

## Cisplatin nephropathy: is cytotoxicity avoidable?

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**Keywords:** kidney; cisplatin; JNK pathway

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### Introduction

Despite the clinical effectiveness of cisplatin as an anti-tumour drug, its nephrotoxic side effect has significantly restricted its use. In spite of prophylactic intensive hydration and forced diuresis, irreversible renal damage occurs in about one third of cisplatin-treated patients. *In vivo* experimental studies have shown acute cytotoxic effects following cisplatin treatment, mostly affecting tubular epithelial cells. Such cytotoxic responses are followed by renal inflammatory and fibroproliferative events in the cisplatin-injected animals [1–3]. Once within renal cells, cisplatin could abnormally reduce ATPase activity, inflict mitochondrial damage, induce cell cycle arrest and impair cellular transport system. The combined effect of these events can induce apoptosis and/or necrotic cell death [4–7]. Cisplatin disrupts the cellular oxidant defence system to induce DNA damage. Treatment with known anti oxidants such as  $\alpha$ -tocopherol, vitamin C, and *N*-acetyl cysteine could counter, to some extent, the reactive oxygen species-mediated toxic effects [8,9]. Studies have shown that cisplatin-mediated generation of free radicals could activate cell death signalling cascade, and in turn could make the tubular epithelial cells sensitive and vulnerable to oxidative-stress-related injuries.

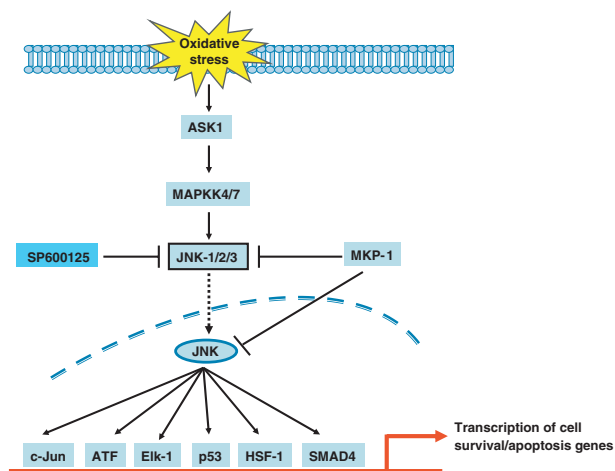
Our understandings of signal transduction pathways during various cellular events, including cell proliferation, differentiation and survival have significantly improved from the elegant research works that were conducted in the last decade. The mitogen-activated protein (MAP) kinase system is one of the most extensively studied pathways that provide an important signalling machinery to convey external stimuli to the nucleus. The MAP kinase family broadly comprises

of c-Jun N-terminal kinase (JNK), p38 MAP kinase, and extracellular signal-regulated kinase (ERK). These signalling pathways can be activated by various overlapping stimuli and are closely associated with enhanced activation of the apoptotic pathway [10]. As cisplatin can activate JNK pathways, such activation is likely to exert its cytotoxic effects by facilitating renal tubular epithelial cell deletion [11–13]. The JNK family, also known as stress-activated protein kinases (SAPKs), are extensively studied in various cell-based systems following cellular injury (Figure 1) [14]. The JNK family consists of JNK1 and JNK2, which are widely distributed, while JNK3 has relatively restricted expression in the heart, brain and testis. JNK, a serine threonine protein kinase, phosphorylates c-Jun, a component of the transcription factor activator protein-1 (AP-1). Interacting with other DNA-binding proteins, AP-1 regulates the transcription of wide range of genes that include numerous cytokines and growth factors. Upon activation, MAP kinases translocate to the nucleus where they activate transcription factors to induce expression of genes that determine the biological response of the cell.

Since individual transcription factors are capable of regulating the expression of set of genes, the signalling components that control the activity of these transcription factors are becoming major therapeutic targets. Studies have shown that activation of the JNK pathway is associated with cisplatin-induced nephrotoxicity [12]. Suppressing JNK pathways therefore provides a potential therapeutic target to minimize *in vivo* cisplatin-induced cytotoxicity. SP600125 is a potent inhibitor of JNK1, 2 and 3 [15], and more importantly it is effective in both *in vitro* and *in vivo* model systems. The pharmacological efficacy of SP600125 makes it an ideal choice for assessing the role of JNK in mediating biological responses. In the current issue of NDT, Francescato *et al.* [16] has studied *in vivo* renoprotective effects of SP600125 following cisplatin treatment. The aetiological diversity, along with multi-stage, multi-factorial molecular events of different stages of chronic kidney diseases [17,18] make it clinically difficult to pinpoint and target one single risk factor to minimize or delay the progression of the disease process. In contrast, the defined initial triggering events, subsequent signalling cascade and eventual nephrotoxic effects following

