Chapter 8
YAP and p73: A Matter of Mutual Specificity in Tumor Suppression

Sara Donzelli, Sabrina Strano, and Giovanni Blandino

Abstract YAP and p73 proteins are key nodes of two distinct tumor suppressor pathways. The HIPPO tumor suppressor pathway to which YAP belongs is the most recent identified in the cancer arena, while that of the p53 family including p73 is the most well studied and characterized. Often in response to anticancer treatment, distinct tumor suppressor pathways can be triggered and cross talk each other. This is well represented by the growing experimental evidence linking HIPPO and p53 family tumor suppressor pathways. Here we mainly focus on the physical and functional interaction between YAP and p73 proteins, their role in drug-induced apoptosis and their implications in tumor suppression.

Keywords p73 • YAP • Apoptosis • Interaction • Pathway

8.1 The p73 Gene

The p73 gene, which is extensively subjected to alternative splicing, encodes proteins that are almost equally distributed among TA and ΔN isoforms. The resulting proteins are members of the p53 family. They are heavily involved in growth suppression, apoptosis, DNA repair, senescence, and differentiation.

S. Donzelli • G. Blandino (✉)
Translational Oncogenomic Unit, Molecular Medicine Area, Regina Elena National Cancer Institute, Rome, Italy
e-mail: blandino@ifo.it

S. Strano
Molecular Chemoprevention Group, Molecular Medicine Area, Regina Elena National Cancer Institute, Rome, Italy

M. Oren and Y. Aylon (eds.), *The Hippo Signaling Pathway and Cancer*,
DOI 10.1007/978-1-4614-6220-0_8,

8.1.1 p53 Family

The first member of the family identified was p53 in 1979, whose tumor suppressor activity is now well established (Lane and Crawford 1979; Linzer and Levine 1979). It is in fact defined "the guardian of the genome," due to its ability to induce cell cycle arrest or apoptosis in the presence of different kinds of cellular stress signals. It is also found mutated in almost 50 % of human cancers (Hainaut et al. 1997; Hollstein et al. 1997).

The other two members of the family, p63 and p73, were discovered in 1997, almost 20 years after discovering p53. Even if they were discovered later than p53, the overall structure and sequence homology suggest that a p63/p73-like protogene is the ancestral gene, whereas p53 evolved later in higher organisms.

p63 and p73 are structurally and functionally similar to p53 sharing the same function. For instance their involvement in tumor suppression (Collavin et al. 2010). However, they also have specific functions that differ from p53, that is, playing important roles in embryonic development and differentiation (Jost et al. 1997; Kaghad et al. 1997; Yang et al. 1998).

The p53 transcription factor family members are characterized by a very similar protein structure composed of an amino-terminal transactivation domain (TA), a proline-rich domain (PR), a core DNA binding domain (DBD), and a carboxy-terminal oligomerization domain (OD) (Blandino and Dobbelstein 2004; Levrero et al. 2000; Melino et al. 2002; Stiewe and Putzer 2002). In contrast to p53, p63 and p73 proteins contain also a sterile-alpha motif (SAM) domain at the carboxy-terminal region. Knowledge of these domains' specific functions is still poorly understood. It seems to mediate the interaction with other proteins not yet identified (Chi et al. 1999). The SAM domain is made up of typical proteins that take part in development regulation, thus supporting the involvement of p63 and p73 in differentiation (Harms and Chen 2005; Irwin and Kaelin 2001; Ozaki et al. 1999).

The DBD is the domain with the highest grade of homology between the three family members, with 65 % of homology between p53 and p73. This results in the activation of overlapping sets of target genes.

Conversely, the OD domain is less conserved among the family members; p53 binds to DNA as a homo-tetramer. While p63 and p73, preferentially form homo-tetramers rather than hetero-tetramers with each other (Davison et al. 1999; Marin and Kaelin 2000).

The gene structure of p53 family members is highly complex and gives rise to different protein isoforms (Mills 2005; Murray-Zmijewski et al. 2006). Among the p53 family members, the p73 gene is the most complex and presents the highest number of isoforms generated by the activity of two distinct promoters on p73 gene and by different alternative splicing events. The resulting proteins may have antagonistic properties and are expressed differently in normal human tissue and cell lines.

8.1.2 p73 Protein Isoforms

The p73 gene is composed of 15 exons spanning over 80,000 bp on chromosome 1p36.32 (Ozaki and Nakagawara 2005). The biology of p73 gene is highly complex, since it can be transcribed in a variety of different isoforms generated by alternative splicing events and by the activity of two distinct promoters, for a total of 45 mRNA variants. These can encode theoretically 36 different p73 protein isoforms (Fig. 8.1).

Alternative splicing events between exons 10–13 at the C-terminal give rise to seven different isoforms (p73 α–η) (De Laurenzi et al. 1998; Kaghad et al. 1997; Melino et al. 2002; Moll and Slade 2004). Among these, p73α is the longest one containing a SAM in the extreme C-terminal region. C-terminal splicing isoforms display different transcriptional and biological properties (De Laurenzi et al. 1998; Ozaki et al. 1999; Ueda et al. 1999). Indeed, p73β has a stronger effect in the transactivation of p53/p73 target genes and in the induction of apoptosis in cancer cells than the full-length p73α (Lee and La Thangue 1999; Ueda et al. 1999). This suggests the existence of a regulatory function for the C-terminal domain (Lee and La Thangue 1999; Ozaki et al. 1999). Moreover, different splicing isoforms are differentially expressed among human tissues and cell lines, thus presenting different biological functions (De Laurenzi et al. 1998; Ueda et al. 1999).

In addition to C-terminal isoforms, alternative splicing events on the p73 gene give rise also to four N-terminal variants initiated at different ATG (ΔN′ p73, Δ2p73, Δ3p73, Δ2,3p73) (Fillippovich et al. 2001; Ishimoto et al. 2002; Murray-Zmijewski et al. 2006). These truncated forms, named ΔNp73 are transactivation-defective and behave as dominant negative isoforms in regard to TAp73 and p53 and act as anti-apoptotic proteins (Pozniak et al. 2000).

The other isoforms of p73 are generated by the activity of two distinct promoters present on the p73 gene: P1, located immediately upstream from the first exon, and P2, located in intron 3 upstream from the transcription starting site for ΔNp73 within exon 3′. The P1 and P2 promoters give rise to full-length TAp73 isoforms, and amino-terminal truncated ΔNp73 isoforms, respectively. The transcripts are exposed to both amino- and carboxy-terminal splicing.

