CLINICAL IMPLICATIONS OF THE p53 GENE

David Sidransky, M.D.

Johns Hopkins University School of Medicine, Department of Otolaryngology, Division of Head and Neck Cancer Research, Baltimore, Maryland, 21205-2196

Monica Hollstein, Ph.D.

German Cancer Research Center, Division 0325, Toxicology & Cancer Risk Factors, Im Nevenheimer Feld 280, D-69120 Heidelberg, Germany

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ABSTRACT

The capacity for malignant growth is acquired by the stepwise accumulation of defects in specific genes regulating cell growth and tissue homeostasis. Although several hundred genes are known to control growth, molecular genetic studies in cancer show that few of these are consistently involved in the natural history of human cancer, and those typically in only certain types of malignancy. Prospects for development of molecular-based diagnostic and therapeutic strategies with widespread application did not look promising, until it was realized that the p53 tumor suppressor gene was defective in approximately half of all malignancies. This discovery generated research efforts of unparalleled intensity to determine how p53 functions at the molecular level, and how to apply this knowledge to clinical ends.

FUNCTIONS OF NORMAL p53

The term p53 originally referred to a 53-kilodalton phosphoprotein, the product of a 20-kilobase gene on the short arm of human chromosome 17. However, both the gene (tumor protein 53, or TP53) and the protein were designated as p53 on the historical grounds that the protein was discovered (1, 2).
well before the gene and that it plays a critical role as a cancer suppressor (3, 4). Normal (wild-type) p53 suppresses outgrowth of genetically damaged, hence potentially neoplastic, cells in two distinct ways: by causing a pause in the cell cycle, and by promoting exit from the cell cycle altogether (programmed cell death, or apoptosis). This dichotomy is thought to allow an appropriate biological response to the two sequelae of DNA damage: Either genome integrity is restored by DNA repair, in which case cells can be released from transient cell cycle arrest, or when damage persists, cells can be permanently eliminated from the population by apoptosis. This function of p53 as “guardian of the genome” may extend to a role in initial monitoring and repair of DNA damage in addition to direct control of cell growth and death (5, 6).

**Cancer-Inhibiting Functions**

**CELL CYCLE ARREST** Suppression of cell transformation is mediated by specific binding of p53 tetrameres to DNA at its recognition motifs in the promoter of the wild-type p53-activated fragment (WAF1) gene (7) (synonyms are CIP1, p21 gene), which codes for a universal inhibitor (p21, or CDKI) of the cyclin-dependent kinases that govern cell cycle progression (Figure 1) (8, 9). When levels of p21 inhibitor rise, the cyclin/CDK complexes it binds to can no longer phosphorylate Rb proteins (retinoblastoma tumor suppressor protein family). Underphosphorylated Rb sequesters the E2F transcription factors required for producing the DNA synthesis machinery (10), and the cell cycle is thus blocked prior to S-phase. Regulation of this G1/S boundary is a critical checkpoint in the cell cycle and is potentially inhibited by p21.

Cyclin/CDK inhibition is sufficient for growth suppression of cells (11), but the p21 inhibitor may also interfere with DNA synthesis directly by binding to proliferating cell nuclear antigen (PCNA) (12, 13), an essential factor in DNA replication. However, p21 levels can also be increased by a variety of other mechanisms independent of p53 transactivation (14, 15), suggesting a p53 bypass strategy for therapeutic drugs that would engineer growth arrest in precancerous cells that have lost p53 function (16).

A second gene under transcription control by p53 affecting cell cycle kinetics is GADD45 (growth arrest DNA damage) (17), which encodes a protein that, like p21, inhibits DNA synthesis by binding to PCNA. The MDM-2 protooncogene is also on the growing list of genes found to contain p53-binding consensus motifs and contributes to cell cycle control by a feedback loop to p53 itself (18). The MDM-2 protein binds to the transcription-promoting domain in the N-terminal of p53, inhibiting this activity (19). Finally, p53 controls its own transcription. Other genes regulated by p53 do not affect growth response per se but may modulate response to therapeutic agents
Block of p53 transactivation and loss of specific p53 DNA binding caused by mutation are the major mechanisms by which tumor suppressor function is subverted in cancer.

