c-Abl Stabilizes p73 by a Phosphorylation-augmented Interaction

Kelvin K. C. Tsai and Zhi-Min Yuan

Department of Cancer Cell Biology, Harvard School of Public Health, Boston, Massachusetts 02115

ABSTRACT

The proapoptotic function of c-Abl is in part mediated by its functional interaction with p73, a p53 homologue. Although it has been shown that c-Abl-mediated p73 activation in response to genotoxic stress is associated with an increase of p73 protein levels, the underlying mechanism remains unclear. We show here that c-Abl increases the cellular p73 abundance through a mode of posttranslational regulation. Analogous to its functional activation of p73, the kinase activity is essential for c-Abl to up-regulate p73 protein levels. Analysis of phosphorylation-resistant mutants of p73 reveals that the effect of c-Abl is mediated by its direct phosphorylation on the p73 protein. Consequence to the phosphorylation is a marked increase of the association between c-Abl and p73 via the binding of tyrosine-phosphorylated p73 to the c-Abl Src homology 2 domain. Of functional importance of this phosphorylation-induced interaction in p73 stabilization is the demonstration that expression of a c-Abl SH2 domain peptide, which impedes phosphorylation-dependent association, results in an almost complete abrogation of c-Abl-dependent p73 accumulation. Importantly, expression of the c-Abl SH2 domain peptide also leads to an efficient inhibition of cisplatin-induced accumulation of endogenous p73, highlighting the biological significance. In keeping with its retained phosphorylation sites, the NH2-terminal truncated (ΔN) isoforms of p73, which are antiapoptotic, are also phosphorylated and stabilized by c-Abl, suggesting a possibility that c-Abl contributes to either pro- or antiapoptotic process depending on the expression profile of p73 isoforms.

INTRODUCTION

c-Abl is an Src-like nonreceptor PTK ubiquitously expressed (1). The c-Abl PTK is localized both in the nucleus and in the cytoplasm, and its kinase activity is tightly regulated through different mechanisms (2, 3). Cytoplasmic c-Abl is associated with the F-actin through the COOH-terminal actin-binding domain and may influence the cytoskeleton locally. Recent studies suggest that c-Abl and its homologue Arg may also play a role in neuronal development (1). In comparison, nuclear c-Abl is involved in the regulation of cell cycle and cellular fate decisions in cellular response to DNA damage. Genotoxic stress, such as ionizing radiation or oxidative stress (4, 5), has been shown to induce an activation of the nuclear c-Abl. DNA damage sensor proteins, including ATM and DNA-dependent protein kinase, phosphorylate and activate c-Abl in response to DNA damage. The other nuclear partners of c-Abl include Rb, p53, and p73, proteins that are involved in the regulation of growth and apoptosis (6).

p73 shares strong structural and functional similarities with p53, such as the ability to activate p53-responsive genes and to induce apoptosis (7). Like p53, p73 contains a transactivation domain, a DNA-binding domain, and an oligomerization domain. Unique to p73, however, is that there are several distinct forms of p73, differing either at the COOH terminus or at the NH2 terminus because of alternative splicing (8). An isoform of p73 truncated in the NH2 terminus has recently been identified in murine developing neurons and human tissues (9, 10). The ΔN isoform of p73 lacks the transactivation domain and may serve to counteract the proapoptotic function of p53 or TA forms of p73 (7). Analogous to p53, p73 responds to certain types of genotoxic agents including ionizing radiation and DNA-damaging agents. The activation pathway of p73 in response to genotoxic stress is distinct from that of p53 and is linked to the c-Abl tyrosine kinase, which phosphorylates and activates p73 (11, 12). The increase in the abundance of p73 protein has been reported to associate with increased apoptotic activity of p73. DNA damage also induces p300-mediated acetylation of p73, which activates the apoptotic function of p73 (13). Interestingly, the acetylation of p73 is also dependent on c-Abl-mediated phosphorylation of p73, highlighting the critical role of c-Abl in the regulation of DNA damage-induced p73 activation.

