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# p73 and p63 protein stability: the way to regulate function?

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**Abstract**

While the p53 homologue p73 has been found to be involved in tumorigenesis, the molecular mechanisms involved in this function are still not fully evident. The presence of two distinct promoters allows the formation of two proteins with opposite effects: while TA-p73 shows pro-apoptotic effects, ΔN-p73 has an evident anti-apoptotic function. The relative expression of the two proteins is in fact related to the prognosis of several cancers. Since both p73 and p63, the other member of the same family, share the ability to interact with each other, it is important to understand the mechanisms that control the degradation and stability of both proteins, and their relative isoforms. p73 and p63 stability is regulated not only by protein modifications (phosphorylation, acetylation) but also by its degradation in the proteasome. To this end, the interaction with Mdm2, p300/CBP, and SUMO-1 are discussed in details.


## 1. Introduction

The p53 protein plays an important role in preventing tumour development and a vast majority of human cancers show evidence for loss of p53 function [1]. p53 is activated in response to cellular stress such as DNA damage or oncogene activation, and functions to inhibit cell growth by causing cell-cycle arrest or apoptosis. Several previous observations suggested the presence of homologues of p53. For example, the regulation of p53 targets was observed independent of p53 regulation [2]. Only recently, however, two homologues of p53, called p63 [3] and p73 [4], have been identified (for review see [5,6]). Since then, an impressive body of data has expanded our knowledge on their function (Fig. 1).

Although p73 and p63 also have an apoptotic activity [7–10] (see also Fig. 2), and are able to activate the p53 target genes, p73 and p63 are rarely mutated in tumours (see for review [6]). However, some tumours express abnormal splicing variants [11] and show an interaction among p73 and polymorphisms at codon 72 of p53 [12], suggesting complex interactions among the members of the family [13,14]. More specifically, the two isoforms, TA-p73 and ΔN-p73, show pro-apoptotic and anti-apoptotic properties, respectively (Fig. 3), with the ΔN-p73 protein being controlled at the promoter level by the TA-p73 protein. This indicates that the tumour-suppressor function of TA-p73 has to be very finely tuned by a dominant negative regulatory loop exerted by ΔN-p73 [13]. Interestingly, this regulatory loop is also activated by p53 itself, with ΔN-p73 being also able to inhibit the function of p53, as well as that of TA-p73 [13]. This regulatory loop is somewhat reminiscent of that of Mdm2. Figure 4 shows both the p53/TA-p73 responsive element on the promoter of ΔN-p73 (Fig. 4A), as well as the regulatory loop exerted by ΔN-p73 (Fig. 4B). Expression of the ΔN-p73 isoforms seems to be linked to poor prognosis in cancer [15,16]. Still, mice deficient for p73 [17] or p63 [18,19] present no spontaneous tumours but defects in neuronal or epidermal development, respectively. This is in keeping with the genetic defect found in patients with p63 mutations [20]. These differences in function among the members of the p53 family (see Fig. 3)

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*Abbreviations:* TA-, full length transactivating isoforms; ΔN-, amino-terminal deleted isoforms, lacking the transactivation domain; TA, transactivation domain; DBD, DNA binding domain; OD, oligomerization domain; PR, proline-rich domain; SAM, sterile alpha motif; TI, transinhibitory domain; NES, nuclear exporting signal; SUMO, small ubiquitin-like modifier; PML, promyelocytic leukaemia protein; SAPK, stress activated protein kinases; JNK, Jun kinase.

