

Cisplatin-Induced Cellular Toxicity and its Mechanisms of Action

Shivangi¹ and Dr. Poonam Dhanda²

¹Research Scholar, Department of Biotechnology

²Research Guide, Department of Biotechnology

NIILM University, Kaithal, Haryana

Abstract: *Cisplatin is a highly effective platinum-based chemotherapeutic agent widely used in the treatment of solid tumors, including cancers of the testis, ovary, bladder, lung, head and neck, and other malignancies. Its anticancer activity primarily results from the formation of platinum-DNA adducts that interfere with DNA replication and transcription and activate cellular DNA-damage responses. However, cisplatin also produces substantial toxicity in normal cells and tissues. Cellular toxicity involves a complex interaction among DNA damage, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, inflammatory signaling, cell-cycle arrest, apoptosis, necrosis, autophagy, senescence, and regulated forms of cell death. Cisplatin enters cells through passive diffusion and transporter-mediated mechanisms, including copper transporter 1 and organic cation transporter 2 in renal cells. Intracellular activation produces reactive platinum species that bind DNA and cellular proteins.*

Keywords: Cisplatin, cellular toxicity, DNA damage, oxidative stress, apoptosis, mitochondrial dysfunction, ER stress, inflammation, ferroptosis, chemotherapy.

I. INTRODUCTION

Cisplatin, chemically known as cis-diamminedichloroplatinum (II), is one of the most important cytotoxic agents used in modern cancer chemotherapy. Its clinical importance arises from its ability to kill rapidly proliferating malignant cells through DNA damage and associated cellular stress responses. Despite the development of newer platinum compounds, cisplatin remains an essential component of treatment regimens for several solid tumors. Its therapeutic usefulness, however, is restricted by dose-limiting toxicities affecting organs such as the kidney, nervous system, and auditory system. The cellular response to cisplatin is complex because the drug acts on both nuclear and cytoplasmic targets rather than through a single pathway.

The classical mechanism of cisplatin toxicity begins with intracellular accumulation and aquation of the drug. Activated cisplatin forms covalent bonds with nucleophilic sites in DNA, producing predominantly intrastrand crosslinks and, to a lesser extent, interstrand crosslinks and DNA-protein crosslinks. These lesions distort the DNA structure and interfere with DNA replication and transcription. DNA damage activates cellular surveillance pathways, including p53-dependent signaling, DNA repair mechanisms, cell-cycle checkpoints, and apoptotic pathways. The ultimate response depends on drug concentration, cell type, DNA repair capacity, p53 status, mitochondrial function, and the balance between pro-survival and pro-death signaling.

Cisplatin-induced toxicity cannot, however, be explained solely by DNA damage. Evidence accumulated during the last decade indicates that cisplatin also affects mitochondria, endoplasmic reticulum, cellular membranes, proteins, and cytoskeletal structures. These effects contribute to reactive oxygen species production, mitochondrial dysfunction, inflammatory signaling, and several forms of regulated cell death.

The kidney is particularly vulnerable because cisplatin accumulates in renal tubular cells. Recent evidence identifies DNA damage, mitochondrial pathology, oxidative stress, endoplasmic reticulum stress, inflammation, apoptosis,

necrosis, autophagy, senescence, and epigenetic changes as interconnected components of cisplatin-induced renal cellular injury.

OBJECTIVES OF THE STUDY

- To examine the cellular mechanisms responsible for cisplatin-induced toxicity.
- To explain the role of cisplatin-induced DNA damage in cellular injury.
- To analyze the contribution of oxidative stress and mitochondrial dysfunction.
- To investigate apoptosis, necrosis, autophagy, ferroptosis, and other regulated cell-death pathways.
- To evaluate the roles of inflammatory and endoplasmic-reticulum stress pathways.
- To summarize mechanisms responsible for cellular resistance to cisplatin.
- To identify potential molecular targets for reducing cisplatin-associated toxicity.

