p53 and cancer therapy: a double-edged sword

Commentary

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When misexpression of the Myc oncoprotein was found to produce enhanced susceptibility to apoptosis (1), it suggested that disabling death may be a fundamental component of neoplastic transformation. It also raised the hope that rekindling such death susceptibility may revert the cancer cell to a hypersensitive state amenable to cure. One of the chief regulators of apoptosis in malignancy is p53, also thought to be the most commonly mutated gene in human cancer.

In this issue of the *JCI*, Bunz et al. (2) analyze the importance of p53 status in the response of human colorectal tumor cells to different chemotherapeutic agents. Exploiting in vitro homologous recombination technology, the authors examine the roles of p53 and its transcriptional target, p21, in sensitivity to adriamycin, ionizing radiation, and 5-fluorouracil (5-FU), the mainstay of current colorectal chemotherapy. Interestingly, although p53 loss conferred relative resistance to 5-FU, it conferred greater sensitivity in the same cells to adriamycin or radiation in vitro. This finding supports the general notion that p53 modulates treatment responsiveness, but it also raises the important notion that p53 may do so in opposite directions for different drugs or treatments. The authors highlight a number of important caveats in this system, such as the imperfect predictability of in vitro and in vivo cytotoxicity assays. However, the strategy employed by this research group, headed by Bert Vogelstein, potentially provides a means for discovering other such treatment-sensitivity patterns, and it may be applicable to a significant portion of currently incurable cancers — specifically those that can be grown in vitro. In addition to its potential for revealing mechanistic insights, the system also offers benefits over animal models, in that it examines true human cancers while still attempting to control for genetic background differences. Strategies such as this may permit treatments to be tailored to specific genetic lesions, if prognostically meaningful correlations are obtained.

What is meant by "prognostically meaningful correlations"? Such analyses would define prognosis, or optimal treatment, based on unambiguous genotypic or gene expression profiles. Certainly, the likelihood of cure for large tumor burdens is usually very low in human cancers. But are there malignancies, even when widely metastatic, that are curable using common chemotherapeutic agents? Clearly, there are, and have been for a while — chief among them, a variety of pediatric cancers and tumors of younger adults. While these do not include carcinomas (the most common of all cancers), the specific mesenchymal, germ cell, and hematopoietic cancers in this group are likely to contain significant clues pertinent to other cancers. One model is that these tumors may have sustained relatively few genetic "hits" and may have less efficiently dismantled their death machinery. In vivo, such tumors may exist in a state of near-simultaneous proliferation and death triggered by stresses such as starvation, hypoxia (3), acidosis (4), or substratum detachment (5). These tumors behave similarly to a variety of experimentally derived animal models of neoplasia, such as rodent fibroblasts transformed by Myc or E1A and Ras. Such models have provided major insights into the actions of a number of cancer genes. In this way, p53 was shown to play a profound role in regulating the apoptotic response of transformed fibroblasts to DNA damage (6–8). Moreover, beyond permitting these fibroblasts from being sensitized to apoptosis by oncogenic transformation, p53 simultaneously carries out cell-cycle checkpoint activities in other cells, which may significantly protect them from genotoxic damage (9).

The hallmark of any successful treatment is a high therapeutic index. p53 may confer a high therapeutic index in specific tumors by simultaneously sensitizing the cancer clone and protecting the host, thus widening the index from both sides. If so, p53 would be expected to play an important role in cancer treatment, with its loss or mutation predicting a substantially worsened prognosis. Certain animal models fit this scenario, as do a number of the highly curable cancers, including acute lymphoblastic leukemia of childhood, Wilms' tumor, and others. Clinical correlations between p53 and prognosis have been found in a number of less successfully treated cancers as well, but these data have been more controversial and, in some cases, confounded by the realization that alternate mechanisms exist to disable p53, such as Mdm2- or papillomavirus E6–mediated degradation (or ARF-mediated regulation of Mdm2). In fact, it may be the case that much as the Rb-cyclinD-cdk pathway is disabled by one means or another in nearly all tumors, p53 function may also be inactivated by diverse means, and to varying extents, in a very high fraction of tumors. Because p53's function remains incompletely understood, downstream lesions of p53 may also be relatively common. Clinical correlation based on p53 genotype may be limited to statements that p53 wild-type status would be necessary for high curability, whereas either p53 retention (wild-type) or mutation could be associated with functional deficiency in p53 and worsened prognosis. Thus, p53 is almost invariably wild-type in highly chemosensitive cancers, whereas it may be either wild-type or mutant in more resistant cancers (neuroblastoma and melanoma being examples of poorly responsive, often p53 wild-type tumors).

