

REVIEW ARTICLE

Pharmacogenetic factors influencing cisplatin-based cancer treatment efficiency

Benny Beldrus Septer^{1,2}, Dogfounianalo Somda^{3,4}, Arsène Ngabo^{4,5}, Amel Elbasyouni^{4*}, Boitumelo Tubutubu⁴, Shadrack Barmasai⁶, Titilayo Kèmi Sophia Nelly Adedjobi^{7,8}, Joel Bidounga⁹, Abel Kolawole Oyebamiji¹⁰, Philip Joel Mwesigwa¹¹, and Samuel Mulondo¹²

¹Center for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya

²Brown School, Washington University in St Louis, Saint Louis, Missouri, United States of America

³Laboratory of Molecular Biology and Genetics, Training and Research Unit in Life and Earth Sciences, University Joseph Ki-Zerbo, Ouagadougou, Burkina Faso

⁴Pan African University Institute for Basic Sciences, Technology & Innovation (PAUSTI), Nairobi, Kenya

⁵Department of Biology, Faculty of Science and Technology, Université Officielle de Bukavu, Bukavu, South Kivu, Democratic Republic of the Congo

⁶Center for Virus Research, Kenya Medical Research Institute, Nairobi, Kenya

⁷Laboratory of Biology and Molecular Typing in Microbiology, Department of Biochemistry and Cellular Biology, Faculty of Sciences and Technology, University of Abomey-Calavi, Abomey-Calavi, Atlantique, Bénin

⁸Laboratory of Research in Biology Medical and Pharmaceutical, National University of Science, Technology, Engineering and Mathematics, Abomey, Zou, Bénin

⁹Department of Biology, Faculty of Science and Technology, Marien Ngouabi University, Brazzaville, Republic of the Congo

¹⁰Department of Industrial Chemistry, Faculty of Science, University of Ilesa, Ilesa, Osun State, Nigeria

¹¹Department of Biochemistry and Molecular Genetics, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

¹²Vaccine and Pharmaceutical Centre, National Livestock Resources Research Institute, National Agricultural Research Organisation, Kampala, Uganda

***Corresponding author:**
Amel Elbasyouni
(elbasyouni.amel@hotmail.com)

Citation: Septer BB, Somda D, Ngabo A, *et al.* Pharmacogenetic factors influencing cisplatin-based cancer treatment efficiency. *Gene Protein Dis.*
doi: 10.36922/GPD025490080

Received: December 4, 2025

Revised: May 18, 2026

Accepted: May 18, 2026

Published online: July 21, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract

Cisplatin remains a cornerstone of chemotherapy for numerous solid tumors; however, its clinical utility is frequently compromised by substantial inter-individual variability in treatment response and the emergence of severe dose-limiting toxicities. This review systematically examines the primary pharmacogenetic and epigenetic factors that underpin these differential clinical outcomes. We evaluated key polymorphisms in genes governing drug metabolism and transport; specifically, those of glutathione S-transferases (GSTs), copper transporters (CTR1, ATP7A/B), and solute carrier (SLC) transporters, which collectively dictate intracellular drug accumulation and inactivation. Furthermore, we analyzed the critical role of the DNA repair machinery, with a particular emphasis on the nucleotide excision repair pathway in mediating cisplatin resistance. Beyond traditional genetic variations, this review explored the emerging effect of epigenetic modifications and noncoding RNAs, including microRNAs, long noncoding RNAs, and circular RNAs, in post-transcriptionally modulating cellular pathways associated with chemoresistance. The

synthesis of these findings underscores the need to integrate robust pharmacogenetic profiling into clinical practice to transition oncology from a standardized protocol to a personalized therapeutic approach. Ultimately, identifying and validating these molecular markers can maximize therapeutic efficacy while mitigating adverse toxicities in individual patients.

Keywords: Cisplatin; Pharmacogenetics; Genetic polymorphisms; DNA repair; Noncoding RNAs; Epigenetic modifications

1. Introduction

Cisplatin is a cornerstone of modern chemotherapy and remains a potent platinum-based compound used in the treatment of numerous solid tumors, including those of the ovaries, bladder, head and neck, and lungs.^{1,2} Its primary mechanism of action involves the formation of platinum–DNA adducts, which obstruct DNA replication and transcription, ultimately triggering apoptosis in rapidly dividing cancer cells.^{3,4} When incorporated into multi-agent regimens, cisplatin has demonstrated remarkable success; for example, it is credited with achieving cure rates exceeding 90% in testicular cancer. Despite its broad efficacy and enduring clinical utility, the application of cisplatin is frequently constrained by two significant and intertwined challenges: profound inter-individual variability in treatment response and the onset of severe, dose-limiting toxicities. Patients presenting with histologically indistinguishable cancers often exhibit drastically different outcomes when administered standard cisplatin regimens. While some patients achieve complete remission, others experience minimal therapeutic benefit or suffer from aggressive tumor recurrence driven by intrinsic or acquired resistance mechanisms.⁵

The therapeutic window for cisplatin is exceptionally narrow. The drug is notorious for inducing severe adverse effects, notably nephrotoxicity, neurotoxicity, and ototoxicity, which often necessitate dose reduction or premature cessation of therapy. The clinical and economic burden of these toxicities is substantial, significantly impacting patients' quality of life and increasing overall healthcare expenditures.

Pharmacogenetics investigates how inherited and somatic genetic variations dictate drug efficacy and toxicity profiles.⁶ By identifying specific molecular markers, pharmacogenetics aims to move oncology beyond a traditional, empirical “one-size-fits-all” paradigm toward precision medicine. In this personalized framework, treatment strategies and dosing schedules are tailored

to a patient's unique genomic architecture to maximize antineoplastic efficacy while systematically minimizing the risk of adverse events.^{7–9}

Despite the robust scientific rationale supporting pharmacogenetic testing, its clinical translation in oncology remains challenging. Current barriers to widespread implementation include the lack of standardized testing infrastructure, delays in obtaining actionable genomic results, evolving evidence bases, and the complexities providers face in interpreting polygenic data.¹⁰ Furthermore, recent advancements have highlighted that traditional DNA polymorphisms account for only a fraction of the observed variability. Emerging research emphasizes the critical role of epigenetic mechanisms and noncoding RNAs (ncRNAs) in modulating drug transporters and DNA repair capacity, adding layers of complexity to cisplatin resistance.^{11,12} Concurrently, innovations in liquid biopsy for circulating biomarkers and the application of machine learning models to predict toxicity are beginning to bridge the gap between genomic discovery and clinical utility.^{13,14}

This review critically examines the pharmacogenetic and epigenetic determinants that govern cisplatin response and resistance. We evaluated key genetic polymorphisms in drug metabolism and transport pathways, alongside variations in the DNA repair machinery. Furthermore, we explored the emerging influence of ncRNAs and epigenetic modifications to identify robust, predictive biomarkers. This review aims to provide a framework for overcoming current translational barriers and advancing personalized cisplatin therapy.

2. Genetic polymorphisms in drug metabolism and transport

The journey of cisplatin from systemic administration to nuclear DNA in a cancer cell is a highly regulated, complex pharmacokinetic process, mediated by host proteins that govern its transport, intracellular metabolism, and

detoxification. Genetic variations, particularly single-nucleotide polymorphisms (SNPs), within the genes encoding these critical proteins can significantly alter their structural conformation and functional kinetics. Consequently, these variations exert a profound influence on both the antineoplastic efficacy and the severity of dose-limiting toxicities associated with the drug.^{15,16} In this section, we critically examine the pharmacogenetics of three pivotal protein families: glutathione S-transferases (GSTs), copper transporters, and the solute carrier (SLC) family of transporters.

2.1. Glutathione S-transferases

Glutathione S-transferases constitute a ubiquitous superfamily of Phase II metabolic enzymes primarily responsible for cellular detoxification. They facilitate this process by catalyzing the conjugation of reduced glutathione to various electrophilic compounds, including cisplatin, thereby neutralizing their cytotoxic potential and facilitating their cellular export.¹⁷ Because this conjugation represents a primary mechanism of cisplatin inactivation, functional polymorphisms in GST genes, particularly *GSTP1*, *GSTM1*, and *GSTT1*, have been extensively evaluated as predictive biomarkers for treatment outcomes.

A prominent example is the *GSTP1* Ile105Val polymorphism (rs1695), which induces an amino acid substitution within the enzyme's active site. This structural alteration significantly modifies the enzyme's substrate affinity and catalytic efficiency.^{18–20} Mechanistically, the Val-105 variant demonstrates a markedly reduced capacity for conjugating certain electrophilic substrates compared to the wild-type Ile-105 allele. Clinical correlation of this kinetic deficiency was demonstrated when the *GSTP1* Ile105Val polymorphism was found to be significantly associated with progression-free survival in Russian cohorts with ovarian cancer, suggesting that reduced detoxification capacity enhances prolonged intracellular drug exposure.²¹ Recent meta-analyses corroborate these findings, confirming that the *GSTP1* rs1695 polymorphism is significantly correlated not only with platinum-induced efficacy but also with the severity of cumulative toxicities, such as neurotoxicity in patients receiving platinum-based regimens.^{22,23}

Furthermore, the basal expression level of the glutathione S-transferase P (GSTP) protein has been identified as a fundamental determinant in the pathogenesis of cisplatin-induced nephrotoxicity. Townsend *et al.*²⁴ elucidated a critical gender-specific disparity, demonstrating that male mice, which exhibit approximately 10-fold higher hepatic GSTP expression than their female counterparts, experience significantly more severe renal damage

following cisplatin administration. Crucially, this sex-dependent difference was completely abrogated in *GstP1/P2*-knockout mice. This paradoxical finding suggests that hepatic GSTP actively contributes to the formation of a nephrotoxic platinum–glutathione conjugate, which is subsequently processed into a reactive thiol within the kidney.