II. MATERIALS AND METHODS

The present paper represents a narrative research review of literature concerning the cellular and molecular mechanisms of cisplatin toxicity. Research articles and review studies published primarily between 2010 and 2023 were considered. Particular attention was given to studies investigating DNA damage, cellular uptake, oxidative stress, mitochondrial dysfunction, apoptosis, cell-cycle regulation, ER stress, inflammation, autophagy, regulated cell death, and cisplatin resistance.

The literature was synthesized thematically rather than statistically because the included studies differed considerably in experimental systems, cisplatin concentrations, cell types, animal models, endpoints, and treatment schedules.

CELLULAR ENTRY AND INTRACELLULAR ACTIVATION OF CISPLATIN

Cisplatin must enter cells before producing its major cytotoxic effects. Cellular uptake can occur through passive diffusion as well as transporter-mediated processes. Copper transporter 1 (CTR1) has been implicated in cisplatin uptake in several cell types, whereas organic cation transporter 2 (OCT2) has an important role in cisplatin accumulation in renal tubular cells. Efflux mechanisms involving ATP7A, ATP7B, and other transport systems can influence intracellular drug concentration and contribute to resistance.

Once inside the relatively low-chloride intracellular environment, cisplatin undergoes aquation. Chloride ligands are replaced by water molecules, generating highly reactive platinum-containing species. These activated molecules interact with DNA, proteins, glutathione, and other cellular nucleophiles.

Table 1. Major stages in cisplatin-induced cellular toxicity

Stage	Major event	Principal cellular consequence
1	Cellular uptake	Intracellular accumulation of cisplatin
2	Aquation	Formation of reactive platinum species
3	DNA binding	DNA adduct and crosslink formation
4	DNA damage response	Activation of p53, p21, c-Abl and repair pathways
5	Oxidative stress	ROS accumulation and antioxidant depletion
6	Mitochondrial injury	Loss of membrane potential and ATP dysfunction
7	ER stress	Unfolded-protein response and stress signaling
8	Inflammation	Cytokine and NF- κ B-related responses
9	Cell-cycle arrest	Inhibition of cellular proliferation
10	Cell death	Apoptosis, necrosis and regulated cell death

CISPLATIN-INDUCED DNA DAMAGE

DNA damage is the best-established mechanism underlying cisplatin's anticancer activity. Cisplatin forms covalent DNA adducts, particularly 1,2-intrastrand crosslinks involving adjacent guanine residues. These lesions bend the DNA helix and interfere with polymerase progression.

The DNA lesions are recognized by DNA damage surveillance systems. Nucleotide excision repair is an important mechanism for removing cisplatin-DNA adducts, while mismatch repair and other DNA damage-response pathways contribute to determining cellular fate. Persistent DNA damage activates checkpoint signaling and can produce cell-cycle arrest or apoptosis.

The DNA damage response is strongly influenced by p53. Following DNA damage, p53 can induce p21 and other target genes responsible for cell-cycle arrest and DNA repair. If the damage is extensive or cannot be adequately repaired, p53 can promote pro-apoptotic pathways. p53 therefore acts as an important molecular decision point between survival and cell death.

Table 2. Major DNA-related mechanisms of cisplatin toxicity

DNA-related mechanism	Molecular effect	Cellular outcome
Intrastrand crosslinks	DNA helix distortion	Replication inhibition
Interstrand crosslinks	Separation of DNA strands prevented	Severe replication/transcription stress
DNA-protein interactions	Protein-DNA complex formation	Impaired DNA processing
Nucleotide excision repair	Removal of cisplatin adducts	DNA repair or resistance
p53 activation	p21 and pro-apoptotic gene induction	Arrest or apoptosis
Mismatch repair signaling	Recognition of abnormal DNA	Stress signaling and apoptosis
c-Abl activation	JNK/p38 and p73 signaling	Pro-apoptotic signaling

OXIDATIVE STRESS AND REACTIVE OXYGEN SPECIES

Oxidative stress is a major contributor to cisplatin-induced cellular injury. Cisplatin can increase the production of reactive oxygen species, including superoxide, hydrogen peroxide, and hydroxyl radicals. Simultaneously, antioxidant defenses may become depleted.

