Dysfunction of the TP53 tumor suppressor gene in lymphoid malignancies

Zijun Y. Xu-Monette, L. Jeffrey Medeiros, Yong Li, Robert Z. Orlowski, Michael Andreeff, Carlos E. Bueso-Ramos, Timothy C. Greiner, Timothy J. McDonnell, and Ken H. Young

Department of Hematopathology, University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biochemistry and Molecular Biology, University of Louisville School of Medicine, Louisville, KY; Departments of Lymphoma and Myeloma, and Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX; and Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE

Mutations of the TP53 gene and dysregulation of the TP53 pathway are important in the pathogenesis of many human cancers, including lymphomas. Tumor suppression by p53 occurs via both transcription-dependent activities in the nucleus by which p53 regulates transcription of genes involved in cell cycle, DNA repair, apoptosis, signaling, transcription, and metabolism; and transcription-independent activities that induce apoptosis and autophagy in the cytoplasm. In lymphoid malignancies, the frequency of TP53 deletions and mutations is lower than in other types of cancer. Nonetheless, the status of TP53 is an independent prognostic factor in most lymphoma types. Dysfunction of TP53 with wild-type coding sequence can result from deregulated gene expression, stability, and activity of p53. To overcome TP53 pathway inactivation, therapeutic delivery of wild-type p53, activation of mutant p53, inhibition of MDM2-mediated degradation of p53, and activation of p53-dependent and -independent apoptotic pathways have been explored experimentally and in clinical trials. We review the mechanisms of TP53 dysfunction, recent advances implicated in lymphomagenesis, and therapeutic approaches to overcoming p53 inactivation. (Blood. 2012;119(16):3668-3683)

Introduction

The TP53/P53 gene (tumor protein p53), initially identified as an oncogene in 1979, has been recognized as a tumor suppressor gene since 1989. Tumor suppressor p53 protein (cellular tumor antigen p53), is “the guardian of the genome,” preserves genome stability under cellular stress, and is involved in various processes of development, differentiation, aging, and disease.

p53 and tumor suppression

Structure and functions

TP53 spans 19,144 bp on chromosome 17p13.1. The dominant TP53 transcript is a 2586-nucleotide (nt) mRNA, including a 5’-untranslated region (UTR) from exons 1 and 2, a 3’-UTR from exon 11, and coding sequence (CDS) from exons 2 to 11, which is translated into the canonical product of p53 consisting of 393 amino acids with several functional domains and motifs (Figure 1).

p53 is expressed in all tissues with a half-life of approximately 20 minutes under normal conditions because of murine double minute 2 homolog (MDM2)–mediated ubiquitination and proteasomal degradation. Under stressed conditions, p53 is transcriptionally induced and stabilized/activated by posttranslational modifications (Figure 1). It is thought that phosphorylation, acetylation, and methylation in stressed cells release p53 from MDM2 inhibition and activate p53, whereas sumoylation and neddylation increase p53 stability by inhibiting ubiquitination and repress p53 function.3,4

The tumor suppressor function of p53 is reflected in its regulation of cell-cycle arrest, DNA repair, apoptosis, senescence, and autophagy, through both transcription-dependent and -independent activities (Figure 2).

Transcription-dependent activities (TAs) of p53 are required for p53-dependent tumor suppression, as demonstrated in mouse models that succumb to thymic lymphomas because of expression of mutant p5398 (Leu25Trp26 to Gln25Ser26), which abolishes p53 TA but retains its transcription-independent function of apoptosis intact.5 TAs of p53 in lymphocytes (supplemental Table 1; Figure 3)6-11 are distinct from TAs in other cells.11

In comparison, transcription-independent activities (TIAs) of p53 are mediated by protein–protein interactions, associated with apoptosis via the intrinsic mitochondrial pathway and autophagy (Figure 4). The induction of apoptosis by cytoplasmic p53 has been demonstrated by retrovirus-mediated exclusive delivery of wild-type (WT) p53 with mitochondrial import leader fusions to p53-null or p53-mutant (p53-mut) lymphoma B cells, with low or no infectivity on normal cells.12 This holds hope for the killing of tumor cells without invoking potentially lethal pathology by massive apoptosis. However, the role of p53 is undermined by p53-independent apoptosis pathways. In BW B-cell lymphoma cells, radical oxygen species (ROS) generation, rather than p53, appears to be the key regulator of apoptosis.13

The role of p53 in autophagy is incompletely elucidated. Cytoplasmic p53 inhibits autophagy by promoting the mammalian target of rapamycin (mTOR) pathway, whereas nuclear p53 stimulates autophagy by transactivating the mTOR inhibitors, damage-regulated autophagy modulator, and several metabolism genes.3,14 Autophagy is also regulated by PI3K-Akt-mTOR, STK11 (serine/threonine kinase 11)–AMPK (AMP-activated protein kinase)–mTOR, Beclin1, Bcl-2, and other molecules.15 Inhibition of autophagy by cytoplasmic p53 has not been investigated in lymphocytes, but induction of autophagy by nuclear p53 has been shown in chronic lymphocytic leukemia (CLL) lymphocytes and is associated with drug resistance to dasatinib.16

The online version of this article contains a data supplement.


© 2012 by The American Society of Hematology

3668 BLOOD, 19 APRIL 2012 • VOLUME 119, NUMBER 16
microRNAs (miRNAs) are endogenous single-stranded RNAs (~22 nt) that bind to complementary sequences of target mRNAs, leading to mRNA degradation or suppression of translation. miRNA genes are transcribed into pri-miRNAs and pre-miRNAs in the nucleus, which are processed into mature miRNAs and

---

**Figure 1.** Schematic structure of TP53 and p53, and numbers of mutations in exons in lymphoid malignancies. (A) TP53 gene structure, p53 functional domains, and posttranslational modifications. Exons are in blue (UTRs) or green (CDS) and are drawn proportionally to their sizes; introns are dark blue and not drawn to scale. Sizes of exons/introns according to NCBI (reference NC_000017.10 sequence). Domains of p53 include transactivation domain (TAD), proline-rich domain (PRD), DBD, nuclear localization sequence (NLS), oligomerization domain (OD), and basic repression (BR) of DBD. Both the TAD and OD have a nuclear export signal (NES). Posttranslational modification of p53 can occur by phosphorylation (P), acetylation (A), ubiquitination (U), methylation (M), neddylation (N), or sumoylation (S). (B) Schematic of p53 protein structure. Shown are positions in the p53 primary sequence for 3 loops (L1, L2, L3) involved in DNA binding, 11 β-strands (S1-S10) as components of 2 anti-parallel β-sheets, and 3 α-helices, including 2 in the helix-loop-helix motif. (C) TP53 CDS mutation numbers in lymphoid malignancies. These mutations are not randomly distributed, as indicated by the finding that mutation numbers (shown on right side and illustrated by the length of red bars) in each exon are not proportional to exon sizes (on the left side). Mutation numbers (unique mutation variants and sample/mutation associations) are according to the IARC TP53 database (R15 release, November 2010).

