

The Tumor Suppressor TAp73

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The tumor suppressor TAp73 is a member of the p53 family, which is inhibited in many human solid and hematological tumors. In contrast to those in the p53 gene, mutations in the p73 gene are very rare in tumors, suggesting that the decrease in TAp73 activity and expression detected in those tumors are caused mainly by coordinated post-translational modifications of TAp73.

Keywords: 73 ; post-translational modification ; ubiquitin ; phosphorylation ; acetylation ; cancer therapy

1. Introduction

The *p53* gene, commonly referred to as the guardian of the human genome, is highly mutated in approximately 50% of human cancers [1][2]. It is a vital tumor-suppressor gene due to the ability of *p53* to induce apoptosis and growth arrest in response to cell stress, genotoxicity, and DNA damage [3]. Overall, *p53* is a master transcription factor of cell cycle inhibitors, such as *p21^{WAF1}* [4][5], as well as several pro-apoptotic genes, including *Bax* and *Bim* [6][7]. *p53* was thought to be a unique gene in the human genome for more than two decades until the discovery of two additional members of its family, *p63* and *p73*, which share a similar structure and function [8][9][10][11]. The tumor suppressor *p53* and its homologs, *p63* and *p73*, play crucial roles in the regulation of several cellular activities such as DNA damage response, development, cellular homeostasis, aging, and metabolism [12][13]. Like other members, *p73* is also expressed as multiple functional isoforms (Figure 1). The *p73* gene has two different promoters, thereby allowing for the generation of two types of isoforms with two opposite functions. The transactivation-*p73* (TAp73) isoforms contain the N-terminal transactivation domain with pro-apoptotic functions, whereas the N-terminally truncated *p73* (Δ Np73) isoforms have anti-apoptotic properties (Figure 1) [11][14][15][16][17][18].

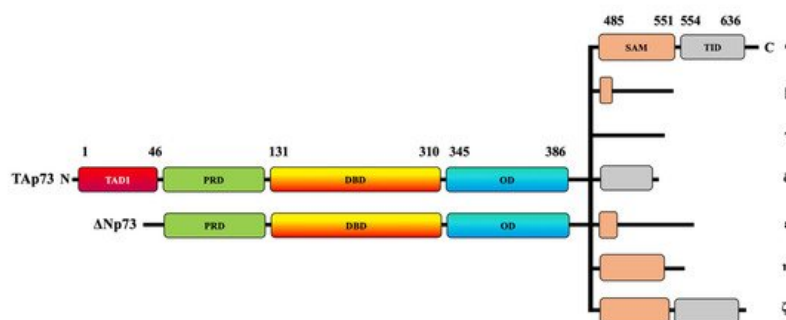


Figure 1. Schematic representation of TAp73 and Δ Np73 domains. The human *p73* protein comprises transcriptional activating domains (TADs) and a proline-rich domain (PRD) at its N-terminal and a DNA-binding domain (DBD). The *p73* C-terminal domain is composed of an oligomerization domain (OD), a sterile alpha motif (SAM) domain, and a transactivation inhibitory domain (TID). At least two N-terminal isoforms, TAp73 and Δ Np73, can be combined with the C-terminal α , β , γ , δ , ϵ , ζ , and η isoforms.

The human *p73* gene contains 14 exons that extend to around 80 kb. The *p73* protein contains approximately eight domains. At its N-terminal, the human *p73* protein comprises transcriptional activating domains (TADs), a proline-rich domain (PRD), and a DNA-binding domain (DBD). The carboxy-terminal (C-terminal) is composed of an oligomerization domain (OD), a sterile alpha motif (SAM) domain, and a transactivation-inhibitory domain (TID) [19][20]. The TID is a post-SAM region and is absent in *p53* [20]. The TAp73 isoforms have multiple variants— α , β , γ , δ , ϵ , ζ , and η —that are expressed due to alternative splicing on the SAM domain located at the C-terminal region [21] (Figure 1). TAp73 α is considered the longest variant because it has the longest SAM domain and the longest C-terminal, whereas *p73* β has a shorter SAM domain and a shorter C-terminal tail [20][22].

