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SHORT REPORT

p53 and p73 in suppression of Myc-driven lymphomagenesis

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Induction of apoptosis by the tumor suppressor p53 is known to protect from Myc-driven lymphomagenesis. The p53 family member p73 is also a proapoptotic protein, which is activated in response to oncogenes like Myc. Here, we have investigated whether p73 provides a similar protection from Myc-driven lymphomas as p53. Confirming previous studies, the inactivation of a single p53 allele ($p53^{+/-}$) strongly reduced the median survival of *Eμ-Myc* transgenic mice from 103 to 39 days and was invariably associated with a loss of the wild-type p53 allele. In contrast, mutational inactivation of a p73 allele ($p73^{+/-}$) reduced the median survival by only 12 days. Lymphomas that developed in the $p73^{+/-}$ background showed no loss of heterozygosity (LOH). Furthermore, gene expression profiling of $p73^{+/+}$, $p73^{+/-}$ and $p73^{-/-}$ lymphomas indicated that $p73^{+/-}$ lymphomas retained p73 transcriptional activity. Subtle gene expression differences between $p73^{+/+}$ and $p73^{+/-}$ lymphomas, however, suggest a haploinsufficient phenotype on some p73 target genes. This might help to explain why $p73^{+/-}$ animals succumbed to disease slightly earlier than their $p73^{+/+}$ littermates (log-rank test $p < 0.0395$) and why p73 often shows monoallelic inactivation in human lymphomas. Together these data demonstrate that in Myc-driven lymphomagenesis p73 has weak tumor suppressor activity compared with p53.

Key words: p53; p73; Myc; tumor suppression; lymphoma

The tumor suppressor p53 is activated by a number of genome-threatening stimuli including DNA damage and expression of oncogenes. For example, Myc overexpression triggers activation of the *Ink4a/Arf* locus resulting in $p19^{ARF}$-mediated stabilization of p53.[1,2] p53 effectively opposes Myc-induced hyperproliferation by killing those cells in which Myc levels exceed a safe threshold. In fact, proapoptotic ARF/p53 signaling has been identified as the major barrier to Myc-induced lymphomagenesis, which must be attenuated in full-blown Myc-driven malignancies.[3]

The p53 family member p73 shares a high degree of structural homology with p53.[4] The highest degree of homology is seen within the central DNA binding domain resulting in the transactivation of an overlapping set of target genes and the ability to induce cell cycle arrest and apoptosis.[5] Transactivation requires full-length p73, called TAp73, which is commonly distinguished from the transactivation-defective ΔNp73 isoform generated by an alternative promoter.[6] The TAp73 promoter is regulated by E2F and activated when pRB control of E2F is lost due to disruption of the pRB circuitry by oncogenes like adenoviral E1A, SV40 large T or c-Myc.[7–9] TAp73 thereby contributes to the proapoptotic response triggered by E2F1, E1A and c-Myc.[8,9] It has therefore been speculated that TAp73 provides a tumor fail–safe mechanism protecting from tumorigenesis by killing oncogene-bearing cells.[10]

In support of this hypothesis, we have recently demonstrated in cell culture experiments that TAp73 indeed poses a barrier to malignant transformation: TAp73 limits the survival of pRB-inactivated cells when these are grown to high cell density for example in soft agar assays.[7,11] However, data on tumor suppressor functions of p73 *in vivo* are still scarce and contradictory. The initial description of p73 knockout mice reported no increased tumor susceptibility.[12] Similarly, p73 did not protect from irradiation-induced T-cell lymphomagenesis.[13] In contrast, Flores *et al.,* recently reported spontaneous tumor development in both $p73^{+/-}$ and $p73^{-/-}$ animals.[14] These tumors, however, were often microscopic in size and occurred late in life. Considering activation of p73's proapoptotic function by oncogenes like c-Myc, we therefore investigated whether p73 protects from Myc-induced lymphomagenesis *in vivo*.