**PROGRAMMED CELL DEATH** In response to DNA damage, p53 can trigger exit from the cell cycle and chromosomal disintegration by an active enzymatic process of cell death (apoptosis) (20). The mechanism of p53-induced apoptosis is not well understood. The equilibrium of bax and bc1-2, two principal and opposing protein components of apoptosis regulation that form neutralizing heterodimer complexes, may be shifted by p53 in favor of cell death (Figure 1). p53 increases levels of the apoptosis-promoting factor BAX, which has the p53 recognition motif in its promoter and represses levels of the apoptosis-blocking protein bc1-2 (21). However, mechanisms not involving transcriptional activation by p53 and pathways entirely independent of p53 have also been described (20). The molecular pathways and gene families regulating cell death in differ-
entiation and development are cell/tissue type specific. Because cell death can also be programmed by p53–independent routes in some cell contexts, this raises the possibility that these alternate mechanisms can be enlisted artificially in an unfamiliar physiological context by new therapeutic drugs (see below). The finding that anticancer drugs may eliminate cancer cells predominantly by apoptosis may place the control of this process by p53 in center stage clinically (22).

**Cellular Control of p53 Activity**

Specific DNA binding of normal p53 protein is negatively regulated by its C-terminal domain, where sites for phosphorylation and tetramerization critical for high activity are located. The capacity for p53 to adopt different conformations and hence assume different activity states is also influenced by its oxidation state and binding to zinc metal ions, potentially serving as sensors of oxidative and genotoxic stress (23). In addition, various cellular processes affect nuclear levels of active protein (24) (e.g., protein and messenger RNA stability, cellular localization, and cytoplasmic sequestering). These multiple routes by which final conformationally active nuclear p53 protein levels can be regulated are important in medical research because they provide the molecular information necessary for designing drugs to reinstall p53-controlled growth suppression.

When genetic damage such as DNA strand breaks occurs in a cell (25, 26) with normally functioning p53, levels of the active protein rise, and the cell cycle is stalled or the process of cell death is induced (27). It is not known what cellular signals decide between these alternatives or convert cell arrest to cell death. Cells deficient in functional p53 are genetically unstable and become permissive for inopportune gene amplification or chromosome loss through DNA strand breakage and rejoining (28–30). Increasing genetic disorder in the form of aneuploidy and detrimental genetic recombination events with loss of genetic material (LOH) can also accumulate in the cell population when unrepaired damage to nuclear macromolecules persists through the stages of cell division. The inability to delay cell division processes increases the probability that DNA damage will remain uncorrected during DNA replication, leading to neoplastic progression.

**ALTERED p53 IN CANCER**

*p53 Gene Lesions in Human Cancer*

**SPORADIC CANCER**  Between 30 and 70% of malignant tumors of almost every organ and histologic subtype have a point mutation in one of the two p53 gene copies and loss of the other allele (31). In addition, loss of p53 function by other
mechanisms may be important in some of the cancers that do not have p53 allele loss or mutation (see below). Most tumor mutations are missense base substitutions in the p53 coding sequence that change a single amino acid in the core domain, which governs conformation and specific interactions with DNA. Sites where mutations are especially likely to occur (hot spots) cluster at points where the protein is in close proximity to DNA or makes direct contact when the tetramer binds to its recognition motif (32). This structural information from X-ray crystallography of p53-DNA complexes corroborates biological data indicating that the feature of p53 crucial for suppression of tumor growth resides in its specific DNA binding and transcription activation functions rather than in its other interactions with cellular macromolecules (Figure 1 and see above).

