Cisplatin and Its Intercellular Cytotoxicity: Mechanism Derived from Different Pathway and Progression Targeting Toxicity Concern

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Abstract: Cisplatin is a metal platinum complex with anticancer activity. It is a cell cycle nonspecific antitumor drug that can produce effective cytotoxicity. It mainly crosslinks with DNA, induces apoptosis, inhibits cell viability and kills tumor cells, and also has a certain effect on RNA and protein of tumor cells. Cisplatin, as a kind of classic anticancer drug, plays an important role in clinical chemotherapy. The emergence of cisplatin resistance is the product of the interaction of multiple mechanisms. In this paper, by consulting the relevant literature on cisplatin in recent years, the paper summarizes cisplatin's main mechanisms and recent research progresses.

1 INTRODUCTION

Antineoplastic drugs, specifically against tumor cells, exert their effects through multiple mechanisms, but more or less have counter-effects present in each type of drugs. 5-fluorouracil (5-Fu), a pyrimidine antagonist, blocks the DNA synthesis by converting to 5F-dUMP and subsequently prevents tumor cell growth by inhibiting cell proliferation (Paul, 2021). However, fluorouracil has a high toxicity in rapidly growing cells, such as bone marrow and intestinal epithelium, and it also causes mild leukopenia (decreasing in white cell counts), thrombocytopenia (decreasing in blood platelets counts), and central nerve system (CNS) toxicity that's inversible (Papich, 2016).

Vinblastine, an anticancer drug often used in the past years binds to microtubules protein tubulin, which leads to the termination of microtubules assembly in metaphase and the chromosome splitting to stop the growth of the cell. Yet, in Zhou's research, vinblastine causes the death of myocardial cells through coronary spasm and cardiac arrest. As a result, heart damage inevitably happened in both vitro and vivo use of vinblastine (Zhou, 2021). In addition, vinblastine leads to hyperpigmentation or bluish-black discoloration over the nose and fingertips along with darkening of the nail beds without any other sources of influences (Chakraborti, 2020). Cisplatin (CP) as a metallic-platinum-containing anticancer drug targets multiple locations to exert its effects on the sexual organs on both male and female, respiration system, pancreas, and breast to block the growth of the tumor in cells (Santos, 2020), and platinum based concurrent chemoradiotherapy becomes a necessary step in cure of locoregionally advanced nasopharyngeal carcinoma or a head and neck cancer with a specific geographic distribution (Zhang, 2019). It generally binds to the mitochondrial DNA and damages the DNA that triggers the immune system to haveresponses to the damage (Papich, 2016). CP affects the level of expressed mtDNA reactive oxygen species (ROS) which disrupts the equilibrium of oxygen, ATP production, and ROS which increases the expression of apoptosis caspases and leads to cell death. Lastly, the release of chemokines and cytokines from DNA damage induced by ROS causes inflammation in cell (Papich, 2016; Zhang, 2019) (figure 1).

Despite the number of routes to control the growth of cancer cells, cisplatin has limitations, so it does not exhibit its full potential. One limitation is resistance which the DNA repair system repeals the outsider

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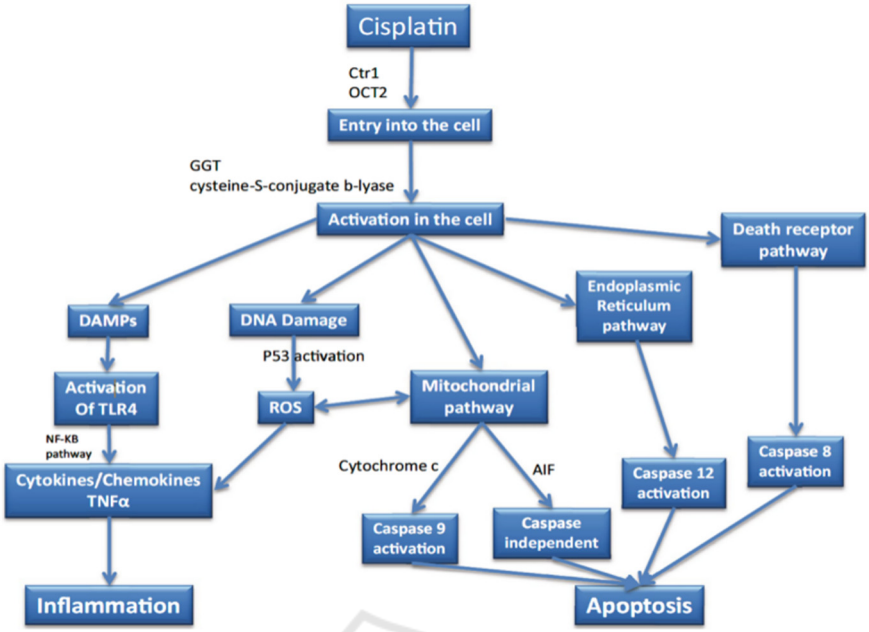

