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Research on the Mechanism of Cisplatin-induced Apoptosis and Methods to Alleviate Its Toxicity

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Abstract. Cisplatin is used as a first-line chemotherapy drug in the treatment of various malignancies, but its clinical application is severely limited by dose-limiting toxicities that affect the kidneys, gastrointestinal tract, lungs, and auditory system. Current studies have elucidated the multifactorial mechanisms behind these toxicities, including mitochondrial dysfunction mediated by oxidative stress, DNA damage-induced apoptosis, and dysregulated cell death crosstalk (such as ferroptosis and necroptosis), as well as organ-specific accumulation regulated by transporters such as OCT2 and CTR1. However, the synergy between multi-organ toxicity mechanisms remains to be fully elucidated. This review systematically analyzed the molecular pathways driving cisplatin-induced organ damage, identified risk factors, and provided target ideas for subsequent research on emerging protective strategies. The main findings showed that targeted inhibition of uptake transporters (OCT2), activation of cytoprotective pathways (PPARαagonists), and regulation of cell death nodes (MLKL/RIPK3 inhibitors) can significantly reduce toxicity without affecting efficacy. This study provides a mechanistic basis for the design of personalized cisplatin regimens and provides a reference for clinical risk stratification. Key unanswered questions include optimizing organ-selective drug delivery systems and defining biomarkers of toxicity susceptibility. Future studies should prioritize combinatorial approaches that simultaneously target oxidative stress and cell death cascades in affected organs to expand the therapeutic window.

Keywords: cisplatin toxicity, oxidative stress, apoptosis, renal protection

1. Introduction

Cisplatin, or cis-diamminedichloridoplatinum(II), represents a cornerstone in the history of metal-based anticancer therapeutics. Discovered serendipitously in 1965 by Barnett Rosenberg during experiments on bacterial cell division inhibition under electric fields, cisplatin's anticancer potential was later validated in preclinical and clinical studies, leading to its approval by the U.S. Food and Drug Administration (FDA) in 1978 for testicular and ovarian cancers [1,2]. As a first-generation platinum drug, cisplatin has since been widely employed in treating various solid tumors, including lung, bladder, cervical, and head-and-neck cancers, owing to its ability to form covalent DNA adducts that disrupt replication and transcription, ultimately triggering apoptosis [3,4]. The primary

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mechanism of cisplatin's cytotoxicity involves the formation of intra- and interstrand DNA crosslinks, predominantly targeting the N7 position of purine bases. These lesions distort the DNA helix, activating DNA damage response pathways such as the nucleotide excision repair (NER) and mismatch repair (MMR) systems. Failure to repair these lesions leads to cell cycle arrest (G1, S, or G2 phases) and subsequent activation of apoptotic pathways via p53-dependent and independent mechanisms [5,6]. For instance, cisplatin-induced DNA damage activates kinases like ATR(Ataxia telangiectasia and Rad3-related protein) and ATM (Ataxia-telangiectasia mutated), which phosphorylate p53, promoting transcription of pro-apoptotic genes, while suppressing anti-apoptotic proteins [7,8]. Mitochondrial dysfunction and reactive oxygen species (ROS) generation further amplify apoptotic signaling through cytochrome c release and caspase cascade activation [9].

Despite its clinical success, cisplatin therapy is limited by intrinsic and acquired resistance, as well as severe off-target toxicities, including nephrotoxicity, ototoxicity, and neurotoxicity. Resistance mechanisms encompass reduced drug uptake (via Copper transportation protein 1 (CTR1) downregulation), enhanced efflux (mediated by ATP7A/B), detoxification by glutathione (GSH), and enhanced DNA repair. Additionally, cisplatin's non-selective biodistribution and interaction with plasma proteins (e.g., albumin) further diminish its therapeutic efficacy. To address these challenges, research has expanded to explore cisplatin's crosstalk with alternative cell death pathways, such as ferroptosis (iron-dependent lipid peroxidation) and necroptosis (regulated necrosis), which may synergistically enhance cytotoxicity or exacerbate tissue damage [9]. Understanding these interactions is critical for developing strategies to optimize cisplatin's therapeutic window.

This review focuses on the molecular intricacies of cisplatin-induced apoptosis, its interplay with other cell death modalities. Elucidation of these mechanisms may provide a foundation for novel therapeutic interventions that utilize cisplatin's apoptotic efficacy while minimizing its adverse effects.