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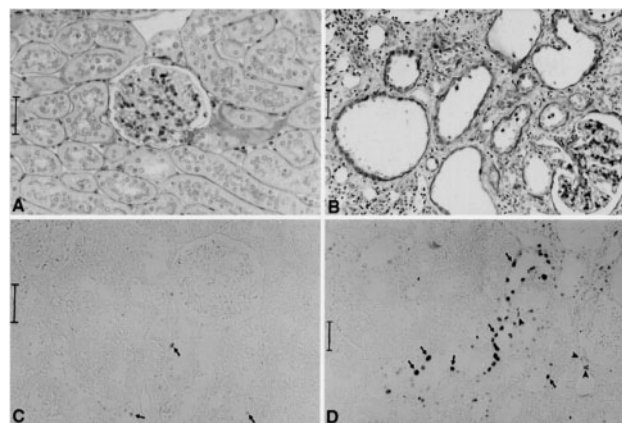
**Fig. 1.** Simplified diagram of activation of JNK pathways and their possible cross talk at the level of downstream targets. Please note that only a few selected molecules are included to keep the diagram simple, yet relevant to this article. Cisplatin, by inducing oxidative stress, is likely to induce apoptosis signal-regulating kinase 1 (ASK1), which by involving JNK signalling pathways, could activate transcription factors to exert cytotoxic effects in the kidney, by disrupting cellular homeostasis.

cisplatin treatment provided the opportunity to molecularly manipulate related pathology.

### Cisplatin-induced cytotoxicity

As mentioned, cisplatin-associated nephrotoxicity begins with tubular epithelial cell deletion (Figure 2). Numerous studies have shown that cisplatin could activate various pro-inflammatory and apoptotic molecules, including caspase-3 and -9, Bax and Fas system [4,19–22]. *In vitro* studies have shown that cisplatin could induce apoptosis in porcine kidney epithelial LLC-PK1 cells through mitochondrial signalling pathways, possibly by activating Bax-induced mitochondrial permeability, with release of cytochrome c, and activation of caspase 9. A role for caspase-3 has also reported in cisplatin-induced apoptosis in LLC-PK1 cells, and could be prevented by bcl-2 [23]. In addition, cisplatin-induced receptor-mediated apoptosis has been detected in various cells lines [24–28]. Increased expression of Fas and its ligand has shown to be associated with cisplatin-induced apoptosis in human proximal tubular epithelial cells [28]. Similar Fas-mediated cisplatin-induced apoptosis has been found in neuroblastoma cells [27], leukaemia cells [26], hepatoma cells [25] and thymocytes [24]. In contrast, Fas-independent cisplatin-induced apoptosis is also reported in various tumours cell lines including in lung cancer cells [29,30]. It appears likely that cisplatin-induced apoptosis does not always take a uniform pathway, and there might be a cell-specific mode of apoptosis following cisplatin treatment [31].

Nuclear fragmentation after cisplatin treatment is a common feature. Deoxyribonuclease I (DNase I) is



**Fig. 2.** Histological features of control rat kidney (A), and cisplatin-treated rat kidney (B); note severe tubulointerstitial injuries, including tubular epithelial cell detachments, cystic dilatation of tubules, and inflammatory cell infiltration in cisplatin-exposed kidney. TUNEL staining shows scattered TUNEL-positive nuclei in the control kidney (C), while increased numbers of TUNEL-positive tubular epithelial cells (arrows) are present in cisplatin-treated rat kidney (D) (A, B: PAS staining; C, D: TUNEL staining; bars = 50  $\mu$ m).

a well-characterized Ca/Mg-dependent endonuclease that is involved in DNA fragmentation during cell death. Recently, *DNase1* null mice have been shown to be resistant to cisplatin-induced renal injury, suggesting a role of *DNase 1* in cisplatin-mediated cell death [32]. Whatever the molecular mechanisms of cell deletion, it is, however, beyond any doubt that necrosis and apoptosis are the immediate cytotoxic consequences of cisplatin treatment, and any therapeutic intervention should be directed towards protecting renal tubular epithelial cells from cytotoxic cell death.

