ISSN 2706-6819 Vol. 7, Issue 1: 91-96, DOI: 10.25236/IJFM.2025.070115

Mitochondrial Pathways in Cisplatin Resistance: A New Perspective on Tumor Therapy Challenges

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Abstract: *Despite its high toxicity and the frequent recurrence of patients due to drug resistance, cisplatin remains one of the most effective and widely used chemotherapeutic agents for treating various solid tumors. Therefore, avoiding cisplatin resistance remains a primary goal in clinical treatment. Increasing evidence highlights the importance of mitochondria in cancer initiation, progression, metastasis, and chemotherapy resistance. This review summarizes current understandings of the role of mitochondria in cisplatin resistance and recent developments in this field, including mitochondrial DNA alterations, increased mitochondrial reactive oxygen species (ROS), and changes in mitochondrial dynamics. It aims to provide new insights into the mechanisms of cisplatin resistance and identify novel therapeutic targets for overcoming cisplatin resistance in tumors.*

Keywords: *Mitochondria, Cisplatin Resistance, Tumors*

1. Introduction

Cisplatin (cis-[PtCl2(NH3)2], DDP) is one of the most potent and widely used drugs for treating various solid cancers, such as testicular cancer, ovarian cancer, head and neck cancer, bladder cancer, lung cancer, cervical cancer, melanoma, and lymphoma[1]. Cisplatin typically binds to genomic DNA (gDNA) or mitochondrial DNA (mtDNA), causing DNA damage, blocking the production of DNA, mRNA, and proteins, inhibiting DNA replication, and activating multiple signaling pathways, ultimately leading to tumor cell necrosis or apoptosis[2,3]. However, in most cases, tumor cells exposed to cisplatin activate various adaptive responses, making them less susceptible to cisplatin's anti-proliferative and cytotoxic effects and eventually restoring their proliferative capacity[4]. Consequently, most patients treated with cisplatin are destined to experience treatment failure and tumor recurrence. Therefore, identifying different pathways and molecular targets may provide new perspectives for overcoming cisplatin resistance.

Mitochondria are the primary sites of cellular energy metabolism. In addition to their core bioenergetic functions through the tricarboxylic acid cycle (TCA), oxidative phosphorylation (OXPHOS), and fatty acid oxidation (FAO), mitochondria also perform anabolic functions, such as the biosynthesis of amino acids, lipids, and nucleotides. Furthermore, they maintain Ca2+ homeostasis and redox equivalents and participate in intrinsic apoptotic signaling pathways, thereby regulating cell death[5]. These diverse functions enable mitochondria to sense cellular stress and confer cells with high plasticity, allowing them to rapidly adapt to challenging microenvironmental conditions. Sixty years ago, Warburg proposed that tumor cells prefer glycolysis over oxidative phosphorylation for energy production, which is associated with mitochondrial dysfunction[6]. In recent years, research on the "Warburg effect" has become more comprehensive, with increasing evidence showing that tumor cells undergo metabolic remodeling when acquiring drug-resistant phenotypes. This process enables cells to adapt to drug pressure by adjusting their metabolic pathways, thereby developing resistance. During this process, various mitochondrial-regulated physiological processes are involved in modulating cisplatin resistance. Mitochondrial DNA (mtDNA) and membrane proteins are primary targets of cisplatin, and cisplatin can impair mitochondrial function, leading to excessive ROS production[7]. This review will elaborate on the mitochondrial-related mechanisms in cisplatin resistance, providing new perspectives for understanding the role of mitochondria in acquired cisplatin resistance and offering potential therapeutic targets for overcoming cisplatin resistance.

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2. Mitochondrial Function and Cisplatin Resistance

2.1. Mitochondrial DNA (mtDNA) Damage and Repair

Studies have shown that mitochondrial DNA is a primary target of cisplatin, and cisplatin-induced mtDNA damage can lead to drug resistance[7]. Cisplatin can bind to mtDNA, forming adducts similar to its interaction with nuclear DNA. However, mtDNA lacks the nucleotide excision repair (NER) mechanism present in nuclear DNA, making it more susceptible to damage[8]. The specific targeting of mtDNA by cisplatin has been confirmed in multiple studies, such as its preferential binding to mtDNA in head and neck squamous cell carcinoma and ovarian cancer cells[9,10]. mtDNA damage leads to mitochondrial dysfunction, including decreased mitochondrial membrane potential, reduced adenosine triphosphate (ATP) production, and impaired activity of mitochondrial respiratory chain complexes. These changes further trigger the production of intracellular ROS, exacerbating oxidative stress and ultimately leading to cell apoptosis or necrosis[10]. The weak repair capacity of mtDNA is a critical factor in cisplatin resistance. Studies indicate that the absence or deficiency of mtDNA damage repair mechanisms enhances cancer cell resistance to cisplatin[8]. Additionally, the upregulation of mtDNA repair proteins may be associated with cisplatin resistance[11].