ΔNp73 lacks a transactivation domain (Figure 1), but it has oncogenic potential, as displayed by its dominant-negative effects on both wildtype p53 and TAp73 [16][17]. Like TAp73, ΔNp73 can be combined with C-terminal isoforms (Figure 1). ΔNp73 usually displaces wildtype p53 and TAp73 at the oligomerization level through competition for the DNA-binding site [23]. The overexpression of p73 induces apoptosis, whereas ΔNp73 can inhibit p73-induced cell death; therefore, the fine balance between the two variants can determine cell fate.

The increasing interest in the *p73* gene has resulted from the very low frequency of its mutations in human cancers [21][24][25]. Indeed, mutations in the *p73* gene are very rare in human tumors compared to those in the *p53* gene, which have been detected in more than 50% of human cancers [2][26][27]. In addition to *p73* gene mutations, *p73* has been also found to be epigenetically silenced in some leukemias and lymphomas through the hypermethylation of its promoter [28][29][30]. Alternatively, the loss of p73 in cancer may result from several post-translational modifications, including the ubiquitin-dependent proteasomal degradation pathway, phosphorylation, acetylation, and small ubiquitin-related modifier (SUMO)ylation. Thus, a deep understanding of p73 post-translational modifications will be extremely helpful in finding and developing new strategies for the prevention and treatment of cancers, especially those with p53 mutations. In this review, we summarize the current knowledge regarding the different pathways implicated in the regulation of p73 at the post-translational level. This review also highlights the growing importance of targeting the post-translational modifications of p73 as a promising antitumor strategy, regardless of the p53 status.

2. Ubiquitination-Dependent p73 Inhibition

In all cells, the intracellular proteins are degraded through the ubiquitin-proteasome pathway (UPP). The UPP contains specific enzymes that bind polypeptide chains to ubiquitin (Ub) and tag them for proteasomal degradation [31][32]. The tagged polypeptides are recognized by the 26S proteasome, a multicatalytic protease complex that degrades large ubiquitinated polypeptides into small peptides. Three enzymes are required for the ubiquitin tagging process: E1, a Ub-activating enzyme; E2, a Ub carrier or conjugating protein; and E3, a Ub protein ligase [33]. The E3 ligases are responsible for ligating Ub to polypeptides or proteins. By contrast, the deubiquitinating enzymes (DUBs) remove Ub from ubiquitinated proteins, thereby promoting protein stability.

The reversible regulation of Ub by E3 ligases and DUBs has received increasing attention for several diseases, including cancers [34][35][36][37]. The ubiquitination pathway affects many tumor-suppressor proteins, including p53 and its homologs, p63 and p73 [38]. Over the last 20 years, researchers have discovered many ubiquitin E3 ligases that directly promote the protein degradation of p53, p63, and p73 by either ubiquitination-dependent or ubiquitination-independent proteasome pathways [39]. TAp73 was shown to undergo ubiquitination and to be inhibited by various E3 ubiquitin-ligase enzymes (Table 1) (Figure 2), such as Itch [40][41][42][43], mouse double minute 2 homolog (MDM2) and its homologue mouse double minute X (MDMX) [44][45][46], p53-induced RING-H2 protein (Pirh2) [47][48][49], tripartite motif 32 (TRIM32) [50], FBXO protein 45 (FBXO45) [51], Cullin4A (cul4A)-dependent ligase (CDL4A) [52], and WW Domain Containing E3 Ubiquitin Protein Ligase 2(WWP2) [53]. PIR2 (p73-induced ring protein 2) is also an E3 ubiquitin ligase for p73 through a mechanism that involves targeting the ΔNp73/TAp73α balance rather than the direct ubiquitination of p73 [54].

