Phosphorylation of mouse p53 at Ser18 occurs after DNA damage. To determine the physiological roles of this phosphorylation event in p53-dependent DNA damage responses, a Ser18 to Ala missense mutation was introduced into the germline of mice. Thymocytes and fibroblasts from the knock-in mice show reduced transactivation of many p53 target genes following DNA damage. p53 protein stabilization and DNA binding are similar in knock-in and wild type mice, but C-terminal acetylation was defective, consistent with a role for Ser18 in the recruitment of transcriptional co-activators. The apoptotic response of knock-in thymocytes to ionizing radiation is intermediate between that of wild type and p53 null thymocytes. Despite impaired transcriptional and apoptotic responses, the knock-in mice are not prone to spontaneous tumorigenesis. This indicates that neither phosphorylation of p53 on Ser18 by ATM nor a full transcriptional response is essential to prevent spontaneous tumor formation in mice.

p53 is the most commonly mutated tumor suppressor gene in human cancers and plays two main roles in cellular responses to stresses. It causes cell cycle arrest or apoptosis, partly depending on the cell types (1, 2). Both p53-triggered responses can protect the genome from accumulating mutations and passing these mutations on to the daughter cells. Structural and functional analyses of p53 have shown that p53 is a transcription factor with a sequence-specific DNA-binding domain in the central region and a transcriptional activation domain at the N terminus. Three additional domains, including a nuclear localization signal, a tetramerization domain, and an extreme C-terminal regulatory domain, are present in the C terminus of p53 (2). The transcriptional activities of p53 are essential for both p53-dependent cell cycle arrest and apoptosis (3, 4).

In response to DNA damage and other sources of cellular stresses, the protein levels of p53 are greatly up-regulated, and its transcriptional activities are significantly induced (2). However, it remains unclear how these stresses signal p53 responses. The p53 protein level is regulated post-transcriptionally, and up-regulation of p53 following DNA damages is mainly due to increased protein stability (5). The interaction between p53 and Mdm2, a transcriptional target of p53, represents a negative feedback regulatory mechanism for the rapid turnover of p53 in normal cells (6, 7). In this context, p53 is degraded through a ubiquitin-dependent pathway, and Mdm2 functions as the p53-specific E3 ubiquitin ligase (8, 9).

Accumulating evidence suggests that phosphorylation of p53 might play important roles in regulating p53 stability and activity (5). Both human and mouse p53 are phosphorylated at multiple sites at the N and C terminus both in vivo and in vitro by a number of kinases. In this context, phosphorylation of p53 at Ser18 occurs rapidly following DNA damage and requires the ATM family protein kinases (10–12). A number of studies have sought to elucidate the role of Ser15 phosphorylation in regulating p53 stability and activity. One study reported that phosphorylation of p53 at Ser15 disrupted its interactions with Mdm2, leading to p53 stabilization (13). Others have argued that Ser15 phosphorylation is required for the acetylation of p53 at C-terminal Lys residues but dispensable for p53-Mdm2 interaction (14–16).

To address the importance of Ser15 phosphorylation in p53 responses to DNA damage, we introduced a missense Ser18 (corresponding to Ser15 of human p53) to Ala mutation into the endogenous p53 gene of mouse embryonic stem (ES)1 cells. Analysis of homozygous mutant p53S18A ES cells indicated that phosphorylation of mouse p53 at Ser18 is important for the maximum induction of p53 protein levels after DNA damage (17). In addition, p53-dependent cell cycle G1 arrest and induction of p21 were impaired in p53S18A-differentiated ES cells (17). However, p53 acetylation at the extreme C terminus is normal in p53S18A ES cells. These previous findings support a role for Ser18 phosphorylation in regulating p53 responses to DNA damage. However, considering that the ES cell is an atypical cell type in the regulation of p53 stability and activity (18), we introduced the p53S18A mutation into mouse germline.

EXPERIMENTAL PROCEDURES

Construction of p53S18A Mice—p53S18A ES cells were described previously (17). The heterozygous mutant ES cells were injected into C57BL6 blastocysts to generate chimeric mice that transmitted the mutation into mouse germline. The germline-transmitted mice were bred with CMV-Cre mice to excise the PGK-neo gene from the targeted alleles. Heterozygous mutant mice were intercrossed to generate p53S18A mice.