Despite the substantial sequence homology shared by p73 and p53, the stability of p73 is controlled by mechanisms distinct from that of p53. p53 is mainly degraded through proteasome-dependent proteolysis, in which MDM2 plays a major role via its E3-ligase activity that is critical for p53 nuclear export and degradation (14). In contrast, much less is known about the regulation of p73 stability. Although binding to p73, MDM2 fails to target p73 for nuclear export or degradation (15, 16). In contrast to p53, which is readily ubiquitinated by MDM2, p73 exhibits a much lower tendency for ubiquitination. Indirect evidence obtained from the effects of proteasome inhibitors suggest that the additional COOH-terminal extension of p73α isoforms regulates its proteasome-dependent degradation (17, 18). The small ubiquitin-like modifier 1 (SUMO-1)-modification of the COOH-terminal Lys627 residue of p73α, which is not present in p73β, might contribute to the preferential degradation of the α isoform (18). Nevertheless, it is still unclear whether the proteasome pathway is the primary degradation route of p73α. How the stability of other p73 isoforms is regulated is also poorly understood.

With the fact that cellular abundance of p73 is increased in c-Abl-mediated apoptotic response to DNA damage but the underlying mechanism remains unclear, we used a system in which constitutively active c-Abl is expressed to study c-Abl-mediated up-regulation of p73. Our results show that c-Abl increases cellular protein levels of p73 in a kinase-dependent manner. The c-Abl-mediated effect on the p73 abundance is predominantly dependent on the phosphorylation of p73 Tyr99, but the phosphorylation of other tyrosine residues may also have a contributing role. We further provide evidence to show that phosphorylated p73 interacts with the SH2 domain of c-Abl. The induced close proximity of c-Abl and p73 may protect p73 from degradation, thereby increasing its protein abundance in cells. The biological significance underlying this SH2-mediated interaction is demonstrated when the c-Abl SH2 peptide, expressed as a miniprotein, abolishes the accumulation of endogenous p73 in response to cisplatin exposure.
MATERIALS AND METHODS

Cell Culture and Plasmids. 293T, MCF-7, U2OS, and COS-1 cells were maintained in MEM supplemented with 10% FBS. HCT116 (p53−/−) cells (provided by Dr. Bert Vogelstein, Johns Hopkins University, Baltimore, MD) were maintained in McCoy’s 5A medium supplemented with 10% FBS and antibiotics. pcDNA-3 (Invitrogen) and pEGFP-C1 (Clontech) are mammalian expression vectors under the control of the cytomegalovirus promoter and carries a FLAG- or GFP-coding sequence upstream from its cloning sites. The expression vector encoding for FLAG-p73α, FLAG-p73β, and GFP-c-Abl (ib isoform) were constructed by standard techniques and were verified by sequencing.

Cloning of Truncated p73 Isoforms and Various p73 and c-Abl Mutants. Primers 5’-CCGGATCCGCCGCTACTAGTATGACTCTGAGG-3’ and 5’-GTCTAGAGCTAGGCTGGATAATGGAGCGTGG-3’ were used to amplify the ΔNp73α and ΔNp73β from TA forms of p73α and p73β present on the pcDNA-3 vector. Primers 5’-CCGGATCCGCCGCTACTAGTATGACTCTGAGG-3’ and 5’-GTCTAGAGCTAGGCTGGATAATGGAGCGTGG-3’ were used to amplify the sequence encoding the c-Abl SH2 domain peptide from full-length c-Abl present on the pcDNA-3 vector. Standard two-step PCR procedures were performed to construct the p73 mutants bearing various tyrosine-to-phenylalanine mutations. The amplicons were purified and digested with BamHI and XbaI and were cloned into pcDNA-3 vector. The kinase inactive K290R mutant of c-Abl and the DNA-binding deficient mutant R292H of p73β were generated by PCR-based methods, as described previously (19).

Transfection and Immunoblot. Cells seeded at a density of ~70% confluence were transfected with indicated amounts of expression vectors by a calcium phosphate precipitation method (for 293T cells) or with LipofectAMINE Plus reagent (Life Technologies, Inc.). In each experiment, suitable amounts of pEGFP-C1 were cotransfected with each construct to determine the transfection efficiency. Cells were harvested 36 h posttransfection and lysed in 200 μl of RIPA buffer [10 mm Tris-HCl (pH 7.5), 1 mm EDTA, 150 mm NaCl, 1 mm DTT, 10% glycerol, 0.2 mm phenylmethylsulfonyl fluoride, 1% NP-40, 0.01% SDS, and 1× protease inhibitors cocktail] by incubating on ice for 1 h, and the extracts were centrifuged at 13,000 rpm for 15 min to remove cell debris. After addition of 5× SDS loading buffer, the samples (20 μg) were boiled at 95°C for 5 min and were subjected to SDS-PAGE. Proteins were then transferred onto a nitrocellulose membrane (Schleicher and Schuell) and probed with the indicated primary antibodies and the horseradish peroxidase-conjugated affinity-purified goat antirabbit IgG. Bound proteins were visualized with an enhanced chemiluminescence detection system (Perkin-Elmer).