2. Organs affected by cisplatin toxicity

2.1. Kidney

Nephrotoxic cellular processes are caused by the intracellular conversion of cisplatin to toxic metabolites and the local accumulation of the drug through the proximal tubular membrane. Therefore, even if cisplatin is not toxic in the blood, its concentration in the kidney may still reach a level that is toxic to humans. According to early studies, cisplatin moves from the basolateral to the apical side of the tubular cells [10]. Cisplatin is cleared from the bloodstream and enters the tubular cells by transporters produced in the basolateral part of the tubule, such as organic cation transporter 2 (OCT2, the major OCT in the human kidney) and, less commonly, CTR1.Then, apically expressed multidrug and toxin extrusion transporter 1 (MATE1) extracts cisplatin from the tubular lumen. Overall, there is a negative correlation between cisplatin nephrotoxicity and MATE1 and a positive correlation with OCT2 and CTR1 expression [11].

Cisplatin induces oxidative stress, a phenomenon characterized by an imbalance between the generation and elimination of ROS. Following treatment with cisplatin, reactive oxygen species (ROS) levels in mitochondria are dramatically increased through multiple pathways, leading to nephrotoxicity.

First off, as cisplatin is an electrophile, it can directly interfere with the way mitochondrial complexes function, thereby increasing the production of reactive oxygen species (ROS). Second, cisplatin impairs mitochondrial energetics by inhibiting the expression of genes involved in fatty

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acid metabolism regulated by peroxisome proliferator-activated receptor α (PPARα). The major energy source for the proximal tubule is fatty acid oxidation. PPARα agonist therapy has been reported to mitigate cisplatin-induced nephrotoxicity in humans [10]. Cisplatin can also deplete mitochondrial energetics by inhibiting mitochondrial glutamate-oxaloacetate aminotransferase, which catalyzes the conversion of glutamate and oxaloacetate as well as aspartate and α-ketoglutarate and is essential for the entry of NADH, the major electron donor for oxidative phosphorylation, into mitochondria.

Moreover, cisplatin also triggers the production of reactive oxygen species (ROS) via NADPH oxidase (NOX). Treatment with cisplatin markedly increases O2 generation in both glomeruli and proximal tubules, correlating with elevated expression of the NOX subunits gp91phox and p47phox. Among the NOX isoforms (NOX1-5), NOX4, found in the nucleus and endoplasmic reticulum [11], is highly expressed in the kidney. Its expression is significantly upregulated in carboplatin-induced acute kidney injury models. By promoting ROS-mediated programmed cell death and inflammation, NOX4 plays a key role in worsening cisplatin-induced kidney damage.

2.2. Gastointestinal tract

Despite nephrotoxicity is the main dose-limiting side effect of Cisplatin, gastrointestinal symptoms are the major problem for patients as a lifelong clinical issue. Cisplatin is mainly absorbed through passive diffusion in the gastrointestinal tract.

The intestine is clinically highly susceptible to cisplatin cytotoxicity, primarily due to the rapid proliferation of gastrointestinal epithelial cells. Cisplatin-induced intestinal toxicity manifests as severe gastrointestinal dysfunction that severely affects treatment compliance. The most common persistent clinical sequelae include nausea, vomiting, anorexia, weight loss, and other complications, which often persist after treatment cessation [12]. Epidemiologically, cisplatin chemotherapy causes diarrhea in approximately 67% of patients, while nausea and/or vomiting affects 70–80%.

Researches have shown that Cisplatin-induced vomiting is related to the increase of 5-hydroxytryptamine (5-HT) concentrations in the intestine and brainstem, which mainly enhances the release of 5-HT by enterochromaffin cells in the gastrointestinal tract, thereby stimulating 5-HT3 receptors (5-HT3 Rs) on vagal afferents to initiate the vomiting reflex. In addition, Cisplatin treatment reduces the overall surface area of villi in the small intestine, which in turn, decreases intestinal motility and alters the digestive and metabolic functions of the small intestine.

As mentioned above, Cisplatin-induced oxidative stress can cause mitochondrial dysfunction, which may be the cause of the activation of multiple signaling pathways that ultimately lead to apoptosis and necrosis of intestinal cells. The sequential events leading to oxidative damage of intestinal cells caused by CP are summarized in the Fig.1 [12].