This paper is available on line at http://www.jbc.org
Western Blotting Analysis—Protein extracts from 4 × 10^6 MEFs or 5 × 10^6 mouse thymocytes were separated by SDS-PAGE on 8% (for Mdm2), 12% (p53), or 15% (p21) polyacrylamide gels and transferred to nitrocellulose membrane. The membrane was blocked with 5% dry milk and probed with a monoclonal antibody against p53 (pAb240; Santa Cruz Biotechnology, Inc.), a polyclonal antibody against p53 (CM-5; Vector Laboratories Inc.), a polyclonal antibody against p21 (Santa Cruz Biotechnology, Inc.), or a monoclonal antibody against Mdm2 (2A10; Oncogene Science). The filter was then incubated with a horse-radish peroxidase-conjugated secondary antibody, developed with ECL Plus from Amersham Biosciences. To determine whether the amount of proteins in each lane was comparable, the filter was stripped and reprobed with a monoclonal antibody specific for p53 or p53 acetylated at Lys379. Rabbit polyclonal antibody against murine p53 acetylated at Lys379 was described previously (3).

Cell Cycle Analysis—Cell cycle G0/S arrest was performed as previously described (19). Briefly, subconfluent MEFs were synchronized at G0 by serum starvation in Dulbecco’s modified Eagle’s medium supplemented with 0.1% fetal calf serum for 96 h. Irradiated or untreated G0 synchronized cells were trypsinized and plated in 10-cm-diameter plates at a density of 1 × 10^6 cells/plate in normal growth medium supplemented with 10 μM bromodeoxyuridine. After 24 h of bromodeoxyuridine labeling, the cells were harvested, fixed in 70% ethanol, and stored at −20 °C. DNA content and DNA synthesis were analyzed by flow cytometry as previously described (19).

p53-dependent Apoptosis in Mouse Thymocytes—Single cell suspension of thymocytes were plated in Dulbecco’s modified Eagle’s medium supplemented with 5% fetal calf serum and 10 μg/ml heparin, pH 7.0, at a density of 10^6 cells/ml and treated with increasing dosages of IR. Ten hours after treatment, the percentages of apoptotic thymocytes were determined by staining with fluorescein isothiocyanate-conjugated Annexin V (Pharmingen) and analyzed by flow cytometry as described (3).

Microarray Analysis—Total RNA was extracted from thymocytes of untreated (5 grays) or irradiated (5 grays) mice 8 h after IR with a Qiagen RNeasy extraction kit. RNA amount and quality were monitored with Agilent Nano6000 RNA chips (Agilent Technologies). Ten micrograms of total RNA from each thymocyte sample were reverse transcribed using Superscript II reverse transcriptase (Invitrogen), converted into double-stranded cDNA, and then biotin-labeled during in vitro transcription using the ENZO RNA Transcript labeling kit (Affymetrix, Sunnydale, CA) according to Affymetrix recommended protocols. Each sample was pre-tested for RNA integrity by hybridization to Affymetrix Test5 chips and then hybridized to Affymetrix Murine Genome U74Av2 microarray slides, which interrogate ~12,600 murine genes (listed at www.affymetrix.com). Data from microarray experiments were evaluated using the Affymetrix MAS 5.0 and DMT software. Following scanning of each oligonucleotide array, the average signal intensity (sum of all intensities/number of sequence) was set to 100.

