Molecular mechanisms of cisplatin induced nephrotoxicity

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1. Background Nephrotoxicity associated with cisplatin (CP) utilization is considered as a great concerning hamper against the exploitation of CP clinical use (Kotb et al., 2021). Till now, there is still a struggle with the high incidence of nephrotoxicity associated with CP use. It was reported that about 25-35% of patients experienced a decline in glomerular filtration, accompanied by an elevation in blood urea nitrogen (BUN), serum creatinine (Scr) levels that indicate the renal insufficiency which takes place upon CP single dose, despite the use of preventive techniques that mainly rely on the use of saline and hydration (Gómez-Sierra et al., 2018; Fang et al., 2021). Further, it was reported that CP is associated with hypomagnesemia, which may persist for years upon its use (Goren, 2003). Importantly, the kidney was delineated to be the most influential site for CP toxicity, particularly the S3 segment of the proximal tubules epithelial cells (PTECs). Further, the concentration of CP in proximal tubules was identified to be roughly 5 times higher than that of it in the serum (Amuthan et al., 2021), regardless of all the accessible attempts that were adopted in order to prevent nephrotoxic effect of CP, around one third of patients on CP therapy still suffer from nephrotoxicity.

Keywords: Nephrotoxicity, cisplatin, molecular mechanisms

2. Pathophysiological mechanisms of nephrotoxicity induced by CP

Despite, full mechanism of CP nephrotoxicity is not fully elicited, multiple pathophysiological events were proposed to define the nephrotoxic effect of CP. These molecular mechanisms involve (1) cellular uptake of CP and its buildup into PTECs by the transport pathway (McSweeney et al., 2021), (2) metabolic conversion of CP into nephrotoxin thiol (Zhang et al., 2021), (3) Oxidative stress and mitochondrial dysfunction (Santos et al., 2007), (4) inflammation (Manohar and Leung, 2018), (5) activation of the p38 mitogen-activated protein kinase (38 MAPK) (Rashed et al., 2011), (6) apoptosis (Ozkok and Edelstein, 2014).

2.1. The contribution of OCT2 in the initiation of CP nephrotoxicity

Indeed, CP uptake into renal PTECs was previously identified as the driver of the CP nephrotoxic impact (McSweeney et al., 2021). The uptake of CP into renal cells is mediated through passive diffusion and transport system (Peres and Cunha Júnior, 2013). Organic cation transporters (OCTs) were implicated in the uptake and transportation of CP into the cells (Koepsell, 2013;
Zhang et al., 2021). Three forms of OCTs were recognized in humans: OCT1, OCT2, OCT3. OCT1, the predominant OCT in the liver, OCT3, the key OCT in the placenta (Koepsell et al., 2007). OCT2 is expressed mainly in the kidney, particularly, the basolateral S3 segment of renal PTECs in both animals and humans (Ciarimboli, 2012; George et al., 2017). Importantly, OCT2 was observed to play a critical role in mediating CP accumulation into PTECs; which in turn contributes mainly to the CP nephrotoxic effect (Kim et al., 2015). Besides, it was documented that 30% of the nephrotoxic effect associated with CP is related to OCT2 uptake (Nieskens et al., 2018). Further, it was evidenced by other studies performed on renal cells the higher toxicity of CP on the basolateral side than apical side linking it to the expression of OCT2 in this segment (Ludwig et al., 2004; Gómez-Sierra et al., 2018). Furthermore, OCT2-deficient animals exhibited a decrease in CP accumulation, which was verified by a reduction in the platinum buildup (Soodvilai et al., 2020). Moreover, pharmacological inhibition of OCT2 by other OCT2 inhibitors, such as cimetidine or imatinib, was demonstrated to have a nephroprotective effect, supported by the results that were indicative of improvement of kidney function, as well as the histopathological outcomings that have highlighted also the amelioration of the renal damage induced by CP (Tanihara et al., 2009; Katsuda et al., 2010). Earlier study revealed that inhibition of OCT2 would have a nephroprotective effect without even compromising the antitumor properties of CP (Sprowl et al., 2013). Besides, diabetic rats were also found to be resistant to the CP-nephrotoxic impact, this is may be related to a downregulation in OCT2 expression in these rats (Najjar and Saad, 2001; Grover et al., 2004; Thomas et al., 2004). Notably, CP analogues that include carboplatin and oxaliplatin were shown to be less nephrotoxic than CP, this is attributed to their inability to interact with OCT2 (Ciarimboli et al., 2005). Eventually, OCT2 represents an important target in the recent novel approaches that attempt to attenuate CP nephrotoxicity.