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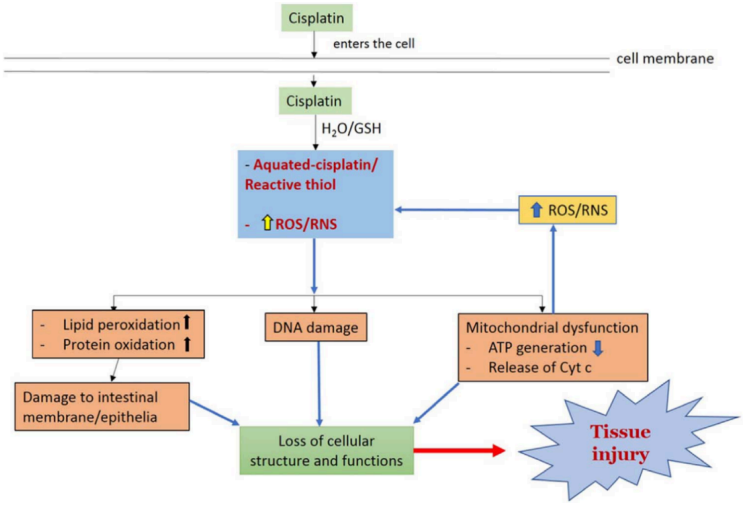

Figure 1: Sequential events leading to oxidative damage of intestinal cells by cisplatin [12]

2.3. Lung

Studies have demonstrated that cisplatin causes lung damage in a dose-dependent manner. Han et al. assessed the shape of lung tissue in bronchoalveolar lavage fluid (BALF), as well as the number of cells and protein content. The experimental group discovered that, in a dose-dependent manner, the quantity of cells and protein content in BALF increased dramatically three days after mice were injected with cisplatin. Additionally, thickening of the lung interstitium and an increase in cell count were noted three days following the injection of cisplatin (20 mg/kg Body Weight). Furthermore, mice who received cisplatin injections had increased lung tissue expression of Ly6G, a marker of monocytes, granulocytes, and neutrophils, than mice in the control group [13].

Secondly, analysis conducted by the experimental group identified the presence of ciliary structural proteins and their breakdown fragments within bronchoalveolar lavage fluid (BALF). This finding provides direct biochemical evidence that cisplatin treatment induces significant structural disintegration of motile cilia on the surface of respiratory epithelial cells. Consequently, the resulting ciliary debris, comprising detached protein fragments, is subsequently released into the airway lumen and recovered in BALF. The underlying pathogenesis of this cisplatin-induced damage to both pulmonary epithelial cells and their ciliary apparatus is mechanistically linked to the drug's capacity to perturb the pulmonary redox equilibrium. This disruption culminates in a state of heightened oxidative stress within the lung tissue microenvironment. The excessive generation of reactive oxygen species (ROS) associated with this stress is a principal mediator of the observed cellular and subcellular structural injury.

2.4. Ear

The main route for cisplatin to enter the cochlea is through the blood vessels in the stria vascularis. After entering the endolymph of the middle ear, cisplatin is absorbed through the apical membrane of sensory hair cells. CTR-1 and OCT-2 enter the supporting cell through facilitated diffusion. When cisplatin is taken up by cells, a water reaction occurs. Cisplatin can bind to negatively charged macromolecules within cells and cause damage, thereby leading to cell apoptosis. Compared with other organs (such as the kidneys, lungs and gastrointestinal tract), the cochlea has a longer ability to preserve cisplatin [14]. In the cochlea of mice and humans, cisplatin cannot be cleared for months or

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years after cisplatin treatment and mostly accumulates in the stria vasculatum area. One of the reasons why cisplatin cannot be cleared from the cochlea for a long time may cause ototoxicity.

According to molecular theory, cisplatin may harm DNA, which would trigger apoptosis and harm the cochlea. Furthermore, one of the main causes of cochlear damage and hearing loss brought on by cisplatin is oxidative stress. Cochlear hair cells undergo mitochondrial-mediated apoptosis when ROS accumulates. Cisplatin's pro-inflammatory characteristics raises the possibility that inflammation and ototoxicity are strongly related. Cell death, cochlear damage, and eventually hearing loss can result from the inner ear's overproduction of inflammatory mediators [14].

