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Mitochondrial Dysregulation and Protection in Cisplatin Nephrotoxicity

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Abstract

Nephrotoxicity is a major side effect of cisplatin in chemotherapy. Pathologically, cisplatin nephrotoxicity is characterized by cell injury and death in renal tubules. The research in the past decade has gained significant understanding of the cellular and molecular mechanisms of tubular cell death, revealing a central role of mitochondrial dysregulation. The pathological changes of mitochondria in cisplatin nephrotoxicity are mainly triggered by DNA damage response, pro-apoptotic protein attack, disruption of mitochondrial dynamics, and oxidative stress. As such, inhibitory strategies targeting these cytotoxic events may provide renal protection. Nonetheless, ideal approaches for renoprotection should not only protect kidneys but also enhance the anti-cancer efficacy of cisplatin in chemotherapy.

Keywords

Cisplatin; Nephrotoxicity; Mitochondria; Apoptosis; Reactive oxygen species

1. Introduction

Since its discovery in late 1960s as a chemotherapy drug, cisplatin has been used to treat a variety of cancers such as testicular, ovarian, and lung cancers. The therapeutic efficacy of cisplatin for certain cancer types is remarkably high. For example, the cure rate of testicular cancer with cisplatin is over 90%. As a result, for over a half century, cisplatin and related platinium derivatives have been a mainstay in chemotherapy of cancer. However, cisplatin is also well-known for its side effects. Particularly, renal disorder has been noted since the initial use of cisplatin in patients. The adverse effect of cisplatin in kidneys, called cisplatin nephrotoxicity, is manifested clinically as lower glomerular filtration rate, reduced serum

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Author contributions

ZD designed the outline of manuscript, YY drafted the manuscript, and ZD and LFY checked and revised the manuscript. All authors declare that they have no conflicting interests.

magnesium and potassium levels [1–3]. It is estimated that about a quarter to one-third of patients undergoing cisplatin treatment experience cisplatin nephrotoxicity [1,4]. Pathologically, cisplatin induces cell injury and death in renal tubules, triggers vascular dysfunction, and activates a robust inflammatory response. Despite years of research, the mechanism underlying cisplatin nephrotoxicity remains unclear and effective renal protective approaches during chemotherapy are still not available. In recent years, there have been significant progresses in understanding how renal tubular cells are injured and die following cisplatin treatment. In this review, we briefly summarize the main pathways of cell death in cisplatin nephrotoxicity and then focus on mitochondrial changes that contributes to renal tubular cell injury and death in cisplatin nephrotoxicity.

2. Kidney tubular cell death in cisplatin nephroxicity

A notable pathological feature of cisplatin nephrotoxicity is cell death in renal tubules. Under this condition, both necrosis and apoptosis are detected in various tubular segments, especially proximal and distal tubules. In vitro in cultured tubular cells, cisplatin induces apoptosis in 10–50 micromolar concentrations and necrosis in much higher concentrations. In vivo studies using animal models indicates the presence of mixed forms of cell death. Mechanistically, multiple pathways of apoptosis have been implicated in cisplatin nephrotoxicity (Figure 1). There is an impressive induction of Fas/ Fas ligand and TNF-α by cisplatin [5,6]. Moreover, deletion of TNF-α receptors protects against cisplatin nephrotoxicity in mice, providing further support for a role of death receptor-mediated extrinsic pathway of apoptosis. Also there is evidence of ER stress in experimental models of cisplatin nephrotoxicity, accompanied by the activation of caspase-12 [7,8], but definitive evidence for the involvement of ER stress pathway of apoptosis remains to be demonstrated. In sharp contrast, convincing evidence has been demonstrated for the pathogenic role of mitochondria-mediated intrinsic pathway of apoptosis in cisplatin nephrotoxicity. In the intrinsic pathway, Bax is activated to accumulate in mitochondria, insert into the outer membrane, and form super-oligomers; meanwhile, Bak (which is constitutively expressed in mitochondria) is activated to oligomerize. The oligomers of Bax and Bak induce porous defects in mitochondrial outer membrane, leading to the release of apoptogenic factors, such as cytochrome c. Cytochrome c, after being released into cytosol, associates with Apaf-1 to activate caspase-9. Bax and Bak activation has been demonstrated during cisplatin nephrotoxicity and more importantly, global knockout of Bax and proximal tubule specific knockout of Bak and Bak render mice resistant to cisplatin-induced cytochrome c release, tubular apoptosis and kidney injury [9,10].