A major conformation effect from any one of an array of single amino acid substitutions would explain several puzzling aspects of p53 tumor biology. One conformationally altered molecule of a p53 tetramer can disturb DNA binding, so that one aberrant allele can be sufficient to compromise tumor suppressor function (hence be selected for) (33, 34). This is a departure from the classic model for tumor suppressor genes in which both parental copies are inactivated before growth suppressor activity in the cell is affected. The relative vulnerability of p53 as a site for genetic lesions in cancer development may thus rest partly on the large number of possible sites where minute damage will cause a major defect, and partly in the fact that damage to just one allele can already compromise suppressor activity and would be selected for during growth. In addition, some p53 mutants may acquire a new, growth-stimulating potential (oncogenic gain-of-function mutations).

GERMLINE MUTATIONS IN P53 The Li-Fraumeni (L-F) syndrome is a rare family cancer syndrome typically characterized by an increased risk of breast, brain, and adrenocortical tumors, sarcomas, and leukemia. Many, though not all, L-F families have germline p53 mutations, and a carrier has a 90% risk of developing cancer by age 70. As is true for somatic p53 mutations, most L-F germline mutations are missense mutations in the core domain of the p53 gene, and the individual L-F mutations are found also in sporadic tumors (35). Children with second cancers, or with sarcomas, have an increased likelihood of carrying either a de novo germline p53 mutation, or a constitutive mutation inherited from a parent not previously identified as a member of a L-F kindred.

Environmental and host factors may influence the penetrance of a constitutive p53 mutation and the spectrum of tumors it elicits among affected family members. It is not clear why the frequent cancers in the classic syndrome do not include several of the common sporadic human cancers in which p53 mutations are frequent (e.g. colorectal cancer) (36).
Assessment of p53 Status in Human Cells

**GENE SEQUENCING**  Genotyping of tumors can be accomplished by polymerase chain reaction amplification of the p53 gene or messenger RNA, and by DNA sequencing. A prescreening step of the polymerase chain reaction products by sensitive gel assays (single-strand conformation polymorphism, denaturing gradient gel electrophoresis) can reduce the labor-intensive work of identifying mutations by direct genetic analysis (37).

**IMMUNOHISTOCHEMISTRY**  A rapid preliminary indication of p53 status in tumors can be performed by immunohistochemical detection of nuclear p53 accumulation. This approach is feasible because mutant p53 in tumor cells usually adopts a conformation more resistant to degradation than the wild-type, increasing the protein half-life by more than a magnitude. Various factors must be taken into consideration in the interpretation of results, however. Protein half-life is affected by cellular context, and prolongation may involve prior loss of the wild-type allele. Mutations that lead to absence of protein, and many that produce a truncated protein, will yield negative results in this assay. Factors that affect the minimal histochemically detectable accumulated protein require standardization for routine clinical application of immunohistochemistry [e.g. fixation (38, 39) and protocol procedures, selection of a uniform panel of primary antibodies (40), and microscope stations equipped with image analyzers to quantify protein accumulation]. Finally, studies where a few cells in early lesions are found to stain with p53 antibody are difficult to interpret. These results may be due to the first few mutant cells in the clonal evolution of a tumor, or wild-type protein may accumulate in nonneoplastic cells in response to genotoxic exposures (e.g. UV light), hypoxia, or other biological changes in cellular environment.

The correlation between the presence of a p53 missense mutation and immunohistochemical staining of a tumor with certain p53 antibodies is high in some cancer types, for example in head and neck tumors, in lung cancers of various cell subtypes, and in colorectal cancer. Frequent nuclear staining without gene structural mutation has been reported for skin melanomas and preinvasive prostate neoplasia. The p53 protein may be biochemically altered by a different mechanism than gene mutation, possibly involving other p53-binding inhibitory proteins.

**FUNCTIONAL TESTS**  These assays are based on the correlation between growth suppressor activity of p53 and its specific DNA binding and transactivation capacity. Human p53 sequences from a tumor or lymphocytes of an individual suspected of carrying a germline mutation are introduced and expressed in yeast tester strains that undergo a phenotypic change, such as colony color, when a
protein genetically engineered to be p53-inducible accumulates. The tests
distinguish between biologically silent germline or tumor mutations and those
that indeed disrupt suppressor activity (41).