---

**p53-regulated miRNA genes in lymphocytes**

MicroRNAs (miRNAs) are endogenous single-stranded RNAs (~22 nt) that bind to complementary sequences of target mRNAs, leading to mRNA degradation or suppression of translation. miRNA genes are transcribed into pri-miRNAs and pre-miRNAs in the nucleus, which are processed into mature miRNAs and

---

**Figure 2.** TAs and TIAs of p53 in lymphocytes. TAs are those that p53 activates or represses in nucleus by binding directly or indirectly to target genes. TIAs include regulation of the intrinsic apoptosis pathway and autophagy through protein-protein interactions in the cytoplasm. Ub indicates ubiquitination.
anti-sense miRNA* in the cytoplasm. There are 1527 human miRNAs transcribed from approximately 800 published miRNA gene loci in the miRBase 18 database (http://www.mirbase.org, released November 2011). Approximately half of mammalian pre-miRNAs are found in non-protein–coding transcripts, and half are located in the introns of protein-coding transcripts from a host gene. miRNAs transactivated by p53 in lymphocytes include miR-15a, miR-16-1 (targeting oncogene MYB, antiapoptotic BCL2 and MCL1), miR-34a (targeting oncogene FOXP1 and BCL2), miR-34b, and miR-34c (targeting ZAP70). The dysregulation of these miRNAs is associated with poor clinical outcomes. miR-15a and miR-16-1 are expressed from intron 4 of the LEU2 gene, a locus deleted in 55% of CLL cases (del13q14). MIR34B and MIR34C loci are deleted in 18% of CLL cases (del11q). MIR34A is located at chromosome 1p36.22 and has been suggested to be a p53-induced tumor suppressor in a CLL mouse model. The promoter of the MIR15A/MIR16-1 cluster has several p53 responsive-elements, and expression of miR-15a and miR-16-1 correlates with p53 expression. p53 induces expression of miR-34a, miRs-34b/34c by directly binding to their promoters. miR-34a overexpression can block cell development, and reduced miR-34a expression has been correlated with inferior overall survival (OS) in patients with diffuse large B-cell lymphoma (DLBCL) and significantly shorter treatment-free survival in CLL patients.

In human lymphoblastoid cell lines, p53 induces let-7 miRNA family members, miRNAs (miR-142-3p, miR-142-5p) that are brought close to the 5' region of MYC because of a translocation. 5 of 7 miRNAs of the miR-17-92 cluster, and other potential oncomirs (miR-155, miR-145, miR-143, and miR-21), although p53 represses the miR-17-92 cluster in colorectal carcinomas. In myeloma cells, p53-inducible miRs-192, -194, and -215 target MDM2 and therefore activate p53. The aberrant expression and clinical importance of these miRNAs are summarized in Table 1.

**Effect of p53 activities in lymphocytes**

p53 simultaneously promotes cell-cycle arrest, DNA repair, and apoptosis, prompting the question as to whether a cell dies or survives after repair. The choice between cell-cycle arrest and apoptosis depends on cell type, cell-cycle stage, extent of DNA damage, p53 level and ratio to p53 isoforms, external survival factors, and internal cellular setting. Lymphocytes are prone to apoptosis under stress compared with other cell types that are prone to permanent cell-cycle arrest, transformation, or mitotic catastrophe leading to p53-independent apoptosis or necrotic death. Lethal hematopoietic syndrome resulting from an acute p53 response is characterized by massive apoptosis. Drugs can modulate the balance of p53 functions. For example, RO-3306, a CDK1 inhibitor, blocks cell-cycle arrest by inhibiting p53-mediated activation of p21 but enhances apoptosis by reducing levels of antiapoptotic Bcl-2, survivin, and MDM2, and thereby caused enhanced apoptosis in acute myeloid leukemia (AML) cell lines with WT-p53.

On the other hand, when the downstream apoptotic pathway is blocked, or p53 is an apoptosis-deficient mutant, p53 in lymphocytes can enhance cell-cycle arrest and senescence, characterized by irreversible growth arrest, and delay lymphomagenesis, as has been shown in several murine lymphoma models. Apoptosis also appears to be affected by autophagy, although the role of autophagy in cell death or cancer remains debatable. Autophagy correlates with drug resistance and tumor progression in several lymphoid malignancies. In a Myc-induced model of lymphoma, inhibition of autophagy by either chloroquine, an
inhibitor of late autophagy, or short hairpin RNA for ATG5, a key autophagy gene, enhanced p53-dependent and -independent apoptosis, suggesting that autophagy is a survival pathway in lymphoma progression. Chloroquine also sensitized dasatinib-resistant CLL and imatinib-resistant CML cells. Oppositely, it has been suggested that cell death induced by bortezomib in multiple myeloma (MM) is via an autophagic pathway.

Loss of p53 function and lymphomagenesis

In p53-deficient mouse models, either absence or loss of function, malignant lymphoma is the predominant tumor type. Loss of phosphorylation of Ser15 and Ser20 in human p53 was associated with lymphomagenesis of p53-mut mice. Chloroquine also sensitized dasatinib-resistant CLL and imatinib-resistant CML cells. Oppositely, it has been suggested that cell death induced by bortezomib in multiple myeloma (MM) is via an autophagic pathway.

Mechanisms of TP53 dysfunction in lymphoid malignancies

TP53 dysfunction in lymphoid malignancies can arise at the DNA, mRNA, or protein level in cis or in trans, as summarized in Table 2 and Figure 5.
Mutations and polymorphisms of TP53 CDS

**Mutations and polymorphisms of TP53 CDS**. Mutations in the TP53 CDS have been extensively studied. The curated International Agency for Research on Cancer (IARC) TP53 somatic mutation database (R15 release, November 2010, http://www.iarc.fr) includes 26 608 unique sample/mutation associations, 6.1% of which are from hematologic tumors.53 TP53 CDS mutations occur less often in hematopoietic neoplasms than in many other tumor types: 19.3% in lymphoid malignancies, 11.1% in myeloid malignancies, and 14.9% in lymphoid/plasmacytic malignancies (Table 3).53 Mutations have a lower occurrence (13.6%) in the US population than in developing countries.53

More than 90% of p53 mutations in hematologic malignancies are point mutations, 79.9% of which are missense mutations. Allele deletions have been reported in CLL, marginal zone B-cell lymphoma (MZL), FL, and DLBCL. TP53 gene duplication is rare, and translocations involving the TP53 gene have not been reported.

