New Leads Suggest a Clinically Relevant Genotype–Phenotype Relationship for the p53 Gene

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The literature dedicated to the functional properties of the p53 gene can make one wish that there were more genes in the human genome and far fewer functions for each protein product. p53, arguably the most heavily studied gene product, can interact with a wide array of nuclear and cytoplasmic binding partners. These interactions, as well as subtle postranslational changes in phosphorylation, acetylation, sumoylation, and other modifications, can modulate the central activity of p53—the transcriptional activation (and occasional repression) of downstream target genes. Although there is increasing evidence for unexpected nontranscriptional roles for p53 (1), the regulation of target gene expression in concert with individual components of parallel and interconnecting cell signaling cascade pathways mediates the primary function of p53, which has been reviewed extensively (2). This function can be summarized as the ability to sense and respond to cellular stresses that can range from dramatic or subtle DNA damage to hypoxia or aberrant growth signals from oncogene activation. The ability of wild-type p53 to restrain cell growth or to kill affected cells that are at risk for aberrant clonal expansion helps explain, therefore, why loss of wild-type p53 function is among the most common mutational events detected in human cancers.

In this issue of the Journal, Ahrendt et al. (3) report their findings on a dataset of 245 patients with operable non-small-cell lung cancer (NSCLC), in which 188 patients with confirmed stage I, II, or IIIa lung cancer were prospectively analyzed for the presence of p53 mutations. p53 mutation status was then examined in relation to matched clinical outcome and demographic information for each patient. The authors detected p53 mutations in approximately 50% of the primary lung cancer samples, and they determined that the presence of a p53 mutation was a statistically significant predictor of poor survival in the subset of patients with stage I disease (n = 106) but not in patients with more advanced stages of disease. The conclusion of the authors, reflecting the hope of investigators throughout the broad field of molecular prognostic factors, is that this type of specific prognostic information may ultimately lead to better treatment strategies and improved outcomes for patients suffering from NSCLC.

Given the large number of similar reports that have preceded this publication [cited within (3)], often with conflicting conclusions, it is worth considering why this particular study may be newsworthy. To put this study into context, one might briefly address some of the reasons why it has been difficult to establish a role for p53 mutations as a prognostic factor in lung cancer and then discuss separately the timeliness of the basic science and the clinical implications of the data. Major strengths of the Ahrendt et al. study (3) are the prospective nature of the data collection, the reliance on sequence analysis (rather than immunohistochemical assays) for scoring p53 mutational status, and the relatively large number of patients entered on the study. The small number of stage I NSCLC patients (n = 106), however, limits the confidence that can be drawn from further subset analyses within this group. The imperfect sensitivity and the uncertain specificity of the two sequencing methods (direct dideoxynucleotide sequencing and p53 GeneChip analysis) used by Ahrendt et al. (3) as well as findings from a previous report (4), which suggested that direct dideoxynucleotide sequence analysis limited to p53 exons 5–9 may miss 17% of the p53 mutations, must be considered in interpreting the mutational data from this study. In addition, quality-control measures need to be established to ensure that the sensitivity of the assays to detect p53 alterations, which are known to arise as an early event in NSCLC (5,6), is not preferentially reduced in small stage I tumors with a low tumor cellularity index compared with stage I tumors with a high tumor cellularity index. Finally, the tumor–node–metastasis (TNM) staging and performance status (a semi-objective assessment of the patient’s overall health) are the key determinants for NSCLC survival. Because the overall survival of advanced-stage NSCLC patients is so short and the percentage of patients entered into relevant biomarker research studies is so small, it might, therefore, be anticipated that it would be difficult to document statistically significant prognostic factors for advanced-stage lung cancer. In contrast, patients with early-stage lung cancer, especially T1N0 stage I patients, exhibit a range of long survival times after definitive surgical resection that can provide more opportunity for correlative analyses to detect statistically significant changes in survival. However, it is suspected that many recurrences (after complete surgical resection) in patients with early-stage lung cancer (especially T1N0 disease) represent a new second primary lung cancer rather than a recurrence of the original tumor that was initially assayed (7). How to incorporate this additional type of data will be an important challenge for the survival analyses of these early-stage lung cancer trials.