Additionally, gene deletions or “null” polymorphisms in *GSTM1* and *GSTT1*, which result in the complete absence of corresponding enzyme activity, have been strongly implicated in the modulation of cisplatin response. The homozygous deletion of these genes leads to a failure in specific detoxification pathways, thereby increasing oxidative stress and cellular damage.²⁵ While this absence can theoretically elevate the intracellular concentration of the active drug, potentially enhancing therapeutic efficacy against the tumor, it simultaneously escalates the risk of severe systemic toxicity. Recent pharmacogenomic evaluations have highlighted the complexity of these pathways, demonstrating that combined genetic polymorphisms, such as those involving *GSTT1* and *NRF2*, synergistically increase patient susceptibility to specific adverse events, such as cisplatin-induced ototoxicity, underscoring the need to evaluate multi-gene interactions rather than isolated SNPs in clinical practice.

2.2. Copper transporters

The cellular influx and efflux of cisplatin are actively regulated by specialized membrane transporters that evolved primarily to maintain copper homeostasis. The remarkable structural and coordination similarities between hydrated cisplatin complexes and copper ions permit the drug to effectively hijack the cellular copper transport machinery.^{26–28}

The high-affinity copper uptake transporter 1 (CTR1, encoded by the *SLC31A1* gene) serves as the primary gateway for cisplatin entry into both healthy and malignant cells.²⁹ Consequently, its expression level at the plasma membrane is a critical rate-limiting determinant of cisplatin accumulation and subsequent cytotoxicity. In a highly detailed single-cell analysis of ovarian carcinoma, Schoeberl *et al.*²⁸ revealed that cisplatin-resistant cell lines (A2780cis) exhibited markedly decreased intracellular concentrations of both cisplatin and copper. This deficit correlated directly with a significant, targeted reduction in total CTR1 protein levels compared to their cisplatin-sensitive counterparts. Recent advancements in the emerging field of cuproptosis (copper-dependent cell death) further validate this mechanism, demonstrating that prolonged cisplatin exposure triggers a protective adaptive response characterized by the significant downregulation

of *SLC31A1* messenger RNA (mRNA) and CTR1 protein, thereby restricting further drug uptake and cementing a resistant phenotype.^{30,31}

Conversely, the P-type ATPases, ATP7A and ATP7B, which normally function as copper-efflux transporters responsible for sequestering excess copper into the trans-Golgi network for cellular export, also recognize cisplatin as a substrate.³² Overexpression of these transporters allows cancer cells to actively pump the chemotherapeutic agent out of the intracellular space, severely blunting its therapeutic effect. Emerging data suggest that ATP7B expression may correlate more closely with the acquisition of acquired cisplatin resistance than either CTR1 or ATP7A. The dynamic interplay between CTR1-mediated influx and ATP7A/B-mediated efflux creates a delicate stoichiometric balance that ultimately dictates the therapeutic efficacy of cisplatin.³³

2.3. Solute carriers transporters

The SLC superfamily encompasses a massive and diverse group of membrane transport proteins responsible for the translocation of nutrients, ions, and pharmacological agents across cellular barriers.³⁴ Several distinct members of the SLC family have been definitively implicated in the systemic disposition and tissue-specific uptake of platinum-based drugs.³⁵

Most notably, the organic cation transporters (OCTs), which belong to the *SLC22A* family, have been shown to robustly facilitate cisplatin uptake. This transport is particularly pronounced in the basolateral membrane of renal proximal tubule cells, where OCT2 (encoded by *SLC22A2*) is highly expressed.^{36,37} This localized transport activity represents a profound double-edged sword: while OCT-mediated uptake into tumor cells may contribute to the drug's intended antineoplastic effect, its massive accumulation in the kidneys is the primary mechanistic driver behind the high incidence of cisplatin-induced nephrotoxicity.³⁸

Because of this direct causal relationship, polymorphisms in SLC transporter genes can drastically influence the rate of cisplatin uptake, leading to profound inter-individual differences in toxicity profiles.³⁹ For example, specific functional variations in *SLC22A2* have been definitively linked to differences in the severity of kidney damage. A landmark systematic review confirmed that the *SLC22A2* polymorphism rs316019 (c.808G > T; Ser270Ala) significantly alters transporter kinetics.⁴⁰ Interestingly, studies have demonstrated that this specific variant actually confers a protective effect, attenuating

both cisplatin-induced nephrotoxicity and ototoxicity by reducing the drug's accumulation in vulnerable normal tissues.^{41,42}

Despite the robust predictive value of these SLC and GST genotypes, their translation into routine clinical practice remains limited. The integration of these biomarkers into standard oncology workflows requires overcoming substantial barriers, including the need for rapid turnaround times for genetic testing prior to chemotherapy initiation and the necessity of developing validated, genotype-guided dosing algorithms. However, identifying patients with high-risk pharmacogenetic profiles holds immense clinical promise, as it would allow oncologists to proactively implement renoprotective strategies, adjust dosing schedules, or select alternative, non-nephrotoxic chemotherapeutic agents to mitigate the risk of severe, life-altering toxicity. Table 1 summarizes key genetic polymorphisms in drug metabolism and transport genes that modulate cisplatin treatment outcomes.

3. Genetic variations in DNA repair pathways

The cytotoxic efficacy of cisplatin is fundamentally dependent on its ability to inflict overwhelming DNA damage, specifically intra- and inter-strand crosslinks, which the cancer cell cannot resolve. Consequently, the intrinsic DNA repair capacity of a tumor dictates its sensitivity to platinum-based agents.⁴³ While multiple repair mechanisms exist, the nucleotide excision repair (NER) pathway is the principal mechanism responsible for recognizing and excising bulky cisplatin–DNA adducts. Genetic polymorphisms in key NER pathway genes (*ERCC1*, *ERCC2/XPD*, *XRCC1*) can significantly alter a patient's DNA repair capacity, thereby modulating both treatment response and the severity of adverse toxicities.^{44–48}

Excision repair cross-complementing group 1 (*ERCC1*) is a rate-limiting enzyme in the NER pathway, responsible for the 5' incision of the damaged DNA strand.⁴⁹ Its expression level serves as a robust predictor of cisplatin efficacy. High *ERCC1* gene expression implies a highly efficient DNA repair capacity, allowing cancer cells to rapidly remove cisplatin adducts and survive, leading to treatment resistance.^{50–56} Conversely, low *ERCC1* expression signifies a diminished repair capacity, rendering cells highly susceptible to cisplatin-induced apoptosis. This inverse relationship was famously validated by Olausson *et al.*⁵⁷, who demonstrated that patients with *ERCC1*-negative non-small-cell lung cancer derived a significant survival

Table 1. Impact of key genetic polymorphisms in drug metabolism and transport on cisplatin treatment outcomes

Gene (polymorphism)	Function	Impact of variant on cisplatin treatment
<i>GSTP1</i> (Ile105Val; rs1695)	Detoxification via glutathione conjugation	Val-105 variant exhibits reduced catalytic inactivation of the drug, correlating with altered progression-free survival and increased risk of cumulative toxicities.
<i>GSTM1/GSTT1</i> (null deletions)	Detoxification via glutathione conjugation	Complete absence of enzyme activity increases oxidative stress, associated with elevated intracellular drug efficacy but a significantly higher risk of systemic toxicity.
<i>SLC31A1</i> (CTR1 downregulation)	Cellular influx of copper and cisplatin	Adaptive downregulation serves as a primary mechanism of acquired cisplatin resistance, severely restricting intracellular drug accumulation.
<i>ATP7A/ATP7B</i> (overexpression)	Cellular efflux of copper and cisplatin	Active extrusion of the drug from the intracellular space, blunting therapeutic impact and contributing heavily to the resistant phenotype.
<i>SLC22A2</i> (Ser270Ala; rs316019)	Renal proximal tubule uptake (OCT2)	This variant alters transporter kinetics, notably conferring a protective effect against cisplatin-induced nephrotoxicity and ototoxicity.

Abbreviation: OCT2: Organic cation transporter 2.

benefit from adjuvant cisplatin-based chemotherapy, whereas those with *ERCC1*-positive tumors did not.

Recent clinical data continue to reinforce this paradigm. A 2025 study on advanced biliary tract cancer confirmed that high *ERCC1* expression remains a poor prognostic factor for cisplatin efficacy, establishing its utility as an independent predictive biomarker.⁵⁸ Furthermore, specific polymorphisms within the *ERCC1* gene, such as the C8092A (rs3212986) and codon 118 C/T (rs11615) variants, alter mRNA stability and translational efficiency.^{59–64} For example, Bradbury *et al.*⁶⁵ found that the *ERCC1* 8092A variant allele was associated with significantly improved overall survival in cisplatin-treated patients with esophageal cancer, potentially due to impaired repair kinetics.

Similarly, *ERCC2*, also known as xeroderma pigmentosum group D (*XPB*), encodes an essential DNA helicase required for unwinding the DNA duplex around the platinum lesion during the initial stages of NER. Polymorphisms in *ERCC2* can critically affect the stability and unwinding function of this helicase, thereby altering overall DNA repair efficiency.⁶⁶ Two of the most extensively studied *ERCC2* polymorphisms are Asp312Asn (rs1799793) and Lys751Gln (rs13181). Recent quantitative functional profiling has demonstrated that the rs13181 C allele is associated with more severe, unresolved DNA damage following cisplatin exposure, mediated through the p53 pathway.