Tumor Mutation Patterns

A typical tumor mutation, regardless of the cancer type, is a missense mutation
in the core region of p53 that disrupts specific DNA binding and transcriptional
activation of downstream genes under p53 regulation. Closer scrutiny of
the exact types of these DNA base changes, however, reveals major differ-
ences among cancer types, and there are also examples of mutation frequency
and patterns that vary in different patient populations with the same cancer
(Figure 2). Cancer mutation profiles have substantiated theoretical models of
mutagenesis and have corroborated predictions based on experimental data in
bacteria and mammalian cells.

Mutations in tumors are changes in base sequence that have bypassed
detection and removal by DNA repair and are selected for during neoplasia
because they provide a growth advantage. Repair and bioselection may vary
with cell type, differentiation stage, age, and genetic background. Mutation
patterns are a composite of spontaneously arising base changes during normal
processes (for example, DNA polymerase errors) and base miscoding events
provoked by carcinogen attack on DNA.

High exposure to a mutagenic cancer agent can induce mutations charac-
teristic of its chemistry with DNA that swamp out spontaneous base-change
patterns. p53 mutations in squamous cell carcinoma (SCC) and basal cell
carcinoma (BSC) of the skin are the best example of a mutation signature by
the major known risk factor for skin cancer, sunlight (42). About 9% of skin
tumor mutations (excluding XP patients) are CC→TT base substitutions, aris-
ing from photodimers at pyrimidine dinucleotides, and are characteristic of
UV light damage to DNA. Fewer than one per thousand internal cancers
harbors this type of p53 mutation (36). The most common single class of
mutation in internal cancers, on the other hand, is a hallmark of spontaneous
change in mammalian DNA: C→T mutations at 5-mCpG dinucleotides. They
account for one of every four tumor mutations and all cancer types combined
and can occur by spontaneous amino group hydrolysis at 5-mC (5-methyl
cytosine). This mutation is characteristic of sequence drift in evolution and of
germline mutations in all types of genes associated with human diseases (43),
including L-F syndrome p53 mutations. One of every two p53 mutations in
colorectal cancer is of this kind and has stimulated research on genetic and
dietary factors that promote deamination of methylcytosine in the intestinal
epithelium. In patients with head and neck cancer, mutations at these CpG
sites are rare and the incidence of p53 mutations is fourfold higher in patients
who smoke cigarettes and drink alcohol compared with those who do not (44).
Figure 2  p53 mutation patterns by organ site. Frequencies of various types of mutations are calculated from the European Bioinformatics Institute (Cambridge, England) database of p53 mutations in human tumors and cell lines (36), updated (n = 3700 mutations). Shown here: Mouth (primarily squamous cell carcinoma of buccal cavity); breast (all types combined); lung (all types combined); colon (all colorectal tumors); bladder (all types); skin (primarily squamous cell and basal cell carcinoma; includes tumors of patients with xeroderma pigmentosum). Classes of base substitution are listed according to a purine to pyrimidine change, by convention (e.g. G→C to A→T refers to both G→C to A→T (G to A) and C→G to T→A (C to T)).
Analysis of tumor mutations provides concrete information relevant to the issue of whether mutations in human cancer originate primarily from potentially mutagenic normal cellular processes or are induced directly by chemical attack of environmental mutagens on DNA. p53 mutation data suggest that both are important and that their relative importance will depend on cancer type as well as on exposure history and genetic background of the patients.

Demographic differences in tumor mutation frequency and pattern for a single cancer type are molecular corroboration of epidemiologic studies on worldwide cancer incidence patterns that have demonstrated the importance of environment in cancer causation. Geographically disparate p53 tumor mutation prevalence and patterns were first shown for hepatocellular cancer in high-incidence versus low-incidence areas of the world (45). A hot spot at p53 codon 249 characterizes mutations in hepatocellular cancer from high-incidence regions such as Qidong, China, whereas in other parts of the Far East where incidence is lower, and in Europe, mutations are heterogeneous and less frequent. A primary risk factor associated with the hot-spot mutation is the mutagenic food contaminant aflatoxin, a potent liver carcinogen.

p53 IN NEOPLASTIC DEVELOPMENT

Timing

Tumors progress through a series of genetic changes during histopathological progression (46). Elucidating the timing of critical genetic changes in different cancers contributes to the development of molecular progression models. These progression models can then be used to target early genetic changes, potentially useful for early detection strategies, and those that occur later between the preinvasive and the invasive, potentially useful for prognostic assays. Moreover, early changes may be particularly attractive as therapeutic targets for intervention.