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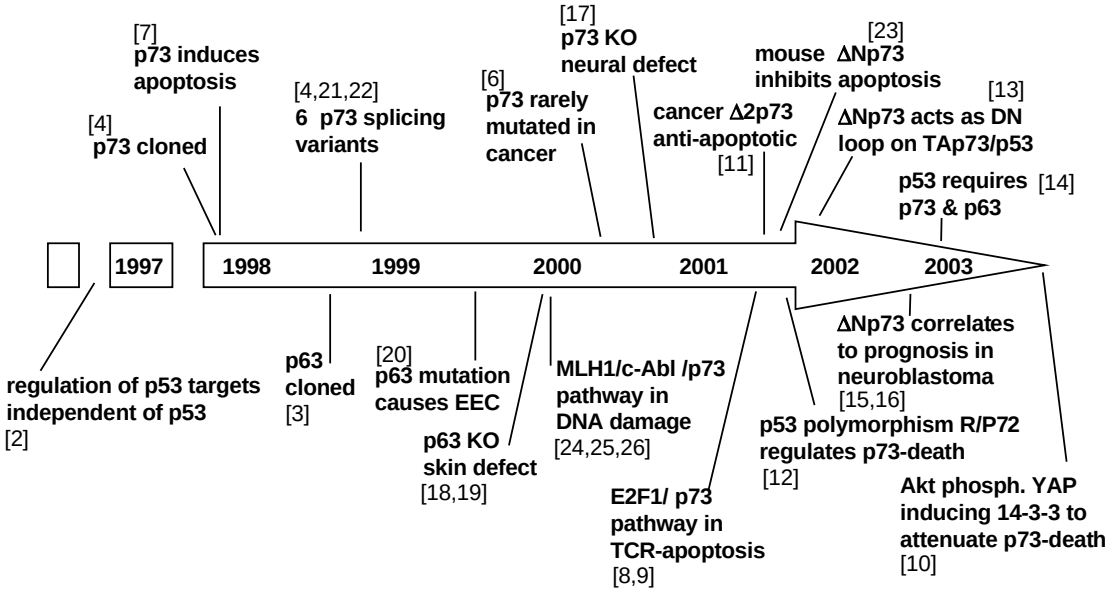


Fig. 1. Timeline of the p53 family. Since the discovery of p73 and p63, a large body of evidence has demonstrated the involvement of p73 in DNA damage as well as in development. Major references are reported.

are quite surprising in light of the 65% of amino acid identity between the DNA binding domain of the three proteins. Indeed, explanations for the observed functional differences can be found in the domains outside of the DNA binding domain. Both p63 and p73 present a wide array of splicing variants (α, β, γ for p63, and α, β, γ, δ, ε, ζ for p73) [4,21,22], and a second alternative promoter which generates a truncated form lacking the transactivation domain (ΔN-p73, as indicated above) [13,23]. The α forms of each of the proteins contain sterile α motifs (SAM domain) which surely play a role in the specific activities of p63 and p73.

The tumour suppressor p53 is a labile protein whose activity is regulated by its degradation and its level of stability. On the contrary, the regulation of the stability of p63 and p73 is still poorly understood, and above all, no degradation pathway has been clearly described yet. The p73 protein undergoes several post-translational modifications [24–28] that regulate the stability and the transcriptional activity of the protein (see Fig. 4C). A recent report [29] suggests a model of intramolecular and inter-splicing-variant interactions, through an internal inhibition domain. This model may allow us to better understand previous studies on p73 and p63 stability.

## 2. p73 and Mdm2

A crucial regulator for p53 is the cellular protein Mdm2, which is able to bind p53's transactivation domain and

