p53 Is Mutated in a Subset of Advanced-Stage Prostate Cancers

Robert Bookstein, Donal MacGrogan, Susan G. Hilsenbeck, Francis Sharkey, and D. Craig Allred

Department of Molecular Biology, Canji, Inc., San Diego, California 92121. R. B., D. M. G., and the Departments of Medicine [S. G. H.] and Pathology [F. S., D. C. A.], The University of Texas Health Science Center at San Antonio, San Antonio, Texas 78284

ABSTRACT

Inactivation of p53, a tumor suppressor gene, contributes to the genesis and/or progression of a substantial fraction of all human cancers, including >50% of breast, lung, and colon carcinomas. Mutated p53 alleles typically contain missense single-base substitutions within exons 5-8 and encode abnormally stable p53 proteins that accumulate to high levels in tumor cell nuclei. To evaluate the frequency, type, and clinical significance of p53 mutation in human prostate cancer, archival tumor material from 150 prostate cancer patients was examined by immunohistochemistry (IHC) with anti-p53 antibodies. Abnormal nuclear p53 accumulation (IHC) was observed in 19 tumors (12.7%) and was strongly related to disease stage (23% of stage III or IV tumors were IHC+ versus 4% of 74 stage 0-II tumors; P < 0.001, Fisher's exact test). The methods of polymerase chain reaction, single-strand conformational polymorphism, and direct sequencing were used to identify mutations, predominantly missense single-base substitutions in exons 5, 7, or 8 in 9 of 14 IHC+ cases but in none of 20 IHC- cases; 5 of these mutations were G:C→A:T transitions at CpG dinucleotides. These data indicate that mutated p53 alleles are quite uncommon in early prostate cancers but are found in 20-25% of advanced cancers, suggesting a role for p53 mutation in the progression of at least a subset of prostate cancers.

INTRODUCTION

Despite its major health impact as the most common cancer in men, prostate carcinoma is relatively poorly understood at the genetic level. It is hypothesized that, as with other neoplasms, mutations of protooncogenes and tumor suppressor genes contribute in some way to the genesis of prostate cancer. Previous studies have demonstrated specific allelic losses of chromosomes 8p, 10q, 16q, and 18q (1, 2) and specific allelic losses of chromosomes 8p, 10q, 16q, and 18q (1, 2) and mutations of Rb3 on chromosome 13q (3, 4) in varying fractions of cases. However, Rb is apparently intact in most prostate cancers, and its mutation may play a modifying role or represent only one of several alternative genetic pathways in prostatic neoplasia. Activated oncogenes also appear to be infrequent in primary prostate tumors; e.g., mutated alleles of the ras gene family have been found in <5% of cases in the United States (5-8).

Another suppressor gene, p53, on human chromosome 17p, is known to be mutated in a majority of colorectal, lung, and breast tumors and also in numerous other cancer types (9, 10). This gene is typically affected by missense point mutations in exons 5-8 that paradoxically stabilize the protein product, leading to massive accumulation in tumor cell nuclei. Wild-type p53 is essentially undetectable by immunochemical methods, and the finding of intense nuclear staining with anti-p53 antibodies strongly suggests the presence of point-mutated p53 (11). Mutations that completely disable gene expression are also observed (12-14). Germline transmission of mutated p53 alleles results in the Li-Fraumeni syndrome, characterized by precocious susceptibility to breast and adrenocortical carcinomas, sarcomas of soft tissue and bone, brain tumors, and leukemia (15-17). These studies indicate that the p53 gene has an extraordinarily broad role in human oncogenesis and that p53 mutations are among the most common genetic changes in human tumors.