Material and methods

Mice

Eμ-Myc transgenic mice[15] were crossed to $p53^{+/-}$[16] or $p73^{+/-}$[12] animals to generate *Eμ-Myc*, $p53^{+/+}$ ($n = 18$); *Eμ-Myc*, $p53^{+/-}$ ($n = 8$); *Eμ-Myc*, $p73^{+/+}$ ($n = 47$) and *Eμ-Myc*, $p73^{+/-}$ ($n = 36$) littermates. *Eμ-Myc*, $p53^{+/+}$ and *Eμ-Myc*, $p53^{+/-}$ were analyzed on a pure C57BL/6 genetic background, whereas *Eμ-Myc*, $p73^{+/+}$ and *Eμ-Myc*, $p73^{+/-}$ were on a mixed C57BL/6 × 129/SvJae background. *Eμ-Myc*, $p73^{-/-}$ mice were generated by crossing *Eμ-Myc*, $p73^{+/-}$ to $p73^{+/-}$ mice. All animals were observed daily for signs of morbidity and tumor development. The first-time palpability of enlarged lymph nodes was recorded as tumor onset. Animals for which data on tumor onset were not available were excluded from the analysis for tumor freeness. Animals were sacrificed when moribund. Individual time values were plotted in the Kaplan-Meier population-event-time course format. Statistical significance was calculated using the 2-sided log-rank test (Prism 4 software, GraphPad).

LOH analysis

DNA was extracted from tail tips or lymphoma tissues by proteinase K digestion in PBND buffer [50 mM KCl, 10 mM Tris-HCl (pH 8.3), 2.5 mM $MgCl_2$, 0.45% NP40, 0.45% Tween-20]. The DNA concentration was determined, and 100 ng were used for multiplex PCR using the primers for the p53 locus 5′-CAG GCT AAC CTA ACC TAC CAC-3′, 5′-ACA GCG TGG TGG TAC CTT AT-3′ and 5′-TGA AGA GCT TGG CGG CGA ATG-3′ or the p73 locus 5′-GGG CCA TGC CTG TCT ACA AAG AA-3′, 5′-CCT TCT ACA CGG ATG AGG TG-3′ and 5′-GAA AGC GAA GGA GCA AAG CTG-3′. PCR products were analyzed by agarose gel electrophoresis.

Microarray experiments

RNA was extracted from a total of 10 *Eμ-Myc* lymphomas from $p53^{+/+}$, $p53^{+/-}$, $p73^{+/+}$, $p73^{+/-}$ and $p73^{-/-}$ mice (2 lymphomas of each genotype) with the RNeasy Mini Kit (Qiagen). Cy3 and Cy5 labeled cDNA probes were generated, after mRNA amplification with MessageAmp II aRNA Kit (Ambion), in a 2-step procedure using the CyScribe Post-Labelling Kit (Amersham Biosciences). Cy3- and Cy5-labeled probes were purified with Qiagen spin

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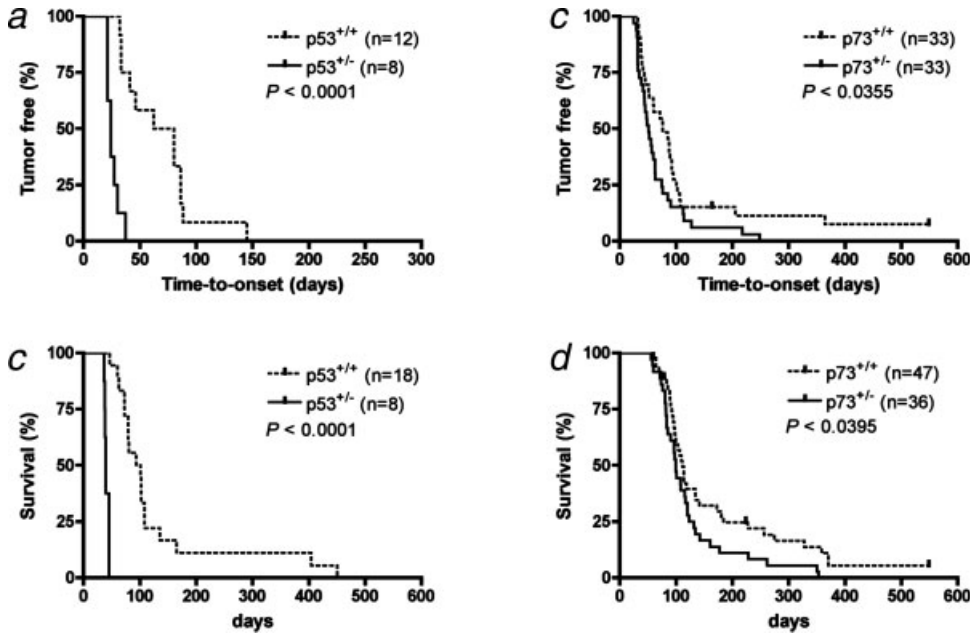