A total of 80.7% of p53 mutants have no transactivation function, 10% have partial function, and 9.3% have transactivation function.54 Many p53 mutants act in a dominant-negative manner to inhibit WT-p53 function. Single allele mutations are frequently followed by loss of heterozygosity, which further promotes tumor development.55 The transcription-independent p53 function is also impaired in many mutants. For example, on doxorubicin treatment,

<table>
<thead>
<tr>
<th>miRNAs</th>
<th>Genes</th>
<th>Locus</th>
<th>Targets</th>
<th>Aberrant expression</th>
<th>Clinical importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-15a</td>
<td>MIR15A</td>
<td>13q14.2</td>
<td>MYB; BCL2; MCL1</td>
<td>Loss or reduced in CLL</td>
<td>Associated with CLL pathogenesis: del13q14 is in 55% CLL</td>
</tr>
<tr>
<td>miR-16-1</td>
<td>MIR16-1</td>
<td>13q14.2</td>
<td>MYB; BCL2; MCL1</td>
<td>Loss or reduced in CLL</td>
<td>Associated with CLL pathogenesis: del13q14 is in 55% CLL</td>
</tr>
<tr>
<td>miR-34a</td>
<td>MIR34A</td>
<td>1p36.22</td>
<td>FOXP1; BCL2</td>
<td>Reduced in DLBCL and CLL</td>
<td>Block pro-B to pre-B development; as a tumor suppressor in CLL mouse model; reduced mir-34a expression correlated with inferior OS in DLBCL and CLL</td>
</tr>
<tr>
<td>miR-34b</td>
<td>MIR34B</td>
<td>11q23.1</td>
<td>ZAP70</td>
<td>Loss or reduced in CLL</td>
<td>Associated with CLL pathogenesis: del11q is in 18% CLL</td>
</tr>
<tr>
<td>let-7a</td>
<td>MIRLET7A1</td>
<td>9q22.32</td>
<td>RAS</td>
<td>Reduced in CLL</td>
<td></td>
</tr>
<tr>
<td>let-7b</td>
<td>MIRLET7B</td>
<td>22q13.31</td>
<td>RAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>let-7c</td>
<td>MIRLET7C</td>
<td>21q21.1</td>
<td>RAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>let-7d</td>
<td>MIRLET7D</td>
<td>9q22.32</td>
<td>RAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>let-7e</td>
<td>MIRLET7E</td>
<td>18p13.41</td>
<td>RAS</td>
<td>Reduced in DLBCL</td>
<td></td>
</tr>
<tr>
<td>let-7f</td>
<td>MIRLET7F1</td>
<td>9q22.32</td>
<td>RAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>let-7g</td>
<td>MIRLET7G</td>
<td>3p21.1</td>
<td>RAS</td>
<td>Differential in DLBCL</td>
<td>Reduced expression correlated with longer EFS in DLBCL</td>
</tr>
<tr>
<td>let-7i</td>
<td>MIRLET7I</td>
<td>12q14.1</td>
<td>RAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-17-3p</td>
<td>MIR17</td>
<td>13q31.3</td>
<td>BIM; p21</td>
<td>Over-regulation correlated with worse clinical outcome in SS</td>
<td></td>
</tr>
<tr>
<td>miR-17-5p</td>
<td>MIR17</td>
<td>13q31.3</td>
<td>PTEN; BIM; p21; E2F1; CCND1</td>
<td>High in DLBCL; differential in CLL</td>
<td>Reduced miR-19a correlated with shorter EFS in DLBCL</td>
</tr>
<tr>
<td>miR-19a</td>
<td>MIR19A</td>
<td>13q31.3</td>
<td>PTEN; BIM; p21; SOCS1</td>
<td>Overexpressed in MM</td>
<td></td>
</tr>
<tr>
<td>miR-19b-1</td>
<td>MIR19B1</td>
<td>13q31.3</td>
<td>PTEN; BIM; p21</td>
<td>Overexpressed in MM</td>
<td></td>
</tr>
<tr>
<td>miR-19a</td>
<td>MIR18</td>
<td>13q31.3</td>
<td>BIM; p21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-21</td>
<td>MIR21</td>
<td>17q23.1</td>
<td>PTEN; PDCD4; SPRY2</td>
<td>Up-regulated in DLBCL and FL</td>
<td>Decreased expression correlated with poor OS in DLBCL</td>
</tr>
<tr>
<td>miR-142-3p</td>
<td>MIR142</td>
<td>17q22</td>
<td></td>
<td>Overexpressed in MM</td>
<td>Up-regulation predicted unfavorable clinical outcome in SS</td>
</tr>
<tr>
<td>miR-142-5p</td>
<td>MIR142</td>
<td>17q22</td>
<td>mriR-142/6-my-c fusion gene overexpressed in B-cell lymphomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-143</td>
<td>MIR143</td>
<td>5q32</td>
<td>Up-regulated in DLBCL and FL</td>
<td>Low in BL</td>
<td></td>
</tr>
<tr>
<td>miR-145</td>
<td>MIR145</td>
<td>5q32</td>
<td>Down-regulated in DLBCL</td>
<td>Up-regulated in DLBCL and FL</td>
<td>Low in BL</td>
</tr>
<tr>
<td>miR-155</td>
<td>MIR155</td>
<td>21q21.3</td>
<td>SHIP1; SOCS1</td>
<td>High in CLL and DLBCL</td>
<td>Overexpressed in NK-cell lymphoma</td>
</tr>
<tr>
<td>miR-192</td>
<td>MIR192</td>
<td>11q13.1</td>
<td>MDM2; IGF1R; IGF1</td>
<td>Down-regulated in MM</td>
<td></td>
</tr>
<tr>
<td>miR-194-1</td>
<td>MIR194-1</td>
<td>1q41.1</td>
<td>MDM2</td>
<td>Down-regulated in MM</td>
<td></td>
</tr>
<tr>
<td>miR-194-2</td>
<td>MIR194-2</td>
<td>11q13.1</td>
<td>MDM2</td>
<td>Down-regulated in MM</td>
<td></td>
</tr>
<tr>
<td>miR-215</td>
<td>MIR215</td>
<td>1q41.1</td>
<td>MDM2; IGF1R; IGF1</td>
<td>Down-regulated in MM</td>
<td></td>
</tr>
</tbody>
</table>

SS indicates Sézary syndrome; and EFS, event-free survival.
p53 mutants in human lymphoma cells can still translocate to mitochondria but cannot induce apoptosis; the latter can be restored by ellipticine. On the other hand, some p53 mutants preserve proapoptotic function but lack the ability to translocate to mitochondria, which can be restored by Tid1.37

TP53 point mutations in lymphoid malignancies occur most often in the p53 DNA-binding domain (DBD; Figure 1), most frequently at codons 248, 273, and 175, similar to the codon distribution pattern in other types of cancer.55 Four of the 5 mutations at these 3 codons (R175H, R248Q, R273H, and R273C) occur in CpG sites, which have elevated mutability (with the exception of R248W). The high frequency of these mutations is also a reflection of functional selection.58 Codons 248, 273 bind to minor and major grooves of DNA, and mutations at codon 175 disrupt p53 structure (Figure 6D).59 Indeed, all 5 mutants have lost transactivation function in a p53-functional assay.54 Codons 176, 158, 244, and 245 also have a high frequency of mutation.

