TP53 in Hematological Cancer: Low Incidence of Mutations With Significant Clinical Relevance

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For the p53 Special Issue

Inactivation of the wild-type p53 gene (TP53) by various genetic alterations is a major event in human tumorigenesis. More than 60\% of human primary tumors exhibit a mutation in the p53 gene. Hematological malignancies present a rather low incidence of genetic alterations in this gene (10–20\%). Nevertheless, epidemiological studies of the hematological malignancies indicate that the prognosis of patients with a mutation in the p53 gene is worse than those expressing the wild-type p53 protein. Correlations between drug resistance, altered apoptosis, and mutations in the p53 gene are found in hematological malignancies and leukemias. These issues, as well as the possibility of exploiting p53 and its various functions for new therapeutic strategies, are discussed in the present review. Hum Mutat 21:277–284, 2003. © 2003 Wiley-Liss, Inc.

**KEY WORDS:** hematological cancer; tumor; p53; TP53; drug resistance; leukemia; lymphoma

**DATABASES:**

TP53 – OMIM: 191170; GenBank: X54156; NM_000546 (mRNA)
http://p53.curie.fr/ (p53 Web Site at Institut Curie)
www.iarc.fr/p53 (IARC p53 Mutation Database)

**INTRODUCTION**

The p53 tumor suppressor gene (TP53; MIM\# 191170) plays a critical role in regulation of cell proliferation mainly through induction of growth arrest or apoptosis. The p53 gene maintains the integrity of the genome, responding to damaged DNA by overexpression and induction of G1 arrest, before initiation of DNA repair. Alternatively, if DNA is not repaired, p53 may induce apoptosis. Mutant p53, on the other hand, cannot arrest cells at G1 and can deregulate apoptosis resulting in malignant transformation and proliferation [Lane, 1992; Levine, 1997; El-Deiry et al., 1994; Sigal and Rotter, 2000].

The loss of p53 function is a key event in tumorigenesis and is associated with various characteristics of tumors, including deregulation of cell cycle, genomic instability, and resistance to chemotherapy [Harris, 1996; Kirsch and Kastan, 1998].

The p53 gene is most frequently mutated in solid tumors [Harris, 1996]. In hematological malignancies p53 mutations are less frequent. Nevertheless, in these tumors a strong correlation was found to be associated with unfavorable prognostic factors and resistance to chemotherapy [Preudhomme and Fenaux, 1997; Krug et al., 2002]. In chronic myeloid leukemia (CML), we and others have reported an increased incidence of p53 mutations in patients in acute phase CML compared with patients in chronic phase [Peller et al., 1998; Prokocimer and Rotter, 1994; Beck et al., 2000]. p53 mutations were suggested to be a prognostic factor especially in the low-risk group of malignant lymphoma [Ichikawa et al., 1997]. We also observed an overexpression of wild-type p53 in lymphocytes of patients with chronic lymphatic leukemia (CLL) [Peller, 1998]. Others have suggested that observed positive immunocytochemistry of p53 concomitant with the presence of mutations in CLL patients may serve as a marker of disease progression and poor prognosis [Cordone et al., 1998].

The scope of the present review is to summarize the most recent studies on p53 mutations in hematological malignancies and their potential use for prognosis in association with deregulation of apoptosis in these tumors. We will also discuss the impact of p53 alterations on chemotherapy resistance as well as the...
role of p53 and related genes and prospects for new therapeutic strategies in these malignancies.

**TP53 MUTATIONS IN HEMATOLOGICAL MALIGNANCIES**

The frequency of p53 mutations in hematological malignancies is relatively low compared to other tumors. Nevertheless, the incidence was found to increase in some cases with disease progression and was associated with a poor prognosis [Preudhomme and Fenaux, 1997; Krug et al., 2002].

Table 1 summarizes recent publications on mutations studies in hematological diseases. In most studies mutations were detected in exons 5 to 8 of the p53 gene, mainly because the investigations were confined to these exons. Among the acute leukemias, acute myeloid leukemia (AML) was found to exhibit a low incidence of mutations (4.5%–9%), prevalent mainly in patients with poor prognosis and complex karyotype. It has been suggested that p53 mutations may be an independent factor for short survival, predominant in elderly patients with unfavorable karyotype [Nakano et al., 2000; Stirwalt et al., 2001]. Similar observations were reported in myelodysplastic syndrome (MDS) [Padua et al., 1998]. However, in patients with AML or MDS previously treated with alkylating agents, the incidence of mutations increased to 27% [Christiansen et al., 2001]. A high incidence of mutations in AML patients has also been described in association with defective DNA mismatch repair and complex karyotype [Zhu et al., 1999b] and in the meta-analysis of a number of studies performed by Krug et al. [2002].