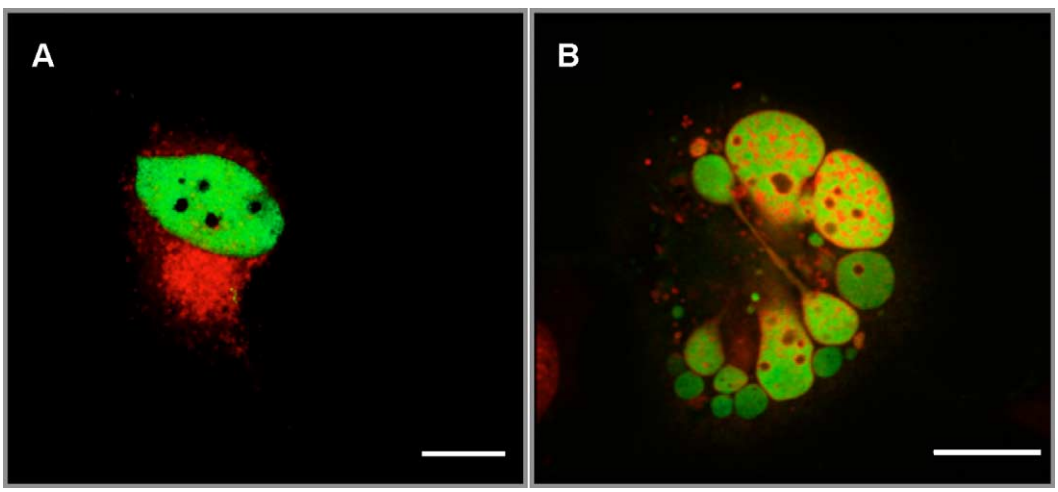


Fig. 2. p73 is a nuclear protein. Subcellular localization of p73 (TA-isoform) in healthy cells (A) and in apoptotic cells (B). In both cases, p73 is nuclear. The protein is identified by the green-fluorescent protein (GFP; green), the red stain indicates the mitochondria (TMRE, panel A), or the fragmenting DNA (propidium iodide, panel B). The p53 negative Saos-2 cells are originated from an osteosarcoma tumor. Apoptosis was induced with cisplatin. Bar indicates 10 μm.