Relevant to the focus of this review, it is important to point out that although death receptor-mediated extrinsic pathway and ER-stress associated apoptosis have been implicated in cisapltin nephrotoxicity, these pathways may converge on mitochondria for tubular cell apoptosis. For example, it is well-known that in the extrinsic pathway, caspase-8 cleaves Bid (a BH3-only pro-apoptotic Bcl-2 protein) resulting in the production of truncated Bid called tBid. tBid moves into mitochondria to activate Bax and Bak to activate the intrinsic pathway of apoptosis to amplify the apoptotic cascade for cell demise (Figure 1). The involvement of mitochondria in these apoptotic pathways supports a central role played by mitochondria in in tubular apoptosis in cisplatin nephrotoxicity.

3. Mitochondrial dysregulation in cisplatin nephrotoxicity

a. ROS production as a result of mitochondrial dysregulation

Physiologically, mitochondria are the "power house" in a cell, which generate the energy compound ATP via oxidative phosphorylation. Nonetheless, during oxidative phosphorylation, the leakage of electrons from the mitochondrial respiratory chain is an intracellular source of free radical generation. Electron leakage is particularly problematic when mitochondria are damaged resulting in reduction or blockade of electron transport. Under such conditions, massive amounts of free radicals in the form of reactive oxygen species (ROS) are produced from mitochondria, which may lead to cell injury and death. In cisplatin nephrotoxicity, a decline in state 3 mitochondrial respiration and calcium accumulation have been observed [11]. Also cisplatin nephrotoxicity is associated with a decrease of cytochrome c oxidase (COX) activity and a reduction in complex IV protein expression. These defects in respiratory chain lead to ROS production from mitochondria. Furthermore, cisplatin treatment reduces mitochondrial MnSOD [12], coupled with decreases in glutathione and succinate dehydrogenase (SDH) activity [13], resulting in drastic decreases in the antioxidant activity in kidney cells. In line with these observations, in cisplatin-treated renal tubular cells mitochondria show a decrease of mitochondrial mass, disruption of cristae, and extensive mitochondrial swelling in late stage [14], which are associated with significant reductions in mitochondrial activity and ATP production. Notably, mitochondrial GSH-reductase (GSH-Rd) activity was reduced, accompanied by a marked decrease in GSH levels and significant ROS formation [15]. Together, these studies indicate a critical role of mitochondrial pathology in oxidative stress during cisplatin nephrotoxicity.

b. DNA damage response in mitochondrial damage in cisplatin nephrotoxicity

Cisplatin-induced tubular cell death is a complex process that involves the activation of multiple signaling pathways [16]. Among them, DNA damage response directly contributes to mitochondrial damage. Cisplatin induces DNA damage by inter- and intra-DNA strand cross-linking, followed by DNA breaks during cell cycle. The resultant DNA damage rapidly activates ataxia telangiectasia mutated and Rad3-related (ATR). ATR activation is indicated mainly by its recruitment of this to DNA damage sites, rather than by an increase in its kinase activity. Intriguingly, ATR recruitment during cisplatin treatment does not take the classical pathway of "9-1-1" protein complex; instead, it depends on the formation of a complex with human mutS homolog 2 (hMSH2), resulting in the formation of nuclear foci at the site of DNA damage [17,18]. ATR, after being activated, further phosphorylates Checkpoint kinase 2 (Chk2), which in turn phosphorylates downstream substrates including p53. The roles played by ATR, Chk2, and p53 in cisplatin-induced renal tubular cell injury and death have been demonstrated by using various inhibitory approaches, including dominant-negative mutants, gene silencing and deficiency [17,18]. Interestingly, the inhibitor of histone deacetylases, suberoylanilide hydroxamic acid (SAHA) also blocks cisplatin-induced phosphorylation of Chk2 and p53, resulting cytoprotection in renal tubular cells [19].