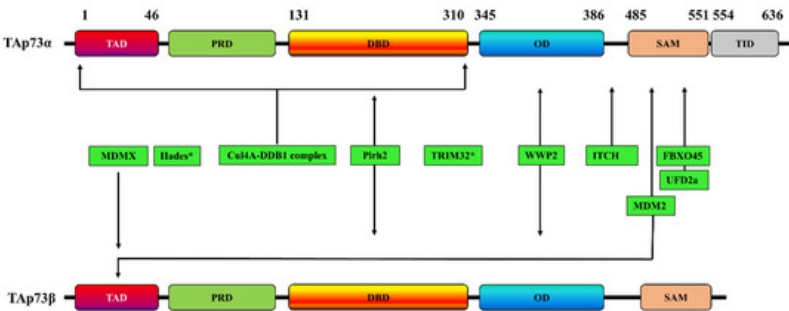


Figure 2. Schematic representation of the interaction sites of various E3 ubiquitin-ligases with TAp73α, TAp73β, or both. * indicates that the p73 interaction site is unknown. TAD: transactivation domain; PRD: proline rich domain; DBD: DNA binding domain; OD: oligomerization domain; SAM: sterile alpha motif; TID: transactivation inhibitory domain.

Table 1. Role of E3 ligases in p73 stability. TRIM32: tripartite motif 32; Cul4A: Cullin4A; MDM2: mouse double minute 2 homolog; Pirh2: p53-induced RING-H2 protein.

E3 Ligase	TAp73 Isoform	p73 Interaction Site	Effects on p73	Refs
ITCH	p73α	PY motif (Met 452–Ala 489)	Proteasome-dependent p73 degradation	[43]

E3 Ligase	TAp73 Isoform	p73 Interaction Site	Effects on p73	Refs
MDM2	p73 α	-	p73 α activity inhibition but without promoting its degradation	[55] [56]
	p73 β	Two residues (F15 and W19)	p73 β activity inhibition but without promoting its degradation	[57]
	p73 α	-	p73 degradation through a mechanism involving the interaction of MDM2 with Itch	[45]
	p73 α and p73 β	N-terminal domain	p73 ubiquitination but without promoting its degradation	[44]
	p73 α	The C-terminal SAM domain (especially the peptide comprising α 4 and α 5 helices of SAM)	-	[58]
MDMX	p73 α	TA domain	Subcellular localization of p73 and inactivation of transcription	[46] [59]
Pirh2	p73 α and p73 β	DNA-binding domain	p73 ubiquitination and repressing p73-dependent transcriptional activity	[47]
TRIM32	p73 α	-	p73 ubiquitination and degradation, inhibiting p73 transcriptional activity	[50]
FBXO45	p73 α	SAM domain	Proteasome-dependent degradation of p73	[51]
UFD2a	p73 α	SAM domain	Ubiquitination-independent p73 degradation	[60]
Hades	-	-	Ubiquitination of p73, promoting its degradation	[61]
Cul4A–DDB1 complex	p73 α	The N-terminal region of p73, encompassing residues 1–320 and including the DNA-binding domain.	p73 monoubiquitination and inhibition of its transcriptional activity without affecting p73 stability	[52]
WWP2	p73 α and p73 β	Oligomerization domain	p73 ubiquitination and its proteasomal degradation in	[53]

2.1. Itch

Itch E3 ubiquitin-protein ligase (Itch) has been reported to be highly expressed in several tumors, including lung cancer, breast cancer, pancreatic cancer, skin cancer, and neuroblastoma, and its inhibition leads to the induction of apoptosis and the inhibition of cell proliferation [38][59][62][63][64]. Itch selectively binds and ubiquitinates p73 α via the PY motif (Met 452–Ala 489) but not p53, thereby leading to a proteasome-dependent p73 degradation [43]. The use of the proteasome inhibitor MG132 or the depletion of Itch using siRNA causes the inhibition of the Itch-mediated p73 degradation and increases p73 expression levels [43]. Similarly, treating cancer cells with DNA-damaging agents, such as doxorubicin, cisplatin, and etoposide, decreases the expression of endogenous Itch in a time- and dose-dependent manner, and this effect is associated with an increase in endogenous p73 levels and enhanced apoptosis [43].

