329 is an ongoing phase 1 study combining TTM with Pt-doublet in advanced NSCLC patients. Further studies are needed to validate these findings in order to use the above agents as adjuncts to conventional Pt based therapy and improve outcomes.

CONCLUSION

Pt-based chemotherapy is the backbone of both curative and palliative treatment for numerous malignancies. Copper transporters, in particular CTR1, play a significant role in intracellular Pt accumulation and have the potential to be used as predictive biomarkers of Pt sensitivity. In addition, modulation of copper transporter expression may be a novel therapeutic strategy to enhance the efficacy of Pt chemotherapy by increasing intratumoral Pt concentration. Specifically, copper chelators and agents that prevent degradation of CTR1, such as bortezomib, are currently being studied in combination with Pt in a variety of solid tumors known to develop Pt resistance.

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