Both immunohistochemical and molecular genetic analyses of p53 have been performed in formalin-fixed, paraffin-embedded tissues from hospital archives (18), which are ready sources of tumor material for prostatic and other cancers. To address questions of frequency, type, and significance of p53 mutation in human prostate cancer, archival tumor and nonneoplastic tissue blocks were collected from 150 patients with prostate cancer for whom complete clinical and pathological information was maintained by tumor registries. Rates and clinicopathological correlates of p53 mutation were estimated by immunostaining representative sections from these 150 tumors. To verify and further characterize mutations, all immunostain-positive cases and 20 immunostain-negative cases were analyzed by PCR, SSCP (19), and direct sequencing of genomic DNA extracted from histological sections.

MATERIALS AND METHODS

Subjects and Materials. One-hundred forty patients (140) of the Audie Murphy Veterans Hospital in San Antonio, TX, were identified via its tumor registry with the diagnosis of prostatic adenocarcinoma between 1987 and 1992 and with treatment by radical prostatectomy (88 cases) or TUR (52 cases). An additional 10 cases of recurrent, stage IV cancer treated by palliative TUR were obtained from Dr. G. Wilding at the University of Wisconsin Comprehensive Cancer Center in Madison, WI. Histopathological grading was done independently of other analyses by one author (F. S.) according to the method of Gleason (20). Staging (0-IV) was based on clinical (56 cases) or pathological (94 cases) assessments of the primary tumor, metastases to regional lymph nodes and distant sites, and histopathological grade, according to standard criteria (21).

IHC. p53 protein accumulation was detected by the use of monoclonal antibody PAB1801 and polyclonal antibody CM-1 (Novocastra Laboratories, Newcastle, United Kingdom), which have been shown to recognize p53 in sections of formalin-fixed, paraffin-embedded tissue (22-24). Positively staining archival tissues were used as controls with each batch of immunostained prostate tumors. Sections (3 μm) were then incubated in 100 mM Tris (pH 7.6) on a Sequenza manual immunostainer, mounted. Immunostained slides were evaluated by light microscopy as described previously (25). In brief, the fraction of positively stained tumor cell...
nuclei was scored on a scale of 0–5, and the intensity of staining was scored on a scale of 0–3. The sum of the two numbers gave the IHC score (range 0, 2–8).

Statistical Analysis. Associations between immunohistochemistry results and other nonparametric indices were evaluated using χ² or Fisher’s exact test.

DNA Extraction. Uniform areas of prostate carcinoma, identified histologically on adjacent hematoxylin/eosin-stained tissue sections, were scraped into microfuge tubes from two or three 10-μm unstained sections on glass slides. Tumor-free lymph nodes or benign prostate tissues were used as sources of somatic DNA. Tissue fragments were deparaffinized with xylene and alcohol as described before (26) and then digested in 100–200 μl of extraction mix (10 mM Tris, pH 8.0–1 mM EDTA–0.5% Tween 20–0.5% Nonidet P-40–250 μg/ml of proteinase K) overnight at 50°C. Samples were then boiled for 10 min and stored at −20°C.

PCR. p53 exons 4 through 9 were amplified in vitro in four segments of ≤450 base pairs (exon 4, exons 5/6, exon 7, exons 8/9) using primers within introns. Primer sequences, kindly provided by D. D’Amico, were as follows: exon 4, 5’-AGAAGCTTGCTCTCCTCAG-3’ and 5’-CTAGTTAGCTTCT-3’; exons 5 and 6, 5’-TGACCTTCACCTGCTTCT-3’ and 5’-CAGAGACCAGCTGTCGTA-3’; exons 8 and 9, 5’-GACCTGATTTCCT-3’ and 5’-CTGGAAATCTTCTCCGTTG-3’. Exon 7 primers were 5’-TCTCTCCCAAGGCGCTCGGCA-3’ (16) and 5’-CAAATGCGCTCTCACCTGGA-3’ (27). An alternative antisense primer, 5’-GATGAGAGGTGGATGTTAGT-3’, was used to assay a sequence polymorphism in intron 7 (Genome Data Base entry 35848). PCR reactions were done in 20-μl volumes containing 1–2 μl of template DNA, 1 μCi [α-32P]dCTP, 40 ng of each primer, and other constituents as described previously (4). PCR conditions were (94°C, 2 min) × 1–(94°C, 1 min; 4°C, 1 min; 92°C, 2 min) × 32–(72°C, 5 min) × 1, where A = 60 for exon 7, A = 50 for exons 8/9, and A = 55 for the remaining reactions. A segment of intron 1 containing a 5-base pair tandem repeat polymorphism was amplified as described in Ref. 28. Negative controls without added template were set up routinely to detect PCR contamination.