Itch and p73 expressions are controlled through several mechanisms. For example, the Itch–p73 interaction was proposed to be under the control of the transcriptional co-activator Yes-associated protein 1 (Yap1), another partner of p73 [40]. Indeed, Yap1 competes with Itch for binding to p73, thereby preventing the Itch-mediated ubiquitination and degradation of p73. Cisplatin increases p73 expression and apoptosis, while the depletion of Yap1 using siRNA blocks these effects [40]. Yap1 interacts with another transcription activator, Runx, to target the promoter of Itch and enhance its transcription, with subsequent support of the degradation of p73 [41]. Nedd4-binding partner-1 (N4BP1) has been also found to compete with Itch for binding to p73 α , thus reducing the ability of Itch to interact with and ubiquitylate p73 α [65]. The Itch/p73 axis is also regulated in chronic lymphocytic leukemia (CLL) cells through the direct regulation of Itch by microRNA 106b (miR106b) [42]. Indeed, the induction of miR106b in CLL cells is associated with a decrease in Itch expression and an increase in the expression of p73 and PUMA, as well as induction of CLL apoptosis [42].

2.2. MDM2/MDMX

MDM2 is a negative regulator of p53; its interaction with the TAD of p53 leads to a ubiquitination-mediated proteasomal degradation of p53 [13][66]. MDM2 also interacts with p73 α and inhibits its function, but it does so without promoting p73 degradation [55][56]. MDM2 also forms a specific complex in vitro and in vivo with p73 β through at least two residues (F15 and W19) [57]. MDM2 overexpression reduces the ability of p73 β to activate transcription but without promoting its

degradation, indicating that MDM2 can directly induce the degradation of the p53 protein but not of its homolog p73 [57]. However, MDM2 has been shown to induce p73 degradation in HeLa cells through a mechanism involving the interaction of MDM2 with Itch [45].

Adriamycin can increase p73 expression and HeLa cell apoptosis, most likely by decreasing the expression of both MDM2 and Itch. Similarly, the MDM2-mediated p73 degradation is inhibited in cells treated with the inhibitor proteasome MG132 [45]. In the same context, MDM2 was reported to use its RING domain to bind to p73 α and p73 β at multiple Lys residues of ubiquitin, thereby promoting the ubiquitination of both isoforms but without inducing their degradation [44]. MDM2 overexpression induces Itch-mediated p73 degradation in MDM2-deficient mouse embryo fibroblasts, whereas its depletion using siRNA induces p73-dependent transactivation and apoptosis [44].

A recent study showed that the MDM2/p73 interaction is established by specific binding between the N-terminus TA domain of MDM2 and the SAM domain of p73 [58]. MDMX, the structural homolog of MDM2, was also shown to negatively regulate p73 [46][59][67]. MDMX physically interacts with p73 α , and its overexpression specifically induces alterations in the subcellular localization of p73 α but not of the p73 homologs p53 and p63 [59]. Both MDM2 and MDMX are capable of binding to the TA domain of p73 [46].

2.3. Pirh2

Pirh2 is a RING finger E3 ligase that induces p53 degradation by promoting its ubiquitination [68][69]. Several studies have reported that Pirh2 acts as an oncogene, and its overexpression in cancer is associated with decreased p53 expression levels [48][49][70]. Pirh2 has also been shown to interact with the DNA-binding domain of both p73 α and p73 β [68][71][72], and its E3 ligase activity promotes p73 ubiquitination both in vivo and in vitro [47][73]. Pirh2 ubiquitinates p73 in vitro via K63-linked chains, while it promotes p73 ubiquitination in vivo by targeting K11-, K29-, K48-, and K63-linked chains [47]. The downregulation of Pirh2 significantly decreases p73 ubiquitination, whereas its overexpression is correlated with an inhibition of p73-dependent translational activity [47]. Pirh2 knockdown in the RKO colon carcinoma cell line inhibits cell growth and increases the levels of p73 and the cell cycle inhibitor p21^{WAF1} [73]. Conversely, the overexpression of Pirh2 in colon and breast cells induces the degradation of p73 via the proteasomal pathway [73]. The exposure of RKO cells to either doxorubicin or camptothecin decreases Pirh2-mediated p73 polyubiquitination [73].