However, the clinical implications of these polymorphisms are highly context-dependent, varying significantly across cancer types, tissue origins, and specific treatment regimens. In bladder cancer, the Gln/

Gln (rs13181) and Asp/Asn (rs1799793) genotypes are associated with increased cancer risk and aggressiveness.⁶⁷ In lung cancer, the *ERCC2* rs13181 TG or TG+GG genotypes are associated with worse overall survival and increased risk of death.⁶⁸ Paradoxically, these same variant alleles can act as positive predictive markers in the context of platinum therapy. Bradbury *et al.*⁶⁵ provided compelling evidence that the variant alleles of both *ERCC2* 312Asn and 751Gln were associated with significantly improved survival in patients receiving cisplatin (adjusted hazard ratios as low as 0.22). In stark contrast, these same variant alleles were associated with significantly worse survival in patients who did not receive cisplatin. This underscores a critical pharmacogenetic concept: a genetic variant that increases general cancer susceptibility (by impairing normal DNA repair) may simultaneously render a tumor highly sensitive to DNA-damaging chemotherapy.

While *ERCC1* and *ERCC2* are core components of the NER pathway, *XRCC1* serves as a key scaffolding protein in the base excision repair (BER) pathway. Although BER is primarily responsible for repairing single-strand DNA breaks and oxidative damage, its role in cisplatin resistance is increasingly recognized.⁶⁹ Recent mechanistic studies reveal an intimate crosstalk between these repair systems; when NER is overwhelmed or defective, BER proteins (such as apurinic/apyrimidinic endonuclease 1 [APE1] and DNA polymerase β [Pol β]) can modulate cisplatin cytotoxicity by attempting to process the crosslinks, often leading to futile repair cycles that trigger apoptosis.^{70,71} Furthermore, mismatch repair proteins can paradoxically shield cisplatin adducts, inhibiting NER proteins from accessing and repairing them, thereby allowing the adducts to persist and induce cell death.⁵⁶

Polymorphisms in *XRCC1*, including Arg194Trp (rs1799782), Arg280His (rs25489), and Arg399Gln (rs25487), have been thoroughly investigated for their association with cisplatin outcomes.^{72–75} Recent studies confirmed that *XRCC1* polymorphisms significantly impact platinum-based chemotherapy outcomes, particularly influencing the severity of cisplatin-induced nephrotoxicity and neurotoxicity in non-small cell lung cancer patients.^{44,76}

Despite the profound predictive potential of DNA repair gene polymorphisms, their clinical translation faces significant hurdles. Contradictory findings across different ethnic populations, for example, specific *ERCC1* variants predicting outcomes in Asian cohorts but failing to replicate in Caucasian populations, highlight the complexity of polygenic inheritance and the limitations of single-SNP analysis. Future personalized medicine

approaches will likely require the integration of multi-gene repair panels with emerging data on the epigenetic regulation and circadian rhythms of these repair pathways to accurately predict cisplatin efficacy and toxicity.⁷⁷ Table 2 summarizes the impact of DNA repair gene variants on cisplatin treatment outcomes, while Table 3 summarizes the influence of genetic variations on major cisplatin-induced toxicities.

4. Noncoding RNAs and chemoresistance

While early pharmacogenetic research focused predominantly on protein-coding genes, the critical role of the noncoding transcriptome in modulating cisplatin efficacy has recently come to the forefront. NcRNAs, which constitute the vast majority of transcribed RNA, act as master regulators of gene expression. By modulating entire cellular pathways post-transcriptionally, specific classes

Table 2. Impact of key DNA repair gene variants on cisplatin treatment outcomes

Gene (polymorphism)	Primary repair pathway	Quantitative impact on cisplatin efficacy	Clinical significance & context	References
<i>ERCC1</i> (C8092A; rs3212986)	Nucleotide excision repair (NER)	The “A” variant alters mRNA stability, reducing DNA repair capacity. Associated with significantly improved overall survival in cisplatin-treated patients.	Serves as a strong positive predictive biomarker for platinum response. Patients with the homozygous variant demonstrate superior outcomes, particularly in esophageal and lung cancers.	58,65
<i>ERCC1</i> (Codon 118 C/T; rs11615)	NER	The “T” allele is associated with reduced <i>ERCC1</i> expression. Meta-analyses show improved objective response rates in platinum-treated patients with the C/T or T/T genotypes.	Demonstrates strong population-specific effects, with predictive value validated more consistently in Asian cohorts compared to Caucasian populations.	44,78
<i>ERCC2/XPD</i> (Asp312Asn; rs1799793)	NER	The “Asn” variant impairs helicase unwinding function. In cisplatin-treated cohorts, the variant allele correlates with a profound survival advantage (adjusted hazard ratio as low as 0.22).	Paradoxical effect: While the variant increases general cancer susceptibility by impairing normal DNA repair, it simultaneously renders the established tumor highly sensitive to cisplatin.	65,67
<i>ERCC2/XPD</i> (Lys751Gln; rs13181)	NER	The “Gln” variant alters the interaction with the p53 pathway. Homozygous variants show significantly higher rates of unresolved platinum-DNA adducts.	Context-dependent clinical utility. It predicts superior response to cisplatin induction therapy but is associated with worse overall survival if platinum agents are not used.	66,68
<i>XRCC1</i> (Arg399Gln; rs25487)	Base excision repair (BER)	The “Gln” variant alters the scaffolding function, disrupting critical crosstalk between BER and NER pathways during crosslink resolution.	Influences the occurrence of “futile repair cycles” that trigger apoptosis. While primarily studied for toxicity, it also modulates overall tumor response to platinum agents.	71,76

Abbreviation: mRNA: Messenger RNA.

Table 3. Influence of genetic variations on major cisplatin-induced systemic toxicities

Toxicity profile	Key implicated genes (polymorphisms)	Pharmacogenetic mechanism	Quantitative risk & clinical impact	References
Nephrotoxicity (acute kidney injury)	<i>SLC22A2/OCT2</i> (Ser270Ala; rs316019)	The “Ala” variant alters the kinetics of the organic cation transporter 2 (OCT2), significantly reducing the active basolateral uptake of cisplatin into renal proximal tubule cells.	Protective effect: Carriers of the variant allele exhibit a substantially lower incidence of severe kidney damage, highlighting OCT2 as a primary mediator of renal accumulation.	38,40
Nephrotoxicity (acute kidney disease)	<i>EPHX1</i> (rs1051740) & <i>TRPA1</i>	Epoxide hydrolase 1 and transient receptor potential ankyrin 1 variants alter local xenobiotic metabolism and inflammatory ion channel responses in the kidney.	Increased risk: Recent data indicate an odds ratio (OR) of 2.8 for developing acute kidney disease in patients carrying specific <i>EPHX1</i> risk alleles.	38,79
Neurotoxicity (peripheral neuropathy)	<i>XRCC1</i> (Arg399Gln; rs25487) & <i>RPRD1B</i>	Reduced systemic DNA repair capacity leads to the rapid accumulation of platinum–DNA adducts in dorsal root ganglion neurons, which lack robust repair mechanisms.	Increased risk: Variants correlate strongly with the early onset and severe progression of cumulative, irreversible peripheral sensory neuropathy.	76,80
Neurotoxicity (severe pain)	<i>TRPV1</i> (rs879207)	Polymorphisms in the transient receptor potential vanilloid 1 channel alter neuronal sensitivity and pain transmission following platinum exposure.	High quantitative risk: Patients with the GG genotype face an almost five-fold higher risk (OR ~5.0) of developing severe, dose-limiting neuropathy.	81
Ototoxicity (irreversible hearing loss)	<i>TPMT</i> & <i>COMT</i> (Met allele)	Variants in thiopurine S-methyltransferase and catechol-O-methyltransferase alter local drug metabolism and oxidative stress responses within the cochlea.	Controversial/FDA-noted: While the FDA label notes <i>TPMT</i> variants as a potential risk factor for pediatric hearing loss, large independent cohorts show conflicting associations. The <i>COMT</i> Met allele appears protective.	82,83

Abbreviation: FDA: Food and Drug Administration.

of ncRNAs, namely long noncoding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs), orchestrate the complex phenotype of cisplatin resistance.⁸⁴

4.1. Long noncoding RNAs

Long noncoding RNAs are transcripts exceeding 200 nucleotides that lack significant protein-coding capacity. They modulate cisplatin resistance through diverse mechanisms, including chromatin remodeling, transcriptional regulation, and acting as competing endogenous RNAs (ceRNAs) or “molecular sponges” for miRNAs.

The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) represents a quintessential example of a resistance-promoting transcript. Recent transcriptomic analyses reveal that *MALAT1* is significantly upregulated in cisplatin-resistant ovarian and lung cancer tissues, with expression levels often correlating with poor progression-free survival.⁸⁵ Mechanistically, *MALAT1* acts as a ceRNA, sequestering tumor-suppressive miRNAs to alleviate their

inhibitory effects on oncogenic targets, thereby promoting invasion, metastasis, and evasion of apoptosis. Similarly, the urothelial carcinoma-associated 1 (*UCA1*) lncRNA drives resistance by sponging miR-129, which directly regulates the expression of *ABCB1*, which encodes a multidrug efflux transporter, thereby reducing intracellular cisplatin accumulation.⁸⁶ Conversely, some lncRNAs act as tumor suppressors; for example, the downregulation of growth arrest-specific 5 (*GAS5*) in resistant cells removes a critical brake on the E2F transcription factor 4 (E2F4)–Poly(ADP-ribose) polymerase 1 (PARP1)–mitogen-activated protein kinase (MAPK) pathway, facilitating uncontrolled proliferation in the presence of platinum-induced DNA damage.⁸⁷ Table 4 summarizes key lncRNAs implicated in cisplatin resistance.