Excessive ROS can damage lipids, proteins, DNA, and mitochondria. Lipid peroxidation compromises cellular membranes, while oxidative modification of proteins can impair enzymes and signaling molecules. Oxidative DNA damage further amplifies the genotoxic effects of cisplatin.

In renal tubular cells, oxidative stress is particularly important because cisplatin accumulation can cause mitochondrial damage and stimulate ROS generation. Contemporary reviews identify oxidative stress as one of the major intracellular stresses involved in cisplatin nephrotoxicity.

Table 3. Oxidative-stress changes associated with cisplatin exposure

Parameter	Effect of cisplatin	Consequence
Reactive oxygen species	↑	Oxidative damage
Lipid peroxidation	↑	Membrane injury
Glutathione	↓	Reduced antioxidant capacity
Superoxide dismutase	Often ↓	Reduced ROS removal
Catalase	Often ↓	Reduced peroxide detoxification
Protein oxidation	↑	Enzyme and structural dysfunction
Oxidative DNA damage	↑	Genotoxic stress
Mitochondrial ROS	↑	Amplification of cellular injury

MAPK AND JNK SIGNALING

Mitogen-activated protein kinase pathways are important regulators of cisplatin-induced cellular responses. Cisplatin can activate JNK and p38 MAPK in response to DNA damage and oxidative stress.

JNK can promote apoptosis by influencing mitochondrial proteins and transcriptional regulators. p38 MAPK can regulate cell-cycle arrest, inflammatory responses, and apoptosis. ERK signaling can have context-dependent effects and may participate in both survival and cell-death responses.

The balance between these signaling pathways contributes to differences in cisplatin sensitivity between cell types.

CELL-CYCLE ARREST AND SENESENCE

Cisplatin-induced DNA damage activates cell-cycle checkpoints. p53 and p21 are important mediators of this process. Temporary cell-cycle arrest allows cells to repair DNA, but persistent DNA damage may result in senescence.

Senescent cells remain metabolically active but permanently lose their ability to proliferate. They can also release inflammatory mediators through the senescence-associated secretory phenotype. Recent evidence indicates that senescence contributes to persistent renal injury and maladaptive repair after cisplatin exposure.

Table 4. Cisplatin-induced cellular responses

Cellular response	Major pathway	Possible outcome
DNA repair	NER, DDR pathways	Cell survival
Cell-cycle arrest	p53-p21	Temporary growth inhibition
Senescence	Persistent DNA damage	Long-term cellular dysfunction
Apoptosis	BAX/cytochrome c/caspases	Programmed cell death
Necrosis	Severe cellular injury	Membrane rupture
Autophagy	Stress-response pathways	Survival or death depending on context
Ferroptosis	Iron-dependent lipid peroxidation	Regulated cell death
Inflammation	NF-κB/cytokines	Secondary tissue injury

AUTOPHAGY

Autophagy is a cellular quality-control mechanism that removes damaged proteins and organelles. Cisplatin can stimulate autophagy as an adaptive response to cellular stress.

The role of autophagy is complex. Moderate autophagy may remove damaged mitochondria and promote cell survival, whereas excessive or dysregulated autophagy may contribute to cellular death. In cisplatin-induced renal injury, autophagy and mitophagy have been implicated in determining the degree of cellular damage and recovery.

Consequently, therapeutic modulation of autophagy requires careful consideration because complete inhibition or excessive stimulation may have different consequences depending on the cell type and stage of injury.

III. DISCUSSION

Cisplatin remains a highly effective anticancer agent because it exploits fundamental vulnerabilities of cancer cells, particularly their dependence on DNA replication and their reduced ability to tolerate genomic stress. The formation of DNA crosslinks is therefore central to its therapeutic action. However, DNA damage alone does not completely explain the drug's toxicity.