The TAD is required for interacting with different transcription coactivators that allow the enhanced expression of p53 target genes. As a result, the TAp73 isoforms are able to induce the expression of different p53-responsive genes, such as p21, GADD45, PUMA, and BAX, controlling growth arrest and apotosis. Conversely, the ΔNp73 isoforms act as dominant negative proteins with anti-apoptotic and pro-proliferative effects by inhibiting TAp73 and p53: the ΔN variants can occupy p53-responsive promoters by preventing on them the transcription machinery recruitment or can interact with TAp73 isoforms generating inactive hetero-tetramers (Pozniak et al. 2000; Yang et al. 2000).

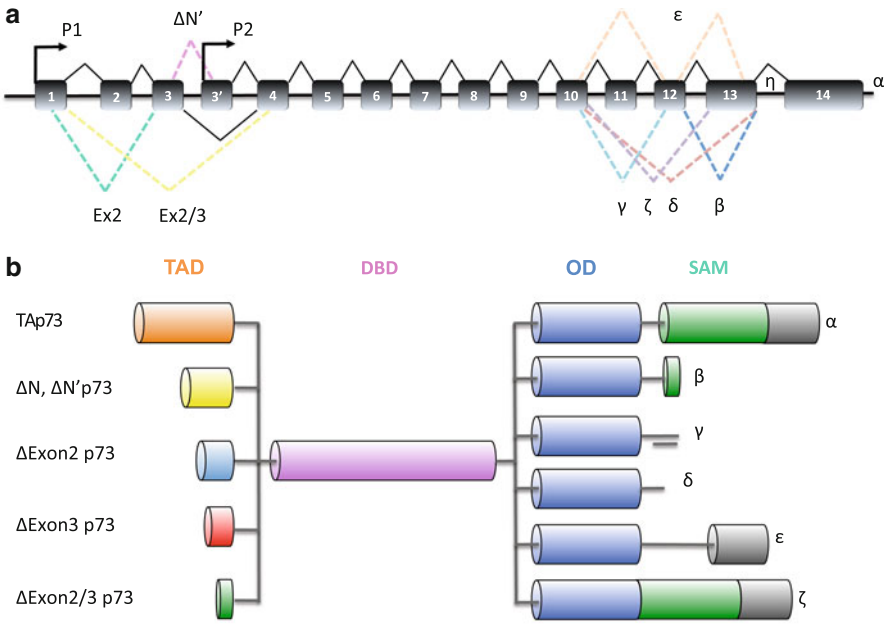

Fig. 8.1 Structure of p73 gene and its isoforms. (**a**) Structure of the human p73 gene. The p73 gene is located on chromosome 1p36.32 and is composed of 15 exons. The transcripts are generated by two alternative promoters (P1 and P2) and undergo alternative splicing events that give rise to different isoforms. (**b**) p73 isoforms. Similar to the other p53 family member, p73 protein is composed of an amino-terminal transactivation domain (TA), a core DNA binding domain (DBD), a carboxy-terminal oligomerization domain (OD), and a sterile-alpha motif (SAM) that is present only in p73 and p63. TA variants are generated by the P1 promoter and possess a functional TAD, while ΔN isoforms, generated by the P2 promoter, lack the TAD domain and thus are transcriptionally inactive. ΔN isoforms can also be generated by alternative splicing events at the first two exons. All the transcripts can also be subjected to alternative splicing events at the C-terminal exons, thus generating a variety of isoforms

8.1.3 p73 Functions

Unlike the p53 gene product that is ubiquitously expressed, the p73 protein shows tissue specificity. In addition, it is involved in defining the developmental stage.

The role of p73 in neurogenesis, sensory pathways, and homeostatic control is revealed by $p73^{-/-}$ mice that present congenital hydrocephalus, hippocampal dysgenesis, loss of peripheral-sympathetic neurons, chronic infections and inflammations, and defects in pheromone detection (Pozniak et al. 2000; Yang et al. 2000).

Differently from $p53^{-/-}$ mice, p73 knockout mice do not show increased susceptibility to spontaneous tumorigenesis, since they die 4–6 weeks after birth (Yang et al. 1999, 2000).

Many of the neurological defects observed in the $p73^{-/-}$ mice are a consequence of neuron absence or loss (Yang et al. 2000). During the development of the nervous system, neurons are overproduced and cells directly compete in order to survive or die, for their growth factors in a process known as naturally occurring cell death. The neurons that are usually committed to surviving during the developmental apoptosis instead die in the p73 knockout mice (Pozniak et al. 2000). In the $p73^{-/-}$ mice, the absence of ΔNp73, the isoform more expressed in murine fetal nervous system, could be responsible for an enhanced neuronal apoptosis (Pozniak et al. 2000, 2002).

Like its homologue p53, p73 has also been implicated in cellular senescence (Alexander et al. 2003; Fang et al. 1999). In p53-depleted tumor cells, the overexpression of p73α and p73β isoforms is sufficient to induce permanent growth arrest with markers of replicative senescence (Fang et al. 1999).

8.1.4 p73 and Apoptosis

A range of chemotherapeutic drugs induce apoptosis via signaling pathways where p53 and/or p73 are central players (Erster and Moll 2005). Chemotherapeutic drugs promote p53 and/or p73 stabilization and activation, which in turn exert transcription-dependent and -independent effects leading to cell cycle arrest or apoptosis. It has been shown that the inhibition of p73 functions reduce the cytotoxicity of chemotherapeutic agents, hence underlying the important role of p73 in controlling cellular sensitivity to some anticancer treatments (Melino 2003; Sayan et al. 2008).

p73 plays an important role in apoptosis as it is involved in the activation of both intrinsic (mitochondria-mediated), extrinsic (death receptor-mediated), and endoplasmic reticulum-mediated apoptotic pathways.

The majority of proteins involved in p73-mediated apoptosis are controlled at the transcriptional level by p73, that is the case of Bax (Di Como et al. 1999; Zhu et al. 1998), PUMA (Melino et al. 2004), Noxa (Wang et al. 2008), CD95 (Muller et al. 2005), and Scotin (Terrinoni et al. 2004).

The activation of Bax, PUMA, and Noxa creates a link between p73 and the mitochondria-mediated cell death pathway (Flinterman et al. 2005; Ramadan et al. 2005). The transcriptional upregulation of CD95 induce the receptor-mediated cell death pathway (Muller et al. 2005), while the induction of Scotin promotes cell death by the induction of endoplasmic reticulum-stress and changes in intracellular calcium levels (Terrinoni et al. 2004).

The p73 exerts also a transcription-independent pro-apoptotic activity: upon death-receptor activation p73 is cleaved by caspases; the p73 fragment and also the full length p73 translocate to the mitochondria where they promote cytochrome c release (Sayan et al. 2008).

As mentioned above, ΔNp73 isoform has a complete opposite effect compared to TA isoform: it prevents apoptosis by different mechanisms. This effect is due principally to its dominant negative effect on TAp73 and p53 transcriptional activity (by competing with TAp73 and p53 for the binding sites on the promoters of their target genes and by the formation of inactive complexes with TAp73 isoforms).