Real Time PCR Analysis—Total RNA was isolated from MEFs or thymocytes with the combination of Trizol (Invitrogen) and RNeasy RNA Cleanup (Qiagen). RNA was treated with RNase-free DNase for 20 min (Roche Applied Science) at room temperature before being reverse transcribed using Superscript II RT (Invitrogen). Real time PCR was performed on an MX-400 machine (Stratagene) with Sybr Green PCR Master Mix (ABI). PCR conditions consisted of a 10-min hot start at 95 °C, followed by 40 cycles of 30 s at 95 °C and 1 min at 61 °C. The average threshold cycle (Ct) for each gene was determined from triplicates of real-time reactions, and levels of gene expression relative to glyceraldehyde-3-phosphate dehydrogenase were determined as previously described (20). The primer sequences for p21, Bax, and cyclin G were described (20). Other primers are listed below: Mdm2 primers, 5′-ATGTCGGGT-ACATGGATGTTGTT-3′ and ACCTGCATCCATCTCACCTCAGA-3′; Noxa primers, 5′-GACCGAGCTCAATGATGTTGTT-3′ and 5′-GTTGCAGCACCTCATGCT-3′; Perp primers, 5′-CACCTGCATCCATCTCACCTCAGA-3′ and 5′-GGCTGAGAGGTTAAGAACGATTACAGGTTGTT-3′; 14–3–3 ε primers, 5′-GCCGAGGTTAAGAACGATTACAGGTTGTT-3′ and 5′-GTTGCAGCACCTCATGCT-3′ and 5′-GGCTGAGAGGTTAAGAACGATTACAGGTTGTT-3′ and 5′-GGCTGAGAGGTTAAGAACGATTACAGGTTGTT-3′; and glyceraldehyde-3-phosphate dehydrogenase primers, 5′-CCAGTAGTCATCCATCTCACCTCAGA-3′ and 5′-GACTGCAGCAGACATCATCCATCTCACCTCAGA-3′.

Chromatin Immunoprecipitation Assay—ChIP analysis of in vivo binding of p53 to p53-dependent promoters was essentially as described (21). For ChIP, 1.6 × 10^6 MEFs in a 10-cm dish were fixed with 1% formaldehyde for 10 min at room temperature. Formaldehyde was neutralized by the addition of 125 mM glycine for 5 min. The cells were washed twice in ice-cold phosphate-buffered saline and collected by scraping in 1 ml of 1% SDS 50 mM Tris, pH 8.0, 100 mM 5-bromodeoxyuridine, 2 mM 5-bromodeoxyuridine, and 0.2 μg/ml phenylmethylsulfonyl fluoride. The lysates were vortexed and insoluble material was collected by centrifugation at 4 °C for 5 min. The pellets were resuspended in 1 ml of 0.25% SDS, 200 mM NaCl, 50 mM Tris, pH 8.0, 100 μg/ml salmon sperm DNA, and protease inhibitors and sonicated to an average fragment size of 0.6 kb using a Microtip on a Branson sonicator. The remaining insoluble material was removed by centrifugation at 4 °C for 5 min. The supernatant was diluted with 2 volumes of 1% Nonidet P-40, 350 mM NaCl and split in three samples. Each ChIP was incubated for 12 h at 4 °C with 10 μl of antibody-coated paramagnetic protein G beads

![Figure 1](http://www.jbc.org/)

**FIG. 1.** p53 stability and activities in wild type and p53S18A thymocytes after IR. A, the protein levels of p53 in wild type and p53S18A thymocytes at various time points after exposure to 5 grays of IR. The time points and genotypes are labeled at the tops of the lanes. p53 and actin are indicated on the right. B, the percentile ratio of nonapoptotic thymocytes in wild type and p53S18A thymocytes treated with 5, 10, and 20 grays of IR to the nonapoptotic thymocytes from untreated controls. The mean values from three independent experiments are presented with error bars.