### Modulation of cisplatin-induced cytotoxicity

In humans following standard-dose regimens, one-third of patients usually develop varying degrees of cisplatin-related side effects. Several strategies have been explored to reduce the side effects of cisplatin therapy. These include the use of less intensive treatment or the replacement of nephro- and neurotoxic cisplatin with the less toxic analogue carboplatin and aggressive hydration with saline, often with the addition of mannitol. However, all have shown limited success. Recent studies are directed more towards reducing the cytotoxic impact of cisplatin. In a human study, amifostine (Ethyol, an organic thiophosphate compound with a cytoprotective potential) produces less renal damage when used prior to cisplatin therapy, compared with patients treated only with cisplatin [33–35]. It is presumed that the active free thiol metabolite can reduce the toxic effects of cisplatin on the kidney, possibly by binding to free radicals generated in the tissues following cisplatin treatment.

Since uncontrolled apoptosis is one of the major early pathological changes in cisplatin nephropathy,

studies have examined the protective role of caspase inhibitors on proximal tubular epithelial cell survival following cisplatin exposure. Cisplatin-induced apoptosis of rat proximal tubular epithelial cell has been shown to be decreased by caspase inhibitors, such as B-D-FMK (pan caspase inhibitor), Z-DEVD-FMK (predominantly caspase-3 inhibitor) and Z-VAD-FMK (predominantly caspase-1 and -3 inhibitor). Although all caspase inhibitors were found to be effective at reducing caspase-3 activity, the cited study found pan caspase inhibitor B-D-FMK as the most effective at preventing apoptosis and increasing cell survival following cisplatin exposure [36]. Caspase inhibitors therefore have the potential to minimize uncontrolled apoptosis in cisplatin nephropathy.

Experimental studies have shown that ebselen (2-phenyl-1,2-benziselenazol-3[2H]-one, is a lipid-soluble seleno-organic compound that potently inhibits lipid peroxidation through a glutathione peroxidase-like action) has a renoprotective effect in cisplatin-treated rats, possibly exerting its beneficial effects by modulating the antioxidant system [37,38]. Use of a novel free radical scavenger, 3-methyl-1-phenyl-pyrazolin-5-one (MCI-186; edarabone) has also been shown to protect the kidneys from developing acute renal failure following cisplatin treatment [39]. Edarabone, a lipophilic compound, is able to trap both hydroxyl radicals and prevent iron-induced peroxidative injuries [40]. Together, these studies suggest beneficial effects of using a free radical scavenger in modulating cisplatin-associated nephrotoxicity [41].

Another approach that appears to have clinical benefit is to target specific signalling components to selectively block the adverse responses. In the cisplatin-treated rat model, Francescato *et al.* [16] found a significantly higher expression of phosphorylated-JNK in the kidney (both in cortex and outer medulla). These results are in agreement with earlier observations, where Sheikh-Hamad *et al.* [12] showed about a 3-fold increase in the JNK1 activity in the corticomedullary junction, along with the induction of pro-apoptotic factors (caspases 1, 2 and 8 and Bax) in the kidneys of cisplatin-treated animals. Since activation of JNK pathway is associated with higher rate of apoptosis, Francescato *et al.* [16] tested the *in vivo* effects of JNK inhibitor SP600125, as a potential renoprotective agent following cisplatin treatment. SP600125 treatment not only reduced cisplatin-induced structural damages of the kidney, but more importantly improved renal function. One of the mechanisms of such renoprotection by SP600125 is believed to be through reducing apoptotic cell deletion, and suppressing inflammatory responses. These results seem to be plausible, as the loss of tubular epithelial cells is the single most important pathology of cisplatin-exposed kidney.

JNK-mediated cisplatin-induced apoptosis is not restricted to kidney cells. MAP kinase phosphatase (MKP)-1 is a negative regulator of MAP kinase signalling. The ability of MKP-1 to dephosphorylate

and inactivate ERK, p38 and JNK have important regulatory roles in MAP kinase signalling (Figure 1) [42]. The activation of the JNK pathway is required for cisplatin-mediated death of primary mouse embryonic fibroblasts. Blockade of JNK activity could protect cells from cisplatin-induced apoptotic cell death. In *MKP-1<sup>-/-</sup>* cells isolated from *MKP-1* null mice, JNK phosphorylation was robust and prolonged following cisplatin treatment, compared with *MKP-1<sup>+/+</sup>* cells, implicating MKP-1 as a negative regulator of cisplatin-induced JNK activation. In the same study, phosphorylation of p38 and ERK1 by cisplatin was comparable between *MKP-1<sup>-/-</sup>* and wild-type cells [43]. These results clearly suggest that MKP-1 specifically targets the JNK pathway in response to cisplatin treatment and that MKP-1 might preferentially inactivate the JNK pathway following cisplatin treatment, to exert cell survival effects. In general, these results are similar to the *in vivo* observations of Francescato *et al.* [16], where JNK inhibitor SP600125 was shown to reduce cisplatin-induced renal tubular epithelial cell death.