Figure 1 – Influence of p53 and p73 on tumor development in *E*μ-*Myc* transgenic mice. Kaplan-Meier plots on (*a*,*b*) lymphoma incidence and (*c*,*d*) overall survival. Both p53 and p73 heterozygous mutant animals showed a significantly different time-to-onset and overall survival compared with their p53 and p73 wild-type controls as determined by 2-sided log-rank test ($p < 0.05$).

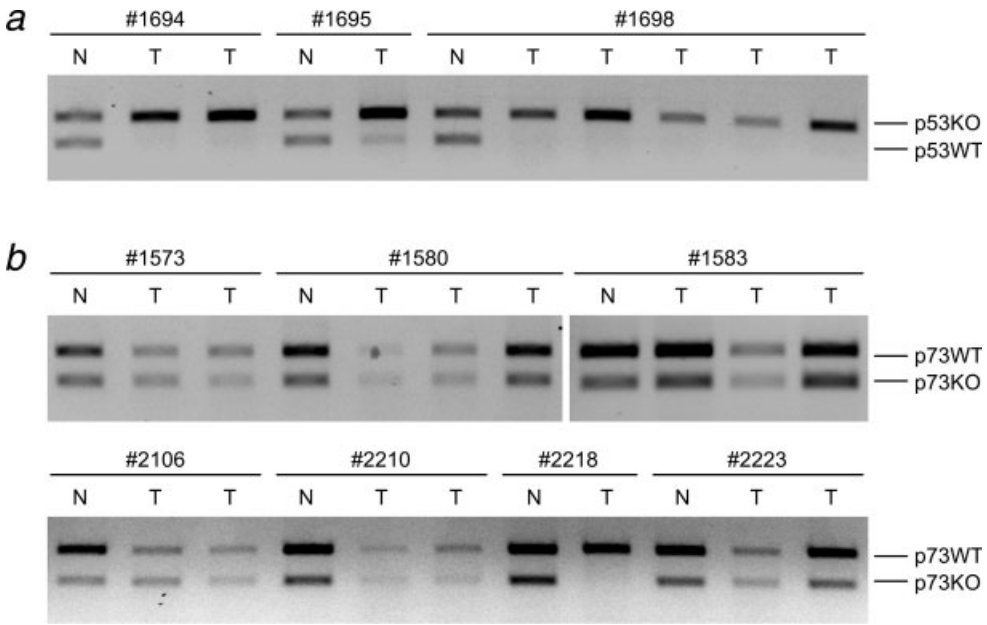

Figure 2 – Loss of heterozygosity (LOH) analysis at (*a*) the p53 and (*b*) the p73 locus by multiplex PCR of normal (tail tip, N) or tumor tissue (lymphoma, T). *E*μ-*Myc*, $p53^{+/-}$ mice: #1694, #1695, #1698; *E*μ-*Myc*, $p73^{+/-}$ mice: #1573, #1580, #1583, #2106, #2210, #2218, #2223.

columns, combined and hybridized to 21.5K cDNA microarrays (IMT, Marburg) for 16 hr at 55°C. Following washing at a stringency of 0.1× SSC/0.1% SDS and 0.1× SSC, the microarrays were scanned and quantitated using Scan Array Express (Perkin Elmer). The background-corrected ratio of the 2 channels were calculated, log 2 transformed and standardized. We used the print-tip-lowess normalization to correct for inherent bias on each chip. We performed 2 microarray hybridizations for each lymphoma sample. Expression data and gene annotations were stored in ArrayExpress (http://www.ebi.ac.uk/arrayexpress/). The R environment (http://www.r-project.org/) was used for gene filtering and normalization of the data. Differentially expressed genes were selected by a fold change of at least 4 and an absolute value of the *t*-statistic of 1.96.