SSCP. Exon 5/6 and 8/9 PCR products were digested with endonucleases AarI (United States Biochemicals, Cleveland, OH) or Syl (New England Biolabs, Beverly, MA), respectively, to separate paired exons (29). Samples were diluted 1:1 with 10 mM EDTA-0.1% SDS, then diluted 1:1 again with sequencing loading buffer (50% formamide–10 mM EDTA–0.25% xylene cyanol–0.25% bromophenol blue), and boiled for 2 min. Samples were placed on ice, and 3 μl per lane were loaded on gels (32 cm x 40 cm x 0.4 mm) containing 5% polyacrylamide in 1× Tris-borate-EDTA (0.089 M Tris-borate, pH 8.3–0.025 M EDTA) with or without 10% glycerol or 1× MDE gel mix (J. T. Baker, Phillipsburg, NJ) in 0.6 × Tris-borate-EDTA. One unboiled sample per gel was loaded to identify renatured products. Electrophoresis of polyacrylamide gels was done at 40 W at RT with a cooling fan or at 4°C (without glycerol only), whereas MDE gels were run at 6–8 W at RT according to the recommendations of the manufacturer. Gels were dried and autoradiographed at −70°C for 1–2 days.

Direct Sequencing. Abnormal SSCP bands were cut out of dried gels and eluted in 10 μl Tris (pH 7.4)–1 mM EDTA overnight at 50°C to obtain pure mutated DNA templates (30). Templates (5 μl) were reamplified in 100-μl volumes with primers (250 ng each) corresponding to the ends of the templates; if aberrant bands were derived from endonuclease-digested PCR products, then internal primers were used as follows: exon 5 antisense, 5’-CAACCAGCCCGTCTCTC-3’; exon 8 antisense, 5’-TCCTCCTCACCAGC-3’.

Remaining PCR constituents and conditions were as described above. Reamplified PCR products were separated from primers by 5% nondenaturing PAGE, visualized by ethidium bromide staining, and eluted from gel slices by the “crush and soak” method (31). Purified DNA was used as template for double-stranded cycle sequencing with [32P]labeled 32P-labeled primers according to kit instructions (Promega, Madison, WI). Products were separated by 6% denaturing PAGE, dried, and autoradiographed overnight at −70°C without an intensifying screen.

RESULTS

Aberrant p53 Accumulation. Nuclear staining of tumor cells (Fig. 1) was observed in 17 (12.1%) of 140 primary and 2 of 10 recurrent prostate cancers (total, 12.7% of 150 cases). The fraction of tumor cells with positively staining nuclei varied from a few percent to 90% (see Table 1). Cell-to-cell staining heterogeneity is a recognized feature of p53 IHC (22, 25, 33). Adjacent, morphologically benign prostate tissue was evaluated overly in 62 of the radical prostatectomy specimens. Nuclear staining of benign epithelium was not seen.

Clinicopathological Correlations. The clinical significance of p53 accumulation was preliminarily investigated by examining correlations with disease stage and histological grade. The rate of IHC positivity was clearly related to stage, increasing from 1 (2.6%) of 38 stage 0-I tumors to 8 (24%) of 33 stage IV tumors (Table 1). IHC results were also strongly associated (P = 0.004) with higher primary T stage, which is a major determinant of overall stage. The largest increases in IHC rate occurred between stages II and III or T2 and T3, which are primarily distinguished by the absence or presence, respectively, of invasion beyond the prostatic capsule (21). A weak association of IHC positivity and increased histological grade (grouped by Gleason scores 2–4, 5–7, and 8–10) failed to reach statistical significance (P = 0.08). There was no relationship between immunostaining result and type of treatment (radical prostatectomy versus TUR).