## Conclusion

Although JNK inhibition in reducing *in vivo* cisplatin-induced renal cytotoxicity is promising, whether or not such an observation will be clinically applicable is another issue and needs further controlled studies. For instance, combined SP600125 and cisplatin treatment does not change the total platinum content of the kidney, in comparison with cisplatin-treatment alone [16]. This raises an important question, how does SP600125 protect tubular cells? In other words, what happens to the platinum that has already been taken up by the tubular epithelial cells? JNK is one of the many pathways (perhaps the dominant one) that might be activated by cisplatin, and theoretically, SP600125 should provide only partial protection. However, urinary malondialdehyde (MDA) level, which the investigators measured to determine the *in vivo* status of oxidative stress, was very similar in the untreated *vs* combined SP600125 and cisplatin-treated animals. Does that imply near complete *in vivo* suppression of oxidant stress by JNK inhibitors following cisplatin treatment? Like all good scientific studies, the results presented by Francescato *et al.* [16] generate as many questions as they do answers. The scientific challenge and clinical utility lie in pursuing those questions.

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*Conflict of interest statement.* None declared

(See related article by Francescato *et al.* Effect of JNK inhibition on cisplatin-induced renal damage. *Nephrol Dial Transplant* 2007; 22: 2138–2148.)

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## HIV-associated renal diseases in Africa—a desperate need for additional study

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**Keywords:** creatinine clearance; epidemiology; glomerular filtration rate; HIV; HIV-associated nephropathy; HIV-associated glomerulonephritis; renal function

Since the emergence of Acquired Immune Deficiency Syndrome (AIDS) more than 25 years ago, renal disease has been recognized as a common and intimately associated complication of Human Immunodeficiency Virus (HIV) infection. It is now known that there are several renal syndromes and diseases associated with HIV infection. These diseases are more or less tightly linked with the viral infection, the expression of HIV genes in the kidney and the interaction of HIV proteins with renal cells. Approximately 50–60% of renal disease associated with HIV infection may be considered “classic HIV-associated nephropathy” (HIVAN) [1–6]. Many studies have suggested a dramatically heightened susceptibility to the development of renal disease in patients of African descent who become infected with HIV [7–11]. In the United States, the incidence of HIV-associated renal diseases, at least progressing to end-stage renal disease (ESRD), has stabilized or decreased [12]. This is undoubtedly due to major scientific advances in the production of highly active antiretroviral therapy (HAART), and the increased access to these medications in the United States and variably in developed countries throughout the world. However, HAART is expensive and is associated with a variety of complications including potential HAART-related nephropathies [13,14].

HAART also requires a life-long commitment and the ability to maintain appropriate specialized medical care [15].

In the United States, an unexpected concomitant of HAART therapy has been to impede our understanding of epidemiologic and pathogenic mechanisms underlying the development of renal diseases associated with the viral infection. The natural history of the renal diseases associated with HIV infection has been radically changed by therapy [14,16]. Most investigators believe HAART to be indicated in patients with renal disease in the presence of HIV infection, but specifically in the case of classic HIVAN, as well as HIV-associated thrombotic microangiopathies and immune complex renal diseases [6,17–21]. Therefore, the independent role of other therapies, such as glucocorticoids or angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), probably cannot be ethically assessed in any contemporary setting. Investigation of pathogenic mechanisms using sophisticated molecular biologic investigative techniques on renal tissue in patients who present with renal disease holds tremendous promise, but may be challenging in the setting of HAART.

Although the cumulative number of patients with AIDS approaches 1 million in the United States [22,23], these figures are dwarfed by the enormity of the epidemic in the rest of the world, and most importantly in Sub-Saharan Africa, where it is estimated that almost 25 million people are living with HIV/AIDS (a tragic prevalence of 5.9% of the population). 2.1 million deaths have occurred because of the epidemic in this part of the world [24].