Figure 1: The overall picture of different pathways involved in cisplatin nephrotoxicity (Manohar, 2018).

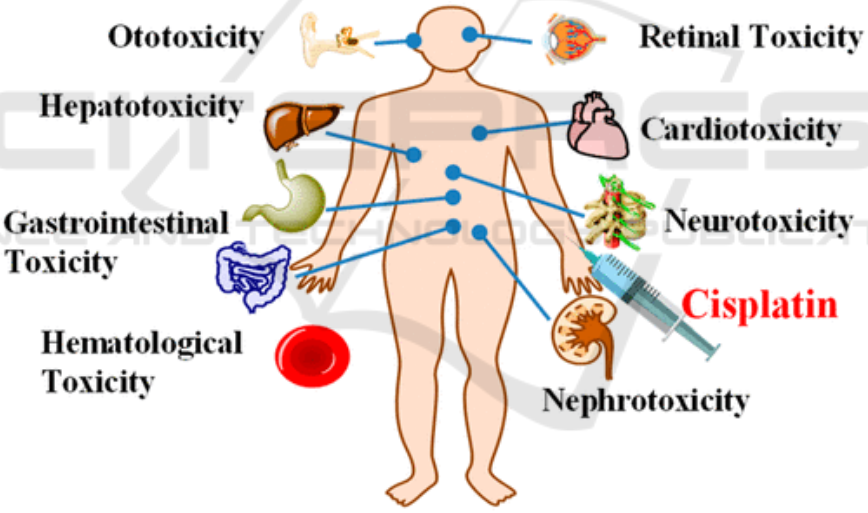

Figure 2: The variety of toxicities produced after cisplatin is injected (Qi, 2019).

cisplatin and lowers the effectiveness of the drug; another limitation is the inactivation of the drug by binding to different proteins which lead to weakened signaling to apoptosis and pro-survival mechanisms (Ghosh, 2019); lastly, cisplatin is highly dosage dependent, and when a higher dose is taken, it leads the different type of toxicities in the body, and the nephrotoxicity is the most common one (figure 2). Those toxicities are not lethal, but they affect the life quality of the patients through discomfort, and subsequently reduce the treatment time and the effect of cisplatin (Qi, 2019). The main focus of this paper is to introduce different pathways hat are derived from DNA damage and the production of ROS and analyze how the resistance occurs.

2 MECHANISM

2.1 DNA Damage and ROS

Cisplatin (CP) contains a platinum atom that can covalently bind to DNA, but only a small percentage of CP is directly bound to DNA, and most of the

binding is through histone H1. H1, platinum (pt), and DNA form a ternary complex. This complex makes the binding between cisplatin to DNA stronger than just them alone, and H1 also strengthens the effect of cisplatin by inhibiting the DNA repair mechanisms (Cheng, 2019). Recently, another paper has proposed another mechanism for the binding of CP to DNA based on dissociative electron transfer (DET), in which cisplatin accepts electrons from DNA to form two reactive radicals and DNA adducts (Li, 2019). Due to the binding, cells activate the repair pathway to fix the DNA adducts (Kleih, 2019), and two types of repair are activated, global repair (GR) and transcription-coupled repair (TCR). Acting on transcribed strands of active genes to repair the modified DNA, TCR is initiated by the translocating RNA polymerases and Escherichia coli RNA polymerase (RNAP). GR, on the other hand, acts on the non-transcribed strands of transcribed genes and is initiated by NER factor UvrA and it removes DNA damage from the entire genome (Yimit, 2019). If the DNA adduct is not being fixed by the repairment, ROS will be produced. ROS is produced during mitochondrial respiration (Kleih, 2019; Yimit, 2019). In most situations, the energy is produced in the form of ATP by mitochondria, and oxygen produced from the ETC will form water molecules. However, some oxygen can escape from this process, and ROS are produced. The overproduction of ROS can cause oxidative stress which disrupts the equilibrium of organelles and lowers the ATP synthesis from the ETC which increases apoptotic factors and decreases in anti-apoptotic factors which lead to cell death and other serious issues.