A result of this effect is the ΔNp73 inhibition of Bax, CD95, and Scotin transcriptional activation (Muller et al. 2005; Rossi et al. 2004). The anti-apoptotic activity of ΔNp73 isoform is also exerted by the activation of the heat shock factor (HSF)-responsive gene expression, such as the anti-apoptotic inducible heat shock protein (Hsp)-72 (Tanaka et al. 2004).

8.1.5 p73 in Cancer

Despite the significant homology to p53, the p73 gene is not a classic Knudson-type tumor suppressor gene (Melino et al. 2002).

The first gene targeting studies in the mouse indicated that p73 was mainly implicated in normal development (Yang et al. 2000). It did not seem to be involved in cancer as $p73^{-/-}$ mice did not display an increased susceptibility to spontaneous tumorigenesis. However, this effect was due to the fact that the construct utilized to generate $p73^{-/-}$ mice deleted the central DBD of p73, so it affected all the p73 isoforms. In addition, the phenotype observed was the result of both TA and ΔN variant depletion, that, as mentioned above, have an opposite biological effect. In fact there are no changes in the balance of TA/ΔN isoforms, and also in their pro-apoptotic and anti-apoptotic effects, respectively.

The role of p73 in cancer prevention was clearly highlighted by the generation of p73 heterozygous mice alone or in combination with p53. It has been shown that $p73^{+/-}$ and $p73^{+/-}$:$p53^{+/-}$ mice present more aggressive tumor phenotypes compared to $p73^{+/+}$ and $p73^{+/+}$:$p53^{+/-}$ mice (Flores et al. 2005).

Moreover, the generation of specific TAp73 knockout mice ($TAp73^{-/-}$), in which the expression of the ΔN isoforms is still maintained, confirmed TAp73 tumor suppression activity. Compared to $p73^{-/-}$ mice, the $TAp73^{-/-}$ mice present less hippocampal dysgenesis, but increased infertility due to genomic instability of the oocyte and demonstrating a very high incidence of spontaneous tumors, particularly lung adenocarcinomas (Tomasini et al. 2009). The $TAp73^{-/-}$ mice phenotype indirectly shows the oncogenic potential carried by ΔNp73 isoforms, highlighting the importance of a proper balance between TA and ΔN isoforms in normal cells in maintaining genomic fidelity.

In contrast to p53 that is mutated in 50 % of human cancers, the p73 gene is rarely mutated having a frequency of 0.5 % (Ikawa et al. 1999; Nimura et al. 1998; Nomoto et al. 1998; Shishikura et al. 1999; Takahashi et al. 1998). Two examples of p73 mutation are P405R and P425L, a somatic and germ line mutation found in primary neuroblastomas (Naka et al. 2001).

Even if the p73 gene is rarely mutated, it shows a significant incidence in the loss of heterozygosity in a number of different tumors.

Moreover, the p73 gene is often upregulated in different cancer types and this is associated with a poor patient survival prognosis (Tannapfel et al. 1999).

With the design of reagents directed toward discriminating different p73 splicing variants, it was possible to verify that the ΔNp73 isoform is the predominately over-expressed one in tumors of the lung, breast, thymus, colon, prostate, skin, ovary, muscle, and other organs, whereas it is not expressed in healthy tissues (Bozzetti et al. 2007; Cam et al. 2006; Casciano et al. 2002; Dominguez et al. 2006a, b; Frasca et al. 2003; Guan and Chen 2005; Uramoto et al. 2004, 2006; Wager et al. 2006).

In vitro and in vivo studies confirmed the oncogenic role of ΔNp73 isoform. It promotes fibroblasts colony formation ability (Ishimoto et al. 2002) and cooperates with k-RAS, c-myc, and E1A in promoting transformation and tumorigenicity (Petrenko et al. 2003).

Other evidence of ΔNp73 oncogenic role is significantly shown from transgenic mice in which ΔNp73 was overexpressed in the liver. The mice displayed an increased proliferation of hepatocytes, with acinar disorganization and the appearance of pre-neoplastic nodules that in the 83 % of cases evolved in hepatic carcinoma (Tannapfel et al. 2008).

However in various studies, like ΔNp73, also TAp73 expression levels were found increased. This greater increase in levels is consistent with those studies demonstrating the ability of TAp73 in transactivating the ΔNp73 promoter and that ΔNp73 in turn stabilizes the TAp73 protein (Becker et al. 2006; Bozzetti et al. 2007; Dominguez et al. 2006a, b; Frasca et al. 2003; Grob et al. 2001; Slade et al. 2004). In these cases, the tumor suppressive activity of TAp73 is counteracted by a dominant negative effect of ΔNp73 that is able to occupy the DNA binding sites on the promoters of p53 and p73 target genes and to form inactive hetero-tetramer with TAp73 (Pozniak et al. 2000).

8.1.6 p73 Regulation

The expression and the activity of p73 isoforms can be modulated at three different levels (Fig. 8.2): (a) transcriptional regulation of P73 gene P1 and P2 promoters that determines which amino-terminal isoform is produced; (b) post-transcriptional regulation of gene expression by the use of alternative carboxy- and amino-terminal splicing; (c) post-translational regulation that has an impact on protein stability, on protein–protein interaction, and on specificity to target genes (Marabese et al. 2007).

(a) As mentioned above, there are two distinct promoters present on the p73 gene: P1 located upstream from the exon 1 and P2 located within intron 3 which give rise to TA and ΔN isoforms, respectively.