2.2. Reactive Oxygen Species (ROS) Regulation

ROS play a significant role in cisplatin-induced cytotoxicity, but abnormal ROS metabolism can lead to cisplatin resistance. Cisplatin-resistant cells utilize multiple mechanisms to combat oxidative stress. These include upregulating key antioxidant enzymes, such as nuclear factor erythroid 2–related factor 2 (Nrf2), superoxide dismutase (SOD), and glutathione (GSH), as well as enhancing their reactive oxygen species (ROS) scavenging capacity. This adaptive response effectively reduces ROS levels and mitigates cisplatin-induced oxidative stress[12]. Second, through metabolic reprogramming, including increasing oxidative phosphorylation and enhancing glutamine dependency, they reduce sensitivity to ROS[13]. Additionally, decreased mitochondrial membrane potential, reduced ATP synthesis, and mtDNA mutations and functional deterioration further exacerbate abnormal ROS metabolism[14,15]. Mitochondria are the primary source of ROS, and their dysfunction can lead to increased or decreased ROS levels, thereby affecting cisplatin sensitivity. Cisplatin-resistant cells often exhibit elevated mitochondrial ROS levels, which may result from impaired mitochondrial electron transport chains or enhanced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity[16]. Moreover, these cells show increased mitochondrial numbers and morphological changes, including fission and fusion, which may affect mitochondrial function and exacerbate ROS production[17]. Simultaneously, the expression levels of key mitochondrial proteins, for example, peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) and mitochondrial transcription factor A (TFAM), also change, influencing mitochondrial biogenesis and ROS metabolism[18].

2.3. Energy Metabolism

A significant mechanism of cisplatin resistance is the metabolic reprogramming of tumor cells to adapt to the toxicity of chemotherapeutic drugs, closely related to changes in glucose, amino acid, fatty acid metabolism, and the TCA cycle. Cisplatin reduces the energy supply of cancer cells by inhibiting glycolysis and the TCA cycle. Studies have shown that inhibiting glycolysis, through the suppression of hexokinase or glucose transporters, can enhance the cytotoxicity of cisplatin. Additionally, the accumulation of glucose metabolites, for example, lactate, is also considered an important marker of cisplatin-induced cell death[19]. The TCA cycle is a central pathway in cellular energy metabolism. In cisplatin-resistant cells, the levels of certain metabolic intermediates, such as malate and oxaloacetate, are elevated. This suggests that these metabolic pathways may be reactivated to support cell survival[19]. Cancer cells enhance fatty acid metabolism and reduce glucose dependence to survive cisplatin-induced oxidative stress[20,21]. The enhancement of fatty acid metabolism is closely related to cisplatin resistance[22]. Platinum(IV) complexes with fenofibrate as the axial ligand can improve the drug sensitivity of tumor cells to cisplatin by inhibiting the metabolism of cholesterol[23].Studies have shown that increased FAO directly leads to cisplatin resistance. Moreover, the upregulation of fatty acid synthesis-related genes is also associated with cisplatin resistance[24]. Research targeting these metabolic pathways provides direction for the development of new anticancer drugs. For example, by inhibiting key enzymes in fatty acid synthesis, glycolysis, or the TCA cycle, the toxicity of cisplatin can be enhanced[25]. Amino acid metabolism also plays a crucial role in cisplatin resistance. Studies have found that supplementation with certain amino acids, for example, proline, can enhance cancer cell resistance

ISSN 2706-6819 Vol. 7, Issue 1: 91-96, DOI: 10.25236/IJFM.2025.070115

to cisplatin. Inhibition of amino acid metabolic pathways, including glutaminase, may potentiate the antitumor effects of cisplatin[26]. These studies not only reveal the molecular mechanisms of cisplatin resistance but also provide important theoretical foundations and practical guidance for the development of new anticancer drugs.

3. Mitochondrial Dynamics and Cisplatin Resistance

3.1. Mitochondrial Fission and Fusion

Mitochondrial dynamics encompass the processes of fission and fusion, which significantly influence cellular metabolic states and apoptotic pathways. Research indicates that in cisplatin-resistant cells, mitochondrial fission and autophagy are increased, while mitochondrial fragmentation and apoptotic cells are reduced, suggesting a potential mechanism for drug resistance. In cisplatin-resistant leukemia cell lines (e.g., L1210/Dk), studies have demonstrated the upregulation of mitochondrial fusion-related proteins (Mitofusin 1 [Mfn1] and Mitofusin 2 [Mfn2]) and concomitant downregulation of fission-related proteins (Dynamin-related protein 1 [Drp1] and Optic atrophy 1 [OPA1]), suggesting that dysregulated mitochondrial dynamics may contribute to cisplatin resistance[27]. The regulation of mitochondrial fission and fusion is also linked to cisplatin resistance, with proteins from the p53 and Bcl-2 families influencing apoptosis through mitochondrial dynamics[28].