RTPCR

RNA extracted from the lymphoma samples (2 of each mouse genotype) was reverse transcribed with Omniscript (Qiagen) and

analyzed by qPCR in triplicates with the Brilliant II QPCR reagent on the Mx 3005P (Stratagene). Results were normalized to GAPDH. Primer sequences and amplification conditions are available upon request.

Results and discussion

To compare the tumor suppressor activities of p53 and p73 in Myc-induced lymphomagenesis we used the well-established *Eμ-Myc* transgenic mouse model in which c-Myc is overexpressed in B-cell progenitors under control of the immunoglobulin heavy chain enhancer.[15] After a protracted subclinical course, *Eμ-Myc* mice develop clonal pre-B and B-cell lymphomas, which closely resemble human non-Hodgkin's lymphomas. Importantly, human non-Hodgkin's lymphomas are known to frequently inactivate p73 alleles by abnormal methylation or deletion suggesting that p73 plays a tumor suppressor role in this tumor entity.[17,18]

To generate B-cell lymphomas with defined genetic alterations in p53 or p73, we crossed the *Eμ-Myc* transgenic to mice heterozygous for germ-line deletions in p53 ($p53^{+/-}$) or p73 ($p73^{+/-}$).[12,16] As previously reported, the onset of *Eμ-Myc* lymphomas in $p53^{+/-}$ animals (Fig. 1*a*) was greatly accelerated compared with $p53^{+/+}$ controls (median time of onset 24 and 71 days, respectively; 2-sided log-rank test $p < 0.0001$). Consistently, the median survival was strongly reduced ($p53^{+/-}$: 39 days, $p53^{+/+}$: 103 days; ratio 2.641, 95% CI 2.164–3.118; Fig. 1*c*). In contrast, the onset of lymphoma development in *Eμ-Myc*, $p73^{+/-}$ mice (Fig. 1*b*) was only slightly accelerated compared with controls (51 and 76 days, respectively; $p < 0.0355$), and the median survival of *Eμ-Myc*, $p73^{+/-}$ animals was not significantly reduced (99 and 111 days; ratio 1.121, 95% CI 0.4873–1.755). However, a slight protective effect of p73 became apparent at later time points (>100 days) resulting in a significantly different overall survival (2-sided log-rank test $p < 0.0395$; Fig. 1*d*). Further examination of *Eμ-Myc* lymphomas from $p73^{+/+}$ and $p73^{+/-}$ mice revealed no differences in histology or tissue distribution (data not shown). Metastasis to the lung or liver was not observed. Of note, we also obtained *Eμ-Myc*, $p73^{-/-}$ animals. Most of them died before weaning, not because of lymphomas, but as a consequence of developmental defects that are commonly seen in p73-knockout mice. The low number of adult *Eμ-Myc*, $p73^{-/-}$ mice therefore precluded a thorough analysis of lymphomagenesis. However, the only 2 *Eμ-Myc*, $p73^{-/-}$ mice that survived beyond weaning developed tumors with a similar latency as *Eμ-Myc*, $p73^{+/+}$ or $p73^{+/-}$ mice. Importantly, these *Eμ-Myc*, $p73^{-/-}$ animals were still alive at 100 days, when all *Eμ-Myc,* $p53^{+/-}$ had already died from lymphomas. We therefore conclude that targeted inactivation of p73 does not enhance Myc-induced lymphomagenesis to a comparable extent as the loss of p53.

The protective effect of p53 results in the invariant loss of the remaining wild-type p53 allele in lymphomas arising in *Eμ-Myc*, $p53^{+/-}$ animals[1,2,19] (Fig. 2*a*). In contrast, we did not observe a loss of heterozygosity (LOH) in lymphomas from *Eμ-Myc*, $p73^{+/-}$ mice ($n = 11$; Fig. 2*b*).