The data by Ahrendt et al. (3), which demonstrate a genotype–phenotype relationship for p53 inactivation, suggest several interesting basic science implications that will extend beyond the identification of a candidate prognostic tool for lung cancer. For example, there is growing evidence that the MDM2 and ARF gene products participate in a feedback loop to regulate p53 function, which is, in turn, a single component within a...
larger DNA/cell-stress-sensing, tumor-suppressor pathway (8,9). Although p53 mutations were detected in 50% of the primary NSCLC tumors (3), it is likely that non-p53 components of this same tumor suppressor pathway have been targeted for genetic or epigenetic alterations in many of the lung tumors retaining a wild-type p53 sequence. The observation by Ahrendt et al. (3) and those of others (10)—that subgroups of lung tumors carrying p53 missense mutations may behave differently from tumors carrying null p53 alleles versus tumors with wild-type p53 sequences—suggests that mutational inactivation of a single tumor suppressor pathway might generate considerable phenotype heterogeneity, depending on which upstream or downstream component within the pathway has been inactivated. More importantly, this phenotype heterogeneity may also help resolve a paradox between in vivo and in vitro data for p53 tumor biology that has lingered for many years. Although there have been substantial in vivo data demonstrating that loss of wild-type p53 function, through the inactivation of both p53 alleles as defined for tumor suppressor genes, is required for human tumorigenesis, this model could not fully explain the unusually high prevalence of missense p53 mutations detected in human tumors. These missense alterations were in contrast to the more usual premature-termination codon alterations seen in other loss-of-function tumor suppressor genes, such as the retinoblastoma gene (11). The in vivo data were also unable to explain the compelling in vitro data for gain-of-function tumorigenic potential observed with many tumor-specific p53 missense mutants (12). The conclusion by Ahrendt et al. (3)—that tumors carrying certain p53 mutations exhibit a more aggressive clinical phenotype than tumors with null or wild-type p53 expression—helps consolidate both the in vitro and the in vivo data, although more information on the in vivo biology of missense p53 mutants is needed.

Two recent studies (13,14) have provided such clues for new directions in the analysis of p53 mutational status as a prognostic factor in cancer. Previous studies (15–17) have demonstrated that certain tumor-specific p53 missense mutations selectively gain the ability to bind and inactivate the p53-related family members, p63 and p73. In addition, a common p53 polymorphism potently modified the ability of mutant p53 to disrupt p73-mediated apoptosis (17). Recent studies (13,14) extend these observations to show that certain p53 mutants on alleles carrying the Arg-72 polymorphism but not on alleles carrying the Pro-72 polymorphism, can inactivate p73 function, resulting in the phenotype of multidrug resistance. This imbalance in apoptosis/survival signals following exposure to genotoxic drugs would also be predicted to exhibit a clinically aggressive phenotype in untreated tumors that may, nonetheless, be intermittently exposed to intrinsic or extrinsic cell stress factors. Therefore, it will be important to further extend these observations by incorporating the status of the Arg/Pro codon 72 polymorphism in the present mutational study (3) and in future trials of p53 status in human tumors.

Ultimately, for a prognostic factor to be clinically useful, there needs to be an algorithm that proposes an effective management option based on test results. However, as of early May 2003, evidence to support the use of adjuvant radiation therapy or chemotherapy for resected early-stage lung cancer is still lacking. The anticipated publication later this year of the results of several large randomized, multicenter trials on the use of adjuvant chemotherapy for early-stage lung cancer will stimulate this debate and help guide clinical practice for this group of patients. The possibility that resected early-stage lung cancer patients with unfavorable p53 status and/or prognosis may also be less responsive to conventional chemotherapy regimens will heighten the need to develop alternate treatment strategies. Finally, because the data of Ahrendt et al. (3) were collected before the widespread use of spiral computed tomography scanning, the biology, genotype, and clinical course of this new group of sub-centimeter T1NO stage I NSCLC patients will need to be reassessed where the focus will, undoubtedly, be on the prevention of secondary tumors rather than solely on the elimination of microscopic metastasis.

References