A low incidence of p53 mutations (5%) was reported in a number of studies on infant acute lymphatic leukemia (ALL). One patient harbored a mutation only at relapse with a translocation t(4;11) [Megenigal et al., 1998]. Three other patients with mutations had a poor clinical outcome [Kawamura et al., 1999] and two patients had an early relapse and exhibited resistance to treatment with adriamycin [Zhou et al., 2000].

Among patients in acute phase, chronic myeloid leukemia has a high percentage of mutations [Peller et al., 1998; Beck et al., 2000; Krug et al., 2002].

Chronic lymphoproliferative diseases, summarized in Table 1, show an exceptionally high incidence of mutations in chronic lymphatic leukemia (CLL) and hairy cell leukemia (HCL) patients. In one study, 2 out of 9 patients with atypical CLL harbored p53 mutations in exon 5 and 7. Both had an aggressive disease with translocation t(11;14) [De Angeli et al., 2000]. Another study demonstrated mutations in 47% of CLL patients with no correlation to disease outcome but with abnormal cytogenetics [Barnabas et al., 2001]. A study by Lazaridou et al. [2000] detected monoallelic deletion of p53 in 29% of cases that appeared late in the course of the disease and was associated with advanced stage. A lower incidence of mutations was reported in 3 out of 19 CLL patients (15%). Two out of 8 (25%) patients with Richter’s transformation of CLL exhibited p53 mutations. The p53 mutations in CLL were associated with multiple cell cycle regulator disruptions which may facilitate the transformation to a more severe disease, Richter’s syndrome.

A surprising observation is the rather high frequency (28%), of mutations in HCL an indolent chronic lymphoproliferative disease with good response to several therapeutic agents. The characteristics of mutations were found to be entirely different from those described in other hematological cancers but, nevertheless, their presence predicted a poor treatment outcome [Konig et al., 2000].

Various types of lymphomas exhibited a frequency of p53 mutations between 10 and 20%. In non-Hodgkin's lymphoma (NHL), p53 mutations were also associated with poor prognosis [Hirose and Kuroda, 1998]. Stokke et al. [2000] observed several p53 aberrations in NHL patients: p53 overexpression, allelic loss, and mutations. These were associated with a high S-phase fraction, poor therapy response, and short survival. There was no evidence that such aberrations led to reduced apoptosis.

Splenic lymphoma with villous lymphocytes, although being an indolent low-grade lymphoma, also revealed a more aggressive disease with lessened survival for patients with p53 abnormalities [Gruzszka-Westwood et al., 2001]. In aggressive variants of mantle-cell lymphoma, p53 inactivation has been detected [Campo et al., 1999] and a high incidence of mutations (67%) was observed concomitant with a translocation t(11;14) [De Angeli et al., 2000]. Furthermore, mutations were observed in 22% of patients with diffuse large B-cell lymphoma, a NHL subtype with the highest mortality. These aberrations in p53 and in other genes were suggested to be involved in disease progression [Moller et al., 1999].

p53 mutations were also detected in human leukemia-lymphoma cell lines [Prokocimer et al., 1998b]. It has been recently observed that p53 gene alterations often emerge in cell lines although the original tumor cells had wild-type p53. A relapse specimen carried an identical mutation to that of the derived cell line. It was suggested that p53 alteration in a minor clone may confer a survival advantage to these malignant cells in vitro and presumably also in vivo [Drexler et al., 2000].