2.2. Metabolic conversion of CP into nephrotoxin thiol
Furthermore, gamma-glutamyl-transpeptidase enzyme, which located in the brush border of renal proximal tubules is involved in the metabolism of CP, converting it into the reactive nephrotoxin thiol, which formed upon conjugation of CP with glutathione (GSH) in the liver, contributing to its nephrotoxic effect (Wainford et al., 2008; dos Santos et al., 2012).
Figure 2. Schematic representation of OCT2-mediating transportation of CP into the PTEC (Zhang et al., 2021).

Figure 3. Illustration showing bioactivation of CP to its nephrotoxin (Zhang et al., 2021).
2.3. Role of oxidative stress in the induction of CP nephrotoxicity

Oxidative stress was recognized as a vital contributor to the etiology of CP nephrotoxicity. CP triggers the surge of reactive oxygen species (ROS), through three mechanisms: first, during the conversion of CP into its highly reactive form, that is characterized by the rapid ability to react with thiol contained molecules like glutathione (GSH), ending up with the depletion and inhibition of antioxidant enzymes activity such as GSH, and superoxide dismutase (SOD), that lead to the disturbance in the balance of redox status homeostasis, ending with the accumulation of ROS and aggravation of oxidative stress status. Second, CP was implicated in the impairment of the respiratory chain of mitochondria. In vitro and in vivo studies performed on renal PTECS documented the inhibitory effect of CP on complexes I to IV of the mitochondrial respiratory chain. Further, they revealed the reduction in the level of intracellular ATP, affecting membrane electrochemical potential (Satoh et al., 2003; Santos et al., 2007; Zsengellér et al., 2012). Thirdly, ROS accumulation can also be mediated via the effect of CP on the cytochrome P450 (CYP450) system, that induces a rise in the level of catalytic iron, in turn leads to production of other potent oxidants (Liu and Baliga, 2003).

Eventually, all these events were involved in the CP-nephrotoxic effect and led to the generation of additional free radicals such as superoxide anion, hydroxyl radical, and hydrogen peroxide that induce a denaturation of renal cells components such as (lipid & protein, & DNA), and accretion of lipid peroxidation products malondialdehyde (MDA), contributing to the activation of additional multiple complexes signaling cascades that result in renal injury, inflammation and apoptosis.

2.4. CP-mediating inflammatory and cytokines activation:

The MAPK-signaling system is an interconnected serine/threonine kinases cascades, that responsible for regulation of vital important processes associated with cell differentiation, proliferation, survival as well (Nguyen et al., 2013). p38 is the critical MAPK, that was described its contribution in CP nephrotoxicity (Yang et al., 2019). Interestingly, authors have linked the initiation of p38 pathway to ROS release which mediated consequently to CP (Tsuruya et al., 2003). Besides, it was clarified that p38 activation would elicit in the production of tumor necrosis factor alpha (TNF-α), that is involved in CP-mediating renal inflammation (Mishima et al., 2006; Yano et al., 2007). Importantly, p38 was suggested to be an important target in order to possess a protective effect on renal cell against CP nephrotoxicity (Thongnuanjan et al., 2016). In addition, the coordination of TNF-α was described in the activation of other proinflammatory cytokines like interleukin-2 (IL-2), interleukin-6 (IL-6) interleukin-β (IL-β), chemokine monocyte chemoattractant protein-1(MCP-1), contributing to CP-inducing renal injury (Ramesh and Reeves, 2002; Miller et al., 2010). Previous study highlighted the importance of pharmacological TNF-α inhibitors and their related protective effects that are associated mainly with the decrease in the expression of these cytokines and chemokines, contributing to the amelioration of CP-mediating nephrotoxic effect (Ramesh and Reeves, 2004).