The lack of LOH, however, does not exclude a loss of p73 activity caused by a reduced expression level, an altered expression ratio of the antagonistic TAp73 and ΔNp73 isoforms or an inactivation of p73 by increased expression of inhibitors. To investigate a possible loss of p73 function we measured p73 activity on the basis of gene expression profiles. For this, we used a total of 10 *Eμ-Myc* lymphomas from $p53^{+/+}$, $p53^{+/-}$, $p73^{+/+}$, $p73^{+/-}$ and $p73^{-/-}$ animals, 2 from each genetic background, for analysis with 21.5 K cDNA microarrays. Both tumors from $p53^{+/-}$ animals showed LOH, whereas the tumors from $p73^{+/-}$ mice did not. Hierarchical clustering of gene expression profiles revealed clustering of p73-null lymphomas separate from all wild-type ($p53^{+/+}$ and $p73^{+/+}$) lymphomas (Fig. 3*a*). One of the 2 $p73^{+/-}$ lymphomas clustered with the $p73^{+/+}$, the other with the p73-null samples. Importantly, lymphomas from $p53^{+/+}$ and $p73^{+/+}$ mice

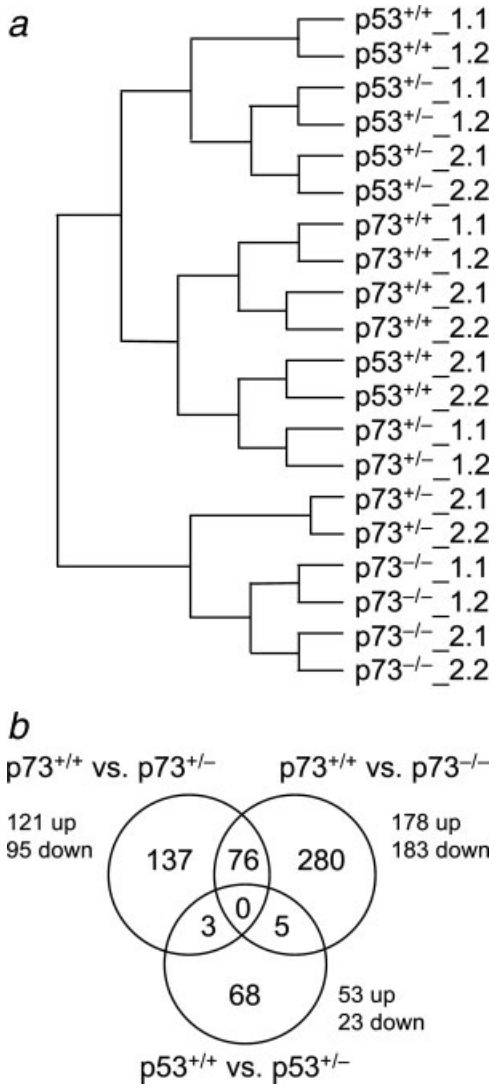

Figure 3 – Microarray analysis of lymphoma tissues. (*a*) Average linkage hierarchical clustering of samples using the Euclidean distance metric. There were 2 technical replicates for each lymphoma sample. (*b*) Venn diagram illustrating overlap of differentially expressed genes.

coclustered with those from $p53^{+/-}$ mice, which are p53-null due to LOH, suggesting general inactivation of p53 in all lymphoma samples.

When comparing the number of differentially expressed genes, the strongest changes were seen in the p73-null lymphomas (Fig. 3*b*). A total of 361 genes were significantly deregulated in p73-null compared with $p73^{+/+}$ lymphomas. This group of genes is enriched in genes of the GO classification ''membrane'' and ''receptor activity'' (DAVID functional annotation, Benjamini score < 0.005). $p73^{+/-}$ and $p73^{+/+}$ lymphomas showed differential expression of only 216 genes, which substantially overlapped with the group of genes deregulated in the p73-null lymphomas. Only 76 genes were differentially expressed between $p53^{+/+}$ and $p53^{+/-}$ samples, and these did not considerably overlap with the genes deregulated by the loss of p73.