A summary of molecular pathophysiology of indolent lymphomas by Capello and Gaidano [2000] clearly indicates that accumulation of p53 in conjunction with other genes’ alterations correlate with the transition from low-grade to high-grade disease.
<table>
<thead>
<tr>
<th>Exon</th>
<th>Mutation type</th>
<th>Frequency</th>
<th>Cell origin</th>
<th>Tumor type</th>
<th>Clinical parameters</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5, 7</td>
<td>Point mutation</td>
<td>2/9 (22%)</td>
<td>PB</td>
<td>aCLL</td>
<td>t(11;14) aggressive disease</td>
<td>DeAngelii et al. [2000]</td>
</tr>
<tr>
<td>5, 6, 7, 8</td>
<td>Point mutation</td>
<td>14/30 (47%)</td>
<td>PB</td>
<td>CLL</td>
<td>high % of mutations, no correlation to disease outcome, abnormal cytogenetics</td>
<td>Barnabas et al. [2001]</td>
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<tr>
<td></td>
<td>Frame shift</td>
<td>3/19 (15%)</td>
<td>CLL</td>
<td>RS</td>
<td>p21, p27, RB, cyclin D aberration</td>
<td>Cobo et al. [2002]</td>
</tr>
<tr>
<td></td>
<td>Microdeletion</td>
<td>2/8 (25%)</td>
<td>RS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4, 5, 7, 9</td>
<td>Structural abnormalities, deletion</td>
<td>10/28 (36%)</td>
<td>PB</td>
<td>CML</td>
<td>AP, abnormalities in Rb, additional karyotypes</td>
<td>Beck et al. [2000]</td>
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<td>of the other allele</td>
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<tr>
<td>5 to 8</td>
<td>NP</td>
<td>6/16 (37%)</td>
<td>PB</td>
<td>B-PLL</td>
<td>Worse clinical outcome, spontaneous apoptosis</td>
<td>Hercher et al. [2001]</td>
</tr>
<tr>
<td>5, 6, 7, 8</td>
<td>Intron 4</td>
<td>9/200 (4.5%)</td>
<td>BM</td>
<td>AML</td>
<td>Complex karyotype, poor prognosis</td>
<td>Nakano et al. [2000]</td>
</tr>
<tr>
<td>5, 6, 7, 8+</td>
<td>Point mutation/frame shift/</td>
<td>21/77 (27%)</td>
<td>BM, PB</td>
<td>MDS, AML</td>
<td>Previously treated with alkylating agent, complex karyotype, short survival</td>
<td>Christiansen et al. [2001]</td>
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<tr>
<td></td>
<td>protein truncation</td>
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<tr>
<td>5, 7, 8</td>
<td>Point mutation/deletion</td>
<td>4/50 (8%)</td>
<td>PB</td>
<td>MDS</td>
<td>Abnormal karyotype, poor prognosis</td>
<td>Padua et al. [1998]</td>
</tr>
<tr>
<td>5, 7</td>
<td>Point mutation</td>
<td>6/43 (36%)</td>
<td>PB</td>
<td>AML, ALL</td>
<td>Defective MSH2(DNA mismatch repair), complex karyotype, MLL translocation</td>
<td>Zhu et al. [1999b]</td>
</tr>
<tr>
<td>5</td>
<td>Point mutation</td>
<td>1/19 (5%)</td>
<td>BM</td>
<td>infant ALL</td>
<td>At relapse, t(4;11), MLL translocation</td>
<td>Megonigal et al. [1998]</td>
</tr>
<tr>
<td>5, 7, 8</td>
<td>Point mutation/Frame shift</td>
<td>3/57 (5%)</td>
<td>PB</td>
<td>Infant B &amp; T-ALL</td>
<td>Poor clinical outcome, multiple mutations, sensitive to Fas-mediated apoptosis</td>
<td>Kawamura et al. [1999]</td>
</tr>
<tr>
<td>5, 6, 7</td>
<td>Frameshift</td>
<td>4/5</td>
<td>Cell line</td>
<td></td>
<td></td>
<td>Zhou et al. [1988]</td>
</tr>
<tr>
<td>7</td>
<td>Point mutation</td>
<td>2/42 (25%)</td>
<td>BM</td>
<td>Infant B-ALL</td>
<td>+/− MDM2 overexpression early relapse and adriamycin-resistance</td>
<td>Zhou et al. [2000]</td>
</tr>
<tr>
<td>5, 6, 7, 8</td>
<td>Point mutation/deletion</td>
<td>17/67 (25%)</td>
<td>PB</td>
<td>HCL</td>
<td>An indolent disease, good response to therapy</td>
<td>Konig et al. [2000]</td>
</tr>
<tr>
<td>5, 7, 8</td>
<td>Point mutation</td>
<td>3/17 (18%)</td>
<td>Frozen tissue</td>
<td>NKT-cell lymphoma</td>
<td>No significant difference in outcome</td>
<td>Petit et al. [2001]</td>
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<tr>
<td></td>
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<td>5/21 (24%)</td>
<td>Paraffin-Embedded</td>
<td></td>
<td></td>
<td>Quintanilla-Martinez et al. [2001]</td>
</tr>
<tr>
<td>5, 6</td>
<td>Point mutation</td>
<td>4/6 (67%)</td>
<td>PB</td>
<td>MCL</td>
<td>t(11;14) aggressive disease</td>
<td>DeAngelii et al. [2000]</td>
</tr>
<tr>
<td>5, 6, 7, 8</td>
<td>Point mutation</td>
<td>8/37 (22%)</td>
<td>Frozen tissue</td>
<td>DLCL</td>
<td>Concomitant with other gene Mutation. Disease progression</td>
<td>Moller et al. [1999]</td>
</tr>
<tr>
<td>4, 8</td>
<td>Point mutation</td>
<td>4/20 (20%)</td>
<td>PB, BM, spleen</td>
<td>SLVL</td>
<td>Aggressive disease, poor prognosis, worse survival</td>
<td>Gruszka-Westwood et al. [2001]</td>
</tr>
<tr>
<td>5, 7, 8, 9</td>
<td>Point mutation</td>
<td>8/83 (10%)</td>
<td>LN</td>
<td>B-Cell NHL</td>
<td>High S phase, poor therapy response, shorter survival</td>
<td>Stokke et al. [2000]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4/40 (10%)</td>
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<td>Cogliatti et al. [2000]</td>
</tr>
<tr>
<td>5 to 8</td>
<td>Point mutation/Frameshift deletion</td>
<td>20/123 (16%)</td>
<td>frozen tissue</td>
<td>AIDS-related NHL</td>
<td>Prognostic factor, short survival, higher frequency in high-grade cases.</td>
<td>Gronbaek et al. [2000]</td>
</tr>
</tbody>
</table>

