

REVIEW ARTICLE

Pharmacogenetic factors influencing cisplatin-based cancer treatment efficiency

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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.

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