**TABLE I**

<table>
<thead>
<tr>
<th>Genes</th>
<th>Wild type</th>
<th>p53S18A</th>
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<tbody>
<tr>
<td></td>
<td>Expt. 1</td>
<td>Expt. 2</td>
</tr>
<tr>
<td>p21</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Mdm2</td>
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<td>1.6</td>
</tr>
<tr>
<td>14–3–3 ε</td>
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<td>6</td>
</tr>
<tr>
<td>TNF-α</td>
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<td>8</td>
</tr>
<tr>
<td>O/Eβ</td>
<td>14</td>
<td>11.5</td>
</tr>
<tr>
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<td>2</td>
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<tr>
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<tr>
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<td>Pig8</td>
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</tbody>
</table>
One μg Pab248 (22) was used per ChIP. Immune complexes were collected with a magnet, washed four times in 1% Nonidet P-40, 350 mM NaCl, 50 mM Tris, pH 8.0, resuspended in 125 μl of 1% SDS, and eluted by heating to 85 °C for 10 min. Cross-linking was reversed by incubation of the eluate for 6 h at 5° C. The samples were diluted with 125 μl of water containing 160 μg/liter proteinase K and incubated for 1 h at 50 °C. DNA was purified by extraction with phenol-chloroform and precipitated with isopropanol and glycogen. Quantitative PCR was performed on a PE5700 PCR machine using a SYBR Master Mix (Perkin Elmer). The PCR cycles were 50 °C for 2 min to digest dUTP-containing DNA and 95 °C for 10 min to activate Taq Gold polymerase, and then there were cycles of 95 °C for 15 s and 60 °C for 1 min repeated 40 times, except for the Mdm2 primers where the annealing temperature was 62 °C. The primer sequences are: Mdm2, forward primer 5'-GGTCAAGTTGGGACACGTCC-3' and reverse primer 5'-AGCGTTTAAATAACCCCAGCTG-3'; PERP distal promoter, forward primer 5'-CACCTATATAAGGCTATGTGTAGAGG-3' and reverse primer 5'-TACAATATCATATGGAGGAATCTAGTCTGTG-3'; and PERP proximal promoter, forward primer 5'-TCACAGGCTATTGGGATGTCC-3' and reverse primer 5'-AACACAGTGTAAGGAGCATGGCT-3'.

For ChIP analysis of histone acetylation at p53-dependent promoters, anti-acetyl histone H3 rabbit polyclonal antibody (Upstate Biotechnology, Inc.) was used to immunoprecipitate acetylated chromatin. The primers to detect the promoters of Mdm2, Noxa, and p21 in thymocytes before and after IR. Histone acetylation at the β-actin promoter was also analyzed as an internal control. The genotypes and time points are labeled on the top. Mdm2, p21, and β-actin are indicated on the right. Wt, wild type.

**RESULTS**

*p53-dependent Activities in Thymocytes after IR—*Mouse thymocytes undergo p53-dependent apoptosis after IR (23, 24). Therefore, to test the functions of p53 phosphorylation at Ser18 in regulating p53 apoptotic activities, we analyzed p53 stabilization and p53-dependent apoptosis in p53S18A thymocytes after IR essentially as described (25). The protein levels of p53 were induced similarly in p53S18A and wild type thymocytes after IR (Fig. 1A). However, p53-dependent apoptosis was significantly impaired in p53S18A thymocytes after IR, indicating that Ser18 phosphorylation was not required for p53 accumulation but was important to fully activate p53 apoptotic activities (Fig. 1B).

To better define the basis for the impaired p53-dependent apoptosis in p53S18A thymocytes after IR, we profiled the global gene expression in both wild type and p53S18A thymocytes before and after IR by microarray analysis. Scatter graphs from duplicate experiments (two sets of treated wild type and p53S18A thymocytes and two sets of untreated controls) show high reproducibility. Upon IR treatment, clear differences be-
tween wild type and p53S18A thymocytes were revealed with respect to overall transcriptional response to IR. In this context, mRNA levels of the known p53-inducible downstream genes p21, Perp, SNK, 14-3-3ζ, and tumor necrosis factor α were increased to considerably higher levels in wild type thymocytes than in p53S18A thymocytes after IR (Table I). However, the impacts of p53S18A mutation on p53-dependent gene expression appear to be promoter-specific, because a number of other known p53 downstream target genes, including Mdm2, Noxa, Bax, Apaf1, and Wig1, were similarly induced in p53S18A thymocytes as in wild type thymocytes after IR (Table I). The differential induction of a number of p53-dependent genes including p21, Mdm2, Noxa, Perp, cyclin G, and 14-3-3ζ in wild type and p53S18A thymocytes after IR was further confirmed by quantitative real time PCR analysis (Fig. 2A).

The promoter-specific effects of S18A mutation on the expression of p53 target genes could be due to the differential requirement of Ser18 phosphorylation in the recruitment of co-activators to the distinct p53-dependent promoters. Therefore, we employed a chromatin immunoprecipitation assay to analyze the histone H3 acetylation at two promoters of p53-dependent genes, Mdm2, Noxa, and p21, in wild type and p53S18A thymocytes with or without IR treatment. As an internal control, histone H3 acetylation at β-actin promoter was also analyzed. Histone acetylation of the Mdm2 promoter was increased to a similar extent in both wild type and p53S18A thymocytes after IR (Fig. 2C). Therefore, histone acetylation of the p21 promoter was reduced in p53S18A thymocytes after IR when compared with that of wild type thymocyte (Fig. 2C). The correlation between the expression levels of Mdm2, Noxa, and p21, and histone acetylation of their promoters suggests that Ser18 phosphorylation is important to recruit co-activators to some but not all p53-dependent promoters.