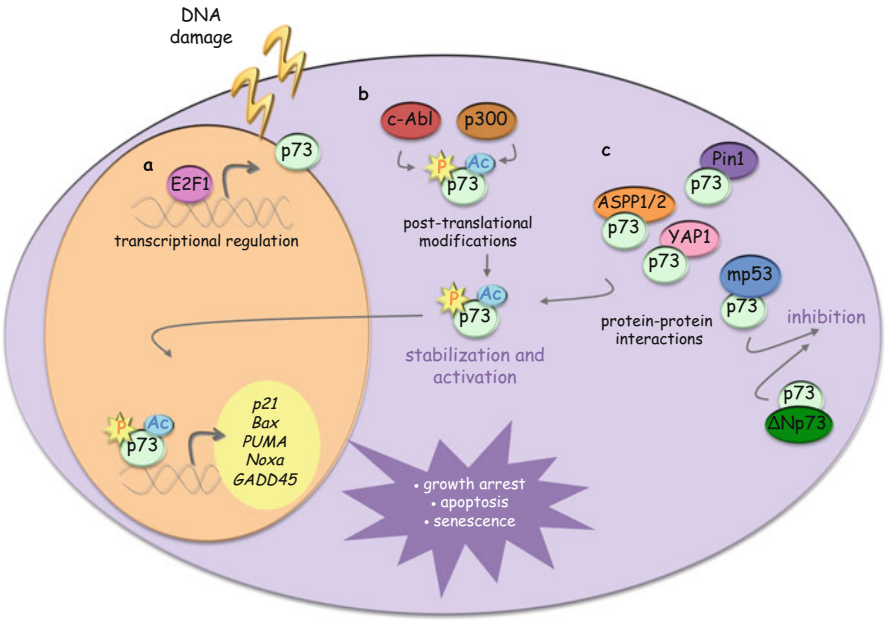

Fig. 8.2 p73 regulation. p73 activity is regulated at different levels: (**a**) transcriptional regulation on P1 and P2 promoters by different transcription factors among which E2F1 on P1 promoter is the best characterized. Upon DNA damage E2F1 binds to its specific consensus sequences on P1 promoter inducing TA isoforms transcription; (**b**) post-translational regulation by protein modifications such as phosphorylation, principally by c-Abl, and acetylation by p300 that stabilize and therefore activate p73; (**c**) physical interaction with other proteins that promote p73 activation (such as ASPP1/2 and YAP) or its inhibition (such as mutant p53 or ΔNp73). Subsequently to its activation, p73 binds to its target genes and, depending on the type of stimulus, it promotes cell growth arrest, apoptosis, or senescence

Binding sites are present on the P1 promoter for different transcription factors such as E2F, Sp1, Myc, c-Myb, AP-2, Egr-1/-2/-3, NFAT, and homeobox proteins (De Laurenzi and Melino 2000). There are also several stretches of CpG islands upstream from the P1 promoter (Ding et al. 1999).

Among the transcriptional regulators of p73, the best characterized one is E2F1. It controls p73 expression under physiological conditions, such as in the G1/S transition or in activation-induced cell death of thymocytes (Irwin et al. 2000; Lissy et al. 2000; Stiewe and Putzer 2000). It has been demonstrated that upon DNA damage E2F1 is subjected to post-translational modifications, such as phosphorylation and acetylation. In addition, it is selectively recruited on the P1 promoter to activate it and to promote a cellular apoptotic response (Ozaki et al. 2009; Pediconi et al. 2003; Urist et al. 2004). E2F1 deacetylation by Sirt1 leads to inhibition of TAp73 transcription (Pediconi et al. 2009). Also methylation and demethylation of E2F1 by Set9 and LSD1 enzymes, respectively, is critical for E2F1 activity on P1 promoter (Kontaki and Talianidis 2010).

E2F1 activity on P1 promoter is also regulated by the interaction with other factors that act as transcriptional repressors, such as C-EBPα, or transcriptional activators, such as YY1 (Marabese et al. 2003; Wu et al. 2008).

In addition to E2F1, cellular and viral oncogene products such as c-Myc and E1A indirectly activated the transcription of p73 (Urist et al. 2004).

A 1-kb regulatory region within the first intron of p73 has also been identified, immediately upstream from the ATG codon of exon 2, containing six consensus binding sites for the transcriptional repressor ZEB1 (Fontemaggi et al. 2001).

Interestingly, the P2 promoter does not contain an E2F1 binding site but possesses a highly efficient p53/TAp73-responsive element. This promoter is activated in response to non-apoptotic DNA damage in a p53-dependent manner to accumulate ΔNp73 proteins and to determine p53/p73-induced cell cycle arrest in cells that do not undergo apoptosis (Grob et al. 2001; Kartasheva et al. 2002; Nakagawa et al. 2002; Vossio et al. 2002). The control of p53/TAp73 on ΔNp73 promoter creates a negative autoregulatory feedback loop that can finely regulate p53 family functions. The loss of these negative feedback loops, occurring in cancer or in infected cells, would result in an indefinite increase in ΔNp73 expression that consequently inactivates p53 and p73, contributing to cancer development (Allart et al. 2002; Stiewe et al. 2002).

(b) The alternative splicing events that occur on the human p73 gene can theoretically give rise to 45 mRNA transcripts which in turn could potentially encode 36 different proteins. The different isoforms are differentially expressed in the human tissues and present specific functions.

(c) Post-translational regulation of p73 includes protein modifications, such as phosphorylation and acetylation and physical interactions with other proteins. These events have an important effect on p73 protein stability and specificity to target genes.

Upon DNA damage, p73 protein is stabilized and thereby activated by the activity of different protein kinases: c-Abl phosphorylates p73 at tyrosine residue 99 (Yuan et al. 1999); Chk1 phosphorylates p73 at serine residue 47 (Gonzalez et al. 2003); PKCδ phosphorylates p73 at serine residue 289 (Ren et al. 2002). All these modifications promote p73 apoptotic activity.

c-Abl also induces p73 phosphorylation in threonine residues adjacent to prolines and the p38 MAP kinase pathway mediates this response (Sanchez-Prieto et al. 2002). Furthermore, p38 phosphorylation of p73 is required for p73 stabilization and recruitment into the nuclear bodies.

The promyelocytic leukemia (PML) protein, in fact, modulates p73 half-life by inhibiting its ubiquitin-proteasome degradation in a PML-nuclear body-dependent manner. PML regulates p73 stability by positively modulating the levels of acetylation, a process that impairs p73 ubiquitination.

As a result, PML potentiates p73 transcriptional and pro-apoptotic activities that are markedly impaired in $PML^{-/-}$ primary cells (Bernassola et al. 2004).

The acetylation of specific p73 protein residues has a pro-apoptotic function effect. Upon doxorubicin treatment p300 acetylates p73 at lysine residues 321, 327 and 331 in a c-Abl-dependent manner (Costanzo et al. 2002). The physical interaction

of p73 with the prolyl isomerase Pin1 promotes p300-mediated acetylation by inducing conformational changes on p73 (Zeng et al. 2000).

Another important post-translational modification that controls p73 stability is the sumolation. Like p53, p73 interacts with the small ubiquitin-like modifier (SUMO) protein which in turn covalently modifies p73α, but not β, on the C-terminal lysine 627 residue and promotes p73α proteasomal degradation (Minty et al. 2000; Rodriguez et al. 1999).

p73 can also be differentially regulated by ubiquitination. NEDL2 ubiquitination within C-terminal proline-rich motif enhances p73 transcriptional and pro-apoptotic activity (Miyazaki et al. 2003). Alternatively, ubiquitination by the ubiquitin E3 ligase Itch potentiates p73 proteasomal degradation. DNA damage causes down regulation of Itch through a poorly characterized mechanism, thus allowing the stabilization and activation of p73 (Agami et al. 1999; Gong et al. 1999; Rossi et al. 2005; Yuan et al. 1999).