A number of genes that were differentially expressed in the microarray experiments were further validated by quantitative RT-PCR (Fig. 4). For example, the NF-κB regulator *Nfkbiz*, the glycogen phosphorylase *Pygl*, the cell adhesion molecule *CadM1*

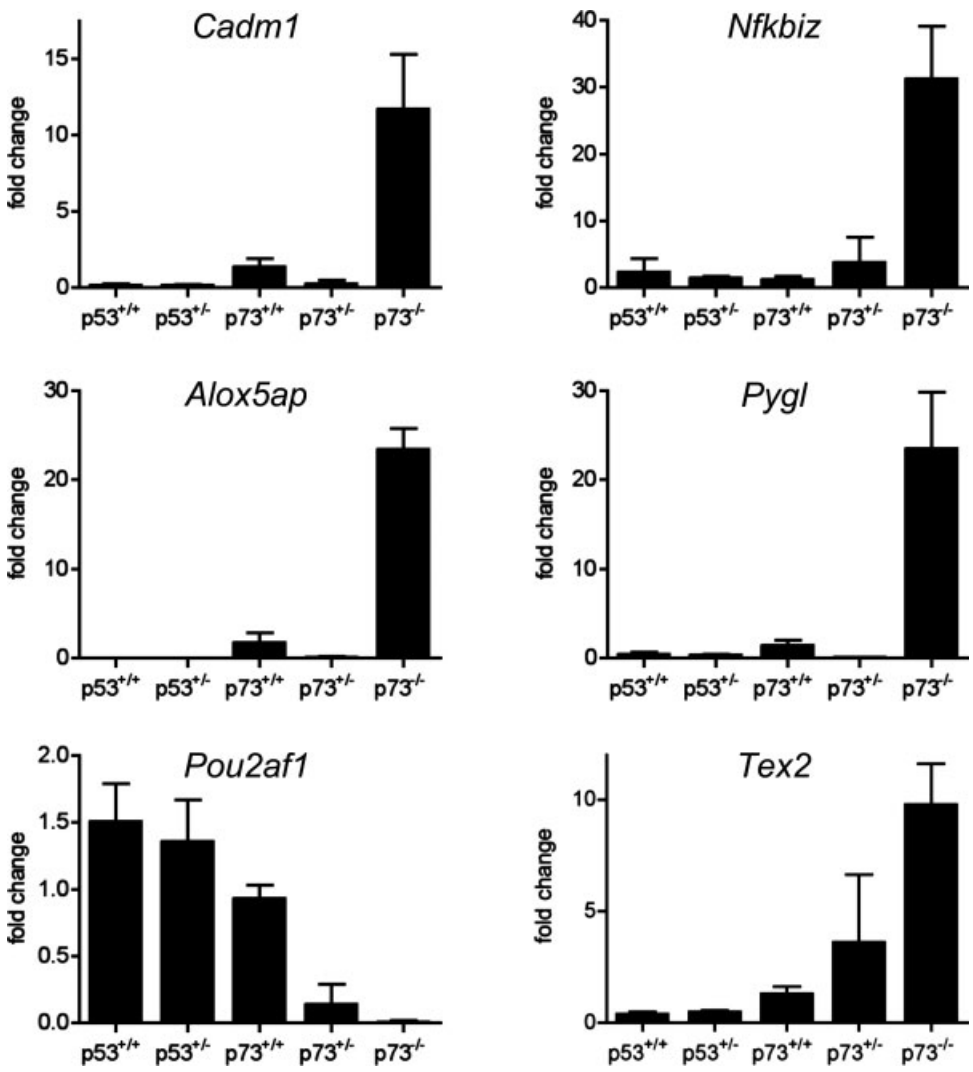

Figure 4 – Validation of microarray results by quantitative RT-PCR. Gene expression data were normalized to expression of GAPDH. Shown is the mean fold change ± SD compared with the $p73^{+/+}$ samples.

and the arachidonate 5-lipoxygenase-activating protein *Alox5ap* were strongly upregulated in the p73-null lymphomas suggesting direct or indirect physiological repression of these genes by p73. Expression of these genes was not changed in $p73^{+/-}$ lymphomas, again strongly supporting the idea that the activity of the remaining p73 allele is not lost during lymphomagenesis. In contrast, expression of the transcriptional coactivator *Pou2af1* and the membrane protein *Tex2* was intermediate in the $p73^{+/-}$ lymphomas compared with p73-null and $p73^{+/+}$ lymphomas, suggesting that p73 is a haploinsufficient transcriptional regulator of a subset of genes including *Pou2af1* and *Tex2*.