PB, peripheral blood; BM, bone marrow; LN, lymph node; NP, not published; CLL, chronic lymphatic leukemia; aCLL, atypical CLL; RS, Richter's syndrome; AP, accelerated phase; MCL, mantle cell lymphoma; DLCL, diffuse large B-cell non-Hodgkin's lymphoma; B-PLL, B-cell prolymphocytic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; T-ALL, T-cell ALL; MDS, myelodysplastic syndrome; HCL, hairy cell leukemia; SLVL, splenic lymphoma with villous lymphocytes; NHL, non-Hodgkin's lymphoma; AML, acute myeloid leukemia.
TP53 AND CHROMOSOMAL ABNORMALITIES

Chromosomal abnormalities are the hallmark of various hematological malignancies [Panayiotidis and Kosti, 1999]. Neoplasia with abnormal karyotypes were also found to harbor p53 alterations [Prokocimer et al., 1998b]. Our study detected a point mutation in codon 272 of the p53 gene in a human T-acute lymphoblastic leukemia (T-ALL) cell line, derived from cells of a patient with resistant ALL carrying two chromosomal abnormalities [Prokocimer et al., 1998a]. Nevertheless, it was observed that karyotypic abnormalities in cell lines undergoing hemopoietic lineage switching had wild-type p53, suggesting that mechanisms other than genetic alterations in p53 are responsible for karyotypic abnormalities [Colley et al., 2000].

In AML, as mentioned earlier, mutations in the p53 gene are infrequent but they were found to be associated with unfavorable complex karyotype abnormality [Stirewalt et al., 2001; Wattel et al., 1994]. Fluorescence in situ hybridization (FISH) analysis of B-lymphoproliferative disorders (B-LPD) of a group of patients with p53 deletions revealed complex cytogenetics including 17p genetic alteration, where p53 is located. It should be noted that the clinical stage of the disease in this group was more advanced and was less responsive to therapy [Shaw and Kronberger, 2000]. Another study with patients with B-LPD revealed unbalanced translocations leading to a monosomy of 17p and to a p53 monoallelic deletion in 11% of the patients. All cases were characterized by resistance to chemotherapy with a poor clinical outcome. It was suggested that genetic abnormalities may allow a risk assessment for individual patients at the time of diagnosis of CLL, giving the opportunity for a risk-adapted management [Callet-Bauchu et al., 1999; Stilgenbauer et al., 2000].

Since it was shown that p53 is involved in the maintenance of chromosome stability, it is possible that p53 alterations in hematological malignancies are primary events in the disruption of the integrity of the genome resulting in complex chromosome abnormalities with a severe disease outcome.

TP53 AND RELATED GENES

The low frequency of p53 alterations in hematological tumors prompted a search for the involvement in carcinogenesis of p53 related genes such as mdm2, p16, p19, and their inter-relations with p53.