**p53 Induction in p53S18A MEFs after DNA Damage**—To define the roles of Ser18 phosphorylation in p53 responses to DNA damage in MEFs, p53 protein levels in p53S18A MEFs at different time points after IR and UV radiation were analyzed by Western blotting. Unexpectedly, we found that p53 was induced to higher peak levels in p53S18A MEFs than in wild type MEFs (Fig. 3, A and B). Because Mdm2-p53 interaction plays a major role in regulating p53 stability, we analyzed p53-Mdm2 interaction by co-immunoprecipitation assay in wild type and p53S18A MEFs at different time points after UV radiation (25). This analysis indicated that p53-Mdm2 interaction was disrupted in both wild type and p53S18A MEFs after UV radiation (Fig. 3C). Therefore, Ser18 phosphorylation was not required to disrupt p53-Mdm2 interaction after UV radiation. However, p53-Mdm2 interaction appeared to be relatively weaker in p53S18A MEFs than that in wild type MEFs at various time points after UV radiation, thus providing the potential basis for the higher protein levels of p53 in p53S18A MEFs after UV radiation. To further understand the basis for the reduced p53-Mdm2 interaction in p53S18A MEFs after UV radiation, we analyzed the induction of Mdm2 mRNA in p53S18A and wild type MEFs after UV radiation by quantitative real time PCR. In contrast to the findings that higher Mdm2 mRNA levels were detected in p53S18A thymocytes after IR, Mdm2 mRNA levels were significantly lower in p53S18A MEFs than in wild type MEFs after UV radiation (Fig. 2B). Mdm2 mRNA levels were also reduced in p53S18A MEFs after IR, indicating that the differential impacts of the S18A mutations on the Mdm2 expression in thymocytes and MEFs were not due to the distinct types of DNA damage (data not shown). The reduced Mdm2 induction in p53S18A MEFs could account for the higher levels of p53 accumulation in these cells after DNA damage. Induction of other analyzed p53-dependent genes was also reduced in
cell cycle arrest in p53S18A MEFs after UV radiation as described (19). The G1/S cell cycle arrest was significantly impaired in p53S18A MEFs after UV radiation, indicating that Ser18 phosphorylation is required for the activation of this p53 activity after DNA damage in MEFs (Fig. 4A). Consistent with this notion, p53-dependent induction of p21 was reduced in p53S18A MEFs after UV radiation (Fig. 2B). Phosphorylation of p53 at the N terminus was suggested to be involved in the nuclear retention of p53 (26). Therefore, one possibility for the impaired p53 activities in p53S18A MEFs after UV radiation was that p53S18A is mostly cytoplasmic. To test this notion, we analyzed the subcellular localization of p53 in MEFs after UV by immunochemical staining with anti-p53 antibody as described (3). Our analysis indicated that p53 accumulated in the nucleus of p53S18A MEFs after UV radiation (60 J/M²). Therefore, there was no apparent developmental defects. Because some p53-dependent responses to DNA damage were impaired in p53S18A mice, these mice might be prone to cancer. Therefore, we monitored the onset of tumorigenesis in more than 55 pairs of p53S18A and littermate or age-matched wild type controls, which are presently between 1 and 2 years old. No apparent increase in spontaneous tumorigenesis was observed in p53S18A mice, suggesting that S18A mutation did not significantly affect p53 tumor suppression activities. It remains to be seen whether challenge of p53S18A mice with carcinogens will reveal enhanced tumor susceptibility or other hidden phenotypes.