Northern Blot Analysis. Total RNA was extracted from cells by the RNeasy Mini kit (Qiagen). RNA (10 μg) was separated on a 1% formaldehyde agarose gel, transferred onto a nylon membrane (Stratagene) and was washed twice with 2× SSC and 0.1% SDS and once with 0.1× SSC and 0.1% SDS at room temperature.

Subcellular Distribution Assay. U2OS cells were grown in 60-mm dishes and were transfected with indicated plasmids. Cells were washed with cold PBS 36 h after transfection, fixed with 4% paraformaldehyde, and permeabilized with ice-cold 0.2% Triton X-100 for 5 min. The slides were then incubated with anti-FLAG antibody (M2, Sigma) at 37°C for 1 h. After washing with PBS three times, the dishes were incubated with secondary antibody (Texas Red-X goat antimouse IgG; Molecular Probes) and DAPI (10 μg/ml; Sigma) for 1 h. After PBS washing, the dishes were mounted with Fluoro- mount-G (Southern Biotechnology Associates) containing 2.5 mg/ml n-propyl gallate (Sigma) and were examined with a fluorescence microscope (excitation wavelength, 490 nm). Images were acquired with a CCD camera (Zeiss).
c-Abl Increases p73 Abundance in a Kinase-dependent Manner. A major challenge in dissecting c-Abl-mediated cellular stress response has been its low kinase activity and lack of the stimulus that can selectively activate c-Abl. To circumvent this limitation, we recently developed vectors that express constitutive kinase-active c-Abl (c-Abl[KA]) proteins (20). These plasmids were used here to study the mechanism of c-Abl-mediated p73 up-regulation without external stimulus or genotoxic stress, which often activates multiple pathways. The abundance of two major TA isoforms of p73, p73α and p73β, expressed from Flag-tagged plasmids, increased significantly in the 293T cells that were cotransfected with a c-Abl(KA) expression vector when compared with that in the control vector-expressing cells (Fig. 1 A, top panel, Lanes 2 and 5). To determine whether this effect is kinase dependent, we tested the kinase-inactive mutant c-Abl [c-Abl(KD)], in which the Lys290 critical for ATP binding was mutated to arginine, for its ability to alter p73 levels. The result shows that inactivation of c-Abl kinase activity resulted in a complete loss of this effect (Fig. 1 A, top panel, Lanes 1–3 versus 4–6). Similar results were also found in H1299 cells and COS1 cells (data not shown).

Subcellular Localization or Transcription Level of p73 Is Not Affected by c-Abl. The c-Abl-mediated induction of p73 levels could occur at levels of either message RNA or protein. Cellular abundance of p73 mRNA was, therefore, determined to distinguish these possibilities. Northern analysis of p73 transcript did not detect a significant difference in the presence or absence of c-Abl, indicating a posttranscriptional mechanism for the c-Abl-mediated regulation of p73 abundance (Fig. 2A). In light of the finding that MDM2-mediated nuclear export of p53 contributes to the subsequent proteolysis of p53 by pro tease (14), we asked whether c-Abl could increase p73 protein stability by affecting p73 distribution using immunofluorescence analysis. When stained with an antibody against FLAG, the cells transfected with Flag-tagged p73β plus pEGFP-C1 empty vector exhibited intense staining of the nucleus, which was visualized by DAPI staining, indicating nuclear localization of p73 (Fig. 2B, top panel). Coexpression of the c-Abl(KA) or c-Abl(KD) did not significantly alter the nuclear distribution of p73β (Fig. 2B, middle and bottom panels). These data exclude the possibility that the c-Abl-mediated increase of p73 abundance is regulated by an alteration of p73 subcellular localization.