2.2 Mitochondrial Pathway

It is known that mitochondria confer bioenergetic plasticity to tumor cells, enabling cells to escape death pathways under stress conditions such as chemotherapy. To date, we recognize the central role of mitochondria, and we recognize that mitochondria are promising pharmacological targets for overcoming cisplatin resistance. Cisplatin-induced cytotoxicity is not caused by the heavy metals themselves, but rather by active metabolites transformed by high concentrations of cisplatin into the intracellular environment. Under cisplatin, mitochondria regulate death receptors by affecting the expression of tumor suppressor proteins (TNF-) and then lead to cell mitochondrial dysfunction which activates AIF, caspases, and other pro-apoptotic factors to induce tumor cell apoptosis (Volarevic, 2019).

The first pathway is the pro-apoptotic factor cytochrome activates caspase-9. This is an apoptotic pattern dependent on proapoptotic factors. This process is after cisplatin stimulated cells, BH3-Interacting Domain Death Agonist (Bid), a member of the Bcl-2 protein family that regulates the permeability of exterior mitochondrial membranes, and apoptosis-promoting gene BCL2-Associated X protein (Bax), a water-soluble-associated protein that belongs to the rabbit anti-human monoclonal antibody. Activation of isoproteins induces increased mitochondrial outer membrane permeability, interferes with mitochondrial function, and induces the automatic release of cytochrome c-mitochondria, which all lead to the activation of Caspase-9 (Bernal-Barquero, 2019). Meanwhile, the reduction in ATP synthesis forces the stressed cells to function in a starvation mode and activate the caspase-induced apoptosis through the release of caspase-9 mediators which is an irreversible cell apoptosis process.

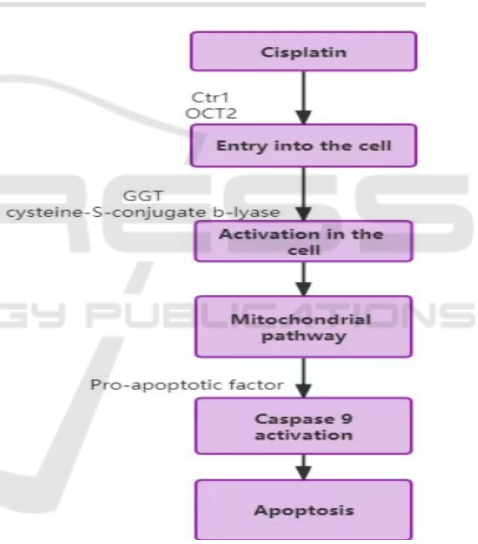

Figure 3: Caspase-dependent mechanism in cisplatin-induced apoptosis.

Although caspase is an important pro-apoptotic factor in apoptosis, there is increasing evidence for a caspase-independent mechanism in cisplatin-induced apoptosis, which is the AIF-induced apoptosis. This is an apoptotic pathway independent of the caspase pro-apoptotic factor (Pabla, 2008).

AIF, the universal apoptosis inducer factor, was the first factor to induce caspase-independent cell apoptosis in 1999. It is present in the inner mitochondrial membrane. It differs from the typical apoptotic process, where AIF transfers from the mitochondria to the cytoplasm and then enters the

nucleus leading to nuclear DNA agglutination, forming 50kb size fragments (Feldman, 2008).