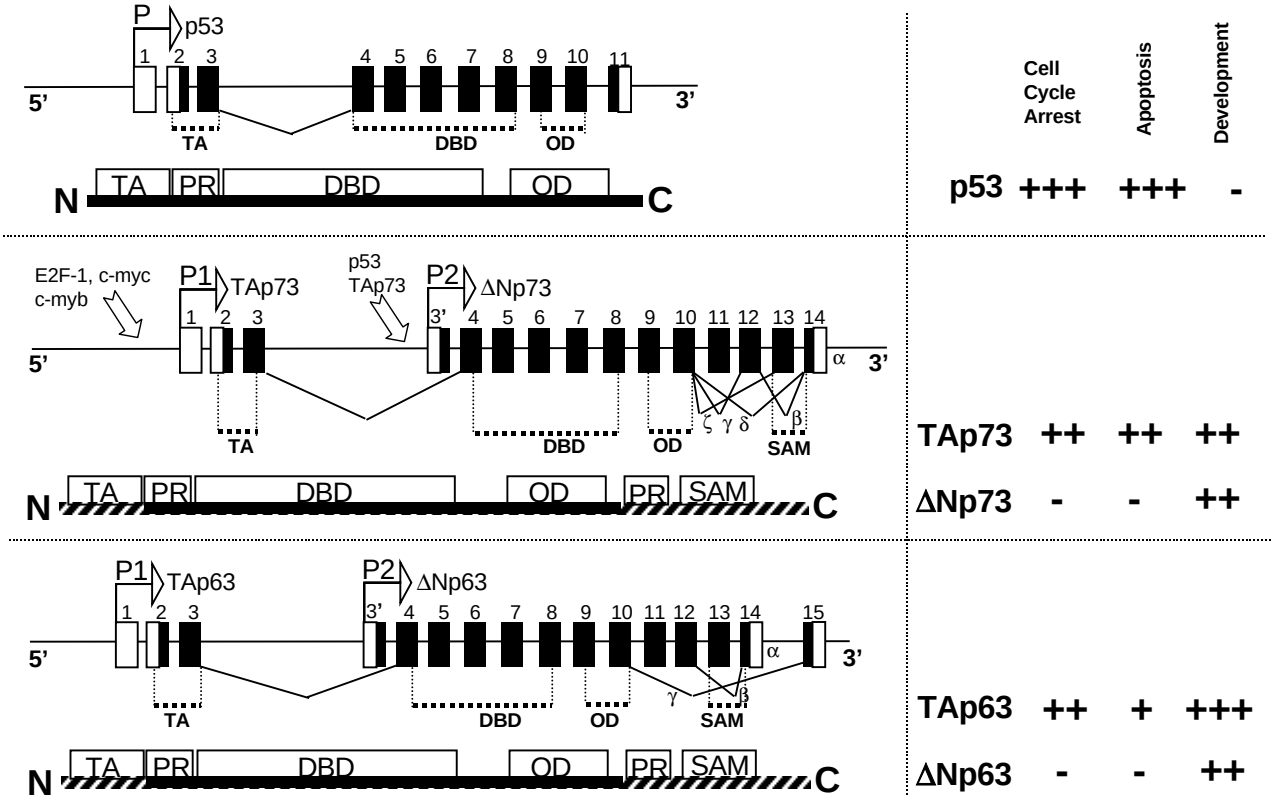


Fig. 3. Structure of the p53 family. The diagrams on the left side represent the overall structure of the TP53, TP73 and TP63 genes. Each gene is outlined both in the structure of the genome (5′–3′), and the organization of the protein (N–C). Exons and introns are not in scale; groups of exons coding for a specific protein domain are indicated. Exons are numbered in arabic numbers; coding sequences are in black, noncoding sequences are in white. The corresponding proteins are reported below each genomic scheme; the main structural domains (TA, PR, DBD, OD, SAM) are indicated. While p53 is a single predominant protein of 393 amino acids coded by 11 exons, p63 and p73 have three extra exons, coding for an extra stretch of 250 residues. The presence of two distinct promoters (P1 and P2) results in the production of a full-length TA-protein (containing the transactivation domain) and a ΔN-protein (without the N-terminal region and its transactivation domain). The presence of alternative splicing isoforms is indicated by the dashed bars in the protein. Abbreviations are reported in the text. The right panels reports the main biological effects of the distinct isoforms.

inhibit its transcriptional activity. Mdm2 can also stimulate the ubiquitination and the proteasome-dependent degradation of p53 [30]. Ubiquitin is a 76 amino acid polypeptide, covalently linked to lysine residues of a protein acceptor by a system of ubiquitin-activating and conjugating-enzymes. Like p53, p73α seems to be degraded by the proteasome pathway, as proteasome inhibitors, such as LLnL and MG132, increase protein levels.

p73α associates with Mdm2 *in vitro* and *in vivo* [31,32], and the interaction involves the N-terminal domains of the two proteins, as for p53. In the case of p73, however, association with Mdm2 does not lead to degradation. The most striking divergence between p53 and p73 resides in the C-terminal, and this part of the protein in p73 is likely to be responsible for the incapacity of Mdm2 to induce degradation. Nonetheless, p73 binding to Mdm2 still has a functional consequence, as Mdm2 binding inhibits p73α transactivating activity. In fact, Mdm2 is able to bind the cofactor p300/CBP, which is necessary for p73 transactivation activity, and has the same binding site as p73. Mdm2 thus acts as a competitor to p73 for p300/CBP binding [32]. The interaction between p53 and p300/CBP is not inhibited by Mdm2, as they use different binding sites in the protein. In addition, the competitive binding of p73α to Mdm2 could result in the protection of p53 from Mdm2-induced degradation.

Another difference between p53 and p73 regulation is the cellular localization induced by Mdm2 interaction [33]. p53's NES is inactive when the protein is in the tetrameric form. Mdm2 induces the ubiquitination of the lysine residues in the C-terminus, allowing the NES to be revealed by a conformational change, so that the protein is exported. p73 C-terminus is different from the p53 one, and lacks the lysines targeted by the ubiquitination. In fact, Mdm2 expression doesn't induce p73β ubiquitination nor exposition of its NES, but p73β aggregates and is sequestered in the nucleus. Its aggregation is independent of Mdm2 ring-domain, necessary for the E3 ligase activity. More recently, a novel protein, Parc, has been found to regulate the subcellular localization of p53 [34]. While this protein seems to be responsible for the abnormal ''Parc-king'' of p53 in the cytoplasm in cancers like neuroblastoma [34], little is known on its possible interactions with p63 and p73, even though the normal nuclear