2.4. TRIM32

Tripartite Motif Containing 32 (TRIM32) a RING protein, is overexpressed in several tumors, including skin tumors. It has E3 ubiquitin ligase properties and plays a role in tumor growth, metastasis, and resistance to anti-cancer drugs [74]. In this context, TRIM32 is involved in the ubiquitination of the tumor-suppressor Abl-interactor 2 (Abi2), resulting in an enhancement of cell proliferation and metastases [75]. TRIM32 also regulates the expression of p73 through the ubiquitination pathway, thereby promoting cell survival and tumor growth [50][76]. A regulatory feedback loop has been reported between TP73 and TRIM32 in human embryonic kidney 293 cells [50]. In HEK293 cells, p73 can act as a transcriptional regulator of TRIM32, and the depletion of p73 significantly decreases TRIM32 expression. TRIM32, in turn, binds to p73 α and promotes its ubiquitination and degradation, thus inhibiting p73 transcriptional activity [50]. The overexpression of TRIM32 inhibits the p73 transcriptional activation of the p21^{WAF1} promoter, thereby enhancing cell cycle progression and cell survival [50].

2.5. FBXO45

Several studies have reported the overexpression of FBXO45 in human cancer and an essential role for FBXO45 in tumorigenesis and progression [77][78][79]. FBXO45 induces the ubiquitination–proteasomal degradation of several tumor-suppressor proteins, such as Par4 (prostate apoptosis response protein 4) [80], F-box/WD repeat-containing protein 7 (FBXW7) [81], and p73 [51]. Through its spla and the ryanodine receptor (SPRY) domain, FBXO45 specifically binds to the SAM domain of p73 α , but not to its homolog p53, thus leading to the proteasome-dependent degradation of p73 both in vitro and in vivo [51]. The silencing of FBXO45 in the BT-20 cells, a p53-mutated cell line, induces the expression of p73 at the protein level [51]. The exposure of FBO45-depleted BT-20 cells to doxorubicin induces apoptosis, indicating that FBXO45 specifically binds to p73 and induces apoptosis via a p73-dependent mechanism [51]. Similar to p73, FBXO45 is also able to interact with Δ Np73 to play a crucial role in its stability in apoptosis and the DNA damage response. However, mutant FBXO45 has shown an impaired function against p73 and does not cause ubiquitination-associated p73 degradation [51].

2.6. UFD2a

Ubiquitin factor 2A (UFD2a), also known as Ubiquitin factor E4B (UBE4B), is an E3/E4 ligase belonging to the U box-type ubiquitin protein ligase family that can catalyze the elongation of the polyubiquitin chain. In response to apoptosis, UFD2a is cleaved by caspase 6, resulting in impaired enzymatic activity and dysfunction, as well as confirming the role of UFD2a in apoptotic signaling [82]. UFD2a physically interacts with p53 in brain tumors to promote p53 polyubiquitination and degradation, thus decreasing p53-mediated apoptotic activity [83]. Similar to its effects on p53, UFD2a regulates the stability of p73 via ubiquitination-independent degradation [60]. UFD2a also physically interacts with the SAM domain of p73 α [60]. The treatment of SH-SY5Y neuroblastoma cells with cisplatin results in a decrease in the expression of UFD2a, while p73 protein expression and apoptosis are increased [60]. The expression of the p73 protein is also increased in UFD2a-depleted cells [60]. Alternatively, the overexpression of UFD2a decreases both p73 α expression and p73-mediated pro-apoptotic activity [60]. Similar findings have been reported in squamous cell carcinoma (SCC) cells [84]. UFD2a knockdown in SCC cells was found to result in p73 accumulation and sensitized the SCC cells to the inhibitory effects of 1,25D3 (the most active metabolite of vitamin D) on cell growth, suggesting that the UFD2a/p73 pathway contributes to the antiproliferative effects of anticancer drugs [84][85].