Detection of Point Mutations. To determine whether p53 accumulation in prostate cancer indicated the presence of characteristic missense mutations and to search for additional mutations not causing nuclear accumulation, four gene segments containing exons 4–9 were amplified in vitro from extracted DNA and screened for altered single-strand conformations by the method of Orita et al. (19). Eighteen IHC+ tumors were available for analysis, of which four consistently yielded nonamplifiable DNA templates. Of the 14 remaining templates, abnormal bands were detected in nine (Fig. 2, Table 2). Reamplification and direct sequencing of these bands (Fig. 3) revealed point mutations in conserved regions or codons that are frequently mutated in other cancers (Table 3). Eight of the nine mutations were predicted...
to lead to amino acid substitutions; one was a single-base deletion of codon 177 that would lead to frameshift, premature translational termination and loss of p53 expression (Fig. 3B). This tumor (no. 3) was found to be heterozygous for a sequence polymorphism in intron 7 (Fig. 4) and thus retained two different p53 alleles. It is therefore hypothesized that the IHC* status of this tumor is due to an undetected point mutation of the other p53 allele. This case is analogous to a heterozygous IHC* breast cancer described previously which contained a single-base deletion in codon 167 (33).

The same analysis was applied to 20 IHC* specimens that were selected with a bias toward higher stage (see legend to Table 2). No SSCP alterations or mutations were detected in DNA from these cases (Table 2). No mutations were detected in exons 4, 6, or 9 after due regard for known neutral polymorphisms (34, 35). Normal migrating products were occasionally sequenced as controls, and no sequence variations were found.

Features of Mutations. Five mutations were transitions (G:C→A:T), all occurring at CpG dinucleotides (Table 3). *Hot-spot* codons 175 (exon 5), 245 and 249 (exon 7), and 273 and 282 (exon 8) were targets of seven of the mutations. The single-base deletion originated at a guanine residue (G:C→A:T), all occurring at CpG dinucleotides (Table 3). *Hot-spot* codons 175 (exon 5), 245 and 249 (exon 7), and 273 and 282 (exon 8) were targets of seven of the mutations. The single-base deletion originated at a guanine residue (G:C→A:T), all occurring at CpG dinucleotides (Table 3).

**Table 3 Summary of p53 mutations**

<table>
<thead>
<tr>
<th>Case</th>
<th>Stage</th>
<th>IHC score</th>
<th>SSCP abnormality</th>
<th>Mutated codon</th>
<th>Mutation (nucleotide)</th>
<th>Mutation (amino acid)</th>
<th>Transition (s)/transversion (v)</th>
<th>CpG?</th>
<th>Germ-line?</th>
<th>Loss of heterozygosity?</th>
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<tr>
<td>1</td>
<td>III</td>
<td>5</td>
<td>Exon5</td>
<td>147</td>
<td>GGT→GGT</td>
<td>Val→Gly</td>
<td>v</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>IV</td>
<td>4</td>
<td>Exon5</td>
<td>175</td>
<td>GCC→CAC</td>
<td>Arg→His</td>
<td>s</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>IV</td>
<td>6</td>
<td>Exon5</td>
<td>177</td>
<td>1 base pair deletion</td>
<td>Frameshift</td>
<td>v</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>III</td>
<td>4</td>
<td>Exon7</td>
<td>245</td>
<td>GGC→AGC</td>
<td>Gly→Ser</td>
<td>s</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>III</td>
<td>5</td>
<td>Exon7</td>
<td>245</td>
<td>GGC→GTC</td>
<td>Gly→Val</td>
<td>v</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>5</td>
<td>Exon7</td>
<td>249</td>
<td>AGG→AGT</td>
<td>Arg→Ser</td>
<td>v</td>
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<td>No</td>
<td>U</td>
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<tr>
<td>7</td>
<td>IV</td>
<td>5</td>
<td>Exon8</td>
<td>273</td>
<td>CTT→TGT</td>
<td>Arg→Cys</td>
<td>s</td>
<td>Yes</td>
<td>NA</td>
<td>No*</td>
</tr>
<tr>
<td>8</td>
<td>IV</td>
<td>4</td>
<td>Exon8</td>
<td>273</td>
<td>CTT→TGT</td>
<td>Arg→Cys</td>
<td>s</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>IV</td>
<td>4</td>
<td>Exon8</td>
<td>282</td>
<td>CGG→TGG</td>
<td>Arg→Trp</td>
<td>s</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

