p53 Point Mutation and Survival in Colorectal Cancer Patients

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Abstract

We have examined the relationship between point mutation of the p53 tumor suppressor gene and survival in colorectal cancer patients. We found that patients with tumors harboring mutated p53 genes showed a significantly poorer prognosis than did those patients with genes without point mutations, and, moreover, patient response to postoperative therapies depended significantly on mutation status in both adjuvant and palliative treatment cohorts. However, not all point mutations were the same functionally; point mutations within the conserved domains of the p53 tumor suppressor gene were inherently more aggressive than tumors with point mutations outside of these domains, and mutations of codon 175 were particularly aggressive. These results suggest that knowledge of a patient's p53 status, both with respect to the presence of point mutations and to the specific nature of the lesion, may be required to accurately predict both the course of the disease and the response of the disease to postoperative therapeutic interventions, especially those therapies based on the induction of apoptosis in the neoplastic cell.

Introduction

The prediction of the biological behavior of a tumor is of primary importance in the management of colorectal cancer patients. Many staging systems have been introduced in an attempt to provide accurate prognostication, but, in general, these provide accurate information about cohorts of patients rather than individuals. Staging systems are often used as a basis for deciding patient management, especially with regard to additional therapies such as radiotherapy, chemotherapy, or combinations thereof (1).

The mainstay of treatment for colorectal carcinoma is surgical resection (1). The intent of surgical intervention may be either curative or palliative, depending on the spread of the disease and the tumor clearance during surgery. Selected patients from both curative and palliative cohorts may be judged to be suitable for additional postoperative treatment in an attempt to either prevent the growth of secondary cancers or to reduce the tumor burden of the patient. Such postoperative therapies may consist of either radiotherapy, chemotherapy, or a combination of both.

Currently, such postoperative therapies are believed to act through the induction of apoptosis, or programmed cell death, in the neoplastic cells (2), and several studies suggest that induction of apoptosis is dependent on the presence of functional copies of the p53 tumor suppressor gene (2–4). More recently, Lowe et al. (5) have shown in a mouse model system that tumors with functional p53 genes respond to radiation and chemotherapeutic agents, whereas those tumors without functional p53 genes do not. Moreover, tumors that were initially responsive to treatment became unresponsive because of the acquisition of p53 point mutations (5). Given that the p53 tumor suppressor gene is one of the most commonly mutated genes in a wide variety of tumors (6–8) these results are potentially of great clinical importance.

Point mutation of the p53 gene occurs in approximately 50% of colorectal carcinomas (6–8) and has recently been shown to be associated strongly with lymphatic dissemination (9) and possibly with a poorer patient prognosis (10). The vast majority of point mutations detected in p53 genes represent missense mutations, which result in amino acid substitutions in the p53 protein (6–8). Such mutant proteins have been shown to have an array of altered biological and biochemical properties, including an extended half-life and the ability to cooperate with activated ras genes to transform cell lines (8). Not all mutant proteins have the same oncogenic potential, although the basis of this is not readily apparent (11).

Nearly 98% of point mutations of the p53 gene detected to date fall in an approximately 600-nucleotide-long stretch of the p53 message, corresponding roughly to exons 4–9 of the p53 gene (6, 7). The p53 protein shows a high degree of evolutionary conservation, but, in particular, five domains (domains I–V) show almost complete conservation from trout to man (12). Four of these domains (domains II–V) occur within the 200-amino acid stretch encoded by the region in which almost all point mutations occur (6, 7).

We have shown previously that point mutation of the p53 gene is associated with disease progression, and in particular, with lymphatic dissemination (9); in this study we wished to examine the influence of p53 point mutation in determining both the course of the disease and how such lesions influence the response to postoperative therapies.

Materials and Methods

Patients and Tumors. The patient cohort is essentially as described previously (9). All tumors selected for DNA sequencing consisted of single adenocarcinomas, and patients with multiple carcinomas of the colorectum, whether synchronous or metachronous, were excluded. Patients with dysplastic adenomas elsewhere in the colon at the time of surgery were also excluded. Patients with synchronous carcinomas were staged Dukes' A–D according to Turnbull's modification of Dukes' original staging (13).

DNA Sequence Analysis. Templates were analyzed by direct sequencing of cDNA-PCR products corresponding to exons 4–9 of the p53 gene by using the dS Cycle Sequencing system (GIBCO-BRL, Gaithersburg, MD). Sequencing was carried out by using a panel of p53 cDNA-specific primers (sequences available on request). Point mutations were confirmed by DNA sequence analysis on both DNA strands.

