Is p21 an oncogene?

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p21WAF1/CIP1 is a cyclin-dependent kinase (cdk) inhibitor, and is a key mediator of p53-dependent cell cycle arrest after DNA damage (1, 2). p21 belongs to the Cip/Kip family of cdk inhibitors and it inhibits proliferation mainly by interfering with cyclin E/cdk2 activity (3). The initial perception of p21 functions was that it might be a tumor suppressor because it inhibits proliferation, and subsequently, tumor suppressor functions for p21 were found in p21/p18 double-deficient mice, where loss of p21 accelerated the incidence and progression of pituitary pathology initiated by the loss of p18 (4). In addition, aging studies in p21-deficient mice have also demonstrated a role for p21 in tumor suppression and showed that mice lacking p21 formed spontaneous tumors by 16 months of age in comparison with 20 months for wild-type animals (5). p21-null mice were also more susceptible to tumorigenesis in response to chemical carcinogens, suggesting that p21 may be a tumor suppressor (6–8).

However, in our 2002 review for this journal (9), we suggested that p21 may also act as an oncogene because it often displays procancer and antiapoptotic activities. Two recent articles support this notion both in mouse models (10) and in patients (11). De la Cueva et al. discovered that elimination of p21 in p53-deficient mice resulted in a substantially longer survival of p53-null (from 6 to 9 months) and p53-haploinsufficient mice (from 11 to 19 months). Furthermore, although multiple different types of tumors spontaneously developed in p53-null mice, only the number of thymic lymphomas was significantly reduced in p21-null mice. Thus, increased survival of p53-deficient mice in the absence of p21 was directly linked to a decrease in the rate of spontaneous thymic lymphomas. Additionally, in the absence of p21, the growth of thymic lymphomas induced by γ-irradiation was substantially delayed in p53-deficient mice, and p21-deficient lymphomas had a higher apoptotic rate than p21-proficient lymphomas. These data support an earlier observation that loss of p21 in the atm-deficient mice leads to a delay in thymic lymphomagenesis (12). De la Cueva et al. suggest that an oncogenic role for p21 in thymic lymphomas may be explained by the antiapoptotic activity of p21 in lymphoma cells.

Additional evidence that p21 may be oncogenic came from phase I clinical trials that used a combination of irinotecan and flavopiridol for the treatment of human solid tumors (11). Tumors in these trials were evaluated by immunohistochemistry for p21 staining, both at pretreatment and within 24 to 48 hours following the second week of therapy. From the six patients who had wild-type p53, p21 remained stable or was nondetectable on the posttreatment biopsy in three patients, all of whom had stable disease or a partial response. In addition, the change in p21 was uninterpretable in two patients with stable disease. Shah et al. suggested that the potentiation of irinotecan by flavopiridol is connected to the suppression of p21 and that low levels of p21 may predict the positive outcome of this combination treatment (11). Similarly, it has been shown that induction of p21 during anticancer treatment in patients with rectal carcinoma was associated with the development of resistance to neoadjuvant radiochemotherapy, with worse outcome of the disease (13). p21 overexpression also significantly compromised the survival of patients with esophageal squamous cell carcinoma and mutations in the p53 gene (14). The role of p21 in spontaneous mouse lymphomas of p53-deficient mice (10) and in cancer patients (11, 13) suggests that p21 may act as an oncogene, either during tumor development or in the course of anticancer treatment. Yet, the most interesting question is why oncogenic activity of p21 is displayed only in mouse thymic lymphomas, but not in other mouse tissues, where p21 also inhibits apoptosis (5–8, 15).

In addition, in some human cancers, p21 expression is a negative regulator of the cell cycle. In fact, it was shown that Notch-mediated p21 repression was associated with reduced cyclin D-cdk4 complex formation and with cell cycle arrest (ref. 20; reviewed in ref. 21). Additionally, phosphorylation of p21 on S130 (22) or T145 (23) negates its...
inhibition of cyclin/cdkks and results in the restoration of cdk2 kinase activity in the presence of p21, as well as cell proliferation. These data suggest that modifications of p21 may change its functional activity. Usually, p21 inhibits apoptosis, but surprisingly, in some cases p21 can promote apoptosis (9, 24). Contradictory functions for p21 in apoptosis may explain its opposing roles in cancer. Finally, p21 can modulate gene transcription by direct association with the promoter region of individual genes or by binding to specific transcription factors/coactivators, thus, modulating their activity (25–29). By directly controlling the activity of various tumor suppressors or oncogenes, p21 may exhibit proancer or anticancer activity in different tumor cells. Further experiments are needed to better define the role of p21 in cancer. It will be critical to determine the exact mechanisms underlying the ability of p21 to play an oncogenic or tumor suppressive role, and to establish additional cellular factors that might alter the function of p21 in tumorigenesis.

References
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