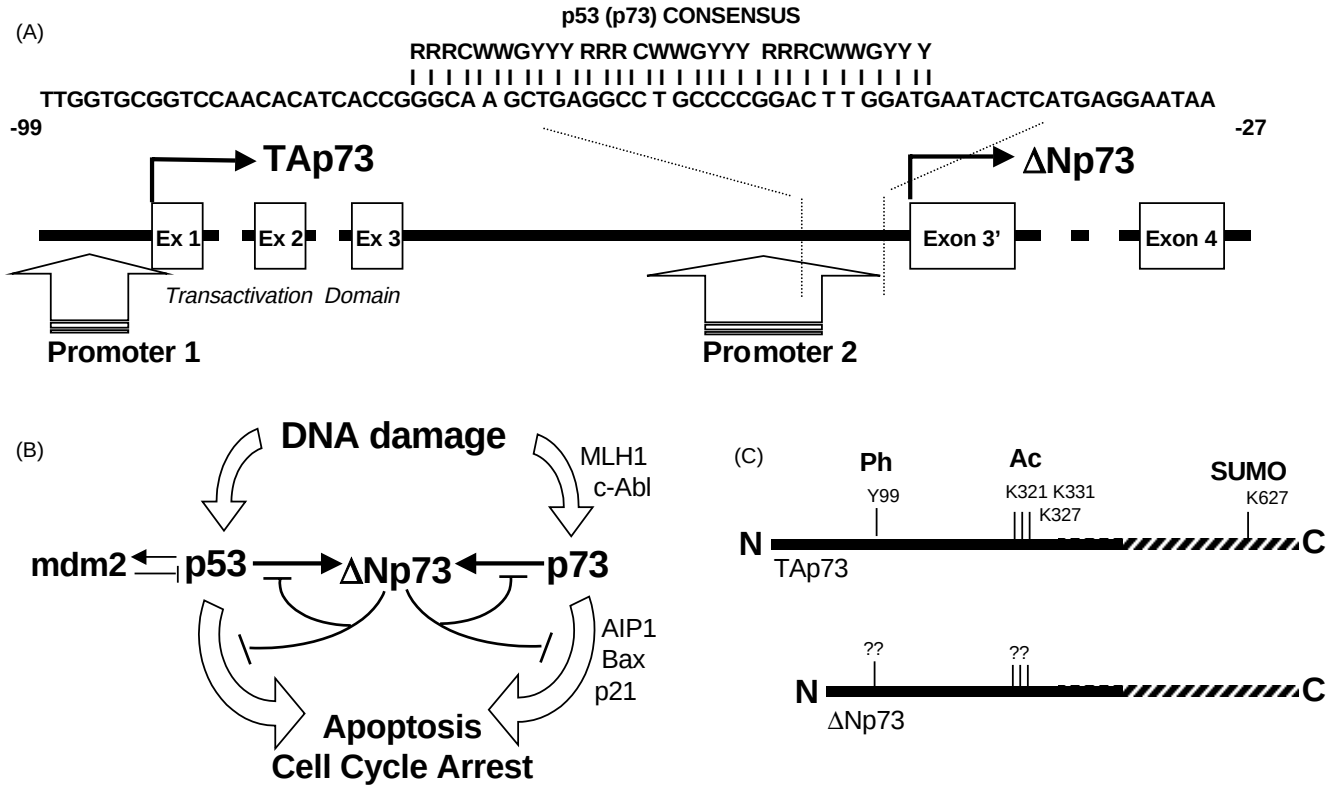


Fig. 4. Regulation of p73's promoters. The two promoters of TP73 are shown in more details; the promoter 1 codifies for the TA-p73 protein, the promoter 2 codifies for the ΔN-p73 protein. A very active p53 resposive elements is present on the P2 promoter (A). This results in the ability of both p53 and TA-p73 to drive the expression of ΔN-p73, which in turn inhibits the function of p53 and TA-p73, creating a dominant negative regulatory loop (B). A simplified organization of the TA-p73 and ΔN-p73 proteins with their post-translational modifications. Abbreviations: Ph, phosphorilation; Ac, acethylation; SUMO, SUMOylation (C).

localization of p73 in neuroblastoma seems to exclude this possibility.