c-Abl-mediated p73 Stabilization Involves a Direct Phosphorylation of the p73 Protein. The kinase-dependent p73 stabilization suggests the possibility that the effect of c-Abl is mediated by its direct phosphorylation of p73. To address this possibility, we tested a previously identified phosphorylation mutant p73Y(Y99F; Ref. 11) for its response to c-Abl. When compared with wild-type p73, the p73(Y99F) mutant appeared to be resistant, albeit not completely, to c-Abl-mediated induction (Fig. 3B, Lane 3 versus Lane 4). The partial response of the p73(Y99F) mutant suggests the presence of additional phosphorylation sites. Anti-phosphotyrosine immunoblotting analysis, indeed, revealed an apparent, but significantly reduced, phosphorylation of the p73Y99F mutant (Fig. 3A, Lane 5). Inspection of the amino acid sequence of p73 identified two additional tyrosine residues, Tyr121 and Tyr240, which have the surrounding sequence conforming to the consensus YXXP motif for c-Abl PTK (22). The corresponding Y to F mutants were then generated for testing their response to c-Abl. The result indicates a partial resistance of the mutants to c-Abl-dependent stabilization (Fig. 3B, Lane 5 versus 6).
TYROSINE PHOSPHORYLATION-DEPENDENT p73 STABILIZATION

The Binding of c-Abl to p73 Is Significantly Enhanced by Its Kinase Activity. Our previous study has shown that the SH3 domain of c-Abl binds to the homo-oligomerization domain of p73 in a kinase-independent manner (11). Tyrosine phosphorylation of p73 would predict an additional binding of p73 to c-Abl that is an SH2 domain-containing protein. To test this possibility, we cotransfected 293T cells with vectors expressing p73β(R292H) and GFP-tagged c-Abl(KA) or c-Abl(KD). The DNA binding-deficient p73β(R292H) was used to minimize the potential cell cycle arrest or proapoptotic functions of the wild-type protein. Cells were harvested 36 h posttransfection and the protein extracts were subjected to pull-down assay using GST-Crk. Both the c-Abl(KA) and c-Abl(KD) proteins were efficiently brought down because of the strong binding of the Crk SH3 domain to proline-rich motifs of c-Abl (Fig. 4, A, top panel, Lane 2 versus Lane 3). To further substantiate this SH2-mediated binding, we tested whether the c-Abl SH2 domain, when expressed as a miniprotein, could modulate the binding of p73 to c-Abl. Significantly, IP-Western analysis indicated that coexpression of the c-Abl SH2 peptide resulted and 7 versus 8). Simultaneous mutations of all of the three-tyrosine residues almost completely abrogated the c-Abl-mediated stabilization effect (Fig. 3B, Lanes 9 versus 10). Taken together, it appears that phosphorylation of p73, mainly on Tyr-99, and Tyr-121 and Tyr-240 to a lesser extent, is essential to c-Abl-mediated p73 stabilization.

Fig. 3. Involvement of multiple p73 tyrosine phosphorylation sites in the regulation of its abundance by c-Abl. A, plasmids (1.0 μg) encoding wild-type p73α or p73α(Y99F) was transfected into 293T cells along with 1.0 μg of c-Abl(KA), c-Abl(KD), or empty vector. Total lysates were immunoprecipitated with the anti-FLAG antibody. The precipitates were analyzed by Western blot using antiphosphotyrosine (p-Tyr) 4G10 or anti-FLAG antibodies. The experiments were repeated, and a representative blot was shown. The values of the densitometry measurements represent the means from duplicated experiments.

domain fusion protein was incubated with cell lysates derived from p73β- and c-Abl(KA)- or c-Abl(KD)-expressing cells. GST fusion proteins of c-Abl SH3 or MDM2 NH2-terminal deletion mutant were included as controls. Interestingly, the c-Abl SH2 domain, indeed, exhibited a strong binding to p73 in c-Abl(KA) (Fig. 4B, top panel, Lane 2), but to neither vector- (Lane 1) nor c-Abl(KD) (Lane 3) expressing cells. In comparison, the c-Abl GST-SH3 domain-mediated binding was not kinase dependent (Fig. 4B, top panel, Lanes 4–6). To further substantiate this SH2-mediated binding, we tested whether the c-Abl SH2 domain, when expressed as a miniprotein, could modulate the binding of p73 to c-Abl. Significantly, IP-Western analysis indicated that coexpression of the c-Abl SH2 peptide resulted
in significantly reduced binding of c-Abl to p73, whereas an irrelevant peptide that corresponded to c-Abl COOH-terminal region (aa residues 969-1145) did not exhibit any apparent effect under the same condition (Fig. 4C, second panel, Lanes 3 versus 4), supporting the hypothesis that the phosphorylation-enhanced association is mediated by the binding of p73 to the SH2 domain of c-Abl.