4.2. MicroRNAs

MicroRNAs are short (19 to 25 nucleotides), highly conserved ncRNAs that bind to the 3′-untranslated regions (UTRs) of target mRNAs, inducing transcript degradation

Table 4. Long noncoding RNAs (lncRNAs) mediating cisplatin resistance

lncRNA	Expression pattern	Quantitative change ^a	Target/mechanism	Regulated gene(s)	Clinical significance & biological function	References
UCA1	Upregulated	Fold change > 2.0	Sponges miR-129	<i>ABCB1 (MDR1)</i>	Drug efflux mediator: Drives resistance by actively reducing intracellular cisplatin accumulation.	88
WDFY3-AS2	Upregulated	Significant	Sponges miR-139-5p	<i>SDC4</i>	Metastasis promoter: Facilitates migration and invasion in resistant phenotypes.	89
GAS5	Downregulated	Significant	Regulates signaling pathways	<i>E2F4-PARP1-MAPK</i>	Tumor suppressor loss: Downregulation removes the brake on cell cycle arrest, preventing cisplatin-induced apoptosis.	87
HOTTIP	Upregulated	Significant	Binds to c-Jun	<i>IL6 → PDL1</i>	Immune evasion: Links chemoresistance with immune escape mechanisms via <i>PDL1</i> upregulation.	90
NRCP	Upregulated	Significant	Regulates signaling pathways	<i>STAT1</i>	Metabolic reprogramming: Drives glycolysis-mediated chemoresistance and metastasis.	91

Note:^a Quantitative changes indicate differential expression between cisplatin-resistant and sensitive phenotypes.

and translational repression. A single miRNA can target hundreds of mRNAs, allowing them to rapidly rewire cellular networks in response to chemotherapeutic stress. The miR-214 transcript is one of the most thoroughly validated drivers of cisplatin resistance. In a landmark study, Yang *et al.*⁹² demonstrated that miR-214 is markedly upregulated in chemoresistant ovarian cancer and directly targets the 3'-UTR of the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene. The consequent downregulation of *PTEN* hyperactivates the phosphoinositide 3-kinase (PI3K)/Akt survival pathway, rendering cells impervious to cisplatin-induced apoptosis. In contrast, specific miRNAs

act as potent chemosensitizers.

Additionally, the downregulation of miR-9 and miR-509-3p is frequently observed in resistant phenotypes; when artificially restored, these miRNAs target critical DNA repair components such as breast cancer 1 (*BRCA1*) and *RAD51*, impairing homologous recombination and reinstating cisplatin sensitivity.^{93,94} The therapeutic potential of manipulating miRNA networks is substantial, though clinical translation remains hindered by delivery challenges. Table 5 details the functional roles of specific miRNAs in the cisplatin response.

Table 5. MicroRNAs (miRNAs) regulating cisplatin sensitivity and resistance

miRNA	Expression pattern	Target gene(s)	Mechanism of action	Clinical significance & role in cisplatin response	References
miR-214	Upregulated	<i>PTEN</i>	Targets 3'-UTR of <i>PTEN</i> , activating the PI3K/Akt survival pathway	Major resistance driver: Promotes cell survival. Exosomal anti-miR-214 can successfully reverse resistance in preclinical models.	88,92
miR-205	Upregulated	<i>PTEN</i>	Suppresses <i>PTEN</i> to promote invasion and migration	Liquid biopsy biomarker: Detectable in serum exosomes of resistant patients; promotes resistance.	95

(Cont'd...)

Table 5. (Continued)

miRNA	Expression pattern	Target gene(s)	Mechanism of action	Clinical significance & role in cisplatin response	References
miR-495	Upregulated	<i>ABCB1</i>	Regulates the drug efflux transporter <i>ABCB1</i> (<i>MDR1</i>)	Efflux mediator: Promotes resistance by actively pumping cisplatin out of the cell.	96
let-7e	Downregulated	<i>PARP1</i>	Targets <i>PARP1</i> to inhibit DNA damage repair	Chemosensitizer: Loss allows robust DNA repair. Restoration improves chemosensitivity in ovarian cancer cells.	97
miR-9	Downregulated	<i>BRCA1</i>	Targets <i>BRCA1</i> , a key component of the error-free homologous recombination (HR) repair pathway	Chemosensitizer: Loss enables efficient repair of platinum adducts. Restoration impairs repair and improves sensitivity.	93
miR-509-3p	Downregulated	<i>HMGA2</i> , <i>RAD51</i>	Regulates HR repair networks	Synthetic lethality target: Enhances the lethality of PARP inhibitors in BRCA-proficient high-grade serous ovarian cancer.	94

Abbreviations: BRCA: Breast cancer susceptibility protein; PARP: Poly(ADP-ribose) polymerase 1; PI3K: Phosphoinositide 3-kinase.

4.3. Circular RNAs and exosomes delivery

Circular RNAs are a recently characterized class of covalently closed, single-stranded RNA molecules that exhibit remarkable stability against exonuclease degradation. This structural resilience makes them highly effective miRNA sponges and exceptionally promising non-invasive biomarkers. Exosomes (30 to 150 nm vesicles) serve as protective transport vehicles, allowing resistant tumor cells to export resistance-promoting circRNAs to neighboring sensitive cells, thereby propagating the resistant phenotype throughout the tumor microenvironment.^{98,99} For example, circ-*CSPP1* is highly upregulated in resistant tissues, where it sponges miR-1236-3p to upregulate Zinc finger E-box-binding homeobox 1 (*ZEB1*), driving epithelial-mesenchymal transition and metastasis.¹⁰⁰ Conversely, the

tumor-suppressive circ-*ITCH* is frequently downregulated in resistant cells, removing its inhibitory sponge effect on miR-106a and allowing uninhibited glycolysis and invasion.¹⁰¹

The discovery of exosome ncRNAs has opened new frontiers in clinical pharmacogenetics. Because these stable vesicles can be isolated from patient serum via liquid biopsy, they offer a real-time, non-invasive window into the tumor's evolving resistance profile. Furthermore, exosomes are currently being engineered as therapeutic delivery vehicles; for example, the delivery of exosome anti-miR-214 has successfully reversed cisplatin resistance in preclinical models of gastric cancer, demonstrating the viability of targeting the noncoding transcriptome to salvage platinum efficacy.⁸⁶ Table 6 outlines the emerging role of circRNAs in cisplatin resistance.

Table 6. Circular RNAs (circRNAs) and exosomal delivery in cisplatin resistance

circRNA	Expression pattern	Localization	Target/mechanism	Regulated gene(s)	Clinical significance & biological function	References
circ- <i>ITCH</i>	Downregulated	Intracellular	Sponges miR-106a	<i>CDH1</i>	Tumor suppressor loss: Downregulation removes inhibition on glycolysis and apoptosis evasion.	101,102
circ- <i>CSPP1</i>	Upregulated	Intracellular	Sponges miR-1236-3p	<i>ZEB1</i> (<i>MMP2/VEGFA</i>)	Metastasis driver: Promotes invasion, migration, and metastasis in resistant phenotypes.	100
circ_103801	Upregulated	Exosomal	Intercellular transfer	<i>Multiple</i>	Resistance propagator: Packaged in exosomes and transferred to sensitive cells, conferring acquired cisplatin resistance.	98,99,103,104

(Cont'd...)

Table 6. (Continued)

circRNA	Expression pattern	Localization	Target/mechanism	Regulated gene(s)	Clinical significance & biological function	References
circ_0008928	Upregulated	Serum exosomes	miR-488/HK2 axis	HK2	Non-invasive biomarker: Regulates glycolysis and cisplatin sensitivity; detectable in patients' serum.	105

Abbreviation: HK2: Hexokinase 2.

5. Epigenetic modifications

Beyond inherited genetic polymorphisms, the dynamic and reversible landscape of epigenetics plays a profound role in orchestrating the cellular response to cisplatin. Epigenetic modifications alter chromatin architecture and gene accessibility without changing the underlying DNA sequence. These mechanisms are increasingly recognized as primary drivers of acquired cisplatin resistance, allowing cancer cells to rapidly adapt to chemotherapeutic stress through extensive transcriptional reprogramming.¹⁰⁶

5.1. DNA methylation

DNA methylation, catalyzed by DNA methyltransferases (DNMTs), typically occurs at CpG islands within gene promoters and results in transcriptional silencing. In the context of cisplatin therapy, the hypermethylation of specific tumor suppressor and DNA repair genes is a critical determinant of treatment efficacy. The most clinically significant example is the methylation status of the *BRCA1* promoter. Hypermethylation of *BRCA1* creates a functional “BRCAness” phenotype, characterized by a severe deficiency in homologous recombination repair. Paradoxically, this epigenetic silencing renders cancer cells highly sensitive to platinum-induced DNA crosslinks, as they lack the high-fidelity repair mechanisms necessary for survival.¹⁰⁷

Conversely, the acquired hypermethylation of other specific genes, such as the mismatch repair gene *hMLH1* or the apoptosis regulator *SLFN11*, is strongly associated with the development of cisplatin resistance. Recent advances have highlighted the therapeutic potential of manipulating these methylation patterns; for example, targeted epigenetic editing of the *BRCA1* promoter using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based technologies significantly increased the sensitivity of ovarian cancer cells to both cisplatin and PARP inhibitors.¹⁰⁸ Furthermore, specific promoter-methylation signatures, such as *CRTAC1* hypermethylation, are emerging as highly predictive liquid biopsy biomarkers for evaluating real-time patient response to platinum therapies.¹¹

5.2. Histone modifications and chromatin accessibility

Histone proteins (H2A, H2B, H3, H4) undergo various post-translational modifications, including acetylation, methylation, and phosphorylation, that dictate how tightly DNA is wound around the nucleosome core. The physical compaction of chromatin directly influences the ability of cisplatin to access DNA and form cytotoxic crosslinks.