The regulation exerted by Mdm2 on p53 is quite complex. Mdm2 induces translation of p53 mRNA from two distinct alternative initiation sites, resulting also in the production of ΔN-p53 (also called p53/47), a shorter amino-terminal truncated protein lacking the transactivation domain [35,36]. This translation requires Mdm2 to interact directly with the nascent p53 polypeptide [35]. ΔN-p53 does not contain the Mdm2 binding site, but it is still able to hetero-oligomerize with p53, negatively regulating its transcriptional and growth-suppressive activities [36]. Therefore, Mdm2 regulates the steady-state protein levels of p53 at two levels: induction of synthesis and targetting its degradation.

While Mdm2 catalyzes the addition of a single ubiquitin to a cluster of six C-terminal lysines in p53, a very recent report demonstrates that p53 is polyubiquitinated by Mdm2 and p300/CBP where the latter acts as an E4 ligase [37].

As discussed above, p73 binds Mdm2, but it is not degraded in the proteasome [31,32], leaving this physical interaction with modest functional effect so far. It is, therefore, tempting to speculate that Mdm2 binding to p73 might produce similar effects to p53: (i) affecting the relative expression of different isoforms, such as ΔN-p73, similarly to ΔN-p53, favouring transactivation of apoptotic versus cell-cycle arrest genes, (ii) facilitating the E4 function of p300/CBP as compared to its acetylase activity, indirectly favouring the degradation of p73, possibly during DNA damage or other stresses.

## 3. p73 and SUMO-1

SUMO-1 is an ubiquitin-like protein, first identified as GAP-modifying protein or SUMO-1. SUMO is also a binding partner of proteins such as PML and CD95 and is essential for PML localization in the PML-oncogene domain. It also covalently modifies IkBα, on the ubiquitin modified lysines, thus inhibiting its degradation. p73α, but not β, can be covalently modified by SUMO (Fig. 3C) [27], on the C-terminal lysine residue 627. This modification seems to potentiate p73α's proteasomal degradation. p73β is a much more powerful transactivator than p73α, this could be because the sumolation of p73α influences other interactions with other proteins, such as c-Abl tyrosine kinase. The involvement of SUMO in PML bodies (also called nuclear bodies) has raised the possibility that p73 interacts with PML in the PML bodies, thus regulating the stability and the function of the protein.

## 4. p73 and the nonreceptor tyrosine kinase c-Abl

c-Abl is a nonreceptor tyrosine kinase that is linked functionally to many key molecules involved in response to DNA damage, including ATM and p53, and also p73α and β after cisplatin induction. In fact, after a cisplatin induction, p73α and β are stabilized and induce apoptosis in a c-Abl-dependent manner, requiring its kinase activity [24,25]. The two proteins interact specifically by a PxxP domain in p73, located between the DBD and the OD, and the SH3 domain of c-Abl. c-Abl is activated, after γ-radiation, presumably by the stress-induced protein kinase ATM.

Moreover, c-Abl activates a group of stress activated protein kinases (SAPK), such as JNK and p38MAP kinase. They are proline-targeted Ser-Thr protein kinases, associated with DNA damage due to UV light or γ-radiation. After cisplatin treatment, p38 is also involved and its activation is sufficient to enhance p73 activity. So, p73 can be stabilized through a tyrosine 99 phosphorylation by c-Abl (shown in see Fig. 4C) and a threonine phosphorylation by p38 [38].

## 5. p63 stability

A variety of signals regulate the C-terminus of p53 which negatively regulates the protein's function. In the same way, the p73 and p63 responses seem to be regulated by their respective C-termini, though these responses are predictably different in the various splice variants presents in these proteins.