Prognostic significance of p53 mutations in lymphoid malignancies. Despite the low frequency of p53 mutations in hematologic malignancies, p53 mutations predict an unfavorable prognosis.51,60 The IARC prognosis dataset indicates that p53 mutations correlate with poor survival for patients with DLBCL, AML, myelodysplastic syndromes, acute lymphoblastic leukemia (ALL), CLL/SLL, FL, MCL, and MM. Our own studies have shown that TP53 mutations in the DBD significantly correlate with poor OS in patients with DLBCL (Figure 6). Concurrent p53 mutations and inactivation of other genes with prognostic impact (eg, p21, p27, ATM, p16INK4a, and ARF) have been correlated with a worse prognosis. As overexpression of p53 often correlates with p53 mutations, p53 immunohistochemical staining has been investigated by others, but its prognostic value has been inconsistent, probably because of different antibodies and different cutoffs for positivity. The combined p53+/p21– immunophenotype might be a better surrogate for p53 mutations with prognostic value.

In a 138 B-CLL cohort, p53 mutations correlated with shorter OS and selective resistance to alkylating agents, fludarabine, and γ-irradiation, but not to some other cytotoxic drugs functioning via p53-independent pathways.61 Moreover, prior chemotherapy is strongly associated with the presence of p53 mutations. Exposure to DNA-damaging alkylating agents has been suggested as being responsible for the development of TP53 mutations and resistance to second-line anti-cancer chemotherapy.61 In a more recent study, however, no clonal evolution of new TP53 mutants was identified after chemotherapy, immunotherapy, or bone marrow transplantation in 181 CLL patients.62

In Lane’s model of p53 function, tumor cells without functional p53 treated with low-dose DNA-damaging agents survive and continue to replicate resulting in mutations and aneuploidy, whereas in cells treated with high-dose DNA-damaging agents, replication attempts result in mitotic failure and cell death.1 In contrast to the prevailing notion that WT-p53 is associated with better prognosis,
it has been suggested that, in the absence of apoptosis, WT-p53 can protect tumor cells treated with ionizing radiation or chemotherapy from mitotic catastrophe or permanent arrest by mediating cell-cycle arrest and DNA repair, and therefore serves as a survival factor. WT-p53 also may serve as a survival factor for tumor cells when p53 induces autophagy that inhibits apoptosis. As reported by Amrein et al, autophagy was induced only in primary CLL lymphocytes expressing WT-p53, and contributed to drug resistance.

Table 3. Mutation numbers and prevalence of TP53 somatic mutations in lymphoid malignancies in IARC database

<table>
<thead>
<tr>
<th>Neoplasms</th>
<th>Sample/mutation associations</th>
<th>Mutation variants</th>
<th>Prevalence‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL)</td>
<td>193</td>
<td>149</td>
<td>10.0% (215/2142)</td>
</tr>
<tr>
<td>Prolymphocytic leukemia (PLL)</td>
<td>11</td>
<td>11</td>
<td>23.5% (12/51)</td>
</tr>
<tr>
<td>Follicular lymphoma (FL)</td>
<td>61</td>
<td>51</td>
<td>11.5% (45/393)</td>
</tr>
<tr>
<td>Mantle cell lymphoma (MCL)</td>
<td>56</td>
<td>51</td>
<td>16.9% (44/260)</td>
</tr>
<tr>
<td>Marginal zone B-cell lymphoma (MZL)</td>
<td>46</td>
<td>51</td>
<td>27.2% (47/181)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
<td>241</td>
<td>165</td>
<td>19.7% (12/630)</td>
</tr>
<tr>
<td>Burkitt lymphoma/Burkitt cell leukemia (BL/L)</td>
<td>126</td>
<td>79</td>
<td>20.8% (72/346)</td>
</tr>
<tr>
<td>Primary effusion lymphoma (PEL)</td>
<td>5</td>
<td>8</td>
<td>6.3% (1/16)</td>
</tr>
<tr>
<td>Mature T-cell lymphoma</td>
<td>23</td>
<td>21</td>
<td>42.8% (12/28)</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma (AILT)</td>
<td>1</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>T-cell large granular lymphocytic leukemia (LGL)</td>
<td>4</td>
<td>4</td>
<td>N/A</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, T cell and null cell type (ALCL)</td>
<td>42</td>
<td>40</td>
<td>30.7% (23/75)</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma (ATCL)</td>
<td>6</td>
<td>6</td>
<td>7.3% (4/55)</td>
</tr>
<tr>
<td>NK/T-cell lymphoma/leukemia</td>
<td>8</td>
<td>7</td>
<td>40.1% (109/272)</td>
</tr>
<tr>
<td>Hodgkin lymphoma (HL)</td>
<td>16</td>
<td>15</td>
<td>12.1% (4/33)</td>
</tr>
<tr>
<td>Plasma cell leukemia/plasmacytoma/multiple myeloma (PCL/PC/MM)</td>
<td>52</td>
<td>42</td>
<td>6.1% (34/556)</td>
</tr>
<tr>
<td>Hairy cell leukemia (HCL)</td>
<td>31</td>
<td>18</td>
<td>26.1% (18/69)</td>
</tr>
</tbody>
</table>

*Sample/mutation association numbers for different malignancies are total numbers of mutation IDs (unique identifier of a sample/mutation association) in IARC database. †Numbers of mutation variants are those of somatic MUT IDs (unique identifier of each gene variation) for different malignancies in IARC database. ‡Prevalence (%) for different malignancies is calculated as the number of cases with mutations divided by the total number of cases analyzed for different malignancies in IARC prevalence dataset.
Polymorphisms of p53 and association with lymphomagenesis. **TP53** has several polymorphisms, most of which occur in introns or UTRs, whereas 8 synonymous and 11 nonsynonymous polymorphisms occur within the CDS.63 The codon 72 polymorphism has been studied regarding its population prevalence and effects on p53 function. The p53 Pro72 variant has stronger transcriptional activity than Arg72, and is twice as stable as the Arg72 in Daudi (human BL) cells. Arg72 is also more susceptible to degradation induced by the human papillomavirus E6 protein. On the other hand, Arg72 has more capacity to induce apoptosis because of its greater ability to localize to mitochondria and lower affinity to the p53 inhibitor iASPP.63