3. Molecular mechanisms of cisplatin-induced apoptosis

3.1. Intrinsic (mitochondrial) apoptotic pathway

Cisplatin-induced apoptosis is tightly linked to mitochondrial dysfunction, a process central to the intrinsic apoptotic pathway. Cisplatin cross-linking with DNA causes damage, activates the ATR/Chk2 signaling pathway, and leads to the phosphorylation of p53. p53 upregulates the pro-apoptotic protein PUMA, which antagonizes the mitochondrial anti-apoptotic protein Bcl-XL and releases Bax and Bak. Bax/Bak oligomerizes on the outer mitochondrial membrane to form channels, promoting the release of cytochrome c, which activates Caspase-9 and downstream Caspase-3 [15]. This pathway is regulated by the Bcl-2 family proteins, where cisplatin downregulates anti-apoptotic Bcl-2 and upregulates pro-apoptotic Bax, shifting the balance toward mitochondrial outer membrane permeabilization (MOMP). Notably, cisplatin-induced mitochondrial ROS generation amplifies apoptotic signaling, further destabilizing mitochondrial integrity [16]. The sequential mechanism is depicted in Fig.2.

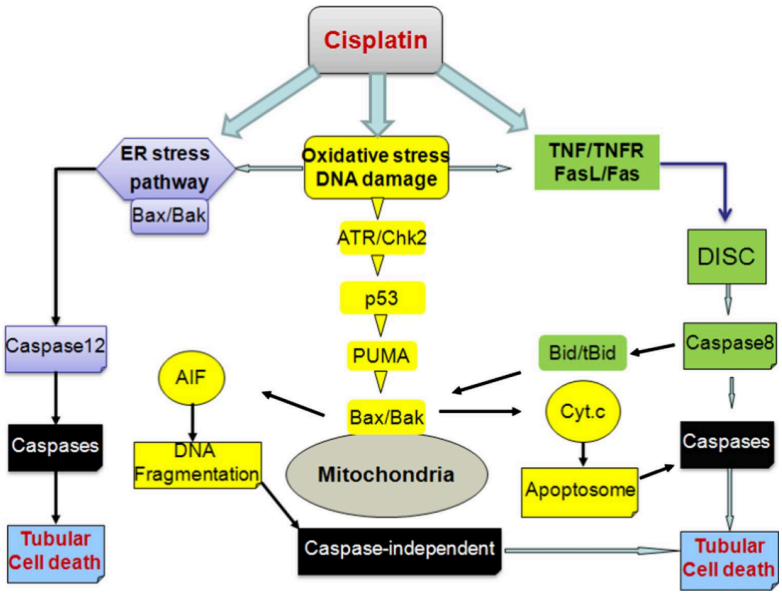

Figure 2: Pathways of apoptosis in cisplatin nephrotoxicity [15]

3.2. Extrinsic (death receptor) apoptotic pathway

TNF-α is the primary mediator of death receptor signaling, which activates the extrinsic pathway. Caspase-8 is activated in cisplatin-treated fibrosarcoma L929 cells when TNF-α binds to TNFR1 and recruits adaptor proteins (TRADD, FADD) to form the death-inducing signaling complex

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(DISC). Bid is broken down by active caspase-8 into tBid, which moves to the mitochondria and works in concert with the intrinsic route to increase Caspase-3 activation and cytochrome c release. However, this route changes to necroptosis through RIPK1/RIPK3/MLKL activation in apoptosis-resistant environments. Fig. 2 also mentions the entire procedure.

4. Crosstalk between apoptosis and other cell death pathway

4.1. Ferroptosis

Ferroptosis is a form of intracellular iron-dependent cell death that is different from apoptosis, necrosis, and autophagy. It is a newly discovered, regulated, non-apoptotic form of cell death. The classic GPX4 regulatory pathway, iron metabolism pathway, and lipid metabolism pathway are three key pathways that initiate the ferroptosis process. Cisplatin has been found to induce ferroptosis, and its potent DNA toxicity damages the already unstable genome of tumor cells, leading to the production of immunogenic DNA fragments. These fragments are believed to play a key role in the ferroptosis process [9].