Typically, AIF has oxidoreductase activity and is involved in mitochondrial ATP generation and redox reactions. When mitochondrial dysfunction occurs, mitochondrial membrane permeability increases, prompting the release of AIF molecules from the mitochondrial cytoplasm, which then translocated to the nucleus according to their nuclear localization sequence and binds to chromosomal DNA. This leads to DNA condensation and degradation, thereby generating caspase-independent forms of apoptosis induction. During cisplatin-induced apoptosis, AIF is cleaved and activated and mediates caspase-independent apoptosis signals, working together with caspase-dependent apoptosis to induce more efficient apoptosis in a complementary manner (Zheng, 2016).

2.3 Inflammatory Pathway

The ROS produced from the DNA damage causes the release of chemokines and other cytokines like TNF-α (Padgett, 2013). Resident kidney cells, such as mesangial cells, glomerular cells, endothelial cells, and renal tubular cells, produce TNF-α locally (Zhang, 2007). Of all these cells, mainly renal tubular cells contribute to the production (Ramesh, 2006).

TNF-α is essential to the generation of pro-inflammatory factors and activation of inflammatory cells. There are two types of TNF-α receptors in a kidney cell: TNFR1 and TNFR2. Different signaling cascades are activated when TNF-α binds to these two receptors. The binding of TNF-α toTNFR2 leads to the inflammatory response (Figure 4). When membrane-bound TNF-α activates TNFR2, it recruits TNFR-associated factor 2 (TRAF2), which then activates NF-κB-inducing kinase (NIK) and subsequently activates IKK complex (Xiao, 2001). Originally, an inhibitory protein IκBα associates with the NF-kappaB dimer, preventing Nf-kappaB from entering the nucleus. Upon activation of IKK complex, IKK phosphorylates IκBα at two N-terminal serines, which triggers ubiquitin-dependent IκBα degradation in the proteasome, resulting in the nuclear translocation of NF-κB dimers (Beinke, 2004; Hayden, 2008). NF-κB dimers then drive the expression of pro-inflammatory genes in innate immune cells, while also controlling the activation of inflammatory T cells (Lawrence T, 2009).

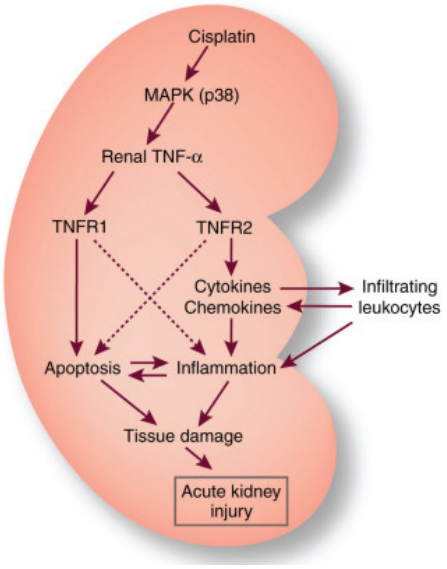

Figure 4: TNF-α production and involvement in cisplatin-induced acute kidney injury (Dong, 2007).

2.4 Autophagy in Kidney

Autophagy is a process in which some damaged proteins or organelles are wrapped by autophagic vesicles with double membrane structure and then sent to lysosomes (animals) or vacuoles (yeast and plants) for degradation and recycling. Because it occurs in both physiological and pathological processes of the body, so far the relevant research has not fully elucidated the role of autophagy in the human body. In the past 20 years, autophagy has always occurred in the research related to cisplatin. Therefore, autophagy is generally considered to be the key to promote cell survival and prevent acute cisplatin nephrotoxicity.

Autophagy protects the kidney from damage during cisplatin exposure, thereby limiting or inhibiting tumor growth, but it may also reduce the efficacy of chemotherapy because of the protection of cancer cells. Autophagy plays an intrinsic protective role in renal tubular cells. Under normal physiological conditions, autophagy in the kidney usually plays a protective cell model of promoting growth to maintain the homeostasis of kidney cells. When the kidney is damaged or in the period of cisplatin exposure, cell stress will rapidly activate induced autophagy to protect the kidney. This autophagy is a form of cytotoxicity that promotes tumor cell death. In addition, there is an unprotected form that does not seem to directly affect cell proliferation or apoptosis (Xu, 2022). When it is proposed that autophagy may inhibit the sensitivity of cisplatin or lead to drug resistance, it is necessary

to distinguish the function of autophagy. In addition, autophagy also plays a role in regulating kidney repair, renal fibrosis, acute renal injury and other renal diseases in the kidney.