Histone acetylation, regulated by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs), is a key determinant of acquired cisplatin resistance.¹⁰⁹ High levels of HDAC expression led to chromatin condensation, physically shielding the DNA from cisplatin attack. Notably, nuclear factor-kappa B (NFκB) signaling drives chemoresistance specifically by inducing robust histone deacetylation, thereby restricting drug access to the genome.¹¹⁰ Consequently, the use of HDAC inhibitors (HDACi) has emerged as a powerful synergistic strategy; by forcing chromatin into an open, relaxed state, HDACi significantly enhances the formation of cisplatin–DNA adducts and restores sensitivity in resistant cell lines.

Beyond acetylation, specific histone methylation patterns, such as the protein arginine methyltransferase 5 (PRMT5)-mediated methylation of *METTL3*, actively facilitate DNA repair mechanisms to promote platinum resistance in high-grade serous ovarian cancer.

5.3. Chromatin remodeling and polycomb group proteins

Chromatin remodeling complexes, such as the switch/sucrose non-fermentable (SWI/SNF) complex, utilize ATP hydrolysis to slide or evict nucleosomes, dynamically regulating the DNA damage response. In cisplatin-resistant cells, altered chromatin remodeling actively influences how DNA adducts are recognized and processed. Chromatin remodeling genes drive resistance by hyperactivating autophagy pathways, allowing cancer cells to survive platinum-induced metabolic stress.¹¹¹

Additionally, polycomb group (PcG) proteins, which function as epigenetic repressors by catalyzing inhibitory histone modifications, frequently silence pro-apoptotic genes in resistant phenotypes. The interplay between these epigenetic regulators creates a formidable barrier to successful chemotherapy.

However, unlike fixed genetic mutations, epigenetic

modifications are inherently reversible. This reversibility has catalyzed the development of “epigenetic priming” strategies, in which epigenetic drugs (DNMT or HDAC inhibitors) are administered prior to cisplatin to reprogram the tumor’s transcriptional landscape, thereby maximizing the efficacy of subsequent platinum-based treatment. [Table 7](#) summarizes the key epigenetic mechanisms influencing cisplatin sensitivity.

Table 7. Epigenetic mechanisms modulating cisplatin sensitivity and resistance

Epigenetic mechanism	Target/Mediator	Description & action	Clinical impact on cisplatin sensitivity	References
DNA promoter hypermethylation	<i>BRCA1</i>	DNMT-mediated silencing of the <i>BRCA1</i> tumor suppressor gene.	Increases sensitivity: Creates a “BRCAness” phenotype with deficient homologous recombination repair, rendering cells highly vulnerable to platinum crosslinks.	107,108
DNA promoter hypermethylation	<i>hMLH1</i> , <i>SLFN11</i> , <i>CRTAC1</i>	Epigenetic silencing of mismatch repair and pro-apoptotic genes.	Drives resistance: Allows cells to tolerate DNA damage. <i>CRTAC1</i> methylation serves as a highly predictive liquid biopsy biomarker.	11
Histone deacetylation (HDAC)	HDACs (HDAC 1, 2, 3)	Removal of acetyl groups from histones, leading to chromatin condensation.	Drives resistance: Physically shields genomic DNA from cisplatin attack. Overcome synergistically by HDAC inhibitors.	109,110
Histone methylation	PRMT5 / METTL3 axis	Addition of methyl groups to histone tails (e.g., H3K27me3) alters gene accessibility.	Drives resistance: Facilitates DNA repair mechanisms and silences tumor suppressor genes.	106
Chromatin remodeling	SWI/SNF Complexes	ATP-dependent sliding or eviction of nucleosomes alters DNA damage recognition.	Modulates response: Can hyperactivate autophagy pathways, allowing cancer cells to survive cisplatin-induced metabolic stress.	111
Polycomb group (PcG) proteins	Epigenetic Repressors	Catalyzing inhibitory histone modifications to silence specific genomic regions.	Drives resistance: Specifically silences genes that promote apoptosis or facilitate DNA damage recognition.	106

Abbreviations: DNMT: DNA methyltransferase; METTL3: Methyltransferase-like 3; PRMT5: Protein arginine methyltransferase 5; SWI/SNF: Switch/sucrose non-fermentable.

6. Conclusion

Personalized oncology requires a fundamental shift from a uniform and empirical treatment strategy to a precision approach tailored to the unique genetic, transcriptomic, and epigenetic profile of each patient. This review has illuminated the different pharmacogenetic factors that dictate an individual’s response to cisplatin. The accumulated evidence demonstrates unequivocally that genetic variations in drug metabolism (GSTs), cellular transport (*SLC22A2*, *CTR1*), and DNA repair pathways (*ERCC1*, *ERCC2*, *XRCC1*) are not minor modulators, but

critical determinants of both therapeutic efficacy and the risk of severe, dose-limiting toxicities.

Furthermore, the expanding roles of the noncoding transcriptome and dynamic epigenetic regulation have added critical new layers of complexity and therapeutic opportunity. The discovery that exosome circRNAs can propagate resistance intercellularly, and that epigenetic silencing of *BRCA1* creates a targetable “BRCAness” phenotype. Together, these multi-omics factors form a comprehensive molecular signature that dictates the ultimate success or failure of platinum-based therapy.

However, despite preclinical and retrospective clinical evidence, significant translational barriers remain in moving these pharmacogenetic findings into routine clinical practice. The translation gap is currently driven by several factors: the lack of standardized, rapid-turnaround diagnostic assays; conflicting data arising from single-gene studies that fail to account for polygenic interactions; and the historical underrepresentation of diverse ethnic populations in pharmacogenomic cohorts, which limits the global applicability of identified biomarkers.

To overcome these barriers and realize the promise of precision cisplatin therapy, future research and clinical implementation must prioritize several key directives. First, the field must transition from single-gene analysis to multi-omics predictive modelling. The integration of genomic polymorphisms, ncRNA expression profiles, and epigenetic signatures using advanced machine learning algorithms will yield composite biomarkers with vastly superior predictive accuracy compared to isolated markers, such as *ERCC1* alone. Second, future clinical validation must rely on large-scale prospective multi-ethnic cohort studies. These trials must be designed not merely to observe pharmacogenetic associations, but to actively test genotype-guided dosing and drug selection strategies against standard-of-care empirical dosing. Third, the development of non-invasive liquid biopsy technologies must be accelerated. The ability to monitor dynamic changes in exosome ncRNAs and circulating tumor DNA methylation during treatment will allow clinicians to detect the emergence of acquired resistance before clinical relapse, enabling timely therapeutic intervention. Finally, regulatory pathways for companion diagnostics must be streamlined, and clinical guidelines must be updated to incorporate actionable pharmacogenetic data. The implementation of pre-treatment genetic screening for high-risk toxicity variants (including the specific *SLC22A2* and *TPMT* polymorphisms) is a highly actionable first step that could immediately reduce the burden of severe nephrotoxicity and ototoxicity.

Ultimately, integrating these complex pharmacogenetic and epigenetic determinants into clinical decision-making will transform cisplatin therapy to maximize therapeutic benefit while minimizing the profound physical and economic costs of ineffective and toxic treatments.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization: Benny Beldrus Septer, Dogfounianalo Somda, Arsène Ngabo, Amel Elbasyouni

Writing–original draft: All authors

Writing–review & editing: Benny Beldrus Septer, Dogfounianalo Somda, Amel Elbasyouni

Acknowledgments

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Ho GY, Woodward N, Coward JIG. Cisplatin versus carboplatin: comparative review of therapeutic management in solid malignancies. *Crit Rev Oncol Hematol*. 2016;102:37-46.
doi: 10.1016/j.critrevonc.2016.03.014
2. Mariconda A, Ceramella J, Catalano A, Saturnino C, Sinicropi MS, Longo P. Cisplatin, the timeless molecule. *Inorganics*. 2025;13(7):246.
doi: 10.3390/inorganics13070246
3. Shahsavani MB, Heidari M, Yousefi R, Moosavi-Movahedi AA. Platinum-based chemotherapeutics in the modern era: From classical DNA-targeting mechanisms to next-generation innovations in cancer therapy. *Chem Biol Drug Des*. 2025;106(6):e70208.
doi: 10.1111/cbdd.70208
4. Tanida S, Mizoshita T, Ozeki K, *et al*. Mechanisms of cisplatin-induced apoptosis and of cisplatin sensitivity: Potential of BIN1 to act as a potent predictor of cisplatin sensitivity in gastric cancer treatment. *Int J Surg Oncol*. 2012;2012:1-8.
doi: 10.1155/2012/862879
5. Elmorsy EA, Saber S, Hamad RS, *et al*. Advances in understanding cisplatin-induced toxicity: Molecular mechanisms and protective strategies. *Eur J Pharm Sci*. 2024;203:106939.
doi: 10.1016/j.ejps.2024.106939
6. Roco Á, Cayún J, Contreras S, Stojanova J, Quiñones L. Can pharmacogenetics explain efficacy and safety of cisplatin pharmacotherapy? *Front Genet*. 2014;5.