Existing studies have found that cisplatin consumes intracellular reduced glutathione (GSH), which is an essential cofactor for glutathione peroxidase 4 (GPX4). After cisplatin inactivates GPX4, it cannot reduce phospholipid hydroperoxides (PLOOH), resulting in the accumulation of lipid peroxides, thereby inducing cell membrane damage and ferroptosis [17].

Since ferroptosis is an iron-dependent mechanism for cell death, one of its features is an increase in the labile iron pool (LIP). According to research, cisplatin can increase the amount of free iron (Fe2+) in cells by causing ferritinophagy or blocking iron transporters such DMT1 and LCN2 [17]. The findings of the protein test in the Ni M et al. experiment demonstrated that cisplatin and shikonin together caused ferroptosis. The levels of lipid peroxidation (LPO), reactive oxygen species (ROS), and Fe2+ rose, according to the results of these tests. It was demonstrated using glutathione peroxidase 4 (GPX4) that cisplatin increased the amount of free iron (Fe2+) in cells [18]. Ferroptosis is caused by excess Fe2+ because it directly catalyzes lipid peroxidation, produces hydroxyl radicals (˙ OH) through the Fenton Reaction, and contributes to the peroxidation of phospholipids to create PLOOH [9,17].

4.2. Necroptosis

Recently, necroptosis, also referred to as regulated necrosis, has been identified as a type of cell death that occurs under conditions of impaired apoptosis. This regulated process has features of both accidental necrosis and apoptosis while both apoptosis and necroptosis are programmed. Similar to necrosis, its morphological characteristics include organelle failure, plasma membrane rupture, and cell swelling [18]. Moreover, energy depletion, reactive oxygen species (ROS) production, and calcium (Ca 2+) buildup are biochemical features of necroptosis. The activation of several important proteins, such as receptor-interacting protein kinase (RIPK)-1, RIPK3, and mixed lineage kinase domain-like protein (MLKL), is linked to the regulation of the necroptosis pathway. By activating nicotinamide adenine dinucleotide phosphate oxidase, suppressing the activity of several antioxidant enzymes, and directly upsetting the mitochondrial respiratory chain, which results in the production of ROS, cisplatin has an impact on mitochondrial function [19]. An increasing number of studies have demonstrated that ROS and the necroptosis pathway interact. Consequently, necroptosis is triggered by cisplatin via a positive feedback loop [9]. Cisplatin promotes RIPK3 recruitment and necrosome formation by directly stimulating RIPK1 autophosphorylation through the generation of

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ROS. On the other hand, when necroptosis is stimulated, RIPK3 activates a number of metabolic regulatory enzymes, which raises energy metabolism and reactive oxygen species (ROS) and intensifies necroptosis activation. MLKL and RIPK3-containing necrosomes can promote aerobic respiration, which raises the production of ROS in the mitochondria [19]. Damage to renal tissue is made worse by this process. Acute kidney damage (AKI) could result from this [9].

5. Conclusion

Cisplatin-induced multi-organ toxicity is driven by interrelated mechanisms such as oxidative stress, DNA damage, and cell death pathway dysregulation. This review summarizes the following key points: (1) Organ-specific accumulation (e.g., OCT2/CTR1-mediated platinum drug uptake in the kidney and cochlear platinum drug retention) exacerbates local damage through mitochondrial dysfunction and reactive oxygen species (ROS) amplification; (2) apoptosis, ferroptosis (GPX4 inactivation/Fe^{2+}overload), and necroptosis (RIPK1/3-MLKL activation) triggered by the p53-PUMA/Bax cascade are intertwined, providing references and ideas for studying multi-target treatments for cisplatin cytotoxicity.

Emerging mitigation strategies—including OCT2 inhibition, PPARα agonists for restoring metabolic homeostasis, and targeting cell death checkpoints (e.g., MLKL inhibitors)—may show preclinical promise in effectively reducing cisplatin-induced cytotoxicity in anti-cancer clinical practice. However, key challenges remain: lack of biomarkers for real-time toxicity monitoring, incomplete understanding of the mechanisms of neurotoxicity, and limited clinical translation of organ-selective delivery systems. Combinatorial approaches that can simultaneously neutralize oxidative stress and modulate death pathway crosstalk should be prioritized in the future and validated repeatedly in animal studies and clinical trials using reliable organoid models. Integrating pharmacogenomics for risk stratification will ultimately enable personalized cisplatin regimens that maximize treatment efficacy while minimizing lifelong morbidity.

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