Because p53 mutations are so common, the timing of their occurrence in different tumor types is of great importance. p53 mutations were initially characterized in colon cancer where they invariably occurred between the preinvasive (adenoma) and the invasive (carcinoma) stage (47). Sequence analysis of p53 has revealed a similar progression in astrocytomas (low to high grade) (48), in squamous cell carcinoma of the head and neck (dysplasia/carcinoma in situ to invasive tumors) (49), and in thyroid cancer (generally in poorly differentiated anaplastic carcinomas) and leukemias (50, 51). These definitive reports are based almost entirely on sequence analysis of the conserved portion of the p53, the region where most mutations occur. Many other studies have been done using immunohistochemical analysis to detect stabilization of mutant p53 protein as a marker of p53 mutation. Many of these
studies have been hindered by a lack of sequence analysis to confirm the presence of these mutations (see above).

**Prognosis**

Although p53 immunohistochemical analysis may in itself be a prognostic indicator, its relationship to p53 mutation by sequence analysis remains to be defined. In certain cancers, p53 mutations through sequence analysis have been compared with overall survival. Several groups have shown that p53 mutation (or 17p loss) is associated with a statistically significant decrease in survival in colon cancer (52, 53). In non-small cell lung cancer, larger studies have shown a difference in survival based on p53 status whereas smaller studies have not (54). However, in head and neck cancer, a growing discrepancy between p53 studies with differences in disease-free and overall survival appears only in immunohistochemistry (IHC) studies and is definitively absent in those employing sequence analysis. Similarly, a large IHC study in bladder cancer was markedly positive, whereas a smaller study based on sequence analysis also correlated with survival; however, p53 was not an independent prognostic factor (55). A large study based on sequence analysis demonstrated a significant decrease in survival for patients with breast cancer, whereas results from IHC approaches are mostly mixed (56, 57). Emerging data suggest that breast cancer mutation analysis is hindered by significant differences in p53 status between different histologic subtypes, whereas in prostate cancer p53 mutations are present by IHC in a small subset of aggressive or metastatic tumors (58). In many other tumor types, immunohistochemical staining based on some of the comments above have been equivocal, occasionally showing a mild decrease or increase in survival or prognosis but usually showing no difference. One must also take into account the fact that staining is more subjective than sequence analysis and that negative trials are less likely to be published. Clearly, controlled trials utilizing both IHC and sequence analysis are required to settle the issue in most tumor types.

**Clonality**

p53 mutations represent clonal genetic alterations that provide these cells with a growth advantage over surrounding cells. Thus, p53 can be used as a marker to test the genetic relationship between separate clusters (i.e. separate tumors) of neoplastic cells. Studies in ovarian cancer have demonstrated identical p53 mutations in scattered peritoneal foci, providing convincing evidence that these foci are derived from a single progenitor cell (59). On the other hand, apparently independent primary tumors of the aerodigestive tract were found to harbor different p53 mutations (60). However, emerging evidence indicates that p53 mutations usually arise later in progression (see above). Therefore, an initial clone arising from an early genetic change may populate a large ana-
tumoral area and eventually give rise to individual lesions that have progressed through independent genetic alterations such as p53 mutation. Thus, the presence of identical p53 mutations is strong molecular proof for clonality, but distinct mutations in most tumor types are not sufficient to exclude the possibility of clonality.