Data Analysis and Statistics. Patient follow-up was determined to be the time between surgery and the last departmental contact (scheduled follow-up, mail response, or telephone contact) or patient death. Median patient follow up was 24 months (interquartile range: 14, 34 months). Survival data was analyzed by Kaplan-Meier plots (14) and the log rank test by using the SPSS computer package (SPSS, Inc., Chicago, IL). Models were tested by using Cox regression analysis, with entry into the model dependent on P < 0.05. Data were entered by using the Forward:Wald method of entry.

Results

The p53 point mutation status was determined for 192 colorectal adenocarcinomas by single-stranded conformational polymorphisms, with the cohort consisting essentially of tumors described previously (9). Point mutations were detected in 57% (109 of 192) of cases. Kaplan-Meier survival plots (14) were generated for patients with or without point-mutated p53 genes (Fig. 1). Log rank analysis of this

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plot showed a significant association between point mutation and a poorer patient prognosis ($P = 0.0054$). Cox regression analysis was used to determine the contribution of several factors toward patient survival. Factors available for entry into the model included Dukes’ Stage, differentiation, and mutation status, as well as patient age and sex. Entry into the model was via the Forward-Wald method and conditional on $P < 0.05$. The final model contained the terms for Dukes’ Stage ($P < 0.0001$) and mutation status ($P = 0.0310$). Overall significance of the model was $\chi^2 = 65.001$ ($P < 0.0001$).

To determine whether there were qualitative differences occurring in the nature of point mutations, we examined 50% of the mutation-positive tumors from the above cohort to determine the exact nature of the point mutation. Hence, 53 templates were subjected to a full DNA sequence analysis. Results are shown in Table 1. The point mutation spectrum determined is representative of the local population (15), which is consistent with, but not identical to, that published on other population cohorts (6, 7), and as such probably reflects regional influences in mutation events (7, 15). Fig. 2 shows an analysis of point mutation distribution with respect to lymph node involvement. We note that point mutations occurring within the highly conserved do-
### Table 1 p53 point mutations characterized in 53 colorectal carcinomas.

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$^a$ Amino acid change, amino acid change in three-letter code.

$^b$ Stage, Dukes' stage of tumor according to Turnbull's modification (13).

$^c$ LN, presence (+) or absence (−) of detectable lymphatic involvement at time of surgery.

$^d$ Dm ATS, presence (+) or absence (−) of detectable distant organ metastasis at the time of surgery.

$^e$ Dm DF, presence (+) or absence (−) of detectable distant organ metastasis at time of surgery or during subsequent follow-up.

$^f$ Follow-up, patient follow-up in months since surgery. Numbers in brackets indicate patient is deceased.

$^a$ CD, point mutation is in (Y) or outside (N) conserved domains.

The p53 gene is involved in the response of tumors to radiation and chemotherapy (5). Therefore, we selected a new cohort of 54 patients who had undergone postsurgical...
patients with point mutations of the p53 gene showed a significantly higher
poorer prognosis than did patients without detectable
point mutations [number of patients, 37; mutation rate, 51% (19 of
37); \( P = 0.038 \) by log rank analysis]. A more substantial difference
was seen in the palliative treatment cases (Fig. 1). The response of
patients to palliative therapy was markedly dependent on the p53
status of the primary colorectal cancer. All of the patients undergoing
palliative postoperative treatment who had point mutations of the p53
gene have died subsequently, in contrast to only one patient who died
from the cohort of patients not showing detectable point mutations
[number of patients, 17; mutation rate, 59% (10 of 17); \( P = 0.0048, \)
log rank analysis].

Fig. 2. Lymphatic dissemination and p53 point mutation. Partial sequence of the p53 protein (amino acids 101—300) showing the distribution of 53 mutants detected by DNA sequence analysis (Table I). +, presence of lymphatic dissemination; —, absence of
lymphatic dissemination. Conserved domains are boxed.

radiotherapy or chemotherapy (or both). Tumors from these patients
were analyzed for point mutations of the p53 gene by single-stranded
conformational polymorphisms as described elsewhere (9, 15).
Point
mutations were detected in 54% (29 of 54) of cases.

Analysis of patient survival with respect to point mutation was then
undertaken by Kaplan-Meier plots (Fig. 1). The two survival curves
are significantly different (\( P = 0.0006 \) by log rank analysis). Patients
with point mutations of the p53 gene showed a significantly higher
patient mortality rate than did those patients whose tumors did not
show evidence of point mutations occurring within the p53 gene.
However, this cohort of patients consists of patients who underwent
either palliative or curative resections. The data was therefore re-
analyzed with respect to the surgical intent. When only curative
resections were considered, a smaller but still significant difference
was found between patients with and without mutations (Fig. 1).