p53, a well-recognized tumor suppressor and transcription factor, is considered as an important mediator in cell death during cisplatin nephrotoxicity [20]. Several p53-target genes have been shown to be up-regulated in during cisplatin treatment of renal tubular cells. These include the pro-apoptotic genes p53-induced protein with a death domain (PIDD) and p53 up-regulated modulator of apoptosis (PUMA-α) [21, 22]. PIDD may activate caspase-2 via the formation of PIDDosome, leading to AIF release from mitochondria and subsequent caspase-independent apoptosis [21], while PUMA-α translocates to mitochondria to interact with and antagonize Bcl-XL, an important anti-apoptotic protein in renal tubular cells [22]. Blockade of Bcl-XL by PUMA-α unleashes Bax and Bak to form oligomer pores on the outer membrane of mitochondria, resulting in the release of cytochrome c release and the activation of caspases. Therefore DNA damage response during cisplatin nephrotoxicity activates the intrinsic pathway of apoptosis via p53 and PUMA-α.

In addition to pro-apoptotic genes, p53 is also responsible for the induction of other genes during cisplatin nephrotoxicity. For example, p21 is induced by cisplatin via both p53-dependent and –independent mechanisms. Interestingly, although known as a cell-cycle arrest protein, p21 also has a remarkable cytoprotective effect in renal tubular cells during cisplatin treatment [23]. p21 inhibits cyclin-dependent kinase 2 (CDK2) to protect tubular cells from cisplatin-induced apoptosis [24,25]. In vivo in rats and mice, inhibition of p21 by antisense oligodeoxynucleotides and p21-deficiency significantly aggravates cisplatin nephrotoxicity [26][27]. A recent study further suggests a remarkable negative feedback mechanism of CDK2-p21 regulation, in which CDK2 phosphorylates p21 to attenuate its inhibition on CDK2 [28]. It remains mysterious as to how CDK2 participates in cell death during cisplatin nephrotoxicity. As a protein kinase, CDK2 may have substrates that are directly or indirectly involved in the regulation of cell injury and death.

c. Mitochondrial dynamics in cisplatin-induced kidney cell death and nephrotoxicity

A significant new development in mitochondrial biology is the recognition of the dynamic nature of these organelles. Now it is appreciated that in physiological conditions, mitochondria constantly under fission and fusion, and the dynamic balance between fission and fusion is crucial to the function and viability of mitochondria [29,30,31]. However, during disease or cell stress mitochondrial dynamics may be disrupted, resulting in mitochondrial fragmentation, membrane leakage, and cell injury and death. The fission and fusion of mitochondria involves complex molecular machineries. Fusion of mitochondria mainly depends on mitofusins-1, mitofusion-2 and OPA1, while fission requires the co-ordination of Drp-1, Fis-1 and other proteins. The first evidence for changes in mitochondrial dynamics during cisplatin nephrotoxicity was demonstrated in 2009, where cisplatin triggered a rapid fragmentation of mitochondria [32]. Importantly, inhibition of Drp-1, the fission protein, preserved the filamentous morphology of mitochondria and protected renal tubular cells from apoptosis. In mice, pharmacological inhibition of Drp-1 also suppressed kidney injury induced by renal ischemia-reperfusion and cisplatin nephrotoxicity [32]. These findings support a critical role for the disruption of mitochondrial dynamics in tubular cell apoptosis and kidney injury. Mechanistically, mitochondrial fragmentation in apoptosis results not only from Drp-1-mediated fission activation but also