In one study, 4 of 25 (17.5%) ALL patients carried the R72P (Arg to Pro) polymorphism.64 No association was found between this polymorphism and the risk or prognosis of AML, CLL, FL, DLBCL, Hodgkin lymphoma (HL), or non-HL (NHL). Conversely, R72P was associated with increased risk of NHL.65 Differential regulation of P1 and P2 has been observed during differentiation of HL-60 cells to granulocytes or monocytes. Expression from P2 was induced 5- to 10-fold during differentiation, whereas expression from P1 remained constant.70 In 2 of 18 (11%) Li-Fraumeni syndrome or Li-Fraumeni syndrome–like families without **TP53** mutations in the CDS and splice junctions, one single nucleotide deletion (A:T) was detected within the C/EBP-like site of the **TP53** promoter.71

Transcription factors and methylation. Numerous transcription factors regulate **TP53** transcription by modulating the **TP53** promoter, possibly in a tissue-specific manner. Conformed transcription factors in lymphocytes include the transcriptional repressors PAX-5, BCL-6, oncogen M, oncprotein TAX, LANA (latency-associated nuclear antigen), and the activators PKCβ and HOXA5. PAX proteins bind to the **TP53** promoter, thereby inhibiting transcription and apoptosis, subsequently important in pro-B-cell differentiation.72 Dysregulation of PAX-5 expression is associated with lymphomagenesis as evidenced by the t(9;14)(p13;q32) in a subset of lymphoplasmacytoid lymphoma.73 BCL-6 binds to the **TP53** promoter and suppresses **TP53** expression, thereby facilitating rapid expansion of the germinal center (GC). Aberrant BCL-6 expression contributes to lymphomagenesis.90,74

**Figure 6.** The prognostic significance of **TP53** mutations in patients with DLCBL. (A) OS (in years) after treatment with the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen among patients with a p53 mutation versus those with WT-p53. (B) OS (in months) after treatment with the rituximab-CHOP regimen among patients with p53 mutations versus those with WT-p53. (C) OS (in years) after CHOP treatment among patients with a **TP53** DNA-binding domain mutation versus those with WT-p53. (D) Location of critical p53 residues in the p53 domain model designed from the published crystal structure. The mutations depicted are associated with poor outcome identified from our group study in 1187 DLBCL cases. The residues are color-coded as follows: green represents mutation from or to proline; deep blue, residues close to zinc sites; light blue, residues close to DNA binding sites; brown, residues far from both zinc and DNA; and orange, cysteine residues implicated in the oxidation-reduction activity of p53.
Hypermethylation of promoters can silence gene expression. Methylation of the TP53 promoter or noncoding exon 1 was found in 8 of 25 (32%) ALL patients with decreased p53 mRNA expression, in 10 of 54 (18.5%) CLL patients, and in 4 of 108 (3.7%) DLBCL patients.

Posttranscriptional dysregulation at the mRNA level in lymphoid malignancies

Alternative splicing. Alternative splicing generates transcript variants that are translated into corresponding isoforms. p53 isoforms expressed in quiescent lymphocytes in a tissue-dependent manner include p53β (p53β9 generated by alternative splicing of intron 9, 341 aa) and p53γ (346 aa) with shorter and different C-terminals compared with p53, Δ40p53s missing 39aa (Δ40p53x, 354 aa; Δ40p53β, 302 aa; and Δ40p53γ, 307 aa) and Δ133p53s missing 132aa (Δ133p53x, 261 aa; Δ133p53β, 209 aa; and Δ133p53γ 214 aa) at the N-terminal regions. Compared with p53 (p53x), these p53 isoforms have different subcellular localization and function, and affect p53 function, but reports have been inconsistent. 

Aberrant expression of several novel p53 isoforms has been reported in lymphoid malignancies. A p53 isoform (Δp53) with loss of 66 aa (257-322) produced by alternative splicing was identified in human bone marrow and HSC93 (human B-cell lymphoma) cells. Δp53 has a selective transactivation function and acts on a different phase of cell cycle than does full-length p53.

A TP53 transcript variant, “Delta Ex6,” has been identified in CLL. Translation produces a truncated p53 isoform (189 aa) devoid of TA function, based on functional analysis of separated alleles. Delta Ex6 and p53β were also found in 1.2% and 2.3% of 1287 CLL cases, respectively. Expression of TP53 Delta Ex6 transgene conferred to 53-/Δβ H1299 cells a proliferative phenotype with loss of intercellular contacts and apoptosis defects.

In PW lymphoma cells treated with L-buthionine sulfoximine, the full-length p53 level was unchanged, whereas a truncated isoform of p53 (~50 kDa) was induced, reaching the highest level when apoptosis was induced irreversibly. In contrast, the rapid shift from a truncated p53 (Δ probably p53β) toward the full-length p53 expression was found responsible for the apoptosis and cytopenia as a response to chemotherapy in 5 AML patients.

Dysregulation of mRNA stability and translation. Recent investigations have identified novel posttranscriptional mechanisms of TP53 regulation in various cancer cell lines, including regulation of mRNA stability (by Wrap53, HuR, Hnf/hematopoietic zinc finger, WIG-1) and translation (by HuR, Hnf, WIG-1, L26, Nucleolin, p53, MDM2) through the 5'-UTR, 3'-UTR, or CDS. If Δ40p53 is possibly generated from an alternative internal ribosome entry site because a stem-loop structure formed in the 5'-UTR of p53 mRNA hampers ribosome scanning and translation, Interestingly, ARF, which increases p53 protein stability by antagonizing MDM2, was required for the nuclear export of p53 mRNA, with the presence of either Hnf or HuR as a prerequisite. These findings suggest that posttranscriptional dysregulation of TP53 may be implicated in lymphomagenesis. A single case of ALL with a one-nucleotide substitution in the 5'-UTR of TP53, which might affect posttranscriptional regulation, has been reported.