The activity of p73 is also influenced by the physical interaction of several proteins. An example of positive regulation is the interaction with ASPP1 and ASPP2. Their binding to p73 DBD specifically stimulates the transactivation functions of p73 on the promoters of pro-apoptotic genes, such as Bax and Puma, except on the promoter of p21 and Mdm2 (Bergamaschi et al. 2004). The ASPP inhibitor family member (iASPP) counteracts this triggering effect on p73 (Bergamaschi et al. 2003; Robinson et al. 2008; Samuels-Lev et al. 2001; Vermeulen et al. 2003).

Also the interaction with the p73 target gene products, Cyclin G and Mdm2, has a negative effect on p73 activity. Cyclin G binding to p73 promotes its degradation, while Mdm2 binding to the transcriptional coactivator p300 causes the disruption of physical and functional interactions between p73 and p300 (Ohtsuka et al. 2003; Zeng et al. 1999).

Of particular interest is the interaction between mutant p53 and p73. The p53 gene is known to be mutated in 50 % of human cancers. The most prevalent types of p53 alterations are missense mutations that occur in the DBD. These mutations result in a very significant loss of DNA binding activity and transactivation capacity (Ory et al. 1994). It is increasingly evident that many mutant p53 forms not only lose their tumor suppressive functions and acquire dominant negative activities, but also gain new oncogenic properties that are independent of wild-type p53 and actively sustain tumor development and progression (Brosh and Rotter 2009). One of the mechanisms by which mutant p53 exerts its gain of function activity is the ability to bind through its mutated DBD and to inhibit its family members, p73 and p63, blocking the transactivation of downstream target genes involved in apoptosis and growth arrest control (Adorno et al. 2009; Di Como et al. 1999; Gaiddon et al. 2001; Marin and Kaelin 2000; Strano and Blandino 2003; Strano et al. 2000). In this regard, some short synthetic peptides, capable to physical disrupt the mutant p53/p73 interaction, have been recently engineered; their effect is to sensitize mutant p53 tumor cells to cisplatin and adryamicin treatments (Di Agostino et al. 2008).

Also the p53 polymorphism in codon 72 (Arg or Pro) influences the interaction with p73, in particular the Arg in the 72 position is required to bind p73 (Marin et al. 2000).

Finally another interactor of p73 that has an important impact on its stability and its activity is the transcriptional coactivator Yes-associated protein 1 (YAP1), a key node of the Hippo signaling pathway. This physical interaction occurs between the PPPPY motif of p73 and the WW domain of YAP and it is specific for only the p53 family members that have a well-conserved PPXY motifs (not p53). The result of YAP protein binding is an enhancement of p73 transcriptional activity upon DNA damage and increase in p73 stability, since YAP promotes the E3 ubiquitin ligase Itch dissociation from p73 (Basu et al. 2003; Strano et al. 2001, 2005). The importance of these interactions will be discussed below.

8.2 YAP

Discovered in 1994 as a 65 kDa binding partner of the Src family kinase c-Yes, chicken YAP (Yes-Associated Protein) was named YAP65 (Sudol 1994). Mouse and human homologs were subsequently cloned and characterized the next year (Sudol et al. 1995).

Two different isoforms have been identified: YAP1 and YAP2, where the principal difference consists in the presence of 1 or 2 WW domains, respectively. Regulation of the switch between the two YAP isoforms is not clear. YAP2 is the major isoform in humans (Komuro et al. 2003).

In general, YAP mRNA is ubiquitously expressed in a wide range of tissues, except peripheral blood leukocytes (Komuro et al. 2003). YAP is also expressed in the full developmental stages from blastocyst to perinatal (Morin-Kensicki et al. 2006).

8.2.1 YAP Functions Discovery

YAP protein was first characterized as a transcriptional coactivator able to bind the PPxY motif of Runx1 (or AML1 for acute myeloid leukemia 1) (Yagi et al. 1999).

Then it was reported that YAP, like its paralog TAZ, presents a 14-3-3 binding site. Affinity purification of the epitope-tagged TEAD2/TEF4 (TEA domain protein 2/transcriptional enhancer factor 4) revealed that YAP is in stable complex with 14-3-3 proteins. In addition, it showed that these proteins seemed to regulate the role of YAP as a coactivator of the TEAD/TEF family of transcription factors (Vassilev et al. 2001). According to these data it was proposed that YAP and its paralog TAZ are 14-3-3 binding transcriptional coactivators regulated by dynamic nucleo-cytoplasmic trafficking. 14-3-3 proteins are phosphoserine- and phosphothreonine-binding signaling regulators for CDC25 phosphates, transcription factors, histone deacetylase, and many others (Yaffe and Elia 2001).

Hence, an important question to pose is which kinases are responsible for phosphorylation of YAP and for linking its regulation to cellular signaling networks? Much support in studying YAP functions came with the identification of Yorkie, the fly ortholog of YAP, that was discovered in a yeast 2-hybrid screening aimed at identifying partners of *Drosophila* M. kinase Warts/Lats (large tumor suppressor) (Huang et al. 2005). This kinase phosphorylates Yorkie resulting in the inhibition of its transactivating and tissue growth-promoting activities (Huang et al. 2005). The kinase Warts/Lats functions downstream from the Hippo kinase (an Ste20 family member) as a key component of a novel signaling pathway important for organ size control (Pan 2007). Thus, the unexpected Yorkie-Lats link suggests the regulation of YAP (and TAZ) by the Hippo-like pathways in mammals. Indeed, several groups have recently shown that mammalians Lats and Hippo-like kinases control the subcellular localization, transcriptional coactivator activities, and biological function of YAP (Camargo et al. 2007; Dong et al. 2007; Oka et al. 2008; Zhang et al. 2008).

Recently, Dupont et al., have identified YAP and its paralog TAZ as nuclear translators of mechanical signals exerted by extracellular matrix stiffness and cell shape. In particular, YAP and TAZ are required for the mesenchymal stem cells differentiation induced by extracellular matrix rigidity and for endothelial cell survival regulated by cell geometry (Dupont et al. 2011).

8.2.2 WW Domain Functions

The WW domain is able to bind short stretches of prolines or PY motifs, therefore mediating the interaction between proteins. The WW domain of YAP belongs to the first of four different classes that differ in terms of sequence of the interacting motif, a PPxY motif in the case of WW type I. The WW domain appears to contain β-strands grouped around four conserved aromatic positions (Bork and Sudol 1994). Other important features of WW domain are the large amount of polar amino acids and the presence of prolines distributed preferentially toward both termini of the linear sequence. One of the C-terminal prolines seems strictly invariant. The length of the domain is of approximately 38 residues as suggested by the length of the second WW module identified in the mouse ortholog of YAP (Sudol et al. 1995).