The current evidence indicates that cisplatin produces simultaneous damage to several cellular compartments. DNA damage initiates the DNA damage response, while mitochondrial dysfunction and ROS generation create additional stress. ER stress alters protein homeostasis, and inflammatory signaling amplifies local tissue injury. The convergence of these pathways determines whether an exposed cell repairs the damage, enters senescence, or undergoes apoptosis or another form of regulated cell death.

The role of mitochondria is particularly important because they function both as sources and targets of oxidative stress. Cisplatin-associated mitochondrial DNA and protein damage can impair respiratory function, increase ROS production,

and facilitate apoptotic signaling. Consequently, mitochondrial protection is an important potential target for reducing toxicity.

Another major development is recognition of regulated cell death beyond conventional apoptosis. Ferroptosis, necroptosis, and other forms of regulated necrosis are increasingly being investigated. The 2023 literature emphasizes that multiple regulated cell-death pathways may operate simultaneously or sequentially during tissue injury.

IV. CONCLUSION

Cisplatin-induced cellular toxicity is a highly complex process involving interconnected molecular pathways. Although DNA damage and formation of platinum-DNA adducts represent the classical basis of cisplatin cytotoxicity, they are only one component of the overall mechanism. Cisplatin also induces oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, inflammation, cell-cycle arrest, senescence, apoptosis, autophagy, necrosis, and other regulated forms of cell death.

The cellular response begins with drug uptake and intracellular activation, followed by DNA binding and activation of DNA damage-response pathways. p53, p21, c-Abl, JNK, p38 MAPK, mitochondrial proteins, caspases, and inflammatory mediators participate in determining cell fate. In renal cells, these mechanisms combine to produce tubular injury and acute kidney injury.

REFERENCES

1. Basu, A., & Krishnamurthy, S. (2010). Cellular responses to cisplatin-induced DNA damage. *Journal of Nucleic Acids*, 2010, 201367.
2. Dasari, S., & Tchounwou, P. B. (2014). Cisplatin in cancer therapy: Molecular mechanisms of action. *European Journal of Pharmacology*, 740, 364–378.
3. Fang, C. Y., Lou, D. Y., Zhou, L. Q., Wang, J. C., Yang, B., He, Q. J., Wang, J. J., & Weng, Q. J. (2021). Natural products: Potential treatments for cisplatin-induced nephrotoxicity. *Acta Pharmacologica Sinica*, 42(12), 1951–1969.
4. Kumar, S., & Tchounwou, P. B. (2015). Molecular mechanisms of cisplatin cytotoxicity in acute promyelocytic leukemia cells. *Oncotarget*, 6(38), 40734–40746.
5. Manohar, S., & Leung, N. (2018). Cisplatin nephrotoxicity: A review of the literature. *Journal of Nephrology*, 31, 15–25.
6. Motwani, S. S., & colleagues. (2023). Cisplatin nephrotoxicity: Novel insights into mechanisms and preventative strategies. *Seminars in Nephrology*, 43.
7. Sanz, A. B., Sanchez-Niño, M. D., Ramos, A. M., et al. (2023). Regulated cell death pathways in kidney disease. *Nature Reviews Nephrology*, 19, 281–299.
8. Tang, C., Livingston, M. J., Safirstein, R., & Dong, Z. (2023). Cisplatin nephrotoxicity: New insights and therapeutic implications. *Nature Reviews Nephrology*, 19, 53–72.
9. Wang, D., & Lippard, S. J. (2005). Cellular processing of platinum anticancer drugs. *Nature Reviews Drug Discovery*, 4, 307–320.
10. Wang, J., & others. (2022). Revisiting the anti-cancer toxicity of clinically approved platinating derivatives. *International Journal of Molecular Sciences*, 23(23), 15410.
11. Zhang, J., (2020). Advances in our understanding of the molecular mechanisms of action of cisplatin in cancer therapy. *Cancers*, 12, 2962.