In addition to binding to p53 protein, MDM2 directly binds to the nucleotides of p53 mRNA corresponding to the MDM2-binding domain (MBD) of p53 and enhances TP53 translation. Cancer-derived silent-point-mutations in the MBD weaken MDM2 binding to p53 mRNA, leading to lower levels of p53 protein and apoptosis. After p53 is translated, the E3 ligase activity of MDM2 leads to the rapid degradation of p53. Δ40p53 stabilizes p53 in the presence of MDM2.

miRNAs targeting the 3'-UTR have emerged as new posttranscriptional regulators. Based on experimental data, 9 miRNAs (mir-25, -30d, -92a, -125b, 504, -1285, -141, -15, -16) have been reported to repress the TP53 gene directly (Table 4). MiRNAs of interest in lymphocytes include miR-15a and miR-16-1 in CLL, miR-25 and miR-30d in MM, and miR-125b. Interaction of miR-15/16:TP53 is an unconventional low-complementary seed match. The regulation of TP53 by miR-15a/miR-16-1 complements mRNA/TP53 feedback circuitry. miRs-15a, -16-1, -25, -30d, and -125b are all highly expressed in GC centroblasts but not in naive (before GC) and memory (after GC) B cells. In addition, these p53-regulatory miRNAs have aberrant expression in lymphoid malignancies. The oncogenic clusters miR-17-92 (containing 2 copies of MIR92A) and miR-106b-25 (containing MIR25) are aberrantly overexpressed in B-cell lymphoma and MM. In contrast, significantly decreased miR-30d expression has been observed in all cases of CLL. miR-125b was overexpressed in DLBCL and FL. Generally, miR-125b was associated with leukemogenesis in mouse models, but all Eμ/miR-125b transgenic mice developed lethal lymphoid tumors with overexpression of antiapoptotic miR-125b.

Posttranslational dysregulation of p53 at the protein level in lymphoid malignancies

p53 degradation. MDM2 mediates polyubiquitination of p53 followed by degradation, both in the cytoplasm and nucleus, and mono-ubiquitination, which enhances nuclear export. Other E3 ligases (Phn2, COP1, and ARF-BP1) also ubiquitinate p53, and MDMX ubiquitination but does not degrade p53. Mutants deficient in MBD can be degraded through oligomerization with WT-p53. Oligomerization of p53 with Δ40p53 lacking MBD increases mono-ubiquitination, nuclear export, and stability of p53.

MDM2 overexpression has been associated with tumorigenesis and poorer prognosis in patients with FL, DLBCL, MCL, MZL, BL, ALL, AML, CLL, MM, and plasma cell leukemia. Malignancies also result from dysregulation of MDM2 regulators (illustrated in Figure 7A). In BL cells, ubiquitin-mediated proteolysis of INK4/ARF and epigenetic silencing of the p16INK4A gene were associated with tumor progression.

Dysfunction of p53 TA. The activity of p53 is fine-tuned by posttranslational modifications and p53-regulators (Figure 7A), adding another mechanism to the ones affecting p53 level. The effects of posttranslational modifications on p53 activity are controversial because of different models and stress conditions used, and interplay between modifications. In addition, p53 has 12 cysteine residues that can be modified by redox, 9 of which are in the DBD. Reduced or oxidized forms of cysteine affect stability, DNA binding, and the transactivation function of p53. Redox modulators influencing p53 include glutathione, REF-1, thioredoxin, metals, and electrophiles. Dysregulation of p53 regulators can result in p53 dysfunction without TP53 mutation. Reduced ASPP1 expression resulting from promoter methylation has been found in 25% of ALL cases (n = 180) and correlates with poorer prognosis. In CLL, loss of ATM function results in a reduced level of p53 and function. MDM2 inhibitors may overcome ATM-mediated resistance to fludarabine in CLL with WT-p53.
Dysfunction of p53 TIA. The regulation of TIA of cytoplasmic p53 associated with apoptosis and autophagy is less elucidated than the regulation of TA of nuclear p53.

Tid1 (mtHsp40) and mono-ubiquitination of p53 promote translocation of p53 to mitochondria. Acetylation of K120 is required for p53 to release BAK from Mcl-1, and for transcription-independent apoptosis. Other posttranslational modifications and redox modulation also affect the translocation. The E3 ubiquitin ligase, CUL-9/Parc, enhances the cytoplasmic function of p53 in vivo. CUL-9/Parc bound to p53 localized in the cytoplasm and activated p53 cytoplasmic function in a mouse model. However, the specific biochemical mechanisms that activate p53 cytoplasmic function remain unclear. Deletion of Cul9 accelerated Etv-Myc-induced lymphomagenesis and attenuated DNA damage-induced apoptosis but had no significant effect on cell-cycle progression.

Downstream dysregulation of the TP53 pathway. Lymphomagenesis can result from dysregulation of downstream p53 effectors by p53-independent pathways. In mucosal-associated lymphoid tissue lymphomas, API2/ mucosal-associated lymphoid tissue 1, the result of the t(11;18)(q21;q21), activates NF-kB signaling and inhibits p53-dependent apoptosis, although p53 is induced and subcellular localization is not changed. Addition of the cytokine IL-6 or thapsigargin (TG, endoplasmic reticulum [ER] calcium-ATPase inhibitor) inhibits p53-induced apoptosis in mouse myeloid leukemic M1-t-p53 cells. Inhibition of apoptosis by IL-6 and TG is partially explained by induction of different p53-independent pathways; p53 transcriptional function was generally not affected. IL-6 did not affect any of the p53-induced proapoptotic genes, whereas TG prevented upregulation of Gadd45 and Dffb. Further investigation showed that IL-6 antagonizes p53 function via the p53-independent PI3K/Akt survival pathway (Figure 7B steps 1-3), which counters both the p53-mediated extrinsic (by inhibiting Fas/CD95 death-inducing signaling complex activation) and intrinsic (by increasing Mcl-1 expression) apoptotic pathways, and activates the NF-kB pro-survival function (by phosphorylation of the NF-kB inhibitor IκB).

In a murine B-ALL cell line dependent on IL-3, after cytokine withdrawal, only cells expressing Bcl-X(L) or active Akt maintain

---

Table 4. Dysregulation of TP53-regulatory microRNAs in lymphoid malignancies.