DISCUSSION

p53 accumulation was detected in 12.7% of 150 prostate carcinomas, but rates varied significantly with tumor stage. Only one case of 38 stage 0–1 cancers was IHC* compared to 22 and 24% in stage III and IV cases, respectively. These results both complement and contrast with those of Visakorpi et al. (35), in which p53 accumulation was examined in 137 consecutive Finnish patients with untreated prostate carcinoma. Using a three-step IHC scoring system of no-, low-, and high-level reactivity, Visakorpi et al. found IHC positivity in 17% of cases overall (11% low level and 6% high level). Statistically nonsignificant trends were observed for higher rates in cases with higher T stage or metastases. The rate of IHC positivity (low + high) in the most advanced Finnish cases was 26%, a figure quite similar to loss of heterozygosity as a second mutation was assessed using polymorphisms in p53 introns 1 or 7 (Fig. 4) or exon 4 (34). The second allele was lost in three cases and apparently retained in three cases (Table 3), although losses in tumors might be masked by sufficient contaminating normal DNA.

Rearrangements Affecting p53. Both IHC and SSCP would fail to detect substantial gene deletions or rearrangements that are occasionally observed in other tumor types. To detect these mutations, DNA extracted from 34 frozen primary prostate carcinomas was analyzed by Southern blotting with a p53 cDNA probe. Bands in all lanes had identical sizes and uniform intensities (data not shown), suggesting the absence of these larger mutational events.
Aptil digestion confirmed that SSCP variation was due to a neutral sequence polymorphism (6% denaturing PAGE) showing loss of heterozygosity in T1 and retention in T5. B, intron 7 single-strand conformational polymorphism (nondenaturing PAGE, RT, 10% glycerol). Apol digestion confirmed that SSCP variation was due to a neutral sequence polymorphism in intron 7. T1 lost one allele compared to matched benign DNA; T3 apparently retained both alleles.

Fig. 4. Intragenic polymorphisms. DNA from paired tumor (T) and benign (B) tissues was amplified as described in “Materials and Methods.” A, intron 1 length polymorphism (6% denaturing PAGE) showing loss of heterozygosity in T1 and retention in T5. B, intron 7 single-strand conformational polymorphism (nondenaturing PAGE, RT, 10% glycerol). Apol digestion confirmed that SSCP variation was due to a neutral sequence polymorphism in intron 7. T1 lost one allele compared to matched benign DNA; T3 apparently retained both alleles.

Ours considering the differences in antibodies, scoring systems, and patient populations between the two studies, Visakorpi et al. did find a significant association between high-level staining and poor clinical outcome, whereas cases with low-level staining were not prognostically different from those with no staining. Clinical outcome could not be meaningfully assessed in our study because of the short follow-up time. In a third immunohistopathological study, p53 accumulation was detected in 17% of 29 prostate cancers, most of which were locally advanced, but not in 34 cases of benign prostatic hyperplasia (37). A variable proportion of positively staining cells was observed ranging from 0.2 to 26% with a mean of 16.7%.