The mdm2 protein targets p53 degradation through ubiquitin-mediated proteolysis [Haupt et al., 1997]. The CDKN2A gene product, p16, inhibits CDK4/6 in the Rb1 pathway. The p19-ARF product interacts with the p53 pathway by binding to mdm2 and promoting its degradation. It is not surprising, therefore, that a mutation in the CDKN2A gene disrupts both the Rb1 and p53 pathways [Pomerantz et al., 1998; Zhang et al., 1998; Drexler, 1998].

Mdm2 protein was overexpressed in AML samples with mutations and/or overexpression of wild-type p53, indicating that accumulation of wild-type p53 was not due to the lack of downregulation of mdm2 in AML patients [Nakano et al., 2000]. In HTLV-I infected T cells from patients with adult T-cell leukemia/lymphoma and established cell lines, p53 stabilization and inactivation was observed in the absence of mutations. In this disorder, mdm2-p19 ARF were expressed at normal levels, thus suggesting that p53 inactivation in these cell lines was not associated with alterations in this pathway [Takimoto et al., 2000]. Another study demonstrated adverse results with overexpression of the mdm2 protein in some mutant human leukemic cell lines, suggesting that normal regulation of mdm2 turnover is altered in tumor cell lines [Pan and Haines, 1999]. A review summarizing genetic alterations of the p15, p16, p18, and p19 genes in human leukemia-lymphoma cells indicated a striking inverse correlation between p16 deletion and the presence of wild-type Rb and no relationship with p53 inactivation [Drexler, 1998]. It is striking that both inactivation of p16 and p53 occur in aggressive variants of mantle cell lymphoma but only one case was reported to exhibit both a deletion in p16 and a point mutation in the p53 gene [Gronbaek et al., 1998]. Otherwise, these two alterations were never found to co-exist in one single tumor. This observation may imply that the two genes are alternative mechanisms in the progression of these tumors [Campo et al., 1999].

Analysis of the status of p16, ARF, and p53 genes in 123 cases of NHL showed that in 40% of aggressive disease cases, one or more alterations of these genes were detected. This compares to only 19% in the low and intermediate grade [Gronbaek et al., 2000]. The overall survival was not different between groups. A significant influence on the outcome of treatment was observed when one of the genes was disrupted, but they differed in a shortened survival when both gene pathways were impaired. These observations suggest the existence of a relationship between p16 and the ARF p53 pathway in the control of lymphoproliferation. This is further supported by a study on aggressive B-cell lymphoma that demonstrated an abnormal expression pattern of p14ARF, more frequent in tumors displaying alterations in the p53, p16, and p27 genes. These tumors revealed aggressive clinical course with shortened survival [Sanchez-Aguilera et al., 2002].

Similar results were obtained when p53, mdm2, and CDKN2A were studied in diffuse large B-cell lymphoma. Overexpression of mdm2 was found in 43% of p53 mutated samples and in 71% of samples with CDKN2A deletions. In this study it was also implied that a second alteration of the p53 pathway
components, such as p19 and mdm2, resulted in an additional growth advantage to the tumor, compared to alteration in only one gene, suggesting that all these genes are involved in disease progression [Moller et al., 1999].

An interesting observation is the expression of mdr-1 via WT1 in vincristine-resistant hematologic cell line mediated by p53. In cells expressing mdr-1, downregulation of p53, and upregulation of WT1 was observed that may contribute to drug sensitivity [Hirose and Kuroda, 1998].

Demonstration of the existence of interrelationships between genes of alternative pathways emphasizes the importance of studying molecular pathways rather than single genes for improved diagnosis and valuable prognosis in hematological malignancies. Cooperating gene alterations may serve as targets for new therapeutic strategies. For a review of other related genes in the p53 family see Bénard et al. [2003].

**TP53 AND APOPTOSIS**

Interrelationships between cellular stress response and apoptosis induced by cytotoxic drugs, as well as the various genes of the death pathway, were extensively discussed by Herr and Debatin [2001]. p53 can be a substrate for jun N-terminal kinase (JNK) activity in JNK signaling-induced apoptosis. JNK either destabilizes p53 by binding, promoting ubiquitin-mediated degradation, or stabilizes p53 by phosphorylation, thus inhibiting degradation. p53-dependent apoptosis consists of parallel or sequential activation of various genes leading to cell death response. This pathway involves, among others, activation of the mitochondrial Apaf-1/caspase pathway, death receptor signaling, CD95, and cleavage of downstream caspases.