<table>
<thead>
<tr>
<th>TP53 3′UTR (top) miRNA (bottom)</th>
<th>Consequential pairing</th>
<th>Seed match</th>
<th>Aberrant expression in lymphoid malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos. 92-98</td>
<td>5′ CUGAGAACCUCUUUGCU-UGGAAUG</td>
<td>7mer-A1</td>
<td>Highly expressed in GC: overexpressed in B-cell lymphoma and MM</td>
</tr>
<tr>
<td>hsa-miR-25</td>
<td>3′ AGUCUGUCUGUGUUCUCAGUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 92-98</td>
<td>5′ CUGAGAACCUCUUUGCU-UGGAAUG</td>
<td>7mer-A1</td>
<td>Overexpressed in B-cell lymphoma and MM</td>
</tr>
<tr>
<td>hsa-miR-92a-1</td>
<td>3′ UGUCUCCUGCCUCUUCAGUU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 287-294</td>
<td>5′ UGACUGUUAAGGGUGAGUGUAACAAA</td>
<td>7mer-A1</td>
<td>Highly expressed in GC: decreased expression in CLL</td>
</tr>
<tr>
<td>hsa-miR-304</td>
<td>3′ GAAGUUGACUGCCUUA-CCAAAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 733-740</td>
<td>5′ AGACUGUUGGUUGUGCUGAGGU</td>
<td>7mer-m8</td>
<td>Highly expressed in GC: overexpressed in DLBCL and FL; caused leukemia and lethal lymphoid tumors in mouse models</td>
</tr>
<tr>
<td>hsa-miR-125b</td>
<td>3′ AGUCUGUCUACUCCAGAGUCCCU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 735-742</td>
<td>5′ GACUUGUUGUAAUGUCAGGGAACA</td>
<td>8mer</td>
<td>Not known</td>
</tr>
<tr>
<td>hsa-miR-504</td>
<td>3′ CUAUUCAGCGGUGCCCAAGA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 802-810</td>
<td>5′ UGGUGUCACGCUUCUUGUGCCAGG</td>
<td>7mer-m8</td>
<td>Not known</td>
</tr>
<tr>
<td>hsa-miR-1285</td>
<td>3′ UCCAGAGGGAACAACUGGCUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 960-966</td>
<td>5′ AGAGAAGGGGCUGACAGUGUGUGU</td>
<td>7mer-m8</td>
<td>Not known</td>
</tr>
<tr>
<td>hsa-miR-141</td>
<td>3′ GGUAAGAAAGGUGUCUGCAUAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 966-973</td>
<td>5′ GGGUGUCACGCUUCUUGUGCCAGG</td>
<td>7mer-m8</td>
<td>Not known</td>
</tr>
<tr>
<td>hsa-miR-1285</td>
<td>3′ UCCAGAGGGAACAACUGGCUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 1065-1071</td>
<td>5′ CCCAGUCGAGCGUAGGGUCAA</td>
<td>7mer-A1</td>
<td>Not known</td>
</tr>
<tr>
<td>hsa-miR-504</td>
<td>3′ CUACUCUGGCUGCCUCCAGA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 1084-1092</td>
<td>5′ GUCAACUUCUUUUAUCUCUGCAAGC</td>
<td>low-complementary seed match</td>
<td>Highly expressed in GC: loss leads to higher level of p53 in CLL</td>
</tr>
<tr>
<td>hsa-miR-15a</td>
<td>3′ GUGUUGUGUAAAGAACUCAAGGAU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos. 1084-1092</td>
<td>5′ GUCAACUUCUUUUAUCUCUGCAAGC</td>
<td>Low-complementary seed match</td>
<td>Highly expressed in GC: loss leads to higher level of p53 in CLL</td>
</tr>
<tr>
<td>hsa-miR-16-1</td>
<td>3′ GGGUUGAUAAGGACCAAGAU</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The second to seventh nucleotide of the miRNA 5′-region is known as the seed. There are 4 types of seed-matched sites on the 3′-UTR of target mRNAs according to Bartel: the 6mer site, which perfectly matches the 6-nt miRNA seed; the 7mer-m8 site, which is composed of the seed match supplemented by a Watson-Crick match to miRNA nucleotide 8; the 7mer-A1 site, which is composed of the seed match supplemented by an A across from miRNA nucleotide 1; and the 8mer site, which is composed of the seed match supplemented by both the m8 and the A1. The hierarchy of site efficacy is as follows: 8mer > 7mer-m8 > 7mer-A1 > 6mer > no site, with the 6mer differing only slightly from no site at all. Interaction of miR-15/16: TP53 is unconventional.
50% glycolysis and are resistant to apoptosis. Conversely, Akt-mediated cell survival requires glucose metabolism or alternative mitochondrial fuel to prevent apoptosis.112 In contrast, Bcl-X(L) expression strongly protects cells deprived of glucose from apoptosis. Altered metabolism resulting from glucose and/or IL-3 deprivation induces Puma and Bim expression and apoptosis; p53 is required for maximal Puma induction. Activated Akt drives glycolysis to suppress Puma expression via metabolism checkpoints that control p53 activity and to reduce Puma protein stability, as well as inhibit cytotoxicity of Bim protein possibly by phosphorylation (Figure 7B step 4). Similarly, survival of several human T-ALL cell lines, possibly highly glycolytic and with activated Akt, also depends on mitochondrial metabolism.112

**Therapeutic approaches to overcome p53 inactivation**

Figure 8 and supplemental Table 2 summarize the drugs and compounds targeting the TP53 pathway reviewed in this article.

To bypass p53 defects, therapeutic gene delivery of p53 and restoring function of p53 mutants have been explored for
chemotherapy-refractory malignancies. However, although activated p53 triggers rapid tumor cell apoptosis in the Eμ-Myt mouse model in vivo, restoration of p53 function potently selects for p53-resistant tumors in which p19ARF or p53 were inactivated. Delivery of downstream miRNAs also has been proposed as a potential therapeutic approach, yet many challenges need to be addressed, including nuclease-mediated degradation, adverse off-target effect, toxicity, and unwanted immune response.

Targeting p53 stability, MDM2 inhibitors increase apoptosis and have therapeutic implications in various lymphoma cells. However, early clinical trials with Nutlin-3a have not shown such effects. In an Eμ-Myt mouse model, both Mdm2−/− and Mdm4−/− delayed onset of B-cell lymphoma with increased p53 activity, but hematopoietic failure and cerbellar hypoplasia in double heterozygous Mdm2−/−/Mdm4−/− mice indicate that caution is warranted in the use of the inhibitors of p53 antagonists. Similarly, Mdm2−/− p53−/−Jnk3−/− mice (Mdm2- null, and encoding the p53R172P mutant lacking apoptosis ability but maintaining cell-cycle arrest function) died of hematopoietic failure. Inhibitors of calpain protease or the proteasome also increased p53 stability and elevated p53 levels and apoptosis. However, in MM, the proteasome inhibitor bortezomib significantly increased basal autophagy that was thought to protect myeloma cell viability. Novel syrbactin analogs exhibiting proteasome inhibitory activity induced proapoptotic ER stress and cell death in MM and B-ALL cells and might substitute for bortezomib.