2.7. Hades

Hades, also referred to as mitochondrial ubiquitin ligase activator of NFKB1 (MULAN), is an E3 ubiquitin ligase. Hades is anchored to the outer membrane of mitochondria through its transmembrane domains, with a conserved C-terminal RING-finger domain with an E3 ligase activity facing the cytosol [61]. Hades interacts with p53 in the mitochondria to reduce p53 stability [86]. Hades polyubiquitinates p53 through an MDM2-independent mechanism, thereby inhibiting the p53-dependent mitochondrial cell death pathway by blocking the interaction between p53 and Bcl-2 [86]. Through its RING-finger domain, Hades also interacts with p73 in etoposide-treated H1299 cells [61]. In response to etoposide treatment, p73 is translocated to the mitochondria to colocalize with Hades [61]. Hades induces the ubiquitination of p73 and its degradation, whereas its depletion using siRNA significantly inhibits p73 degradation, indicating that Hades is involved in the ubiquitination-dependent degradation of p73 [61].

2.8. The Cul4A–DDB1 E3 Ubiquitin Ligase Complex

The CDL4A complex targets various proteins that are involved in several signaling pathways, including the DNA damage response and the cell cycle [87][88][89], and it contributes to the degradation of several proteins through the ubiquitin-proteasome pathway. In this context, Cul4A has been reported to interact with p53 to promote its proteasomal degradation [90]. Through damage specific DNA binding protein 1(DDB1), the CDL4A complex can directly bind to the N-terminal region of p73, which encompasses residues 1–320 and includes the DNA-binding domain, thereby inducing p73 mono-ubiquitination and inhibiting p73-dependent transcriptional activity without affecting p73 stability at the protein level [52]. The depletion of DDB1 induces the expression of several known target genes of p73, such as *p21^{WAF1}* and *PUMA* [52]. Clinically, high expression levels of Cul4A in human breast carcinomas are associated with the repression of target genes of p73, indicating that Cul4A is a potent inhibitor of p73 transcriptional activity in cancer [52].

2.9. WWP2

WWP2, an E3 ubiquitin ligase, has an important role in different cellular functions and ubiquitinates, and it decreases the expression of the tumor-suppressor genes *PTEN* [91] and *p73* [53] through the proteasomal pathway. Through its WW3 domain, WWP2 specifically interacts with the oligomerization domain of both p73 α and p73 β but not with p53 [51]. This results in p73 ubiquitination via a K48 linkage, with the subsequent induction of p73 degradation in the proteasome [53]. Interestingly, WWP2 depletion dramatically decreases p73 ubiquitination and increases its expression at the protein level [53].

3. Conclusions

The downregulation of the tumor suppressor TAp73 represses the transcription of several anti-proliferative and pro-apoptotic genes in many human solid and hematological tumors. This, in turn, inhibits apoptosis and enhances cell proliferation. Via its structural domains, which show a high degree of similarity with those of p53, TAp73 interacts with several E3 ubiquitin ligases, kinases, and deacetylases. These proteins, which work together to orchestrate the multiple anti-proliferative and pro-apoptotic functions of TAp73, also offer multiple promising candidates for cancer therapy. Since mutations in the *p73* gene are very rare in tumors, unlike the case for the *p53* gene, the decrease in both activity and quantity of TAp73 detected in various human tumors could arise, in large part, from coordinated post-translational modifications of TAp73. This review has highlighted the multiple post-translational modifications underlying TAp73

regulation in cancer cells and the growing importance of targeting their trigger enzymes as a promising antitumor strategy. Thus, understanding the post-translational modifications involved in TAp73 regulation will allow for the identification of new targets and the exploration of new drugs that can increase the expression of TAp73. This will allow cancer cells to undergo apoptosis, regardless of their p53 status, through the reactivation of several pro-apoptotic genes.

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