How to keep kidneys safe while shrinking tumors: the conundrum of cisplatin action

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CISPLATIN HAS BEEN A MAINSTAY of chemotherapy of various solid tumors for years. A significant body of investigations into its therapeutic effects has two important components. The first, predominantly explored by oncologists, studies the mode of cytotoxic action on tumor cells and ways of preventing resistance to cisplatin. The second, combating cisplatin nephrotoxicity, is a domain of nephrologists. The two rarely intersect, although it is not unreasonable to think that common mechanisms may be in place. In this vein, both groups of investigators are focusing on regulators of cell cycle and determinants of cell death. Members of the cyclin-dependent kinase (Cdk) family, of which 11 are known so far, form noncovalent complexes with A-E cyclins, each responsible for control of a specific point in the cell cycle. The retinoblastoma gene, mutated in a rare tumor that gave the name to the gene, has been found to be aberrant in many other cancers (see a review in Ref. 3). Its protein product (pRb), a member of the pocket protein family, is a key regulator of the E2F family of transcription factors, which consists of seven known members, in turn being critical for cell proliferation and apoptosis. Therefore, a big question is how to enhance the therapeutic effect of cisplatin and at the same time not compromise the kidney. This requires a more detailed view of the individual participants and their function in specific cells.

Lessons learned from E2F knockout mice convincingly demonstrated that these transcription factors [E2F1-3 (activators), E2F4-5 (repressors)] critically participate in cell proliferation and apoptosis. Proapoptotic actions are likely mediated via induction of caspase expression and/or the p53 pathway (reviewed in Ref. 2). E2F1−/− mice are prone to develop sarcomas of the reproductive tract, lymphomas, and lung tumors, presumably due to the defect in p53-dependent apoptosis of damaged cells. Since pRB binds to both activator and repressor E2Fs, it may differentially affect downstream E2F functions.

Cytotoxicity and, specifically, nephrotoxicity of cisplatin has been attributed by different investigators to production of reactive oxygen species, activation of Bax, increased secretion of TNF-α, activation of TLR4, etc. Attempts to alleviate cisplatin nephrotoxicity have been reported using a variety of gaseous molecules (nitric oxide, carbon monoxide, ozone), antioxidants, allopurinol, kinase inhibitors, adenosine receptor blockers, fibrates, and herbal medications, to name a few. Megyesi et al. (5) have previously demonstrated cisplatin-induced p21 resulting in the inhibition of Cdk2, representing a natural protective mechanism. Notably, as elucidated by Yu et al. (10) in this issue of the journal, Cdk2, a target of E2F1, also shown upstream activity: inhibition of Cdk2 prevented overexpression of E2F1, curtailed apoptosis, and ameliorated renal dysfunction. When tubular epithelial cells in culture were transduced with adenoviral E2F1-binding protein, thus reducing its free pool available for transcriptional control, protection against cisplatin toxicity was achieved. In contrast, overexpression of E2F1 was associated with cell death. E2F1 knockout mice (studied before development of tumors) appeared to be markedly protected against cisplatin nephrotoxicity. Whether this protection was due to the blunted accumulation of caspases or reduced p53 induction remains unknown. Nevertheless, the reader is presented with an important, elegantly executed study, spanning cellular-organismic levels of integrity, which should be of interest not only to nephrologists but to oncologists as well.

If the same mechanism is involved in the antitumor action of cisplatin, obviously it should be preserved at least in tumor cells. O’Connor and Lu (6) showed that various stressors like hypoxia, UV irradiation, cisplatin, or etoposide all induce the expression of E2F1, thus linking chemotherapeutics to stress and, parenthetically, potentially expanding the findings of Yu et al. (10) to other forms of acute kidney injury. Notably, the induced E2F1 was found to be transcriptionally inactive. On the other hand, adenoviral E2F1 gene transfer sensitized melanoma cells to apoptosis induced by topoisomerase II inhibitors, but not to cisplatin (4). In the osteosarcoma U2OS cell line, overexpression of E2F1 did not change cell sensitivity to cisplatin but increased it to M phase-acting vinblastin and paclitaxel (8). In contrast, Wang et al. (9) associated cytotoxicity of cisplatin with the induction of E2F1-mediated apoptosis. In ovarian cancer, rapid development of resistance to cisplatin was attributed to deregulation of E2Fs in a way that downregulation of E2F1 and E2F2 accompanied by upregulation of E2F4 and E2F7 in the tumors were associated with the favorable prognosis (7). Most recently, Berthet and Kaldis (1) have summarized a large body of investigations into the cell cycle regulators in tumor and nontumor cells, emphasizing the existing differences between them: inactivation of inhibitory pathways, like INK4 and p53, and differences in susceptibility to Cdk inhibition in tumor cells. Hence, there is no consistency and uniformity in the action of E2F1 in different tumor cells, although cisplatin may exert effects on some tumors which are different from those on the kidney.

It is my belief that to reconcile these two seemingly irreconcilable trends, killing tumors and sparing kidneys, both should be kept in mind in future studies. For instance, what would be the response of the tumor and the kidney to cisplatin in E2F1 knockout mice studied at a more advanced age, when they have already developed sarcomas, lymphomas, or lung malignancy? Would renoprotection compromise the killing of tumor cells or are the pathways discreet? Moreover, tumor xenograft models could be utilized to study dual effects of
cisplatin. Such a coalescence of oncological and nephrological interests should have a far-reaching translational applicability.

REFERENCES