fusion arrest [33]. This "push and pull" mechanism ensures the rapid fragmentation of mitochondria during cell stress or apoptosis. In renal tubular cells, Drp-1 activation seems dependent on calcineurin-mediated dephosphorylation [34]. Upon activation, Drp-1 moves from cytosol to mitochondria to activate mitochondrial fission; on the other side, fusion arrest during apoptosis depends on Bak, a pro-apoptotic Bcl-2 family protein residing on mitochondrial outer membrane (Figure 2). Bak and its homolog Bax are known to provide the gateway for mitochondrial outer membrane permeability in apoptosis. However, the specific role of Bak in mitochondrial damage was unclear. In 2007, Bak was suggested to regulate mitochondrial dynamics during apoptosis [35], suggesting a distinct role of Bak. Normally, Bak interacts with both mitofusins 1 and 2. Upon cell stress or apoptotic induction, Bak dissociates from mitofusins-2 and binds tightly with mitofusins-1 (Figure 2). This "binding partner switch" of Bak is a key to mitochondrial fragmentation because a Bak mutant that does not dissociated from mitofusins-2 cannot induce mitochondrial fragmentation [35]. The role of Bak in mitochondrial fragmentation has been demonstrated in vivo. Specifically, Bak-deficient mice do not increase mitochondrial fragmentation in renal tubular cells upon injury as wild-type animals [36]. It appears puzzling as to how mitochondrial fragmentation, a morphological change, contributes to mitochondrial damage and cell death. However, fragmented mitochondria have been shown to be sensitized to Bax insertion and oligomerization [37]. Thus mitochondrial fragmentation may participate in apoptosis by facilitating Bax insertion and oligomerization, and consequent leakage of apoptogenic factors, such as cytochrome c, for the activation of apoptosis (Figure 2). Collectively, these studies reveal the disruption of mitochondrial dynamics and its important pathogenic role in cisplatin nephrotoxicity. Thus, cisplatin not only induces PUMA expression to antagonize Bcl-XL to free Bax/Bak, it also triggers mitochondrial fragmentation to facilitate Bax insertion and oligomerization in mitochondrial outer membrane to cause leakage of apoptotic factors, such as cytochrome c (Figure 2).

d. Autophagy in cisplatin-induced kidney cell death and nephrotoxicity

Autophagy is a cellular process of bulk degradation of damaged organelles such as mitochondria and other macromolecules in the cytoplasm. Recent studies have demonstrated the induction of autophagy in experimental models of cisplatin nephrotoxicity. Autophagy is induced early during cisplatin treatment of renal tubular cells, prior to apoptosis [38,39]. In vivo in mice, cisplatin induces the formation of autophagic vesicles and autophagosomes in mouse kidneys [38]. Notably, inhibition of autophagy pharmacologically increases tubular cell apoptosis in both in vitro and in vivo models [38,39], suggesting a protective role of autophagy in cisplatin nephrotoxicity. This conclusion has been further substantiated by more recent studies using renal proximal tubule-specific autophagy gene ablation models [40,41]. Consistently, a protective role of autophagy has been demonstrated in renal ischemia-reperfusion injury [42,40]. Autophagy during cisplatin treatment of renal tubular cells can be partially inhibited by the p53 inhibitor pifithrin-alpha, suggesting that p53 is involved in autophagic signaling in this model [38]. In addition, Bcl-2 overexpression can also suppress autophagy during cisplatin treatment [38], supporting the idea that Bcl-2 may interact with Beclin-1 (also called Atg6) to antagonize its autophagic activity. The main substrates of autophagy include dysfunctional mitochondria. Is mitochondrial damage a trigger of autophagy during cisplatin treatment of tubular cells? Does mitochondrial

fragmentation required for the autophagy of mitochondria (called mitophagy)? Future investigations should address these important questions to gain new insights into the response of renal cells and tissues to cisplatin and identify renoprotective targets.

4. Mitochondrial protective agents for cisplatin nephrotoxicity

5.1 Antioxidants

As discussed, mitochondrial damage and consequent activation of apoptosis contributes critically to renal tubular cell injury and death in cisplatin nephrotoxicity. In this disease conditions, oxidative stress is not only considered as a cause of mitochondrial damage but also an important consequence of mitochondrial dysregulation due to the boost of electron leak in respiratory chain. Therefore, antioxidants may beak the vicious cycle between mitochondrial damage and oxidative stress to have renoprotective effects during cisplatin nephrotoxicity.