- doi: 10.3389/fgene.2014.00391
7. Gupta P. Pharmacogenetics, pharmacogenomics and ayurgenomics for personalized medicine: A paradigm shift. *Indian J Pharm Sci.* 2015;77(2):135.
doi: 10.4103/0250-474X.156543
 8. Naderi N, Jolfayi AG, Azimi A, Maleki M, Kalayinia S. Pharmacogenomics in cardiac therapy: Personalizing treatment for heart health. *Biomed Pharm.* 2025;190:118392.
doi: 10.1016/j.biopha.2025.118392
 9. Sadee W, Wang D, Hartmann K, Toland AE. Pharmacogenomics: Driving personalized medicine. *Pharmacol Rev.* 2023;75(4):789-814.
doi: 10.1124/pharmrev.122.000810
 10. Shriver SP, Adams D, McKelvey BA, *et al.* Overcoming barriers to discovery and implementation of equitable pharmacogenomic testing in oncology. *J Clin Oncol.* 2024;42(10):1181-1192.
doi: 10.1200/JCO.23.01748
 11. Yu X, Jia L, Tang Q, Zhou Q, Wang G, Wang S. Regulation of cisplatin resistance in lung cancer by epigenetic mechanisms. *Clin Epigenetics.* 2025;17(1):145.
doi: 10.1186/s13148-025-01961-6
 12. Zhang J, Yu Q, Zhu W, Sun X. Recent advances in the role of circRNA in cisplatin resistance in tumors. *Cancer Gene Ther.* 2025;32(5):497-506.
doi: 10.1038/s41417-025-00899-4
 13. Crupi E, De Padua TC, Marandino L, *et al.* Circulating tumor DNA as a predictive and prognostic biomarker in the perioperative treatment of muscle-invasive bladder cancer: A systematic review. *Eur Urol Oncol.* 2024;7(1):44-52.
doi: 10.1016/j.euo.2023.05.012
 14. Okawa T, Mizuno T, Hanabusa S, *et al.* Prediction model of acute kidney injury induced by cisplatin in older adults using a machine learning algorithm. *PLoS ONE.* 2022;17(1):e0262021.
doi: 10.1371/journal.pone.0262021
 15. Dasari S, Bernard Tchounwou P. Cisplatin in cancer therapy: Molecular mechanisms of action. *Eur J Pharmacol.* 2014;740:364-378.
doi: 10.1016/j.ejphar.2014.07.025
 16. Pervushin NV, Yapryntseva MA, Panteleev MA, Zhivotovsky B, Kopeina GS. Cisplatin resistance and metabolism: Simplification of complexity. *Cancers.* 2024;16(17):3082.
doi: 10.3390/cancers16173082
 17. Townsend DM, Tew KD. The role of glutathione-S-transferase in anti-cancer drug resistance. *Oncogene.* 2003;22(47):7369-7375.
doi: 10.1038/sj.onc.1206940
 18. Malempati S, Agrawal N, Ravisankar D, *et al.* Role of GSTP1 functional polymorphisms in molecular pathogenesis of colorectal cancer. *Hum Gene.* 2024;42:201335.
doi: 10.1016/j.humgen.2024.201335
 19. Romero A, Martín M, Oliva B, *et al.* Glutathione S-transferase P1 c.313A > G polymorphism could be useful in the prediction of doxorubicin response in breast cancer patients. *Ann Oncol.* 2012;23(7):1750-1756.
doi: 10.1093/annonc/mdr483
 20. Saadat M. Evaluation of glutathione S-transferase P1 (GSTP1) Ile105Val polymorphism and susceptibility to type 2 diabetes mellitus, a meta-analysis. *EXCLI J.* 2017;16:1188-1197.
doi: 10.17179/EXCLI2017-828
 21. Khrunin A, Ivanova F, Moiseev A, *et al.* Pharmacogenomics of cisplatin-based chemotherapy in ovarian cancer patients of different ethnic origins. *Pharmacogenomics.* 2012;13(2):171-178.
doi: 10.2217/pgs.11.140
 22. Jawad R, Mshimesh B, Al-Mayah Q. Glutathione-S-transferase pi-1 polymorphisms as predictors of the severity and onset of the development of cumulative oxaliplatin-induced neurotoxicity in patients with colorectal cancer. *World Acad Sci J.* 2025;7(5):1-13.
doi: 10.3892/wasj.2025.369
 23. Kim W, Cho YA, Kim DC, Lee KE. Association between genetic polymorphism of GSTP1 and toxicities in patients receiving platinum-based chemotherapy: A systematic review and meta-analysis. *Pharmaceuticals.* 2022;15(4):439.
doi: 10.3390/ph15040439
 24. Townsend DM, Tew KD, He L, King JB, Hanigan MH. Role of glutathione S-transferase Pi in cisplatin-induced nephrotoxicity. *Biomed Pharm.* 2009;63(2):79-85.
doi: 10.1016/j.biopha.2008.08.004
 25. Alnasser SM. The role of glutathione S-transferases in human disease pathogenesis and their current inhibitors. *Genes Dis.* 2025;12(4):101482.
doi: 10.1016/j.gendis.2024.101482
 26. Abada P, Howell SB. Regulation of cisplatin cytotoxicity by Cu influx transporters. *Met-Based Drugs.* 2010;2010:1-9.
doi: 10.1155/2010/317581
 27. Kuo MT, Chen HHW, Song IS, Savaraj N, Ishikawa T. The roles of copper transporters in cisplatin resistance. *Cancer Metastasis Rev.* 2007;26(1):71-83.
doi: 10.1007/s10555-007-9045-3
 28. Schoeberl A, Gutmann M, Theiner S, *et al.* The copper transporter CTR1 and cisplatin accumulation at the

- single-cell level by LA-ICP-TOFMS. *Front Mol Biosci.* 2022;9:1055356.
doi: 10.3389/fmolb.2022.1055356
29. Howell SB, Safaei R, Larson CA, Sailor MJ. Copper transporters and the cellular pharmacology of the platinum-containing cancer drugs. *Mol Pharmacol.* 2010;77(6):887-894.
doi: 10.1124/mol.109.063172
 30. Xu L, Cao X, Deng Y, *et al.* Cuproptosis-related genes and agents: implications in tumor drug resistance and future perspectives. *Front Pharmacol.* 2025;16:1559236.
doi: 10.3389/fphar.2025.1559236
 31. Yao L, Jiang B, Xu D. Strategies to combat cancer drug resistance: focus on copper metabolism and cuproptosis. *Cancer Drug Resist.* 2025;8:15.
doi: 10.20517/cdr.2025.41
 32. Kalayda GV, Wagner CH, Buß I, Reedijk J, Jaehde U. Altered localisation of the copper efflux transporters ATP7A and ATP7B associated with cisplatin resistance in human ovarian carcinoma cells. *BMC Cancer.* 2008;8(1):175.
doi: 10.1186/1471-2407-8-175
 33. Yoshizawa K, Nozaki S, Kitahara H, *et al.* Copper efflux transporter (ATP7B) contributes to the acquisition of cisplatin-resistance in human oral squamous cell lines. *Oncol Rep.* 2007;18(4):987-991.
doi: 10.3892/or.18.4.987
 34. Pizzagalli MD, Bensimon A, Superti-Furga G. A guide to plasma membrane solute carrier proteins. *FEBS J.* 2021;288(9):2784-2835.
doi: 10.1111/febs.15531
 35. Brecht K, Schäfer AM, Meyer Zu Schwabedissen HE. Uptake transporters of the SLC21, SLC22A, and SLC15A families in anticancer therapy—Modulators of cellular entry or pharmacokinetics? *Cancers.* 2020;12(8):2263.
doi: 10.3390/cancers12082263
 36. Ciarimboli G, Deuster D, Knief A, *et al.* Organic cation transporter 2 mediates cisplatin-induced oto- and nephrotoxicity and is a target for protective interventions. *Am J Pathol.* 2010;176(3):1169-1180.
doi: 10.2353/ajpath.2010.090610
 37. Nieskens TTG, Peters JGP, Dabaghie D, *et al.* Expression of organic anion transporter 1 or 3 in human kidney proximal tubule cells reduces cisplatin sensitivity. *Drug Metab Dispos.* 2018;46(5):592-599.
doi: 10.1124/dmd.117.079384
 38. Ahmed S, Eu-ahsunthornwattana J, Thamrongjirapat T, *et al.* EPHX1 and ERCC2 polymorphisms are associated with cisplatin-induced nephrotoxicity and prognosis in Thai cancer patients. *PLoS ONE.* 2025;20(6):e0324699.
doi: 10.1371/journal.pone.0324699
 39. Selim MS, Kassem AB, El-Bassiouny NA, Salahuddin A, Abu El-Ela RY, Hamza MS. Polymorphic renal transporters and cisplatin's toxicity in urinary bladder cancer patients: current perspectives and future directions. *Med Oncol.* 2023;40(2):80.
doi: 10.1007/s12032-022-01928-0
 40. Zazuli Z, Vijverberg S, Slob E, *et al.* Genetic variations and cisplatin nephrotoxicity: A systematic review. *Front Pharmacol.* 2018;9:1111.
doi: 10.3389/fphar.2018.01111
 41. Lanvers-Kaminsky C, Sprowl JA, Malath I, *et al.* Human OCT2 variant C.808G>T confers protection effect against cisplatin-induced ototoxicity. *Pharmacogenomics.* 2015;16(4):323-332.
doi: 10.2217/pgs.14.182
 42. Zhang J, Zhou W. Ameliorative effects of SLC22A2 gene polymorphism 808 G/T and cimetidine on cisplatin-induced nephrotoxicity in Chinese cancer patients. *Food Chem Toxicol.* 2012;50(7):2289-2293.
doi: 10.1016/j.fct.2012.03.077
 43. Duan M, Ulibarri J, Liu KJ, Mao P. Role of nucleotide excision repair in cisplatin resistance. *Int J Mol Sci.* 2020;21(23):9248.
doi: 10.3390/ijms21239248
 44. Barba A, López-Vilaró L, Ferre M, *et al.* ERCC1 and ERCC2 polymorphisms predict the efficacy and toxicity of platinum-based chemotherapy in small cell lung cancer. *Pharmaceutics.* 2024;16(9):1121.
doi: 10.3390/pharmaceutics16091121
 45. Lee MS, Liu C yu, Su L, Christiani DC. Polymorphisms in ERCC1 and ERCC2/XPD genes and carcinogen DNA adducts in human lung. *Lung Cancer.* 2015;89(1):8-12.
doi: 10.1016/j.lungcan.2015.05.001
 46. Miras I, Vázquez-Gutierrez I, Estévez-García P, Muñoz-Galván S. DNA repair pathways in ovarian cancer: Implications for therapy and resistance. *Biomed Pharm.* 2025;193:118719.
doi: 10.1016/j.biopha.2025.118719
 47. Obiedat H, Alrabadi N, Sultan E, Al Shatti M, Zihlif M. The effect of ERCC1 and ERCC2 gene polymorphisms on response to cisplatin based therapy in osteosarcoma patients. *BMC Med Genet.* 2018;19(1):112.
doi: 10.1186/s12881-018-0627-4
 48. Psyrri A, Gkotzamanidou M, Papaxoinis G, *et al.* The DNA damage response network in the treatment of head and neck squamous cell carcinoma. *ESMO Open.* 2021;6(2):100075.
doi: 10.1016/j.esmoop.2021.100075