How might loss of p53 produce resistance to one drug but sensitization to another? Similar associations have been previously described between p53 loss and treatment sensitization (10, 11), a somewhat surprising notion if p53 were a major effector of apoptotic death. One explanation relates to the distinct cell-cycle arrest and apoptosis activities modulated by p53. p53's cell-cycle arrest activity (mediated at least in part by p21/Cip1/Waf1) maintains genomic stability. In cells where p53 activation predominantly stimulates this checkpoint effect (rather than apoptosis), p53 would function as a survival gene, and its loss would be expected to sensitize the cell to genotoxic stress. Conversely, for cells in which p53 stimulation predominantly produces an apoptotic output, loss of p53 may confer relative treatment resistance. So, presumably the key to predicting the consequence of p53 loss lies in understanding which p53-dependent action is the dominant output of a specific treatment in a given cell.

To complicate matters, there is evidence that p53's apoptotic output might occur through more than one mechanism. Although p53 is a bona fide transcription factor and uses this function to activate apoptosis-promoting genes (12, 13), independent evidence suggests that it may also trigger apoptosis via a transcription-independent route in certain contexts (14–16). It is therefore possible that the specific apoptotic pathway downstream of p53 may vary for a given cell and a given stress or drug treatment.

Given this assortment of potential p53-regulated cellular events, it is possible to envision diverse, even opposite, consequences of deleting p53 on the survival of a cell. In primary rodent fibroblasts, DNA damage activates p53 for p21-mediated cell-cycle arrest; loss of p53 would sensitize the cell to such damage (via p53-independent apoptotic or nonapoptotic death). In oncogene-transformed rodent fibroblasts for which apoptosis is the dominant p53 response (via one or more pathways), loss of p53 would confer resistance relative to wild-type counterparts. In complex human carcinomas, it is possible that persistence of wild-type p53 is an indication that downstream apoptotic elements have been lost. Thus, the apoptotic response mediated by p53 in these cells may mimic only limited aspects of its behavior in oncogene-transformed rodent fibro-blasts. And while certain triggers might employ p53-dependent, transcription-mediated apoptosis (such as 5-FU in the report of Bunz et al.), other triggers such as DNA damage might fail to induce p53-dependent apoptosis, either because of downstream genetic defects in these cells or because of the nature of colonic epithelial cells themselves. For example, perhaps transcription-independent apoptosis is more essential for the DNA damage–induced apoptosis pathway. These alternative scenarios of protective versus sensitizing roles for p53 loss in cancer highlight the most important comparison, which is also the most difficult to assess: the sensitivity of a given tumor cell relative not to the same cell lacking p53, but relative to the normal host. Moreover, through a better understanding of the mechanistic details connecting p53 to the death machinery, clearer views of this process may emerge.

The importance of apoptosis as a death pathway in cancer treatment has come under recent question, particularly by members of the radiobiology community (17). This valid concern has arisen from observations that slower, nonapoptotic death plays a significant role that is missed in short-term viability assays. In addition, as described above, neither the gene status of p53 nor other global apoptosis modulators are highly predictive of treatment outcome in all cancers, particularly the poor-prognosis ones. From this perspective, it is noteworthy that the exceptions, such as oncogene-transformed rodent fibroblasts, may not be special cases, but perhaps should be viewed as the instructive cases whose behavior we should seek to emulate for the more highly evolved treatment-resistant cancers. Indeed the treatment responses of widely metastatic but sensitive childhood tumors are typically dramatic, complete, and rapid (even associated with life-threatening tumor lysis syndrome), with profound cell death occurring over the course of a few days. This behavior obviously reflects a fundamentally different cell-death mechanism from that seen in other less successfully treated cancers.

In colorectal cancer, while 5-FU rarely cures widely metastatic disease, it may confer clinically meaningful treatment responses in specific clinical subgroups. The vast majority of other agents (including adriamycin) do not. Loss of p53 occurs in approximately 80% of colorectal tumors (18). Clinical correlates of 5-FU response in colorectal cancer have suggested that p53 wild-type status predicts greater likelihood of response (19, 20), further validating the observations of Bunz et al. Of course, the most meaningful endpoint is always treatment response in real people with real cancers, and ironically, the outcomes are often known from clinical trials before the theory is well understood. Still, attempts to isolate genetic variables within the complexity of human cancer cells will likely lead us to the day when cell death pathways are successfully harnessed in the treatment of cancer and other diseases.

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