YAP has been found to interact with many proteins whose functions are often different between them and the majority of these interactions mostly occur through WW domain. For example, YAP is able to bind the cytosolic tail of the Erb4 receptor. Upon binding to its ligand, this receptor undergoes cleavage by intra-membrane proteases that free the cytosolic portion. Despite the fact that this interaction occurs in the cytoplasm, YAP is needed to regulate the activity of the cleaved part of Erb4 only once it gets into the nucleus (Komuro et al. 2003; Omerovic et al. 2004).

In addition YAP1 was also found to partner Smad7, enhancing the inhibitory activity of Smad7 against the TGFbeta/Smad1,-2,-3,-5 signaling complex (Ferrigno et al. 2002). The interaction with PEBP2 (an RUNX transcription factor) was the first example of YAP1 as a coactivator of transcription. The WW domain of YAP1

interacts with the PY motif present in the transcription activation domain of PEBP2. In this occasion, YAP1 was reported for the first time to have strong intrinsic transactivation activity (Yagi et al. 1999).

8.2.3 YAP Activity Regulation

The principal mechanism through which YAP protein activity is regulated consists in the control of its cellular localization: YAP exerts its activity into the nucleus and when it is retained into the cytoplasm it is inactive. The nucleo-cytoplasmic shuttling of YAP is dependent on post-translational modifications of the protein, mainly phosphorylations, that promote YAP binding and therefore sequestering by 14-3-3 protein. The residue mainly undergoing phosphorylation is the serine 127 and the first kinase identified as responsible for this modification was Akt/PKB (Basu et al. 2003). It was proposed that in response to DNA damage Akt/PKB is activated. It induces YAP phosphorylation and subsequently retention into the cytoplasm. Therefore suppressing its ability to induce apoptosis through the transcriptional activity of p73 (Basu et al. 2003; Strano et al. 2005).

Other kinases demonstrated to be able to phosphorylate serine 127 residue of YAP are LATS1 and LATS2 (Hao et al. 2008; Oka et al. 2008; Zhao et al. 2007).

As previously mentioned, YAP was firstly discovered as a protein interacting with the two tyrosine kinases c-Yes and c-Src, so it is reasonable to expect post-translational modifications of YAP by these two proteins. In fact, the ability of c-Src/Yes to bind to YAP and to phosphorylate its tyrosine residues promoting YAP recruitment of RUNX2 to subnuclear sites was demonstrated, which in turn results in RUNX2 activity inhibition (Zaidi et al. 2004).

Also the kinase c-Abl is involved in YAP activity regulation. Upon DNA damage, c-Abl phosphorylates the tyrosine 357 residues of YAP promoting its stability and its affinity for p73 (Levy et al. 2008). As mentioned above, c-Abl has an effect also on p73: c-Abl phosphorylation of p73 tyrosine 99 residue promotes its apoptotic activity (Agami et al. 1999).

8.2.4 YAP Protein Structure

YAP protein is composed of several distinct domains (Fig. 8.3): a proline-rich region at the N-terminal, important for the interaction with the SH3 domain of many proteins, among which is c-Yes; two tandem WW domains in the middle, the name originates from the presence of two tryptophan residues, which appear to be conserved along evolution and play an important role in the domain structure and function (Huang et al. 2000; Sudol et al. 1995; Sudol and Hunter 2000); an Src homology domain 3 binding motif (SH3 BM) PVKQPPPLAP; a coiled-coil domain (CC); a C-terminal capped by TWL sequence, a PDZ domain ligand.

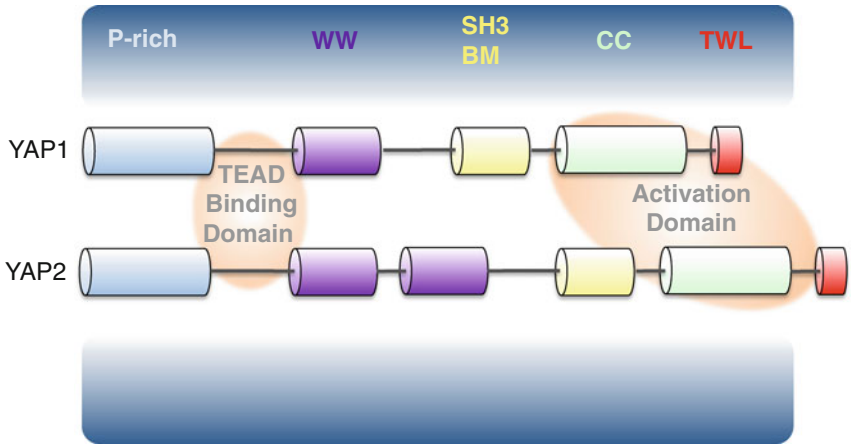

Fig. 8.3 Schematic representation of YAP protein. YAP gene encodes for two isoforms: YAP1 and YAP2. The main differences between YAP1 and YAP2 consist in the presence of 1 or 2 WW domains, respectively. YAP is a 65 kDa protein with several distinct domains: a proline-rich region at the N-terminal, one or two tandem WW domain in the middle followed by an Src homology domain 3 binding motif (SH3 BM), a coiled-coil domain (CC), and a C-terminal capped by TWL sequence, a PDZ domain ligand. The N-terminal is responsible for the interaction with the TEAD transcription factors family, and the C-terminal rich in serine, threonine, and acidic residues was shown to be a strong transcription activator

The N-terminal of YAP was mapped to be the TEAD family transcription factors interaction domain, and the C-terminal of YAP rich in serine, threonine, and acidic residues was shown to be a strong transcription activator.

8.2.5 Role in Animal Development

Different studies highlight the role of YAP in the control of organ growth. In fact, it was demonstrated that the disruption of the Hippo signaling pathway in *Drosophila* M. has a big impact in the growth of imaginal discs (Pan 2007). Moreover, YAP protein mutations are correlated to abnormal size and shape of fly wings (Zhao et al. 2007). Also in mice YAP has been demonstrated to play a pivotal role in cell growth control. YAP overexpression in mice liver induces a reversible increase of its size (Camargo et al. 2007; Dong et al. 2007).

At the molecular levels, the effects of YAP overexpression seem to depend on the inhibition of cell differentiation, partially by stimulating the Notch signaling pathway causing an expansion of multipotent-undifferentiated cells that maintain their ability to differentiate upon YAP gene expression inactivation (Camargo et al. 2007).

The involvement of YAP in the control of bone homeostasis and inhibition of osteoblast activity has also been demonstrated (Zaidi et al. 2004).