Again, patients with point mutations of the p53 gene showed a
significantly poorer prognosis than did patients without detectable
point mutations [number of patients, 37; mutation rate, 51% (19 of
37); \( P = 0.038 \) by log rank analysis]. A more substantial difference
was seen in the palliative treatment cases (Fig. 1). The response of
patients to palliative therapy was markedly dependent on the p53
status of the primary colorectal cancer. All of the patients undergoing
palliative postoperative treatment who had point mutations of the p53
gene have died subsequently, in contrast to only one patient who died
from the cohort of patients not showing detectable point mutations
[number of patients, 17; mutation rate, 59% (10 of 17); \( P = 0.0048, \)
log rank analysis].

Discussion

The specific biological and biochemical properties of mutant p53
proteins have been the subject of intense investigation. The observa-
tion that nearly 80% of mutations of the p53 gene are point mutations
leading to amino acid substitutions (missense mutations) has lead to
the speculation that such mutants may confer an additional growth
advantage over and above that resulting from the loss of suppressor
function (6). This speculation is apparently supported by experiments
that show a “gain of function” for p53 mutants (16). These observa-
tions would suggest that tumors with p53 point mutations would show
a growth advantage over tumors with no p53 mutation. In patient
terms, a growth advantage of a tumor would correlate to a poorer
patient prognosis, and we show here that patients with p53 point
mutations show a significantly poorer prognosis than do patients who
do not show such mutations.

However, it has been observed that not all point mutations are
functionally equivalent (11), and the data generated by DNA sequenc-
ning support this. We find that point mutations occurring within the
evolutionarily conserved domains show a significantly poorer prog-
nosis than do those mutations occurring outside these domains. We
further note that lymphatic dissemination, and the occurrence of
subsequent distant organ metastasis are strongly associated with point
mutations occurring within these regions. Moreover, point mutations
within these regions clearly show differential aggressiveness, with
codon 175 mutants being particularly aggressive.

In this report, we have shown three levels of increasing risk for
colorectal cancer patients: (a) patients with point mutations of the p53
gene show a poorer prognosis than do patients without point muta-
tions; (b) patients with point mutations in the conserved domains
show a poorer prognosis than do those with mutations outside these
domains; and (c) patients with mutations of codon 175 show the
poorest prognosis of all. Detecting point mutations of the p53 gene is
technically demanding and determining the specific nature of the
lesion by DNA sequencing is even more so. However, work from
other areas has shown that routine screening of colorectal carcinomas
for p53 point mutations may become a prime prerequisite in deter-
mining patient management. Recently, Lowe et al. (5) have shown
that the status of the p53 gene plays an integral role in determining a
tumor’s responsiveness to adjuvant therapies. Tumors that have no
p53 or have mutated p53 evince treatment resistance to both chemo-
therapy and radiotherapy, probably by disruption of the cells’ apop-
totic pathways (5). Moreover, initially sensitive tumors may become
resistant by the selection of cells containing mutated p53 (5). Indeed,
in confirmation of this, in the two experimental cohorts reported here,
the response of patients with point-mutated p53 genes to therapies that
are believed to act via the induction of apoptosis is significantly

Table 2  Conserved domain mutations and disease dissemination.
The distribution of p53 mutations was analyzed by Fishers’ exact test in respect to
disease dissemination, both at the time of surgery and during patient follow-up.

<table>
<thead>
<tr>
<th>CD#</th>
<th>LN#</th>
<th>DM ATS#</th>
<th>DM ATSd</th>
<th>DM DF#</th>
<th>DM DFd</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN-#</td>
<td>LN+#</td>
<td>DM ATS-#</td>
<td>DM ATSd</td>
<td>DM DF-#</td>
<td>DM DFd</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>32</td>
<td>12</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>( P = 0.0018 )</td>
<td>( P = 0.0033 )</td>
<td>( P = 0.0033 )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\# CD, absence of detectable lymphatic involvement at time of surgery.
\# LN, presence of detectable lymphatic involvement at time of surgery.
\# DM ATS, absence of detectable distant organ metastasis at time of surgery.
\# DM ATSd, presence of detectable distant organ metastasis at time of surgery.
\# DM DF, absence of detectable distant organ metastasis at time of surgery or during
subsequent follow-up.
\# DM DFd, presence of detectable distant organ metastasis at time of surgery or during
subsequent follow-up.
\# CD, mutation present in one of the conserved domains.
\# LN, mutation present outside of the conserved domain.
\# NS, not significant.
p53 AND PROGNOSIS

poorer (as judged by patient survival) than it is for patients who do not show evidence of point-mutated p53 genes in their primary colorectal adenocarcinomas.

Hence, in colorectal cancer patients, point mutation of the p53 gene plays a pivotal role, in both determining, to some extent, the biological behavior of colorectal carcinomas, as well as modifying the effectiveness of postoperative therapies. As such, correcting defects of the p53 tumor suppressor gene would seem an ideal target for novel gene-based therapies for the treatment of metastatic colon carcinoma.

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References

p53 Point Mutation and Survival in Colorectal Cancer Patients

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