3.2. Mitophagy

The role of mitophagy in cisplatin resistance is complex and dualistic. Meng Y et al.[29] found that in cisplatin-resistant ovarian cancer cells, the Cullin-RING Ligase 4 Complex (CUL4A/DDB1), also known as $CRL4^{CUL4A/DDB1}$, maintains mitochondrial morphology and function by regulating mitochondrial fission and the PTEN-induced putative kinase 1 (PINK1) / Parkin signaling pathway, thereby promoting drug resistance. Knockdown of $CRL4^{CUL4A/DDB1}$ leads to mitochondrial dysfunction and suppresses tumor growth by inducing mitophagy. Xiao Y Y et al.[30] observed that in gastric cancer, cisplatin-resistant cells (e.g., SGC-7901/DDP) exhibit significantly enhanced mitochondrial fission and mitophagy, with metformin further promoting mitophagy via the AMPK-PINK1/Parkin pathway, protecting cancer cells from cisplatin toxicity. Conversely, Meng Y et al.[29] also noted that while targeting $CRL4^{CUL4A/DDB1}$ to induce mitophagy can clear dysfunctional mitochondria, excessive autophagy disrupts mitochondrial homeostasis, ultimately inhibiting the growth of resistant ovarian cancer cells. Chen W et al.[31] discovered that unc-51-like kinase 1 (ULK1) knockdown combined with p53 activation suppresses mitophagy and induces pyroptosis, effectively reversing cisplatin resistance. Given the complexity of mitophagy, future strategies should consider cancer type, molecular pathways, and microenvironmental characteristics to develop precise therapeutic approaches targeting mitophagy.

4. Mitochondrial-Mediated Apoptotic Pathways and Cisplatin Resistance

Mitochondrial-mediated apoptotic pathways play a central role in cisplatin-induced cell death, regulated by various molecular mechanisms. Low H B et al.[32] found that dual-specificity phosphatase 16 (DUSP16) inhibits c-JUN N-terminal kinase (JNK) and p38 activation, reducing BAX accumulation in mitochondria and thereby decreasing apoptosis. Tumor necrosis factor α-induced protein 2 (TNFAIP2) enhances ROS clearance by activating the NRF2 pathway, inhibiting JNK phosphorylation and its apoptotic pathway[33]. In head and neck squamous cell carcinoma, cAMP response element-binding protein 5 (CREB5) suppresses mitochondrial apoptosis via the Mitochondrial Topoisomerase I (TOP1MT) axis, leading to cisplatin resistance[34]. These studies provide a theoretical foundation and practical guidance for developing new anti-resistance strategies.

5. Mitochondrial-Targeted Strategies in Overcoming Cisplatin Resistance

Mitochondrial-targeted compounds, for instance, iridium (III) complexes and Elesclomol, enhance cisplatin sensitivity by inducing mitochondrial damage. Some iridium (III) complexes bind to DNA, while others disrupt redox balance, demonstrating potent anti-tumor activity, particularly in photodynamic therapy, where they generate ROS upon light activation, selectively killing cancer cells and combating resistance[35]. Elesclomol, a mitochondrial metabolism-targeting anticancer drug, was initially recognized as an oxidative stress inducer but is now also known to inhibit cancer through

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cuproptosis induction[36]. Targeting mitochondrial DNA and membrane proteins, specific nanoparticle delivery systems can improve drug uptake. Self-assembling nanoparticle (NP) platforms composed of amphiphilic lipids and polyethylene glycol (PEG) effectively deliver Pt(IV) prodrugs that resist thiol-mediated detoxification via glutathione (GSH) depletion, offering a promising approach to enhance safety and efficacy[37]. Targeting mitochondrial metabolic reprogramming, Lu H et al.[38] developed a self-assembling nanocarrier system, LND-SS-Pt-TPP/HA-CD, which delivers prodrugs to intracellular mitochondria, where cisplatin and lonidamine (LND) act synergistically. Cisplatin causes mtDNA damage, inducing mitochondrial dysfunction and mitophagy, while LND reduces hexokinase II (HK II) levels, disrupts mitochondria, and blocks energy supply through glycolysis inhibition, ultimately killing cisplatin-resistant lung cancer cells. The mitochondrial-targeting small molecule IR-780, combined with cisplatin, overcomes cisplatin resistance by inducing mitochondrial dysfunction and ROS elevation, reducing intracellular GSH levels, and triggering mitochondrial-mediated cell death[39].

6. Conclusion

Mitochondria play multifaceted roles in cisplatin resistance, involving energy metabolism, ROS regulation, apoptotic pathways, and dynamic changes. By delving deeper into the mechanisms of mitochondrial involvement in drug resistance and developing mitochondrial-targeted therapeutic strategies, new avenues for overcoming cisplatin resistance may emerge. Future research should further explore the interactions between mitochondria, the tumor microenvironment, and the immune system, as well as how these findings can be translated into clinical applications.

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