8.2.6 YAP in Tumorigenesis

From *Drosophila* M. genetic studies, the first clues about important roles of YAP in tumorigenesis was shown. In these studies ectopic expression of Yorkie leads to an increase in cell proliferation and tissue overgrowth (Huang et al. 2005). Consistent with this, YAP expression is elevated in gastric adenocarcinoma (Lam-Himlin et al. 2006) and the gene is amplified in liver cancer (Zender et al. 2006) and in mouse mammary tumors (Overholtzer et al. 2006). Furthermore, YAP and TAZ are highly expressed in a wide spectrum of human cancer cell lines and various primary tumors (Chan et al. 2008; Dong et al. 2007) supporting these two proteins as oncogenes. In non-transformed mammary epithelial cells, overexpression of YAP induces epithelial-to-mesenchymal transition, suppression of apoptosis, growth factor-independent proliferation, and anchorage-independent growth (Overholtzer et al. 2006). Likewise, the overexpression of TAZ triggers MCF10 mammary epithelial cells to undergo morphological changes, resembling cell transformation (Chan et al. 2008; Lei et al. 2008). Ectopic expression of TAZ also induces cell proliferation, overcomes contact inhibition, and leads to tumorigenesis in nude mice (Lei et al. 2008). Similarly, overexpression of YAP causes loss of contact inhibition (Dong et al. 2007). Other additional studies support the oncogenic role of YAP (Hao et al. 2008; Overholtzer et al. 2006), whereas other works support the idea that YAP might be a tumor suppressor by interacting with p73 (Matallanas et al. 2007; Oka et al. 2008; Strano et al. 2001), and is important for c-Jun-dependent apoptosis (Danovi et al. 2008). Moreover, a recent study showed that YAP acts as tumor suppressor in breast cancer (Yuan et al. 2008), despite being oncogenic when it is overexpressed in the mammary cell line MCF10A (Overholtzer et al. 2006).

8.2.7 YAP and its Role in Transcription

At the functional level, YAP serves as a coregulator for various transcription factors. YAP shares some transcription factor partners, including TEFs/TEADs (Vassilev et al. 2001) and RUNX proteins (Yagi et al. 1999; Zaidi et al. 2004). In addition, YAP is also known to interact with p73 (Basu et al. 2003; Levy et al. 2008; Strano et al. 2001, 2005). Among all these targets, only the interaction with the TEFs/TEADs appears to be conserved from fly to humans (Vassilev et al. 2001).

The domain of YAP responsible for the interaction with TEFs/TEADs transcription factors is localized at the N-terminal of YAP; it binds to the C-terminal domain of TEAD2/TEF4 (Vassilev et al. 2001; Zhao et al. 2007).

Interestingly, TEAD1 and TEAD2 double knockout mice display similar phenotypes as Yap knockouts (Sawada et al. 2008).

Another important interactor of YAP is the transcription factor RUNX2, which exerts a significant role in skeletal mineralization because it stimulates osteoblast differentiation of mesenchymal stem cells, promotes chondrocyte hypertrophy, and contributes to endothelial cell migration and vascular invasion of developing bone. Like other RUNT domain proteins, RUNX2 is a context-dependent transcriptional activator and repressor of genes that regulate cellular proliferation and differentiation.

YAP was identified as a binding partner of mammalian RUNX proteins in yeast two-hybrid screens wherein the proline-rich activation domain of RUNX1 was used as bait (Yagi et al. 1999). YAP was subsequently shown to interact with full-length RUNX2 in osseous cells via co-immunoprecipitation of endogenous proteins and co-immunofluorescence (Zaidi et al. 2004). RUNX2 recruits YAP to subnuclear foci and to the osteocalcin gene promoter, but does not affect its nucleo-cytoplasmic shuttling (Zaidi et al. 2004). The Y residue in the PPPYP motif of RUNX2 is essential for the interactions with YAP (Zaidi et al. 2004). There is no indication showing that YAP can bind to DNA, but when fused to the GAL4-DBD, YAP acts as a transcriptional coactivator of a heterologous GAL-dependent reporter (Yagi et al. 1999; Zaidi et al. 2004). Accordingly, YAP doubled the RUNX2 (PEBP2aA1)-dependent activation of the IgC-α promoter in p19 cells and a dominant-negative of YAP construct blocked RUNX2-dependent activation of osteocalcin promoter in NIH3T3 cells. However, a full-length version of YAP was not tested on the osteocalcin promoter (Yagi et al. 1999). Zaidi et al. (2004) showed that YAP repressed RUNX2-dependent activation of the osteocalcin promoter in NIH3T3 cells and four other cell lines. Thus, YAP-mediated repression of RUNX2 activity on the osteocalcin promoter is cell-type independent. YAP-mediated repression of RUNX2 instead seems to be dependent on promoter context: YAP blocks RUNX2-dependent activation of TGFβR1 promoter and enhances RUNX2-dependent repression of its own promoter. However, it does not affect RUNX2 transcriptional effects on the p6OSE2 or p21 promoters (Zaidi et al. 2004). These data indicate that RUNX2 can recruit YAP to promoter regions, but the effects of YAP on the expression of RUNX2 target genes is dependent on the cohort of other DNA binding proteins and co-factors brought to the gene by specific DNA sequences and protein–protein interactions. Transcriptional repression of RUNX2 by YAP is dependent on Src-induced activation and phosphorylation of YAP (Zaidi et al. 2004). Tyrosine phosphorylation of YAP is required for its subnuclear co-localization with RUNX2 but not for its nucleo-cytoplasmic transport (Zaidi et al. 2004). Thus, YAP is a signal-responsive and context-dependent regulator of RUNX2 activity that may facilitate gene expression in response to extracellular signals or oncogene activation.

8.3 YAP and p73

8.3.1 YAP Is a Transcriptional Coactivator of p73

Looking for p73 interacting proteins, it was found by Strano et al., that YAP1 was able to bind through its WW domain a PY motif present on the C-terminal region of

