

FOCUS ON RESEARCH

p53 — Master and Commander

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The gene known variously as p53, TP53, and Trp53 is currently featured in nearly 45,000 published articles listed in PubMed — a remarkable number suggesting that the protein product of this gene, p53, is one of the most important molecules in biology. When it was discovered in 1979, the p53 phosphoprotein (molecular mass, 53 kD) was postulated to have “a crucial role in the modulation of the transformed state.”¹ This idea has found support in innumerable studies, including the one reported on by Poeta et al. in this issue of the *Journal* (pages 2552–2561), in which somatic mutations in TP53 were associated with a poor outcome after surgical treatment of squamous-cell carcinoma of the head and neck. In particular, mutations that resulted in a shortened, and presumably malfunctioning, p53 protein or that interfered with the DNA-binding domain of p53 were independent predictors of a poor prognosis. So what is p53, and why is it important in cancer?

The p53 protein functions primarily as a multitarget transcription factor (see diagram). This means that it controls the expression of a wide range of genes with disparate functions. Additional cancer-related functions continue to be discovered, but thus far, its known functions include cell-cycle regulation, senescence, apoptosis, repair of DNA damage caused by genotoxic agents, angiogenesis, and regulation of oxidative stress.² Such a broad range of relevant

functions places p53 in a controlling position with respect to many cancer-related processes. With such a long list of interacting partners, it is not surprising that alterations in TP53 are very often found in cancer³ — indeed, it is probably the mutated gene most frequently found in cancer cells.

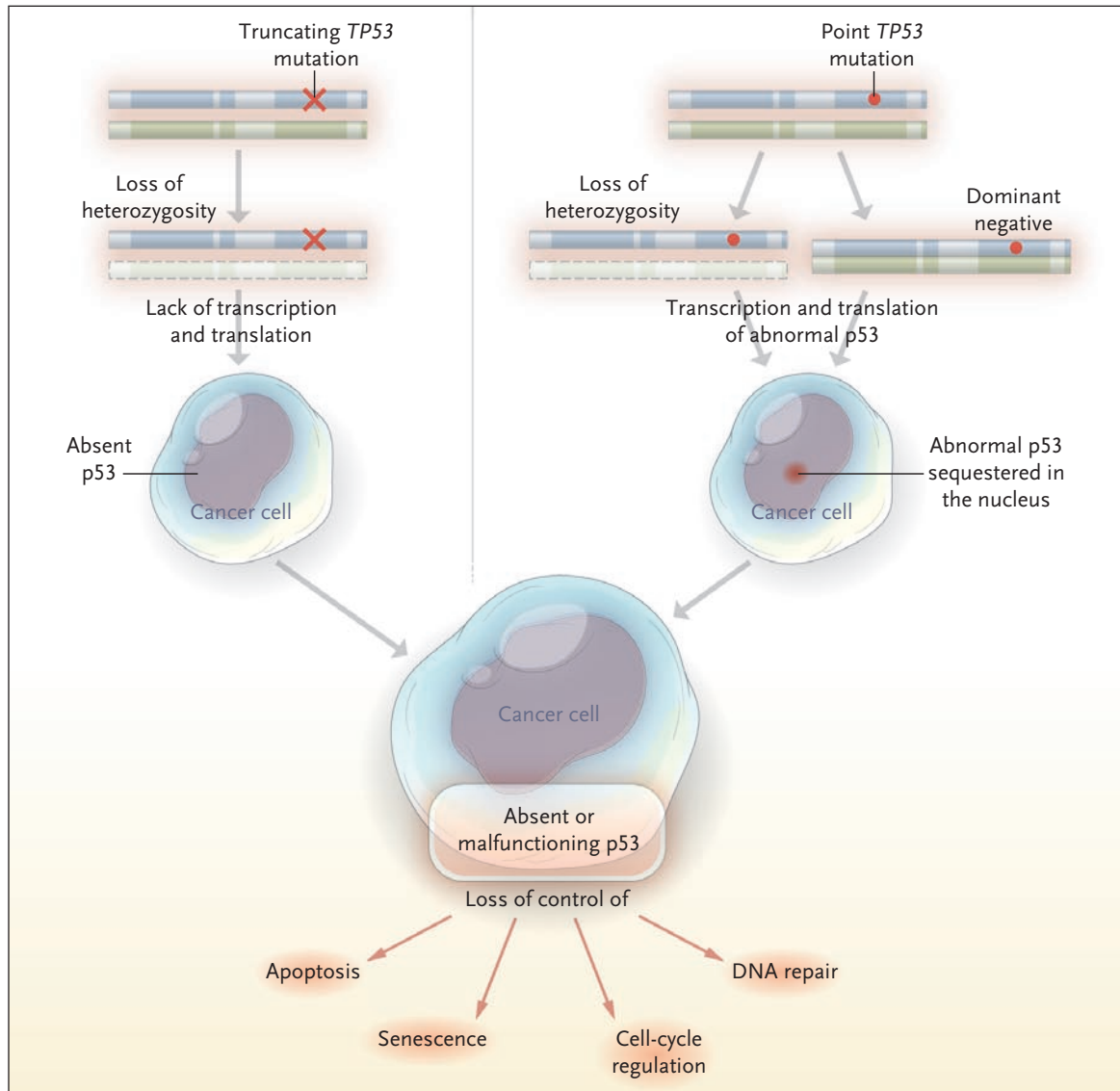
The important question for clinicians is whether all this knowledge is useful in the management of cancer. Despite the abundance of data, it has been hard to show that TP53-mutation status can really have an influence. For example, the expert panel of the American Society of Clinical Oncology on the use of tumor markers in breast cancer recently concluded that the current data are insufficient to support a recommendation for using p53 measurements in the treatment of women with breast cancer.⁴ This is also true for other less thoroughly investigated cancers, such as head and neck cancer.