3 CISPLATIN RESISTANCE

The main disadvantage of cisplatin therapy is its resistance to cancerous cells. Resistance to cisplatin varies with the kind of cancer. For example, small cell lung, testicular, ovarian, head and neck cancers are highly susceptible to cisplatin, while non-small cell lung cancers and colorectal cancers are highly resistant to cisplatin (Ghosh S, 2019). For to solve this thorny problem, current treatments are taken from the following perspectives: reducing cellular drug uptake, reducing drug influx or increasing efflux, cell thiol detoxification, changing drug targets, and repairing DNA (Ghosh S, 2019; Zhang, 2018). There are four primary positions for resistance to cisplatin in the human body as followed.

3.1 Resistance to Drugs When Circulating Through the Blood Stream

As cisplatin is injected intravenously, it flows into the blood before entering cancerous cells. Proteins in the blood may bind to cisplatin, particularly proteins that contain groups of thiols, such as human serum albumin (the carrier of fatty acids in the blood). When the body needs energy, fat cells will release fatty acids into the blood, which will be collected by serum proteins and transported to the place where they are needed. And cysteine (a common amino acid in an organism.). Binding of this protein results in the inactivation of cisplatin.

3.2 Resistance to Drug Influx or Outflow Through Cell Membranes

A decrease in inflow and an increase in cisplatin efflux leads to a decrease in drug accumulation in cancer cells. Fulnos et al. mentioned that the decrease in cisplatin build-up was due to a decrease in drug uptake rather than an increase in drug efflux (Wang, 2016). In the human body, extracellular cisplatin lowers the concentration of Ctr1, so that the dose of its intracellular cisplatin is significantly reduced, resulting in drug resistance. In addition, the two copper carriers, ATP7A and ATP7B, contribute to the flow of cisplatin from the cells, exacerbating drug resistance.

3.3 Resistance To Cisplatin Is Present in The Cytoplasm

By binding to glutathione and metallosulfur proteins (low-molecular-weight proteins with metal-binding capacity and high induction properties), the GSH and cisplatin complex is then excreted using an outlet pump with gs-coupling. There have been reports suggesting that GST either aids in this response or occurs spontaneously (Holzer, 2006).

3.4 Resistance After Cisplatin-DNA Binding

NER is the most effective way to eliminate DNA damage to produce resistance to cisplatin. To restore expression of gene integrity, the NER system removes damaged nucleotides from the two strands to resynthesize DNA. Cells overexpressed with the NER would be far less cisplatin conscious. The MMR (miss match repair protein) protein is a very essential protein that is commonly used to repair DNA-cisplatin injuries. If it can be fixed, those cells can still survive. In place of this, apoptosis is caused (Ghosh S, 2019). As a result, drug resistance takes place.

3.5 Toxicity

Cisplatin induces different levels of nephrotoxicity, ototoxicity, and neurotoxicity depending on the dose and the individual difference. The nephrotoxicity is the most severe one. Cisplatin-induced Acute kidney injury (AKI) involves proximal tubular injury, apoptosis, oxidative stress, inflammation, and vascular injury in the kidneys, which followed by acute renal failure, chronic kidney disease if the toxicity remain untreated and the medicines are keep in using. From Fang's studies, it shows that natural products have the ability to against oxidants, inflammatory, and apoptosis, which regulate the damage caused by cisplatin. As example, ginseng and pomegranate reduce ROS that's produced from cisplatin by restoring the antioxidant enzymes, which decreases the inflammation and subsequently the level of nephrotoxicity in the body (Fang, 2021).

Cisplatin causes hearing damage that is irreversible, high frequency hearing loss. Cisplatin mainly damages the outer sensory hair cells, and it also could have impacts on the spiral ganglion neurons (SGNs) in the cochlea. To prevent the harm,

the main goal is to prevent inflammation, oxidation, and apoptosis occurring in the cells. Alpha-Lipoic acid according to research can lower the ROS levels, and strengthen the hearing ability. In addition, neurotrophins have also been proposed in the treatmentof ototoxicity, because hair cells maintain a healthy SGNs by releasing neurotrophic factors, and ototoxic damages conduct degeneration of SGNs. Moreover, because neurotrophins' receptors are present in neurons but not in cancer cells, it maximizes the effect of chemotherapy without interrupting other treatment on cancer cells (Santos, 2020).

