Clinical implications of \( p53 \) mutations

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Abstract. The ultimate goal of basic cancer research is to provide a theoretical foundation for rational approaches to improve cancer therapy. Our extensive insight into the biology of the \( p53 \) tumour suppressor and the clinical behaviour of tumours harbouring \( p53 \) mutations indicates that information concerning \( p53 \) will be useful in diagnosis and prognosis, and may ultimately produce new therapeutic strategies. At the same time, efforts to understand the clinical implications of \( p53 \) mutations have revealed conceptual and technical limitations in translating basic biology to the clinic. The lessons learned from \( p53 \) may lay the groundwork for future efforts to synthesize cancer gene function, cancer genetics and cancer therapy.

Key words. Apoptosis; chemotherapy; prognosis; tumor suppressor; cancer genetics; clinical outcome.

Introduction

Despite extraordinary advances in our understanding of cancer, basic cancer research has yet to make a substantial impact on the treatment of human malignancy. Most cancer patients continue to receive highly toxic drugs derived from empirical screens, and the best therapy remains complete surgical resection of the tumour. Still, underlying the massive effort to identify the molecular defects in cancer cells is the premise that this information will eventually produce better diagnostic and prognostic tools, and ultimately suggest rational strategies for the development of more effective therapies.

The high frequency of \( p53 \) mutations in diverse human cancers implies that loss of \( p53 \) function is central to tumour development. Consequently, much effort has been devoted to understanding \( p53 \) biology, from its precise three-dimensional structure to its evolutionary significance [1, 2]. Similarly, a large number of clinical studies have asked whether information concerning the basic biology of \( p53 \) can be used for diagnostic or prognostic benefit, or ultimately to suggest strategies to improve cancer therapy. These studies provide valuable insight into the clinical significance of \( p53 \) mutations, but at the same time have revealed fundamental limitations in extrapolating basic research to patients. These studies may provide lessons to guide future work in exploiting \( p53 \) or other cancer genes for improved cancer treatment.

Biological activities of \( p53 \) and tumour development

Research over the last several years has revealed that \( p53 \) has a remarkable number of biological activities, including cell-cycle checkpoints, apoptosis (programmed cell death), senescence, maintenance of genomic integrity and control of angiogenesis (reviewed in refs 3–9). One can envision that disruption of any one of these processes might promote tumour progression. For example, loss of a DNA damage-inducible G1 checkpoint might promote tumour growth by increasing the frequency with which genetic damage is fixed as mutation. By contrast, inactivation of hypoxia or oncogene-induced apoptosis might provide a selective advantage to cells acquiring \( p53 \) mutations, allowing them to more readily emerge [10–13]. Still, it is not known which of these \( p53 \) activities is most critical during the course of tumour development – that is, what provides the selective pressure to mutate \( p53 \)?
**p53 mutation as a prognostic indicator**

Irrespective of which p53 function(s) account for its tumour suppressor activity, the nature of p53 biology and the consequences of p53 loss predict that tumours with p53 mutations should be inherently more aggressive than tumours bearing wild-type p53 genes. For example, loss of a G1 checkpoint and genomic integrity could increase the mutation rate, allowing p53 mutant tumours to evolve more rapidly. Loss of apoptosis or enhancement of angiogenesis would accelerate tumour expansion, and perhaps promote metastasis by allowing tumour cells to better survive foreign environments. Finally, inactivation of senescence programmes might more readily allow developing tumours to bypass a molecular clock that would otherwise provide a brake to tumour growth by limiting cell division. All of these factors, alone or in combination, predict an ominous outcome for patients harbouring p53 mutations.

Owing to the fundamental role of p53 in tumour development, clinical studies have asked whether p53 can be a prognostic indicator in various tumour types. These studies typically ask whether p53 mutations affect the disease-free interval or, ultimately, patient survival. In general, p53 mutations are associated with more aggressive cancers of higher tumour grade, and in many instances, p53 mutations correlate with reduced patient survival independently of tumour grade or stage. Among the tumour types for which substantial data are available, p53 mutations are associated with poor prognosis in certain lymphomas [14] and leukaemias [15–17], carcinomas of the breast [18–24], liver [25], colon [26], endometrium [27], and lung [28, 29], soft-tissue sarcomas [30], Wilms’ tumour [31], transitional cell carcinoma of the bladder [32], head and neck squamous cell carcinoma [33], and glioma [34].

Perhaps the most well-studied situation relating p53 status to patient prognosis is breast carcinoma, a tumour type where there is a clear need for better prognostic indicators. Early diagnosis and surgical resection of node-negative (i.e., nonmetastatic) breast cancer can be curative without requiring adjuvant chemotherapy. However, a percentage (20–30%) of these patients relapse; hence, good markers of relapse (a poor prognosis) might identify those patients in need of adjuvant therapy while sparing those patients who have a low risk of recurrence [35]. Early studies using p53 immunohistochemistry as a surrogate marker of p53 mutations were ambiguous; however, more recent studies using DNA sequencing now clearly indicate a striking association between p53 mutations and poor prognosis. Indeed, p53 may be the most clear-cut indicator of tumour recurrence in breast cancer identified to date [21].

Although the biological explanation underlying the association between p53 mutations and poor prognosis is not known, p53 mutant tumours possess characteristics consistent with functional studies using model systems. For example, tumours with p53 mutations can display reduced apoptosis and a high degree of genomic instability [36, 37], or increased angiogenesis in some cancer types [38, 39]. Also, some studies suggest that p53 mutant tumours more readily immortalize in cell culture, suggesting that they have lost growth controls that appear as increased proliferative capacity in cell culture [40].

Of course, the ultimate goal of identifying prognostic indicators is that they might eventually guide oncologists in the design of appropriate treatment regimens. While the clinical utility of p53 as a prognostic indicator remains uncertain, it seems likely that this information will be useful in conjunction with other indicators. Despite its promise, technology used to determine p53 status is nonuniform and suffers from other serious limitations (see below). Clearly, for p53 to be used routinely to predict prognosis, it will be necessary to standardize the methodology.

**p53 and the cytotoxicity of anticancer agents**

p53 can be activated by a large number of cellular stresses, including ribonucleotide depletion, hypoxia, oxidative stress and certain mitogenic oncogenes [11, 41–43]. Perhaps the best-studied activator of p53 is DNA damage, which can promote p53-dependent arrest or apoptosis depending on the genetic background of the cell or its tissue of origin [44–46]. Since most commonly used cytotoxic drugs either directly or indirectly damage DNA, one can easily imagine that p53 status might affect the outcome of cancer therapy. The precise nature of this impact, however, is not intuitively obvious.

**p53 and the G1 checkpoint**

p53 is involved in a DNA damage-inducible G1 checkpoint and, albeit indirectly, a mitotic spindle checkpoint. The role of p53 in the radiation-induced G1 checkpoint suggests that p53 promotes cell-cycle arrest to facilitate accurate DNA repair; consequently, loss of p53 might allow the persistence of unrepaired damage, leading to enhanced radiation toxicity. However, studies using isogenic fibroblasts from normal and p53 knockout mice found no difference in radiation-induced loss of clonogenic survival, suggesting that this was not the case [47].