Of course, clinical recommendations must take into account what is happening in the real world of patient care, not just the results of randomized, controlled trials. For example, Poeta et al. used microarray technology to identify TP53 mutations. The use of this approach raises questions about the general applicability of the findings, but as the costs of these types of comprehensive genomic analyses continue to decrease, there will be an increasing demand to introduce the technology into the

clinic. Indeed, the study by Poeta et al. and other recent investigations suggest that we are not too far from the era of molecularly tailored medicine,⁵ and it is reasonable to predict that knowledge of TP53 status will be central to this field.

In simple terms, oncologists want to know whom to treat and how to treat them. There are three ways in which oncologists could use knowledge of TP53. First, the choice of cancer treatment could be influenced by the status of TP53 in the tumor — patients with a tumor that bears a TP53 mutation would receive one type of treatment, whereas patients without such a mutation would receive a different treatment. But there are thorny details: changes in p53 function can render a tumor sensitive to one type of chemotherapy but resistant to another. Moreover, as shown by Poeta et al. and others, not all apparently deleterious TP53 mutations have the same effect; at the very least, mutations will have to be categorized into subgroups before physicians can decide how the information should be used. For these reasons, the design of the prospective studies that will be required to validate findings based on retrospective analyses will be complex.

Second, small molecules could be specifically designed to target p53 directly, or perhaps indirectly, using the technique of synthetic lethality, in which cells are killed only when two independent path-



Effect of *TP53* Mutations on the Role of p53 in Cancer-Related Processes.

ways are blocked. This approach is specific to cancer cells because only they will have abnormal p53; when a second pathway is interrupted by the chosen drug, cancer cells are killed but normal cells are not. This technique has been used successfully to kill cells deficient in the *BRCA1* or the *BRCA2* protein and is now being used in patients with germ-line mutations in the *BRCA1* or the *BRCA2* gene

who have had a relapse after initial treatment for breast or ovarian cancer. It is an attractive approach, because *TP53* mutations that result in a malfunctioning p53 protein are so common in cancer.

A third avenue is gene therapy using *TP53* itself. Despite early enthusiasm, it has not proved easy to develop successful gene therapy, and recent well-publicized

catastrophes have cast doubt on the whole field. Moreover, it has become apparent that *TP53* not only is a cancer gene but also has a broad role in the functioning of the entire organism.² Thus, altering the function or even the level of p53 protein may have profound effects on normal cells. For example, slight overexpression of p53 in all cells in a mouse resulted in premature ag-

ing. In humans, the Arg72→Pro polymorphism in p53 results in a slight reduction in the activity of the protein. This change is associated with a small but probably significant increase in cancer risk but also appears to be associated with an increased life span. Perhaps p53, when functioning normally, acts to regulate stem-cell renewal and thus has opposing effects on cancer and longevity through the expansion or reduction of the stem-cell pool.

It thus appears that p53 touch-

es on many parts of our lives — growth, health, longevity, and death. More, perhaps, than a “genome guardian,” p53 seems to be master and commander of key cellular processes that help to determine our fate. Controlling this molecule when it has gone awry may prove to be difficult. As has been widely observed, replacing malfunctioning commanders with new ones that are designed to work better is fraught with its own dangers.

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1. Lane DP, Crawford LV. T antigen is bound to a host protein in SV40-transformed cells. *Nature* 1979;278:261-3.
 2. Vousden KH, Lane DP. p53 In health and disease. *Nat Rev Mol Cell Biol* 2007;8:275-83.
 3. Greenblatt MS, Bennett WP, Hollstein M, Harris CC. Mutations in the p53 tumor suppressor gene: clues to cancer etiology and molecular pathogenesis. *Cancer Res* 1994; 54:4855-78.
 4. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* (in press).
 5. Varmus H. The new era in cancer research. *Science* 2006;312:1162-5.
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