**DISCUSSION**

To investigate the functions of Ser18 phosphorylation in regulating p53 stability and activity, we analyzed the p53 responses to various types of DNA damage in a number of primary cell types, including MEFs, thymocytes, and ES cells (17). These studies demonstrated that Ser18 phosphorylation plays important roles in regulating p53 stability in response to genotoxic stresses in different cell types. In p53S18A ES cells, we previously showed a delayed and reduced p53 induction after DNA damage (17). However, here we show that the maximum levels of p53 induction induced by IR are similar in wild type and p53S18A thymocytes. In addition, higher than normal levels of p53 proteins accumulate in p53S18A MEFs after UV radiation, probably because of weaker interaction between p53 and Mdm2. The difference in p53 stabilization and acetylation in p53S18A ES cells and fibroblasts after UV radiation suggests that regulation of p53 is atypical in ES cells, as suggested by Aladjem et al. (18). Therefore, it is important to study the effects of p53 phosphorylation site mutants in various primary cell types in order to draw conclusions on the in vivo function of

**Fig. 5. ChIP analysis of DNA binding of p53 to p53-dependent promoters in wild type and p53S18A MEFs 18 h after UV radiation (60 J/M²).** Shown are the results of quantitative PCR analysis of the percentage of promoters of p53-dependent genes Mdm2 (A), p21 (B), and Perp (C) bound by p53 in wild type (Wt) and p53S18A MEFs 18 h after UV radiation. The mean values from three independent experiments are presented with error bars.
the phosphorylation event. In this context, during our studies of the Ser^{18} phosphorylation site mutant, we analyzed the effects of S23A mutation on p53 stabilization in ES cells, MEFs, and thymocytes after DNA damage. Our results lead to the conclusion that the S23A mutation had no effect on p53 stabilization after DNA damage in all three primary cell types analyzed (25).

The normal or higher than normal levels of p53 induction in p53^{S18A} MEFs and thymocytes after DNA damage highlight the importance of Ser^{18} phosphorylation in activating p53 functions. The findings that p53-dependent cell cycle G1 arrest and apoptosis are impaired in p53^{S18A} cells after DNA damage indicate that Ser^{18} phosphorylation is important for the activation of p53 activities after these genotoxic stresses. The impaired p53 activities in p53^{S18A} cells after DNA damage are not due to abnormal subcellular location of p53 after DNA damage, because p53 accumulated similarly in the nucleus of wild type and p53^{S18A} cells after DNA damage. The impaired p53 activities are also not due to defective sequence-specific DNA-binding of p53^{S18A} to p53-dependent promoters because p53 binds to a number of p53-dependent promoters normally in p53^{S18A} cells after DNA damage. The greatly reduced acetylation of p53 to the C terminus in p53^{S18A} MEFs after UV radiation might account for the impaired p53 activities, because these acetylation events were shown to be required to recruit transcriptional co-activators to p53-dependent promoters (27, 28). Our findings also indicate that p53 acetylation at the C terminus is not required to activate the sequence-specific DNA binding activities of p53, a conclusion consistent with several published studies (27, 28).

Another novel finding from our studies is that the roles of Ser^{18} phosphorylation in regulating the transcription of p53 target genes appear to be promoter-specific. In this context, although the induction of many p53-dependent genes was impaired in p53^{S18A} thymocytes after IR, induction of some p53-dependent genes was normal in p53^{S18A} thymocytes after IR when compared with those in wild type thymocytes after IR. It is possible that the unaffected promoters, such as Mdm2 promoter, contain DNA-binding motifs bound by other transcriptional factors, which function redundantly with p53 in the recruitment of the transcriptional machinery. In addition, this promoter-specific role may sometimes depend on the cell types, for example, the induction of Mdm2 is enhanced in p53^{S18A} cells after DNA damage. The greatly reduced acetylation of p53 to the C terminus in p53^{S18A} MEFs after UV radiation might account for the impaired p53 activities, because these acetylation events were shown to be required to recruit transcriptional co-activators to p53-dependent promoters (27, 28). Our findings also indicate that p53 acetylation at the C terminus is not required to activate the sequence-specific DNA binding activities of p53, a conclusion consistent with several published studies (27, 28).

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Cell Type- and Promoter-specific Roles of Ser\textsuperscript{18} Phosphorylation in Regulating p53 Responses

Connie Chao, Manfred Hergenhahn, Matthias D. Kaeser, Zhiqun Wu, Shin'ichi Saito, Richard Iggo, Monica Hollstein, Ettore Appella and Yang Xu

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