The Tyrosine Phosphorylation-mediated Stabilization Is Responsible for DNA Damage-induced p73 Accumulation. The fact that both the increase of p73 abundance and the binding of p73 to c-Abl are kinase dependent led us to ask whether there was any causal relation between the increased binding and the stability. Disruption of the phosphorylation-mediated interaction between p73 and c-Abl, if it played any role, would abrogate the ability of c-Abl to stabilize p73. With the finding that expression of the c-Abl SH2 domain resulted in impaired binding of p73 to c-Abl, we assessed the effect of the SH2 domain on p73 stability. Remarkably, the ability of c-Abl to increase p73 abundance was abolished by the c-Abl SH2 domain peptide in a dose-dependent manner (Fig. 5A, top panel, Lanes 3–6). In contrast, coexpression of the c-Abl COOH-terminal peptide (aa 969-1145) did not have any detectable effect (Fig. 5A, top panel, Lane 7), supporting the hypothesis that the induced interaction between the SH2 domain of c-Abl and tyrosine-phosphorylated p73 is responsible for the kinase-dependent p73 stabilization. Having used the kinase-active c-Abl-expressing system to demonstrate that c-Abl stabilizes p73 via a mode of phosphorylation-dependent regulation, we asked whether the similar mechanism is responsible for DNA damage-induced p73 accumulation at the level of endogenous protein. Again, the c-Abl SH2 domain was used to interfere with the tyrosine phosphorylation-induced p73-c-Abl interaction. Simian COS-1 cells, which express detectable p73 (21), were transfected with a control vector or with various amounts of Flag-c-Abl SH2 peptide (Fig. 5B). The cells were exposed to cisplatin (25 μM) at 24 h posttransfection and were harvested at 24 h after addition of the drug for Western analysis. Consistent with the published result (12), anti-p73 immunoblotting analysis revealed cisplatin-induced p73 accumulation in the vector-expressing cells (Fig. 5B, top panel, Lanes 1 versus 2). Significantly, the ability of cisplatin to induce p73 protein levels was compromised by the expression of the c-Abl SH2 peptide in a dose-dependent manner (Fig. 5B, Lanes 3–5). Together, it appears that c-Abl-dependent tyrosine phosphorylation is responsible for the DNA damage-induced p73 accumulation.

The Protein Levels of ΔN Isoforms of p73 Are Also Induced in Kinase-active c-Abl-expressing or Cisplatin-treated Cells. The ΔN isoforms of p73 exhibit antiapoptotic functions by counteracting p53 and TAp73 transactivation activities in a dominant-negative fashion (10). It was of interest to examine whether c-Abl could also affect the protein stability of ΔN isoforms of p73 because the phosphorylation sites are retained in the truncated proteins. To test this possibility, we subjected the ΔN version of both p73α and p73β to analysis for their response to c-Abl-mediated stabilization. In agreement with the retained phosphorylation sites, the cellular abundance of ΔNp73α and ΔNp73β in c-Abl(KA)-, but not in c-Abl(KD)-expressing cells was markedly increased (Fig. 6A). To examine the biological relevance of this observation, we exposed TA or ΔN isoforms of p73-expressing cells to cisplatin. Western analysis indicated that the protein levels of both TA and ΔN isoforms were significantly elevated in cisplatin-treated cells. The opposite activities of TA and ΔN isoforms of p73 in apoptotic cell death would predict that c-Abl might have either pro- or antiapoptotic functions, depending on which isoform is predominantly expressed. To test this possibility, we transfected c-Abl(KA) along with TA or ΔN isoforms of p73α into HCT116 (p53−/−) cells. As shown in Fig. 6C, coexpression of TA-p73α, but not of ΔNp73α, with c-Abl(KA) resulted in a significant increase in the number of apoptotic cells, consistent with the notion that c-Abl differentially regulates cell growth depending on the expression of TA or ΔN isoform of p73.