We showed that nuclear staining for p53 protein was strongly associated with aberrant bands by SSCP and with mutations characterized at the sequence level. Mutations must be clonal (identical and present in most tumor cells) to be detected by these methods. The coexistence of shifted and normally migrating bands in tumor lanes is best explained by contamination of templates with DNA from benign stromal cells and by the heterozygosity of tumor cells themselves. On the other hand, all cases with abnormal SSCP patterns had IHC scores of 4 or more, whereas mutations could not be found in three IHC+ tumors with lower scores, despite the fact that virtually all mutations associated with p53 accumulation are located in exons 5–8 (9). In the study of Visakorpi et al. described above, tumors with no or low-level immunoreactivity shared similar biological and clinical properties, unlike the group with high-level staining. These observations indirectly suggest that low-level immunoreactivity may not correlate with p53 mutation. If our low-scoring tumors are lumped into one category, then only one of 74 stage 0-II tumors was “positive” versus 13 (19%) of 69 stage III-IV tumors (P < 0.0004). Better methods for quantifying p53 expression may be necessary for optimal discrimination of staining categories.

The association of p53 accumulation and advanced stage suggests that p53 mutation may play a role in prostate tumor progression. Indeed, Effert et al. (38) suggested this explicitly based on analysis of a single patient with prostate cancer. Different portions of the primary tumor were found to contain wild-type or mutated sequences at p53 codon 172, whereas a lymph node metastasis was apparently homogeneous for the mutated sequence. It was proposed that a clone with mutated p53 arose within the primary tumor that was able to outgrow other tumor cells and also to metastasize. In colon, bladder, and brain cancers, p53 mutation is often acquired in concert with disease progression as a late event in human oncogenesis (39–41). On the other hand, p53 mutation apparently functions as an early event in tumors of Li-Fraumeni syndrome patients (15–17). Regardless of the precise timing of p53 mutation, introduction of wild-type p53 invariably suppresses the growth or tumorigenicity of cell lines derived from cancers of many types, including prostate (42).

The locations and forms of p53 mutation in each cancer type may reveal clues about mutational mechanisms (9, 43). The eight substitution mutations characterized in this study included five G:C→A:T transitions that alter one base of the dinucleotide sequence CpG in four hot-spot codons (nos. 175, 245, 273, and 282). These CpG dinucleotides are highly methylated in several cell types, and their mutation is thought to occur by spontaneous deamination of methylcytosine (9, 43). A larger sample size is required to determine whether this type of endogenous mutational mechanism is indeed favored in prostate cancer as it is in colon cancer and lymphoma/leukemia (9). In other respects, mutations were typical for any human cancer, including their location in certain conserved regions and the predominance of mutations at the base pair G:C rather than A:T.

IHC+ cases with normal SSCP patterns (Table 2) may be explained in two ways. (a) SSCP is not perfectly sensitive, although detection rates of up to 90% are reported (34). (b) it has been proposed that p53 accumulation may occur without p53 mutation because of other genetic or epigenetic effects affecting the "p53 pathway" (44, 45). Thus, p53 accumulation might not be entirely synonymous with mutation but could be biologically significant nonetheless. These possibilities cannot be distinguished here. Conversely, “knockout” mutations abating expression of both wild-type alleles are also considered biologically significant; for example, p53 mutations in lung cancer cell lines comprised up to 40% of nonsense and splice site mutations (29). We sought to detect such mutations in two ways, (a) by SSCP analysis of exons 4–9 in 20 IHC+ tumors and (b) by Southern blot analysis of 34 radical prostatectomy specimens. No mutations were found in these tumors, despite a bias toward advanced-stage cases. Although exons 1, 2, 3, 10, and 11 were not examined by SSCP, these results certainly suggest that knockout mutations of p53 are not frequent relative to stabilizing point mutations.

Although these studies point to a role for p53 in progression of prostate cancer, many neoplasms arise and progress to advanced stages without this mutation. In fact, the frequency of p53 accumulation and apparent mutation is rather low compared to that of breast, colon, esophagus, and lung cancers. Different types of malignancies evidently share a number of alternative oncogenic pathways but vary in the rates that they are utilized. Given the relatively low frequencies of mutation of ras, Rb, and p53, it is apparent that the most common genetic pathways for prostatic neoplasia are yet to be defined.

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