Several chemicals targeting redox enzymes and compounds with antioxidant properties have been tested for their efficacy in suppressing cisplatin nephroxicity. AH-SOD, a cationic superoxide dismutase (SOD) derivative, can effectively dismute superoxide radicals in situ and inhibit cisplatin-elicited oxidative stress in renal mitochondria resulting in renal protection [43]. Also a small molecular mass SOD-mimetic, Cu(2)(II)(3,5-DTBS)(4)(Eth)(4), shows similar protection through preventing the activation of cellular mechanisms that lead to proximal tubule kidney cell death during cisplatin treatment [44]. Selenium, a beneficial nutrient with antioxidant activity, can ameliorate some of the characteristic features of cisplatin-induced impairments in mitochondria, such as decreases in mitochondrial respiratory function, enzymatic activities in the respiratory chain, and glutathione peroxidase [45]. Curcumin as a natural polyphenolic compound can replenish the mitochondrial lipid peroxidation (LPO) levels and protein carbonyl (PC) content against the mitochondrial toxicity of cisplatin in kidneys [46]. In addition, alpha-Lipoic acid (LA), a thiol-containing antioxidant, can attenuate cisplatin-induced tubulointerstitial injuries through the inhibition of mitochondrial Bax translocation in rats [47].

Cisplatin induces mitochondrial damages, including a decrease of mitochondrial mass, a reduction in the oxidative phosphorylation complexes, and low levels of MnSOD. All these changes can be significantly prevented by epicatechin treatment [48]. Moreover, the mitochondrial-targeted antioxidants, MitoQ or Mito-CP, can dose-dependently prevent cisplatin-induced mitochondrial injury and dysfunctionm whereas they do not diminish cisplatin's anti-cancer effect [49]. The beta-blocker Carvedilol also has strong antioxidant properties against sulfhydryls oxidation in proteins and cardiolipin and redox state unbalance induced by cisplatin [50]. In addition, cimetidine, a pharmacological inhibitor of organic cation transporters (OCT2), can act as an antioxidant to reduce the generation of superoxide anion [51]. Interestingly, OCT2, along with the copper transporter (Ctr1), are responsible for the uptake of cisplatin into renal tubular cells. Therefore, inhibition of OCT2 (by cimetidine) and blockade of Ctr1 may synergistically suppress cisplatin uptake and nephrotoxicity [52].

b. Inhibitors of mitochondrial pathway of apoptosis

The intrinsic pathway of apoptosis is centered on mitochondria and plays a critical role tubular cell death in cisplatin nephrotoxicity. As discussed above, the key events in the intrinsic pathway include Bax and Bak activation on mitochondrial outer membrane followed by the formation of porous defect and consequent release of apoptotic factors, such as cytochrome c. Minocycline, a tetracycline derivative, can up-regulate Bcl-2, resulting in the suppression of Bax accumulation in mitochondria, preservation of mitochondrial membrane integrity, and prevention of cytochrome c release and apoptosis during cisplatin treatment of renal tubular cells [53]. Nutlins, a small molecule antagonist of murine double minute 2 (MDM2), seems to directly suppress the activation of Bax and release of cytochrome c from mitochondria [54]. Bezafibrate as a fibrate class of peroxisome proliferator-activated receptor-alpha (PPAR-alpha) ligand, can prevent the mitochondrial translocation of proapoptotic Bax, consequently, ameliorate proximal tubule cell death during cisplatin nephrotoxicity [55]. Furthermore, knockout of Bax in mice leads to a significantly preservation of renal function under cisplatin treatment [9]. AR9273, an inhibitor of soluble epoxide hydrolase that inhibit the conversion of epoxyeicosatrienoic acids into less active eicosanoids, can also block mitochondrial Bax induction during cisplatin nephrotoxicity and interestingly, these anti-apoptotic effects may involve p38 mitogen-activated protein kinase (MAPK) signaling [56]. A recent study has further demonstrated that cisplatin-induced mitochondria dysfunction can be attenuated through increasing cGMP-dependent protein kinase I (PKG-I) activity. PKG-I activation lead to decreased Bax/Bcl-2 ratio and caspase 3 activity, and a beter preservation of mitochondria membrane potential ($\Delta\psi m$) [57], revealing a new signaling pathway in the regulation of mitochondrial injury and apoptosis in cisplatin nephrotoxicity.