**Alternative Modes of p53 Inactivation**

Many but not all tumors contain p53 mutations and thus several avenues have been pursued to identify alternative mechanisms for inactivation of the p53 gene. An important endogenous pathway of p53 inactivation is by interaction with cellular protein MDM-2 (see above). Although mutations have not been described in primary tumors, amplification of MDM-2 appears to be the preferred mechanism for abrogating p53 function in some tumor types. The best evidence is derived from sarcomas, where approximately one third of primary tumors contain amplification of MDM-2 associated with increased transcription and expression of the gene product, and lack p53 mutations (61). Southern blot amplification of MDM-2 or overexpression by IHC has also been shown in a subset (usually <10%) of breast, lung, brain, and bladder cancers. In most of these studies, p53 mutations are also exclusive, confirming the notion that these two events independently abrogate the p53 pathway.

The best studied system for exogenous inactivation of p53 is the interaction of wild-type p53 with the E6 protein encoded by certain high risk types of human papillomavirus (HPV) (62). Several studies have demonstrated that the HPV E6 and E7 oncoproteins can cooperate to immortalize several types of cells (63). E6 has been shown to bind p53 and to mediate p53 degradation through the ubiquitin pathway (64, 65). Functional studies have also demonstrated that introduction of E6 into cells abrogates the p53-dependent G1 cell cycle arrest induced after exposure to DNA damage (66). The role of HPV infection in the progression of primary cervical cancer now appears convincing. Epidemiologic studies have implicated high risk HPV (subtypes 16 and 18) in the pathogenesis of preinvasive lesions and cervical cancer. The great majority of cervical carcinomas are HPV positive and several studies have shown that p53 mutations are relatively rare in these tumors, again suggesting mutually exclusive pathways for p53 inactivation (67). Cases of primary tumors both with HPV and with p53 mutation, although rare, have led to speculation that other pathways (e.g. E7 protein abrogating the Rb pathway) might be important for tumor progression. Furthermore, mutant p53 may still confer an additional growth advantage for affected cells. Unanswered questions remain, however. It is not known why only a fraction of HPV-infected women develop cancer. Investigators have demonstrated less than one copy of the HPV genome (per cell) in primary tumors with clonal genetic alterations and
HPV infection. This observation may be related to viral integration in the host genome associated with a lack of productive infection. Other studies have occasionally shown HPV sequences in esophageal, head and neck, and bladder tumors, but these tumors have a high incidence of p53 mutation, and the precise role, if any, of HPV in these neoplasms remains to be elucidated.

**DIAGNOSTICS**

*Exfoliated Cells*

The identification of clonal genetic alterations is an emerging and powerful tool for the detection of human malignancy (68). Because p53 mutations are so ubiquitous, they are excellent candidate markers for molecular studies. Although p53 mutations occur often between the preinvasive and the invasive state, many of these lesions are still small, and detection of p53 mutations can be used for detection of preclinical cancers. Initial scientific studies have demonstrated the feasibility of this approach using the polymerase chain reaction followed by cloning and plaque hybridization to demonstrate the presence of rare p53 mutations in the urine of patients with bladder cancer (69). This approach was useful retrospectively for the detection of a clonal p53 mutation several years before the clinical diagnosis of bladder cancer in the case of Vice President Hubert H. Humphrey (70). This case thus demonstrated that morphologic analysis of cytologic samples could be greatly augmented by the use of molecular techniques to detect these clonal p53 mutations.

Similar strategies have been used to detect mutations of p53 in sputum samples of patients who went on to develop clinical lung cancer (71). In all cases, the primary tumors that were resected contained the identical p53 mutation identified in the sputum. Moreover, in one of these cases the diagnosis was confirmed 13 months before the clinical diagnosis, providing an important window for potential early detection and surgical resection. The main limitation to these approaches remains the wide variety of p53 mutations and the inability by current technology to detect these rare mutations without great cost.