Patients with hematological malignancies are commonly treated with a variety of cytotoxic agents including DNA damaging drugs, antimetabolites, mitotic inhibitors, purine analogues, or inhibitors of topoisomerase. All these induce cellular stress, usually beyond the capacity of the DNA repair machinery, that in turn elicit apoptosis.

p53-induced apoptosis in various hematological tumors is often impaired and thus p53-independent pathways may take over. For example, in pediatric acute lymphoblastic leukemia primary leukemic cells and derived cell lines exhibited Fas(CD95)-mediated apoptosis with high levels of Fas expression in p53 mutant cells but not in p53 wild-type cells [Zhou et al., 1998].

Inhibition or promotion of apoptosis related to resistance and sensitivity to chemotherapy were investigated [Masedehors et al., 2000]. B-CLL lymphocytes exhibited a constitutive altered ubiquitin-proteasome system with alterations in the regulation of wild-type p53 proteolysis. Specific inhibition of the ubiquitin system with lactacystin caused accumulation of wild-type p53 in B-CLL but not in normal lymphocytes. This suggested that the ubiquitin-proteasome system may be modified in malignant cells, thus increasing the sensitivity to apoptosis induction in these cells [Masedehors et al., 2000]. Another study on B-CLL that investigated the mechanism of nucleotide cytotoxicity in this disease, showed that p53-mediated apoptosis is the most rapid cytotoxic pathway activated by purine analogues but can be replaced by a p53-independent apoptotic pathway [Pallis et al., 2001]. In AML patients, subpopulations of leukemic cells could be detected by their high- or low-uptake of daunorubicin. The high uptake cells were those that resulted in induction of apoptosis. This intraclonal heterogeneity in drug uptake probably contributes to relapse in AML patients [Palucka et al., 1999]. Patients with AML exhibit chemotherapy resistance linked to cellular resistance to apoptosis. Furthermore, it was demonstrated in cells from patients and cell lines, that p53 directly affects mitochondrial transmembrane potential in leukemic cells and depolarization of mitochondria triggered apoptosis. Mutant p53 failed to exert this depolarization, resulting in resistance to apoptosis [Pallis et al., 2001].

Two independent in vitro studies have demonstrated the induction of apoptosis via a p53-independent pathway in malignant lymphocytes. One study used arsenic trioxide on malignant lymphocytes and achieved growth inhibition and apoptosis [Zhu et al., 1999a]. The other used arsenic-interferon α to induce apoptosis in HTLV-I transformed cells [El-Sabban et al., 2000]. Both studies failed to demonstrate a change in p53 expression.

It thus seems that deregulation of apoptosis is a major event in the development and progression of lymphoproliferative diseases like CLL and some types of lymphoma. Understanding the mechanism that underlie apoptosis is therefore expected to identify new targets for treatment of these disorders.

**SUMMARY AND PROSPECTS FOR NEW THERAPIES**

The frequency of p53 mutations in hematological tumors is low compared to other cancer types. Nevertheless, in those cases of lymphoproliferative diseases with aberrant p53, the gene plays a pivotal role in development and progression of the disease. The involvement of p53 in chromosomal abnormalities and in resistance to DNA-damaging drugs was demonstrated in various leukemias and lymphomas. Impaired apoptosis is a major cause of malignant cell proliferation in these disorders. p53 cooperating with other genes was also found to take part in the pathophysiology of hematological cancers. Deciphering the various pathways of these genes’ functions and
their interrelationships can be used as potent tools in developing new therapeutic strategies.

Primary attempts were directed at antisense therapies. For example, it was observed that both antisense oligonucleotides to the mdm2 and p53 in lymphoblastoid cell line induced apoptosis in these cells only if they expressed wild-type p53 [Capoulade et al., 2001]. Cotter [1999] reviewed the potential use of antisense therapy in hematologic malignancies. It was noted that one new therapeutic approach was based on “silencing” genes involved in the prevention of apoptosis: for example, using antisense oligonucleotides to bcl-2 in follicular lymphoma with t(14;18) with overexpression of bcl-2. In tumors with mutant p53, antisense oligonucleotides against mdm2 was reported to restore wild-type p53 expression. All these demonstrate that normal cell growth can be restored by molecular manipulation.

The recent development of improved wild-type p53 vectors, as well as advances in gene therapy at large, places the defined group of hematological disorders (in which genetic abberations are well correlated with diagnosis and prognosis) as a prime target for gene therapy.

It is expected that these newly designed therapies may efficiently overcome chemoresistance, frequently observed in leukemias and lymphomas patients.

REFERENCES


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