Cisplatin-induced cytotoxicity: is the nucleus relevant?

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CISPLATIN IS A POTENT CHEMOTHERAPEUTIC agent widely used for the treatment of cancer. However, cisplatin is frequently associated with nephrotoxicity, manifesting as acute kidney injury accompanied by hypokalemia and hypomagnesemia (6). Overdose of cisplatin has been reported to cause a wide array of effects, including kidney and liver failure, myelosuppression, neuropathy, ototoxicity, and blindness (16). Cisplatin nephrotoxicity is dose dependent and may correlate with the cumulative dose of the drug (4, 14). The exact mechanism by which cisplatin produces renal damage is unknown. After a single dose of cisplatin, there is preferential sequestration of the drug in the kidneys, liver, intestine, and testes, with concentrations in the kidneys reaching levels higher than 37 times those in plasma (9). Morphological changes after cisplatin-induced kidney injury are most prominent in S3 segments of proximal tubules, where loss of brush-border membrane, cell swelling, nuclear condensation, and focal areas of tubular cell apoptosis and necrosis are seen (15). The reasons for the selective injury of S3 segments after cisplatin administration are unclear. It was hypothesized by Dobyan et al. (3) that cisplatin accumulates selectively in S3 segments secondary to secretion by the adjacent pars recta; alternatively, hemodynamic changes caused by cisplatin may lead to decreased circulation in the vasa recta, causing damage to the most susceptible adjacent regions that include S3 segments.

Cisplatin induces damage to tumors via induction of apoptosis; this is mediated by activation of death receptor-mediated apoptotic signaling mechanisms as well as mitochondrial pathways (2). In addition, cisplatin causes DNA cross-linking, inhibiting cell proliferation (20). However, cisplatin also binds to plasma and cellular proteins, accounting for the difficulty in clearing the drug from the circulation and tissue. Of note, the drug binds irreversibly to sulfhydryl groups of low- and high-molecular-weight molecules (10), and this binding correlates with a fall in the concentration of sulfhydryl moieties in the kidney, especially in the mitochondrial and cytosolic fractions (8), inhibiting a number of sulfhydryl-containing enzymes, including ATPases, thymidylate synthetase, glyceraldehyde-3-phosphate dehydrogenase, glucose-6-phosphate dehydrogenase, γ-glutamylcysteine synthetase, and ribonucleotide reductase (1). The depletion of sulfhydryl groups, which include glutathione, may alter the redox state and contribute to cisplatin-induced cytotoxicity. Thus the toxicity of cisplatin may result from a combination of factors that include, but may not be limited to DNA cross-linking, inhibition of enzymatic activity, and depletion of the antioxidant pool.

In an interesting and elegant work, Yu et al. (19) demonstrated that cisplatin initiates apoptosis from the cytoplasm and suggest that nuclear events may not be critical for the initiation of cisplatin-induced cytotoxicity, at least, not in kidney cells. Cumulative data from this group have demonstrated the involvement of CDK2 in cisplatin-induced cell death in vivo and in vitro (13, 18), and inhibition of CDK2 by p21 protects from cisplatin-induced injury (11, 12, 17). Of interest, deletion of the nuclear localization signal from p21 does not alter its protective action against cisplatin cytotoxicity (17), suggesting that the protective interaction between p21 and CDK2 may not occur in the nucleus. Indeed, active cdk2-cyclin complexes are detected in both nucleus and cytoplasm (7), and translocation of cdk2 from the nucleus to the cytoplasm was reported to occur after the apoptotic stimulus (5). This finding is intriguing, as CDK2 is a cell cycle regulator, and by default, active CDK2 is expected to reside in the nucleus. Yu et al. (19) demonstrate the presence of cdk2 activity in cytoplasts, and as was observed in nucleate cells (13, 18), inhibition of cdk2 in cytoplasts blocked cisplatin-induced apoptosis. These data suggest that cisplatin-induced apoptosis may be initiated from the cytoplasm, in a manner that does not require nuclear contribution. Additionally, they find that cdk2 localizes to the ER and Golgi compartments, suggesting that phosphorylation of substrates in these compartments by CDK2 in response to cisplatin may play an important role in cisplatin-induced cytotoxicity and that CDK2 activity may be critical for cell death signaling originating from the endoplasmic reticulum (ER). Accordingly, inhibition of CDK2 in cytoplasts attenuates ER stress induced by various stressors, such as tunicamycin, which inhibits N-glycosylation, brefeldin A, which causes disassembly of the Golgi and accumulation of secretory proteins in the ER, and thapsigargin, which inhibits the ER Ca2+-ATPase.

Cumulatively, the data by Yu et al. (19) demonstrate that while cisplatin cytotoxicity may be augmented by nuclear events, it may be initiated from the cytoplasm; cdk2 activity, which normally promotes cell cycle progression, is important for promoting apoptosis in response to cisplatin; and finally, subcellular localization of cdk2 may determine its substrate specificity, which in turn determines cell fate. Thus CDK2 may regulate a critical checkpoint in stressed cells; determining whether the cells are viable, and hence can proliferate, or are damaged, and hence committed to apoptosis.

REFERENCES