49. Chen LH, Shen TC, Li CH, *et al.* The significant interaction of excision repair cross-complementing group 1 genotypes and smoking to lung cancer risk. *Cancer Genom Proteom.* 2020;17(5):571-577.
doi: 10.21873/cgp.20213
50. Arora S, Kothandapani A, Tillison K, Kalman-Maltese V, Patrick SM. Downregulation of XPF-ERCC1 enhances cisplatin efficacy in cancer cells☆. *DNA Repair.* 2010;9(7):745-753.
doi: 10.1016/j.dnarep.2010.03.010
51. Bellmunt J, Paz-Ares L, Cuello M, *et al.* Gene expression of ERCC1 as a novel prognostic marker in advanced bladder cancer patients receiving cisplatin-based chemotherapy. *Ann Oncol.* 2007;18(3):522-528.
doi: 10.1093/annonc/mdl435
52. Du P, Li G, Wu L, Huang M. Perspectives of ERCC1 in early-stage and advanced cervical cancer: From experiments to clinical applications. *Front Immunol.* 2023;13:1065379.
doi: 10.3389/fimmu.2022.1065379
53. Friboulet L, Olaussen KA, Pignon JP, *et al.* ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. *N Engl J Med.* 2013;368(12):1101-1110.
doi: 10.1056/NEJMoa1214271
54. Kiss RC, Xia F, Acklin S. Targeting DNA damage response and repair to enhance therapeutic index in cisplatin-based cancer treatment. *Int J Mol Sci.* 2021;22(15):8199.
doi: 10.3390/ijms22158199
55. Liu J, Zhang L, Mao P, *et al.* Functional characterization of a novel transcript of ERCC1 in chemotherapy resistance of ovarian cancer. *Oncotarget.* 2017;8(49):85759-85771.
doi: 10.18632/oncotarget.20482
56. Rocha CRR, Silva MM, Quinet A, Cabral-Neto JB, Menck CFM. DNA repair pathways and cisplatin resistance: an intimate relationship. *Clinics.* 2018;73:e478s.
doi: 10.6061/clinics/2018/e478s
57. Olaussen KA, Dunant A, Fouret P, *et al.* DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med.* 2006;355(10):983-991.
doi: 10.1056/NEJMoa060570
58. Sakamoto Y, Morizane C, Okusaka T, *et al.* Impact of ERCC1 on the outcomes of chemotherapy in advanced biliary tract cancer. *Sci Rep.* 2025;15(1):33862.
doi: 10.1038/s41598-025-07058-7
59. Koutsoukos K, Andrikopoulou A, Dedes N, Zagouri F, Bamias A, Dimopoulos MA. Clinical perspectives of ERCC1 in bladder cancer. *Int J Mol Sci.* 2020;21(22):8829.
doi: 10.3390/ijms21228829
60. Palomba G, Atzori F, Budroni M, *et al.* ERCC1 polymorphisms as prognostic markers in T4 breast cancer patients treated with platinum-based chemotherapy. *J Transl Med.* 2014;12(1):272.
doi: 10.1186/s12967-014-0272-4
61. Tan LM, Qiu CF, Zhu T, *et al.* Genetic polymorphisms and platinum-based chemotherapy treatment outcomes in patients with non-small cell lung cancer: A Genetic epidemiology study based meta-analysis. *Sci Rep.* 2017;7(1):5593.
doi: 10.1038/s41598-017-05642-0
62. Woelfelschneider A, Popanda O, Lilla C, *et al.* A distinct ERCC1 haplotype is associated with mRNA expression levels in prostate cancer patients. *Carcinogenesis.* 2008;29(9):1758-1764.
doi: 10.1093/carcin/bgn067
63. Yin M, Yan J, Martinez-Balibrea E, *et al.* ERCC1 and ERCC2 polymorphisms predict clinical outcomes of oxaliplatin-based chemotherapies in gastric and colorectal cancer: A systemic review and meta-analysis. *Clin Cancer Res.* 2011;17(6):1632-1640.
doi: 10.1158/1078-0432.CCR-10-2169
64. Zhang T, Ma SC, Zhao Y, Zhao D, Ling XL. Association between the ERCC1 rs11615 polymorphism and clinical outcomes of oxaliplatin-based chemotherapies in gastrointestinal cancer: a meta-analysis. *Onco Targets Ther.* 2015;8:641-648.
doi: 10.2147/OTT.S80913
65. Bradbury PA, Kulke MH, Heist RS, *et al.* Cisplatin pharmacogenetics, DNA repair polymorphisms, and esophageal cancer outcomes. *Pharm Genom.* 2009;19(8):613-625.
doi: 10.1097/FPC.0b013e32832f3010
66. Tamura D, Khan SG, Merideth M, *et al.* Effect of mutations in XPD(ERCC2) on pregnancy and prenatal development in mothers of patients with trichothiodystrophy or xeroderma pigmentosum. *Eur J Hum Genet.* 2012;20(12):1308-1310.
doi: 10.1038/ejhg.2012.90
67. Islam MdA, Mubashshira S, Rahman MdM, Kabir Y. Contribution of ERCC2 rs13181 (Lys751Gln) and rs1799793 (Asp312Asn) polymorphisms to the risk of bladder cancer in Bangladesh. *Cancer Genet.* 2024;288-289:126-132.
doi: 10.1016/j.cancergen.2024.11.002
68. Zhang H, Li Y, Guo S, *et al.* Effect of ERCC2 rs13181 and rs1799793 polymorphisms and environmental factors on the prognosis of patients with lung cancer. *Am J Transl Res.* 2020;12(10):6941-6953.
69. Kulkarni A, McNeill DR, Gleichmann M, Mattson MP, Wilson DM. XRCC1 protects against the lethality of induced