*Minimal Residual Disease*

p53 mutations can also be used as markers of tumor spread. In the case of head and neck cancer, patients with invasive primary tumors were sequenced to identify the p53 mutation present in the primary tumor (72). In approximately one half of these patients, p53 mutation was detected, and a probe was synthesized that could detect rare cells carrying the same p53 mutations in apparently normal surgical margins and lymph nodes. With this approach, investigators demonstrated that rare neoplastic cells were often left behind after apparently
complete surgical resection. Many of these patients would have been significantly upstaged if lymph node analysis based on molecular analysis had been included. In many of these cases, the positive molecular margin predicted the precise location of tumor recurrence. This type of approach may also be useful for many types of tumors where p53 mutations are common (see above).

Serum Antibodies

A humoral immune response to mutant p53 has been seen in all types of cancers tested, with the possible exception of gliomas (73). Current estimates of antibody production in cancer patients range from 5–40%, based on simple ELISA tests (73-75). At most, only 1% of control group samples will show detectable titers. It is not clear why only certain patients are able to mount an immune response to mutant p53. Possible explanations for this selective anti-p53 response include loss of tolerance due to accumulation of the more stable mutant forms, association of the mutant p53 with heat-shock proteins (76), and increased immunogenicity due to conformational tertiary changes induced by specific mutations (76, 77). A prerequisite for antibody synthesis in most malignancies appears to be a missense mutation, but this by itself is not sufficient to determine whether or not antibody will be present. Certain p53 mutations in combination with specific class-I and -II HLA antigens involved in processing and presenting the p53 oncoproteins may determine whether an immune response will occur (78). Instances where p53 antibodies in asymptomatic individuals have heralded the development of clinical cancer months to years later suggest that serum screening of high-risk groups may be an appropriate addition to early detection screening strategies (79, 80). Moreover, antibody titers drop sharply after therapy, which implies that monitoring the efficacy of a therapy or the presence of an occult recurrence with anti-p53 titers may be possible. Preliminary work suggests that breast cancer patients with serum p53 antibodies have a lower survival and those with lung cancer have a higher survival, but the value of p53 antibodies in determining prognosis is still unclear (81, 82).

THERAPEUTIC OPPORTUNITIES

The role of p53 in response to DNA damage induced by radiation or chemotherapy has prompted significant interest in alternative strategies for therapy of human cancers (83). An important hypothesis has emerged proposing that primary tumors with p53 mutation may not recognize DNA damage and thus may not induce the normal apoptotic pathway for self-destruction. It would follow that most human tumors with abrogated p53 pathways would be relatively resistant to most therapeutic agents. This in turn would explain the severe resistance of most epithelial tumors to commonly used agents (84, 85).
p53 may also induce suppression of angiogenesis, potentially critical for the early neovascularization seen in primary tumors. Mutant p53 is unable to suppress this process in gliomas, and p53 may also directly affect transcription of thrombospondin-1, an angiogenesis inhibitor (86, 87).

Strategies to circumvent this critical apoptotic decision point in p53 mutant tumors might provide therapeutic advantages (88). However, it is already clear that p53 induction of apoptosis in response to DNA damage varies according to cell type. Some studies on epithelial cells have shown little difference in response to radiation-induced change regardless of p53 status (89). Conversely, leukemias and other hematologic malignancies appear to depend on this critical recognition by wild-type p53 for apoptosis (83). This notion is strengthened by resistance to therapeutic agents in hematologic neoplasms with p53 mutation. Thus, the role of p53 in the apoptotic pathway, the presence of different genetic changes in different tumor types, and the milieu (e.g. growth factors, etc) in which the neoplastic cell resides may all be critical in determining response to these agents.

Future studies should determine if p53 status is a major determinant of DNA damage response in vivo by following large numbers of patients with a single tumor type and assessing clinical response based on p53 status. Preinvasive lesions that contain wild-type p53 may be reversible by induction of apoptosis and could usher in an era of effective chemoprevention. Agents or strategies to bypass p53 mutation and suppress angiogenesis may deprive early lesions of the necessary microenvironment needed for tumor growth. Moreover, new drugs or agents that could bypass mutant p53 or induce an independent apoptotic pathway may be more effective in treating the most common and most resistant epithelial neoplasms.

Literature Cited