5. Conclusion and Perspectives

Mitochondrial dysregulation plays an important pathogenic role in cisplatin nephrotoxicity, especially in renal tubular cell injury and death. Under this disease condition, mitochondria are low in function, display striking morphological and structural changes, and as the stress is pro-longed, become permeabilized at their membranes. Preservation of mitochondrial function and integrity may therefore protect against cisplatin nephrotoxicity. However, it is important to note that a renoprotective strategy in cisplatin nephrotoxicity must consider the response of cancer cells. In other words, an ideal approach should protect kidney cells but not cancer cells. A recent study [58] has identified PKC-delta as a novel pathway of tubular cell death in cisplatin nephrotoxicity. Importantly, in several tumor-bearing animal models, inhibition of PKC-delta protects kidneys and enhances cancer therapy effects of cisplatin. Similar thoughts are applicable for the agents targeting other pathways including the mitochondrial pathway. For example, Nutlin-3 protects kidney tubular cells, but it is also known to kill cancer cells [59], making it a good candidate to pre-clinical tests in tumor models. Another example is minocycline, which is potent in protecting kidneys, has anti-cancer potentials [60]. Can these chemical be used during cisplatin chemotherapy to protect kidneys and further improve cancer therapy?

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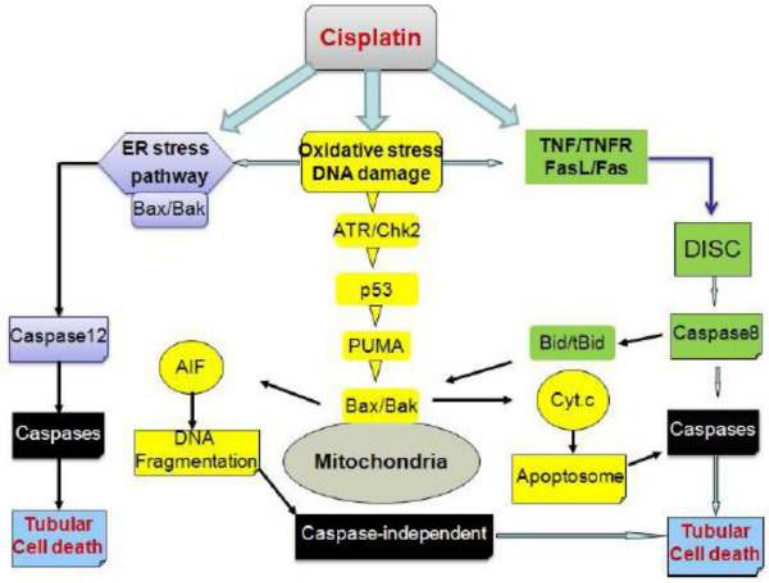

Figure 1.
Pathways of apoptosis in cisplatin nephrotoxicity.

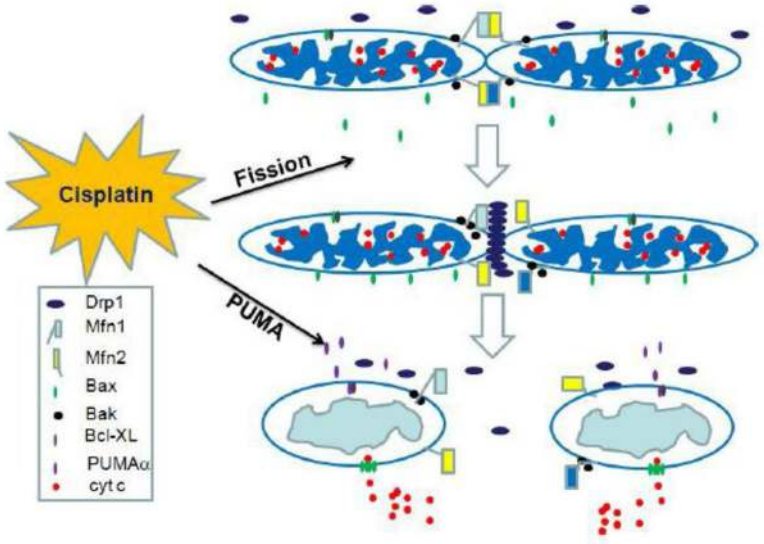

Figure 2.

Cisplatin induces PUMAα expression and triggers mitochondrial fragmentation, leading to Bax/Bak-mediated outer membrane permeabilization and release of apoptotic factors such as cytochrome c.