Serber *et al.* [29] identify a new 71 amino acid domain in the C-terminus of the p63α protein, which is able to inhibit the transactivation domain. In this model, a molecule of TA-p63α is folded and inactivated by the interaction transactivation domain (TA)/transinhibitory domain (TI). This could explain why TA-p63α is a less efficient activator than TA-p63β. In the same way, the ΔN-isoforms, which lack the TA domain, are not able to equally inhibit the TA-p63 proteins. In fact, ΔN-p63α has a stronger dominant negative effect than the β and γ forms. Moreover, the SAM-containing proteins are more stable, as the TI domain, bound to the TA, hides the sites used by the degradation pathway. Therefore, the p63 proteins are not only regulated in their transcriptional activity but also in the stability levels of the various isoforms. The complexes between TA-p63 isoforms and ΔN-p63α or the TA/TI intramolecular folding increase the half-life of the proteins and keep them in an inactive form. This pool of protein is ready to be used in case of a stimulus such as DNA damage or a developmental signal. The SAM domain may play a role in the activation of the protein, binding other activating partners, such as kinases which could phosphorylate the TA or TI domain and thus open the protein in an active form. The high sequence homology between p63 and p73 predicts that these results could possibly be relevant also for p73 regulation.

According to Lee and La Thangue [39], p73β is much more active because it is more stable: the C-terminus seems to alter the p73 half-life. p73β, but not α, increases after LLnL treatment, suggesting that the regulation of endogenous p73 involves an ubiquitin-dependent proteasome pathway, and that the SAM domain of the α form negatively regulates this degradation pathway. This paradox could be explained by some small differences in the two protein sequences, or by different systems used to explore the protein's stability.

## 6. Conclusion

Even if the p53 stability and degradation pathway has been well studied, the mechanisms elucidated for p53 are rarely applicable to p63 or p73. It is clear that p73 and p63 stability is regulated not only by protein modifications (phosphorylation, acetylation) as in the case of p53, but also by the relative amounts of the individual splicing variants, thus at the level of the splicing machinery, which implies yet unknown regulators. This much higher complexity may be due to the fact that p73 and p63 are phylogenetically older than p53. They are not just involved in apoptosis but also in neuronal or epidermal development, which requires a high capacity to respond to diverse stimuli in space and time during embryogenesis. p53 can be seen as a simpler form of these two proteins, ''specialized'' in inducing cell death, so understanding p63 and p73 stability regulation cannot be achieved by drawing simple analogies to p53 pathways. The identification of novel pathways of p63 or p73 stability makes the puzzle more complicated and shows that a lot remains to be understood, in particular, about the degradation pathways of p73 and p63 TA- and ΔN-forms.

## 7. Summary

The p53 family now includes three distinct proteins, p53, p63, and p73, involved both in DNA damage and in development. The two latter proteins are expressed in several isoforms due to either the use of two distinct promoters (TA- and ΔN-isoforms), or to alternative splicing of the last four exons. The ΔN-isoforms lack the transactivation domain, and thus do not seem to act normally as transcription factors. At least for p73, the TA- and ΔN-isoforms are strongly linked to each other, with TA-p73 able to transactivate the expression of ΔN-p73, which in turn inhibits the function of TA-p73. This dominant negative regulatory loop exerted by ΔN-p73 is triggered both by TA-p73 and by p53. Consequently, p73, and in particular ΔN-p73, has been found the be involved in tumourigenesis.

Several post-translational modifications regulate the stability and the transcriptional activity of p73. p73 associates with, but it is not degraded by Mdm2. Nevertheless, this interaction could act as a competitor and thus allow a degree of protection of p53 from Mdm2-induced degradation. Lysine 627 of p73 is modified by SUMO-1, but this occurs only for the alpha isoforms, suggesting distinct regulations for the individual isoforms. c-Abl can phosphorylate tyrosine 99, while p38 induces a threonine phosphorylation. Acetylation seems to occur at lysines in the 321–331 region.

The p63 protein seems also to be regulated by its C-terminal region. Here an inhibitory domain seems to regulate the activity of the transactivation domain located at the other end of the protein, suggesting an intramolecular folding that is able to increase the lifetime of the protein and keep it in an inactive form.

Clearly, the degradation mechanisms of p63 and p73 are quite different from those acting on p53. Despite the mechanisms described above for p63 and p73, the molecular mechanisms controlling p63 and p73 degradation have not been formally identified. These are crucial to the understanding of the regulation of activity of these proteins and their isoforms in the cell.

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