Nuclear factor-kappa B (NF-κB) transcription factor, appears to be activated in response to CP-mediating surge of ROS, which in turn contributes to its translocation into the nucleus upon degrading its inhibitory protein IκBα, resulting in the activation of other robust inflammatory response, including TNF-α which itself plays a key role in the trigger of additional inflammatory related cytokines, contributing to recruitment of further inflammatory cells into the renal tissue (Aggarwal et al., 2004; Ramesh et al., 2007; Sung et al., 2008; Sánchez-González et al., 2011).

CP-mediating cellular stress also seems to be participated in the release of myeloperoxidase (MPO), which is mediated by activated neutrophils. MPO is known to possess influential properties contribute importantly to inflammation and oxidative stress as well (Loria et al., 2008). Nowadays, MPO was suggested as an important contributor to CP nephrotoxicity (Amirshahrokhi and Khalili, 2015).

In addition to ROS, nitrosative stress was also been in CP-induced renal injury (Chirino et al., 2008). It was demonstrated that there is induction in nitric oxide synthase (iNOS) synthesis consequently to CP administration; which results in an increase in nitric oxide production, that ends up with peroxynitrites formation, which has involved mainly in CP-mediating renal injury via reacting with superoxide anions (Peres and Cunha Júnior, 2013). Notably, the excessive production of nitrosative stress and ROS would have a crucial
role in the initiation of other apoptotic cascades, which contribute to progressive renal injury and cell death (Çetin et al., 2006).

### 2.5. CP-mediating apoptotic nephrotoxic effect:

P53 was proposed to be an important mediator that contributes to the nephrotoxic effect of CP, evoking apoptotic renal injury. Following a DNA-damaging action mediated by CP, p53 activation occurs, resulting in cell cycle arrest. p53 exerts a role in activating pro-apoptotic Bcl-2 family protein p53 up-regulated modulator of apoptosis-alpha, which in turn contributes to the buildup of pro-apoptotic Bcl-2-associated X protein (BAX) in mitochondria and inhibition of anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) as well, provoking a disturbance in equilibrium maintained between pro- and anti-apoptotic proteins. Besides, the liberation of cytochrome C in response to activated BAX is induced, eliciting activation of executioner caspase-3 (Yao et al., 2007). Interestingly, several other reports have also linked the activation of p53 to the p38 MAPK pathway, associating it with CP-mediating apoptotic renal injury. In addition to p53-related pathways, the surge of ROS caused by CP has also been involved in the activation of BAX and its associated responses, in a p53-independent manner which also triggers caspase-3 activation and eventually ends with apoptotic renal cell injury (Karasawa and Steyger, 2015).

![Figure 4](image_url). Schematic representation of CP-mediating apoptotic nephrotoxic effect (Karasawa and Steyger, 2015).

### Conclusion

Accumulation of CP via OCT2 is considered as an important contributor to the enhancement of ROS release, which has a role in the exacerbation of oxidative stress status and the decrease induced in the antioxidant activity, eventually resulting in renal injury. Consequently, the trigger of inflammation is induced via activation of transcription factor NF-κB, promoting the production of several inflammatory cytokines such as TNF-α, IL-6, IL-2, and also activation of p38 MAPK, which in turn plays a role in the activation of other inflammatory and apoptotic pathways like p53, as well. Therefore, inhibition of OCT2 would have an ameliorating effect, suggested by a decrease in accumulation of CP into renal cells, attenuating oxidative, inflammatory, and apoptotic nephrotoxic effects of CP.

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