Neurotoxicity in some situations is pherpieral toxicity which is the loss of proprioception or feeling of one's position and body parts (Santos, 2020). Agomelatine, an antioxidant, has been proven on its ability to prevent cisplatin-induced neurotoxicity in the mouse hippocampal neuronal cell line by areduce oxidative stress and inflammation (Cankara, 2021). Additionally, Cisplatin has been discovered toreduce serotonin-regulated pharyngeal pumping activity independent of neurons such as dopamine and glutamates (Wellenberg, 2021). However, two of serotonin derivatives, -feruloylserotonin and coumaroyl serotonin has ability to significantly reduce the level of ROS by increase the level of glutathione peroxidase in the kidney, which reduce the neurotoxicity caused by cisplatin (Park, 2019).

4 RESEARCH AND APPLICATION OF RELATED TECHNOLOGIES

At present, there are still a lot of scientific problems to be solved in this field. In view of the above four processes, cisplatin resistance in human body has been treated in recent years. In view of that drug resistance of cisplatin in the process of blood circulation, Nanoparticles coupled with platinum drugs is also one of the effective ways to solve drug resistance, The combination of nanoparticles and platinum has the following advantages: they can carry more platinum compounds and the targeting drugs to locate cancer cells more accurately, and we can add some hydrophilic molecules to increase drug solubility. Thus, this combination to spread in tumor sites widely. That is not only soars efficiency, but also declines the toxic and adverse effects of drugs (Zhu, 2016). When cisplatin develops drug resistance through the inflow or outflow of cell membrane, we usually use cisplatin sensitizers, which can improve the sensitivity to drugs at normal doses, among which thiazides are typical representatives. It can reduce cisplatin outflow by inhibiting P-glycoprotein (P-gP) in drug-resistant KBV20C cells, and increase the concentration of cisplatin in cells, thus enhancing the cytotoxicity of cisplatin (Choi, 2014). As a new drug delivery system, nano-micelles have great potential advantages in reducing the toxic and side effects of cisplatin and exerting the best therapeutic effect. For the inactivation of platinum drugs, for example, PEG-b-PBEMA micelles loaded with tetravalent platinum were prepared by combining platinum complexes with glutathione consumer-quinone methylate by pharmaceutical means. By improving the efficiency of platinum uptake, reducing intracellular glutathione level and reducing platinum inactivation, the cisplatin resistance of tumor cells can be reversed (Han, 2018). Cisplatin binds to DNA to produce drug resistance. At present, it is mainly by inhibiting the expression of DNA damage repair related proteins to inhibit DNA damage repair and improve platinum drug resistance. PolyADPribose polymerase (PARP) is a kind of DNA damage repair enzyme, and its inhibitor can play a synergistic role in combination with platinum drugs by inhibiting DNA damage repair (Li, 2021), which can enhance the anti-tumor activity of drugs and effectively overcome tumour resistance to cisplatin.A membrane glycoprotein PD-1, which is expressed on the surface of various different immune cells, is paramount in both diseases and adaptive immune responses. Xiaoguang Liu et al. first confirmed that PD-1 plays an important role in regulating cisplatin induced muscle atrophy (Liu, 2022) by regulating autophagy of skeletal muscle.

5 CONCLUSION

Cisplatin nephrotoxicity is a complex process caused by multiple factors. Therefore, it is crucial to understand how the several pathways combined to cause cell dysfunction. This review focuses on two of the pathways: the mitochondrial pathway and the inflammatory pathway (figure 1), both originated from DNA damage. In the mitochondrial pathway, caspase-independent mechanism triggered by AIF leads to apoptosis. In the inflammatory pathway, ROS triggers the release of cytokines and chemokines which leads to inflammation. These contributes to the cisplatin intercellular cytotoxicity. A fascinating area for future study is to compare the different pathways to determine if there's generality in these mechanisms. This may give new insight into renoprotection during cisplatin treatment.

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