DISCUSSION

Despite substantial sequence homology shared by p73 and p53, the stability of the two proteins appears to be regulated through distinct mechanisms. p53 is mainly degraded by the MDM2-mediated pathway (14). Interference of MDM2-dependent p53 destruction is believed as the principle mechanism for DNA damage-induced p53 accumulation. In contrast, MDM2 plays little role in the regulation p73 stability (15, 16), and how p73 is induced in response to DNA stress is less clear. Using a system that expresses constitutive kinase active c-Abl, we demonstrate that p73 is stabilized by c-Abl via a mode of phosphorylation-induced interaction, in which the phosphorylated tyrosine residues of p73 bind to the SH2 domain of c-Abl, resulting in profound increase of c-Abl/p73 association. The close apposition induced by this interaction may prevent p73 from access to factors involved in its degradation, thereby increasing its abundance. Support of this notion comes from the finding that disruption of this phosphorylation-induced interaction by the expression of the c-Abl SH2 peptide abrogates c-Abl-dependent p73 stabilization. The biological relevance of the finding is highlighted by the demonstration that the binding of p73 to the SH2 domain of c-Abl is kinase dependent and is required for c-Abl-dependent stabilization.
c-Abl induces apoptosis in TAp73- but not in Np73/H9262 means from duplicated experiments. Compared with levels in the absence of c-Abl coexpression. The values represent the were deduced from densitometer analysis and were expressed as fold of increase as blot using the indicated antibodies. Relative amounts of various isoforms of p73 proteins were cotransfected with 1.0 g of c-Abl(KA) or with a control vector into 293T cells. The cells were harvested 36 h after transfection and analyzed by Western A, c-Abl stabilized various isoforms of p73. Plasmids (1.0 g) encoding TA or DN isoforms of p73 were cotransfected with 1.0 g of c-Abl(KA) or with a control vector into 293T cells. The cells were harvested 36 h after transfection and analyzed by Western blot using the indicated antibodies. Relative amounts of various isoforms of p73 proteins were expressed as fold of increase as means and SEs from three independent experiments.

B, cisplatin induced stabilization of both TA and DN isoforms of p73. HCT116 (p53-/-) cells were transfected with 0.25 g of TA-p73α or DNp73α, treated with 25 mM cisplatin for 24 h and harvested for immunoblotting. C, c-Abl induces apoptosis in TA-p73α but not in DNp73α expressing cells. Cells with sub-G1 DNA contents were counted (see “Materials and Methods”) and the results were expressed as means and SEs from three independent experiments.

that this mechanism is also applicable to the cisplatin-induced endogenous p73 accumulation.

Some tyrosine kinases preferentially phosphorylate peptides recognized by their own SH2 domains (22). In vitro analysis has shown that c-Abl SH2 domain preferentially binds to a synthetic peptide phosphorylated by its own protein kinase activity (22). Recently, the nuclear transcription factor c-Jun, after phosphorylation by c-Abl on Tyr170, could further interact with c-Abl via the SH2 domain of c-Abl (26). Similar intriguing interaction has been demonstrated between c-Abl SH2 domain and the RNA polymerase II COOH-terminal repeated domain (27), which allows the processive phosphorylation of its multiple tyrosine residues. Our results corroborated these findings by showing the interaction between c-Abl SH2 domain and phospho-tyrosine residues of p73.

Multisite phosphorylation is a common feature of many protein kinase substrates, which may enable events such as multisite docking interactions, integration of different kinase pathways, subcellular localization, protein activity, and the response to regulators (28, 29). Recent evidence also points to multisite phosphorylation as an important way of tuning protein stability and degradation. The F-box protein Cdc4 captures the cyclin-dependent kinase inhibitor Sic1 for ubiquitination and subsequent degradation only when six or more sites of Sic1 are phosphorylated (29). The c-Abl tyrosine kinase phosphorylates p73 on tyrosines 99 as well as on tyrosines 121 and 240, albeit to a lesser extent. It is probable that the multisite phosphorylation of p73 by c-Abl generates a specific phosphotyrosine motif to which the SH2 domain exhibits high affinity. Consistent with this notion is the substantially induced binding of p73 to c-Abl in the kinase-active c-Abl-expressing cells. An additional line of evidence to support this model is the abrogation of this induced interaction by the expression of the c-Abl SH2 peptide. The enormously increased interactions on phosphorylation might protect p73 from degradation. Additional investigations are still required to address this issue.

Of interest is the finding that DNp73, which is antiapoptotic, is also stabilized by c-Abl, suggesting an antiapoptotic function to the c-Abl tyrosine kinase. Both c-Abl and p73 have been associated with neural development. In developing neurons in mice, p73 is primarily present as truncated forms that carry out antiapoptotic functions (10). A plausible corollary is that this mechanism is also applicable to the cisplatin-induced endogenous p73 accumulation.

REFERENCES
c-Abl Stabilizes p73 by a Phosphorylation-augmented Interaction
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