- oxidative DNA damage in nondividing neural cells. *Nucleic Acids Res.* 2008;36(15):5111-5121.
doi: 10.1093/nar/gkn480
70. Kothandapani A, Dangeti VSMN, Brown AR, *et al.* Novel role of base excision repair in mediating cisplatin cytotoxicity. *J Biol Chem.* 2011;286(16):14564-14574.
doi: 10.1074/jbc.M111.225375
 71. Slyskova J, Sabatella M, Ribeiro-Silva C, *et al.* Base and nucleotide excision repair facilitate resolution of platinum drugs-induced transcription blockage. *Nucleic Acids Res.* 2018;46(18):9537-9549.
doi: 10.1093/nar/gky764
 72. Ruwali M. Role of genetic variations in determining treatment outcome in head and neck cancer. *Eur Med J.* 2017;2(4):114-121.
doi: 10.33590/emj/10313625
 73. Yuan Z, Li J, Hu R, Jiao Y, Han Y, Weng Q. Predictive assessment in pharmacogenetics of XRCC1 gene on clinical outcomes of advanced lung cancer patients treated with platinum-based chemotherapy. *Sci Rep.* 2015;5(1):16482.
doi: 10.1038/srep16482
 74. Zhang Y, Wang M, Gu D, *et al.* Association of XRCC1 gene polymorphisms with the survival and clinicopathological characteristics of gastric cancer. *DNA Cell Biol.* 2013;32(3):111-118.
doi: 10.1089/dna.2012.1840
 75. Zhao J, Zhi Z, Zhang M, *et al.* Predictive value of single nucleotide polymorphisms in XRCC1 for radiation-induced normal tissue toxicity. *Onco Targets Ther.* 2018;11:3901-3918.
doi: 10.2147/OTT.S156175
 76. Permatasari L, Afifah N, Ishmatullah M, Intania R, Halimah E, Barliana M. Genetic navigation: A narrative review of XRCC1 polymorphism impact on platinum-based chemotherapy outcomes in NSCLC patients. *Cancer Manag Res.* 2025;17:383-395.
doi: 10.2147/CMAR.S501420
 77. Kang TH. Circadian rhythm of NER and ATR pathways. *Biomolecules.* 2021;11(5):715.
doi: 10.3390/biom11050715
 78. Liu M, Qiu Z, Yang Q. Association between ERCC1 gene polymorphism (rs11615) and colorectal cancer susceptibility: A meta-analysis of medical image fusion and safety applications. *Comput Math Methods Med.* 2022;2022:9988513.
doi: 10.1155/2022/9988513
 79. Wang C, Deng G, Niu S, Meng X. Genetic polymorphisms of TRPA1 does affect risk of cisplatin induced nephrotoxicity in Chinese population. *Transl Oncol.* 2025;60:102486.
doi: 10.1016/j.tranon.2025.102486
 80. Dolan ME, El Charif O, Wheeler HE, *et al.* Clinical and genome-wide analysis of cisplatin-induced peripheral neuropathy in survivors of adult-onset cancer. *Clin Cancer Res.* 2017;23(19):5757-5768.
doi: 10.1158/1078-0432.CCR-16-3224
 81. Zhang X, Trendowski MR, Wilkinson E, *et al.* Pharmacogenomics of cisplatin-induced neurotoxicities: Hearing loss, tinnitus, and peripheral sensory neuropathy. *Cancer Med.* 2022;11(14):2801-2816.
doi: 10.1002/cam4.4644
 82. Iațentiu A, Iațentiu IM, Frăsinaru OE, *et al.* The role of genetic and non-genetic factors in the occurrence of cisplatin-associated ototoxicity. *Int J Mol Sci.* 2025;26(10):4787.
doi: 10.3390/ijms26104787
 83. Yang JJ, Lim JYS, Huang J, *et al.* The role of inherited TPMT and COMT genetic variation in cisplatin-induced ototoxicity in children with cancer. *Clin Pharmacol Ther.* 2013;94(2):252-259.
doi: 10.1038/clpt.2013.121
 84. Zhou X, Ao X, Jia Z, *et al.* Non-coding RNA in cancer drug resistance: Underlying mechanisms and clinical applications. *Front Oncol.* 2022;12:951864.
doi: 10.3389/fonc.2022.951864
 85. Cui Y, Li G, Zhang X, Dai F, Zhang R. Increased MALAT1 expression contributes to cisplatin resistance in non-small cell lung cancer. *Oncol Lett.* 2018;16(4):4821-4828.
doi: 10.3892/ol.2018.9293
 86. Wang X, Zhang H, Bai M, *et al.* Exosomes serve as nanoparticles to deliver anti-miR-214 to reverse chemoresistance to cisplatin in gastric cancer. *Mol Ther.* 2018;26(3):774-783.
doi: 10.1016/j.ymthe.2018.01.001
 87. Long X, Song K, Hu H, *et al.* Long non-coding RNA GAS5 inhibits DDP-resistance and tumor progression of epithelial ovarian cancer via GAS5-E2F4-PARP1-MAPK axis. *J Exp Clin Cancer Res.* 2019;38(1):345.
doi: 10.1186/s13046-019-1329-2
 88. Wang J, Ye C, Liu J, Hu Y. UCA1 confers paclitaxel resistance to ovarian cancer through miR-129/ABCB1 axis. *Biochem Biophys Res Commun.* 2018;501(4):1034-1040.
doi: 10.1016/j.bbrc.2018.05.104
 89. Wu Y, Wang T, Xia L, Zhang M. LncRNA WDFY3-AS2 promotes cisplatin resistance and the cancer stem cell in ovarian cancer by regulating hsa-miR-139-5p/SDC4 axis. *Cancer Cell Int.* 2021;21(1):284.
doi: 10.1186/s12935-021-01993-x

90. Shang A, Wang W, Gu C, *et al.* Long non-coding RNA HOTTIP enhances IL-6 expression to potentiate immune escape of ovarian cancer cells by upregulating the expression of PD-L1 in neutrophils. *J Exp Clin Cancer Res.* 2019;38(1):411.
doi: 10.1186/s13046-019-1394-6
91. Rupaimoole R, Lee J, Haemmerle M, *et al.* Long noncoding RNA ceruloplasmin promotes cancer growth by altering glycolysis. *Cell Rep.* 2015;13(11):2395-2402.
doi: 10.1016/j.celrep.2015.11.047
92. Yang H, Kong W, He L, *et al.* MicroRNA expression profiling in human ovarian cancer: *miR-214* induces cell survival and cisplatin resistance by targeting *PTEN*. *Cancer Res.* 2008;68(2):425-433.
doi: 10.1158/0008-5472.CAN-07-2488
93. Sun C, Li N, Yang Z, *et al.* miR-9 regulation of BRCA1 and ovarian cancer sensitivity to cisplatin and PARP inhibition. *J Natl Cancer Inst.* 2013;105(22):1750-1758.
doi: 10.1093/jnci/djt302
94. Sun C, Cao W, Qiu C, *et al.* MiR-509-3 augments the synthetic lethality of PARPi by regulating HR repair in PDX model of HGSOC. *J Hematol Oncol.* 2020;13(1):9.
doi: 10.1186/s13045-020-0844-0
95. He L, Zhu W, Chen Q, *et al.* Ovarian cancer cell-secreted exosomal miR-205 promotes metastasis by inducing angiogenesis. *Theranostics.* 2019;9(26):8206-8220.
doi: 10.7150/thno.37455
96. Zou Z, Zou R, Zong D, *et al.* miR-495 sensitizes MDR cancer cells to the combination of doxorubicin and taxol by inhibiting MDR1 expression. *J Cell Mol Med.* 2017;21(9):1929-1943.
doi: 10.1111/jcmm.13114
97. Xiao M, Guo J, Xie L, *et al.* Let-7e suppresses DNA damage repair and sensitizes ovarian cancer to cisplatin through targeting PARP1. *Mol Cancer Res.* 2020;18(3):436-447.
doi: 10.1158/1541-7786.MCR-18-1369
98. Hamdy NM, Noureldein MH, Gouhar SA, *et al.* Diagnostic and therapeutic potential of exosomal circRNAs in cancer: decoding the circular code toward precision medicine. *Cancer Cell Int.* 2025;25(1):432.
doi: 10.1186/s12935-025-04053-w
99. Li X, Liu H, Xing P, *et al.* Exosomal circRNAs: Deciphering the novel drug resistance roles in cancer therapy. *J Pharm Anal.* 2025;15(2):101067.
doi: 10.1016/j.jpha.2024.101067
100. Li Q hui, Liu Y, Chen S, *et al.* circ-CSPP1 promotes proliferation, invasion and migration of ovarian cancer cells by acting as a miR-1236-3p sponge. *Biomed Pharm.* 2019;114:108832.
doi: 10.1016/j.biopha.2019.108832
101. Lin C, Xu X, Yang Q, Liang L, Qiao S. Circular RNA ITCH suppresses proliferation, invasion, and glycolysis of ovarian cancer cells by up-regulating CDH1 via sponging miR-106a. *Cancer Cell Int.* 2020;20(1):336.
doi: 10.1186/s12935-020-01420-7
102. Luo L, Gao Y, Sun X. Circ-ITCH correlates with small tumor size, decreased FIGO stage and prolonged overall survival, and it inhibits cells proliferation while promotes cells apoptosis in epithelial ovarian cancer. *Cancer Biomark.* 2018;23(4):505-513.
doi: 10.3233/CBM-181609
103. Pan Y, Lin Y, Mi C. Cisplatin-resistant osteosarcoma cell-derived exosomes confer cisplatin resistance to recipient cells in an exosomal circ_103801-dependent manner. *Cell Biol Int.* 2021;45(4):858-868.
doi: 10.1002/cbin.11532
104. Ye H, Hu X, Wen Y, *et al.* Exosomes in the tumor microenvironment of sarcoma: from biological functions to clinical applications. *J Nanobiotechnol.* 2022;20(1):403.
doi: 10.1186/s12951-022-01609-0
105. Shi Q, Ji T, Ma Z, Tan Q, Liang J. Serum exosomes-based biomarker circ_0008928 regulates cisplatin sensitivity, tumor progression, and glycolysis metabolism by miR-488/*HK2* axis in cisplatin-resistant nonsmall cell lung carcinoma. *Cancer Biother Radiopharm.* 2023;38(8):558-571.
doi: 10.1089/cbr.2020.4490
106. Lumpp T, Stößer S, Fischer F, Hartwig A, Köberle B. Role of Epigenetics for the efficacy of cisplatin. *Int J Mol Sci.* 2024;25(2):1130.
doi: 10.3390/ijms25021130
107. Dedes N, Lontos M, Haidopoulos D, *et al.* Epigenetics in ovarian cancer: A review of current knowledge and future perspectives. *Biomedicines.* 2025;13(11):2820.
doi: 10.3390/biomedicines13112820
108. He W, Zhu H, Zhang S, *et al.* Epigenetic editing of *BRCA1* promoter increases cisplatin and olaparib sensitivity of ovarian cancer cells. *Epigenetics.* 2024;19(1):2357518.
doi: 10.1080/15592294.2024.2357518
109. Natu A, Verma T, Khade B, *et al.* Histone acetylation: a key determinant of acquired cisplatin resistance in cancer. *Clin Epigenetics.* 2024;16(1):8.
doi: 10.1186/s13148-023-01615-5
110. Almeida LO, Abrahao AC, Rosselli-Murai LK, *et al.* NFκB mediates cisplatin resistance through histone modifications in head and neck squamous cell carcinoma (HNSCC). *FEBS Open Bio.* 2014;4(1):96-104.

doi: 10.1016/j.fob.2013.12.003

111. Oh SY, Kim J, Lee KY, *et al.* Chromatin remodeling-driven

autophagy activation induces cisplatin resistance in oral squamous cell carcinoma. *Cell Death Dis.* 2024;15(8):589.

doi: 10.1038/s41419-024-06975-1