Provenance of the protective property of p21

Karl A. Nath

Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, Minnesota

IN THE CURRENT ISSUE of American Journal of Physiology-Renal Physiology, the study by Yu et al. (26) significantly advances an important line of investigation initiated by these investigators in 1996 (17) and which steadfastly interrogated the functional significance of the induction of p21WAF1/CIP1/SDI1 (p21) in the acutely injured kidney (13–18, 22, 26). p21 is a member of the Cip/Kip family of proteins, which promote cell cycle arrest by binding to and inhibiting cyclin-dependent kinases (cdk), the latter, when coupled with specific cyclins, facilitates the orderly procession of the cell cycle (21, 24). It was initially observed that in response to diverse acute insults, prompt and prominent upregulation of p21 occurred in the kidney (17), a finding that led these investigators to question why a cell cycle inhibitor would be strongly expressed in a disease process that obligates cell proliferation in the recovery program that nurses the kidney back to normalcy. Was this induction of p21 obligates cell proliferation in the recovery program that nurses the kidney back to normalcy. Was this induction of p21 maladaptive and inimical, adaptive and salutary, or quite simply, a functionally inert and unengaged epiphenomenon?

An answer was provided in subsequent studies in p21 null mutant mice (13, 16): the induction of p21 was clearly beneficial to the acutely stressed kidney as indicated by the heightened structural and functional impairment of the kidney when p21−/− mice were subjected to a nephrotoxin such as cisplatin or to acute renal ischemia (13, 16). To explain the basis for the protective effects of p21 induced in the kidney following exposure to cisplatin, these authors suggested that the inhibitory effect of p21 on the cell cycle would proscribe cells with damaged DNA from progressing through the cell cycle, thereby forestalling the cellular demise that would otherwise occur (16). While this thesis was entirely consistent with the understanding of the biology of p21 that existed at the time, it became increasingly apparent that the raison d'être of p21 extended way beyond its restraining effect on the cell cycle, that the function of p21 was multifaceted, and that its nature became increasingly apparent that the raison d'être of p21 extended way beyond its restraining effect on the cell cycle, that the function of p21 was multifaceted, and that its nature was nuanced (4, 5, 7, 8, 10, 19, 21, 24, 25). For example, evidence was accrued that p21 influenced transcriptional programs, signaling pathways, and other mechanisms that broadly determine cell fate and phenotype; notably, p21 influenced cell survival, commonly preventing apoptosis on the one hand, but on the other, and quite uncommonly, fostering apoptosis (4, 5, 7, 8, 19, 25). The antiapoptotic effects of p21 seemed distinct from its inhibitory effects on the cell cycle and emanated from cytoplasmic rather than nuclear expression of the protein (3).

The functional effect of p21 in cisplatin-induced toxicity in renal epithelial cells was probed by Megyesi, Price, and Safirstein and collaborators (14, 18, 22) in a series of studies that produced clear and consistent conclusions: cells deficient in p21, when exposed to cisplatin, exhibited decreased survival and increased apoptosis, and conversely, overexpression of p21 by adenoviral vectors markedly reduced cisplatin-induced cell death. Moreover, the beneficial effects of p21 appeared independent of an action on the cell cycle and were channeled through caspase-dependent and caspase-independent processes (22).

These findings, in turn, led to the issue of the basis of such cytoprotective effects of p21. Several possibilities existed, as p21 possesses numerous domains that facilitate binding to proteins relevant to cell survival, including binding domains for procaspase-3, ASK1, c-Myc, GADD45, and calmodulin; indeed, antagonism of some of these proteins has been incriminated as the basis for the survival effects of p21 (3–5, 7, 19, 25). The present findings of Yu et al. (26), however, demonstrate that the antiapoptotic effects of p21 originate from the domain that binds cdk2, one of the major targets inhibited by p21 as it arrests the cell cycle. These intriguing findings may seem initially surprising, because cdk2 is a critical contributor to the progression of the cell cycle and yet the antiapoptotic effects of p21 are considered independent of its inhibition of the cell cycle. Concordance of these considerations is readily apparent when one recognizes the compartment-specific effects of cdk2 (4, 8, 9, 11). Cyclin/cdk complexes easily commute between the nuclear and cytoplasmic compartments (4, 8, 11), and once within the cytoplasm, and as shown by Shankland and collaborators (9) in mesangial cells, these complexes exert far different effects on cell fate; in contrast to the proliferative effects of these complexes in the nucleus, cytoplasmic localization of these complexes may trigger apoptosis (4, 8, 9, 11).

Besides elucidating the origins of the antiapoptotic actions of p21, this study uncovered new and therapeutically exciting insights regarding the pathogenesis of cisplatin-induced nephrotoxicity, an adverse effect that may significantly limit the utility of a highly effective chemotherapeutic agent (2) and one that is the focus of substantial investigation (12, 20, 23). It would be of considerable interest if cdk2 activity contributes to the nephrotoxicity of cisplatin in vivo because inhibiting this activity may mitigate such toxicity, the clinical feasibility of which is aided by the current clinical evaluation of several cdk inhibitors as chemotherapeutic agents (6).

In summary, the study by Yu et al. (26) uncovers the provenance of the protective effects of p21 against cisplatin-induced cytotoxicity, and in the process, discovers a novel mechanism that may underlie such toxicity. It thus represents an illuminating continuation of an important investigative path begun by this laboratory a decade ago which, along the way, led to novel biological insights regarding p21 and which now approaches a potential therapeutic stratagem for reducing the risk of cisplatin-induced nephrotoxicity.

REFERENCES
1. Al-Douahji M, Brugarolas J, Brown PA, Stehman-Breen CO, Alpers CE, and Shankland SJ. The cyclin kinase inhibitor p21WAF1/CIP1 is