Drugs targeting the dysregulated p53-dependent apoptosis pathway include Bcl-2 anti-sense oligonucleotides for CLL, XIAP inhibitor for CLL and ATLL, small-molecule inhibitors of Bcl-2/Bcl-X(L) for CLL, MCL, splenic marginal zone lymphoma, and Bcl-2-dependent lymphomas. Stabilization and activation of p53 also can overcome downstream apoptosis pathway defects. MDM2 inhibitor Nutlin-3a induced increased apoptosis in a preclinical model of DLBCL with WT-p53 and Bcl-2 overexpression because of t(14;18)(q32;q21). Similarly, Nutlin-3a induced apoptotic death in ALK-positive anaplastic large cell lymphoma. Interestingly, Nutlin-3a also enhanced doxorubicin cytotoxicity in p53-mut anaplastic large cell lymphoma and DLBCL. This synergistic effect was suggested to be a result of p73 up-regulation.

The potential of anti-cancer drugs that function through p53-independent apoptosis pathways also has been explored. Hexavalent chromium Cr(VI) induced both p53-dependent and p53-independent apoptosis in U937 lymphoma cells without functional p53.
Ca\(^{2+}\)-calpain pathway and mitochondrial pathway played significant roles in Cr(VI)-induced G2 block and p53-independent apoptosis. ROS generation was involved in both pathways, whereas c-Jun–N-terminal kinase and FAS activation were not detected.\(^{123}\) The proapoaptotic function of the Ca\(^{2+}\)-calpain pathway in p53-deficient U937 cells is opposite to the inhibition of apoptosis by calcium mobilizer TG in M1-t-p53 cells,\(^{110}\) and by calpain in LY-ar lymphoma cells with functional p53.\(^{115}\) Indeed, TG induced autophagy when used alone and increased apoptosis when combined with autophagy inhibitors in MM,\(^{24}\) increased ER stress and apoptosis in human MM and B-ALL.\(^{119}\) induced apoptosis in murine lymphoma cells,\(^{124}\) and induced differential apoptosis in human T-cell lymphomas with or without PLC\(\gamma\)1 phospholipase.\(^{125}\) Therefore, both apoptosis and autophagy can be induced by calcium flux, ROS, are affected by the proteasome or protease, and have an effect on mitochondria. It will be interesting to investigate further whether and how apoptosis and autophagy induced by these drugs regulate each other in lymphomas and how their interaction varies according to p53 status.

Similarly, apoptin, DNA topoisomerase I inhibitor, gallium maltolate, Avicins, ionizing radiation combined with arsenic trioxide or staurosporine, cisplatin combined with rituximab or fludarabine, can induce p53-independent apoptosis pathways in lymphoma cells regardless of p53 status.\(^{123,126-133}\) Nonapoptotic cell death mechanisms are also implicated in jasmonates (plant stress hormones)-induced cell death of murine B-lymphoma with severe ATP depletion, resulting from compromised oxidative phosphorylation in mitochondria. The authors suggested that apoptotic death in p53-wt cells is p53-independent, whereas nonapoptotic death, probably necrosis, is responsible for p53-mut cell death.\(^{134}\)

Noncanonical autophagy (Beclin1-independent) and apoptosis were simultaneously induced by a novel small-molecule compound C1 via ROS production and subsequent activation of extracellular signal-regulated kinase and c-Jun-N-terminal kinase in various cell lines.\(^{135}\) More importantly, autophagy triggered by C1 is tumor cell specific, occurring in lymphoma cells but not reactive lymphocytes.\(^{135}\)

In conclusion, TP53 pathways through TA and TIA of p53 play important roles in determining cell death or cancer progression. miRNAs, new executors in the TP53 pathway, further add to the complexity of the global regulatory network of p53 functions. Identifying key executors in the TP53 pathway can help stratify patients and develop novel therapeutic strategies. The paradoxical roles of p53 in autophagy by TA and TIA reveal novel p53 functions, but the cytoplasmic autophagic function of p53 in lymphocytes remains unclear. Dysfunction of p53 in lymphoma patients can result from deletion, mutations, and dysregulation of TP53 gene expression and p53 activities. These mechanisms provide lymphoma cells multiple ways to inactivate the functions of the TP53 pathway. Proper function of the TP53 pathway is crucial for tumor suppression and achieving favorable outcome in lymphoma patients. Currently, therapeutic approaches attempt to restore WT-p53 function and maintain p53-dependent and -independent apoptosis yet face problems, such as treatment-induced selection of p53-resistant clones, hematopoietic failure, and inefficient or nonspecific miRNA delivery. Mitochondrially targeted delivery of p53 provides hope for tumor-specific killing without adverse effects. However, TIA of p53 is not sufficient for tumor suppression and TA of p53 is required for tumor suppression in other models. Challenges also come from the fact that these agents could induce autophagy, senescence, or apoptosis in different clinical and biologic contexts. Complicated interactions of autophagy and apoptosis lead to cell death in one scenario but survival of tumor cells in other scenarios. This uncertainty related to drug resistance has been observed with proteosome inhibitors, calcium mobilizers, suberoylanilide hydroxamic acid, and many other drugs. Inhibition of autophagy has been shown to be a new anti-cancer treatment. On the other hand, autophagy and necrosis may represent alternative approaches to cell death for apoptosis-resistant tumors only if they lead to, but not protect from, cell death. More attractively, some of these drugs specifically target only tumor cells that harbor genetic lesions or defective pathways. Further investigation to elucidate the mechanisms underlying these results will lead to the advent of effective therapeutic intervention.

Acknowledgments

The authors thank Maitrayee Goswami and Virginia Mohlere from the Department of Scientific Publications for technical and publication editing support. The authors apologize for not including many excellent references because of space limitations.

K.H.Y. was supported by the University of Texas MD Anderson Cancer Center Institutional R&D Fund, Institutional Research Grant Award, the Myeloma SPORE Development Research Program Award, Gundersen Medical Foundation Award, and Forward Lymphoma Fund. This study is supported in part by the National Cancer Institute, National Institutes of Health (R01CA138688 and 1RC1CA146299, Y.L., K.H.Y.) and the MD Anderson Cancer Center SPORE in Multiple Myeloma (P50CA142509, R.Z.O.).

Authorship


Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Ken H. Young, University of Texas MD Anderson Cancer Center, Department of Hematopathology, 1515 Holcombe Blvd, Houston, TX 77230-1439; e-mail: khyoung@mdanderson.org.

References


www.bloodjournal.orgFrom www.bloodjournal.org by guest on October 4, 2017. For personal use only.


24. Wilson HA, Allred DV, O’Neill K, Bell JD. Activities


Dysfunction of the TP53 tumor suppressor gene in lymphoid malignancies

Zijun Y. Xu-Monette, L. Jeffrey Medeiros, Yong Li, Robert Z. Orlowski, Michael Andreeff, Carlos E. Bueso-Ramos, Timothy C. Greiner, Timothy J. McDonnell and Ken H. Young