In summary, the gene expression profiles were largely characterized by the p73 but not the p53 genotype of the animal. This is consistent with the concept that the ARF/p53 pathway is commonly inactivated in most *E*μ-*Myc* lymphomas. The animal's p53-genotype determines the latency of tumor development by affecting the rate of p53-inactivation, but once p53 is inactivated and the tumor is present the gene expression profile becomes independent of the original p53-genotype. In contrast, p73-null tumors were clearly distinguishable from wild-type tumors indicating that the p73 genotype of the host was retained in the tumor. $p73^{+/-}$ lymphomas, however, revealed a haploinsufficient phenotype with respect to some target genes (*e.g. Pou2af1*, *Tex2*) providing a possible clue to the slight but significant difference in overall survival between *E*μ-*Myc*, $p73^{+/+}$ and *E*μ-*Myc*, $p73^{+/-}$ animals.

Together, our data indicate that p53 is certainly the dominant suppressor of Myc-induced lymphomagenesis. p73 contributed small but statistically significant protection, which became apparent from the overall reduced survival of p73-compromised mice (Fig. 1*d*). Considering that p73 is believed to be one of the downstream mediators of Myc-induced apoptosis, it was rather surprising that p73 showed no stronger impact on Myc-driven lymphomagenesis. Although p73 was essential for apoptosis following ectopic expression of c-Myc in Saos-2 cells,[8] c-Myc sensitized p73-knockout MEFs showed similar levels of etoposide-induced apoptosis as wild-type MEFs.[20] One explanation could therefore be that p73 induction by Myc is not as ubiquitous as previously believed but rather restricted to certain tissues or stress conditions. Alternatively, p73 might not be able to trigger apoptosis in pre-B cells so that there is no pressure to inactivate p73 in this cell type. In addition, it has been reported that c-Myc can physically associate with p73, which impairs the transcriptional activity of p73 on target promoter like Bax and p21.[21] p73 inactivation could therefore be dispensable, if the transactivation function of p73 is efficiently controlled by Myc through direct protein–protein interactions. On the other hand, it has also been reported that p73 stimulates the interac-

tion of Max with c-Myc resulting in increased Myc-Max DNA binding.[22] Together, these studies indicate that p73 is not simply a proapoptotic target of Myc but rather forms a more complex network with Myc that is far from being understood.

Our data on the role of p73 in lymphomagenesis are not in agreement with other studies. Perez-Losada *et al*. demonstrated that p73-heterozygous mice showed no significant difference in lymphoma latency, spectrum or frequency after gamma radiation compared with their wild-type counterparts.[13] In addition, the frequency of spontaneous lymphoma development in p53-compromised mice was irrespective of p73 status.[13,14] Consistently, p73 is dispensable for the p53-dependent apoptosis of T lymphocytes.[23] Importantly, irradiation-induced lymphomas and lymphomas occurring in p53-compromised mice are typically T-cell lymphomas, whereas *E*μ-*Myc* mice develop lymphomas of B cell origin.[15] The reduced survival of $p73^{+/-}$ animals in our study would therefore be in agreement with a lymphoma protective effect of p73 restricted to the B-cell lineage.

Interestingly, the small tumor suppressor activity of p73 that became apparent appeared insufficient to drive complete p73 inactivation by LOH during lymphomagenesis. An explanation might be the haploinsufficiency of p73 in regulating a distinct set of genes with *Pou2af1* and *Tex2* being examples. The fact that this subset of target genes was deregulated in the p73 heterozygous state raises the possibility that genes protecting from lymphomagenesis were already inactivated by monoallelic p73 inactivation. In this case, there would be no further advantage of inactivating the remaining wildtype allele by LOH. In fact, recent studies have suggested that complete p73 inactivation might even impair cell proliferation.[24,25] Monoallelic p73 inactivation would thus provide a compromise between the loss of tumor suppressor functions and impaired cell proliferation. This could help to understand the poorer survival of *E*μ-*Myc*, $p73^{+/-}$ animals and also the inactivation of single p73 alleles by either deletion or promoter methylation, which has been observed in ~30% of human lymphomas.[17] Which of the differentially expressed genes determine survival needs further investigation. Likewise, it remains to be seen whether reduced or monoallelic expression of p73 in lymphomas might have a stronger impact on the response to chemotherapy, which would help to predict patient prognosis and to select and fine-tune optimal treatment protocols.

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