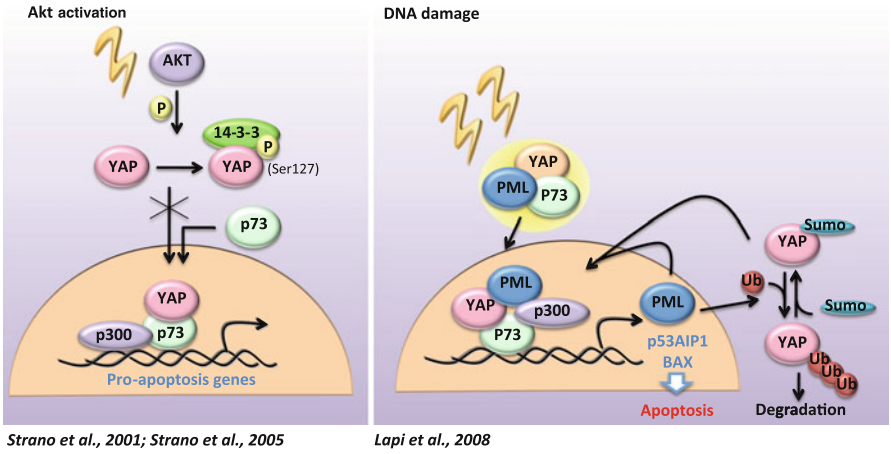

Fig. 8.4 YAP and p73 functions in apoptosis. YAP and p73 cooperate with each other to promote apoptosis upon DNA damage. In particular, YAP exerts an important role in the regulation of p73 stability and transcriptional activity by promoting p300 recruitment on p73 target genes. As shown in the *left panel* Akt-mediated phosphorylation of YAP protein has a negative effect on p73 transcriptional activity because it causes 14-3-3 binding to YAP and its consequent retention into the cytoplasm. In the *right panel*, the pro-apoptotic autoregulatory feedback loop is represented in which PML, YAP, and p73 are involved. Upon DNA damage, PML promotes YAP recruitment into the nuclear bodies where it binds to and activates p73. The YAP/p73 complex protein binds to the promoters of the apoptotic target genes recruiting also p300 and thus promoting their transcriptional activation. Among the target genes there is also PML, that in turn promotes the pro-apoptotic activity of YAP/p73 complex by favoring its stability

p73 (Strano et al. 2001). All the members of the family were checked for this interaction and the shorter members, p73γ and p63γ, and p53 themselves were excluded from the list. Therefore, YAP seems to be selective in choosing its partners among this family of transcription factors, a choice that may guide cells toward a defined outcome when they need YAP function. In 2005, Strano et al., demonstrated that p73 is required for the nuclear translocation of endogenous YAP in cells exposed to cisplatin and that YAP is recruited by PML gene into the nuclear bodies to promote p73 transcriptional activity (Strano et al. 2005). They found that YAP contributes to p73 stabilization in response to DNA damage and promotes p73-dependent apoptosis through the specific and selective coactivation of apoptotic p73 target genes and reinforcement of p300-mediated acetylation of p73 (Fig. 8.4, left panel). Altogether, these results identify YAP as an important determinant for p73 target gene specificity through p300 recruitment and p73 acetylation. In fact, using chromatin-immunoprecipitation, it was shown that upon DNA damage the complex PML-YAP-p73 recruits the acetyl-transferase p300 and together go into the regulatory regions of pro-apoptotic genes and upregulate their transcription (Strano et al. 2005).

Moreover, a YAP effect on p73 protein stability has been demonstrated due to the ability of YAP to bind the same region of p73 usually bound by the ubiquitin-protein ligase Itch. In this way, YAP prevents proteasome-mediated degradation of p73.

8.3.2 *YAP, p73, and PML Are Involved in a Pro-apoptotic Autoregulatory Feedback Loop*

Another important player in the YAP-p73 axis is the PML tumor suppressor gene.

The PML gene, involved in the chromosomal translocation t(15;17) of acute promyelocytic leukemia (APL), encodes a protein that localizes to the PML-nuclear bodies, that has been shown to play an important role in growth suppression, apoptosis, and senescence. In addition, it is induced upon different cellular stress signals and pro-apoptotic stimuli, such as ionizing radiations (Ferbeyre et al. 2000; Pearson et al. 2000). Its tumor suppressor activity has also been demonstrated in PML$^{-/-}$ mice: they present resistance to the lethal effects of γ radiations and to apoptosis induced by CD95 (Salomoni and Pandolfi 2002).

As mentioned before, Strano et al., in 2005 showed how PML is also important in p73-mediated apoptosis in response to cisplatin treatment (Strano et al. 2005).

Afterwards in 2008, Lapi et al. emphasized the existence of an autoregulatory feedback loop in which PML, YAP, and p73 are involved (Fig. 8.4, right panel) (Lapi et al. 2008). In more detail, by using a gene expression microarray analysis in human colon cancer cells HCT116 treated with cisplatin, they found that PML expression is positively modulated by the protein complex p73/YAP. PML is not a specific p73 target gene, since it is controlled by p53 (de Stanchina et al. 2004). In fact, the authors demonstrated how p53 can synergize with p73/YAP complex in the transcriptional regulation of PML during the apoptotic response of HCT116 cells. However, they showed that in particular cellular contexts, in which p53 is not present or mutated, p73 is still able to induce PML expression and nuclear bodies formation. Moreover, by using a constitutively active mutant of AKT that restrains YAP into the cytoplasm, they stressed the important role of YAP as a coactivator of p73 in the transactivation of PML.

The existence of an autoregulatory feedback loop is due to the ability of PML to control YAP stability. In fact, the authors proved the presence of a physical interaction taking place between the WW domain of YAP and the PVPVY motif of PML. This interaction has an effect on YAP half-life since it promotes YAP sumoylation that prevents YAP ubiquitination and therefore its proteasomal degradation.

PML upregulation by p73/YAP complex has an effect also on p73 transcriptional activity itself, in fact, as mentioned before, PML promotes p300-mediated acetylation of p73, that in turn induces the p73 pro-apoptotic response (Bernassola et al. 2004).

8.4 Conclusions

It is becoming increasingly clear that the efficiency and the efficacy of a tumor suppressor response can also be based on the number of engaged tumor suppressor pathways. The existence of an autoregulatory feedback loop between YAP, p73, and

PML, which closely links three different tumor suppressor pathways, might hold promise for anticancer therapeutic approaches. YAP which appears to bridge p53 and PML tumor suppressor activities might turn to be an intriguing and potentially attractive therapeutic target whose modulation maximizes distinct tumor suppressor activities.

References

Adorno M, Cordenonsi M, Montagner M, Dupont S, Wong C, Hann B, et al. A mutant-p53/Smad complex opposes p63 to empower TGFbeta-induced metastasis. Cell. 2009;137:87–98.

Agami R, Blandino G, Oren M, Shaul Y. Interaction of c-Abl and p73alpha and their collaboration to induce apoptosis. Nature. 1999;399:809–13.

Alexander K, Yang HS, Hinds PW. pRb inactivation in senescent cells leads to an E2F-dependent apoptosis requiring p73. Mol Cancer Res. 2003;1:716–28.

Allart S, Martin H, Detraves C, Terrasson J, Caput D, Davrinche C. Human cytomegalovirus induces drug resistance and alteration of programmed cell death by accumulation of deltaN-p73alpha. J Biol Chem. 2002;277:29063–8.

Basu S, Totty NF, Irwin MS, Sudol M, Downward J. Akt phosphorylates the Yes-associated protein, YAP, to induce interaction with 14-3-3 and attenuation of p73-mediated apoptosis. Mol Cell. 2003;11:11–23.

Becker K, Pancoska P, Concin N, Vanden Heuvel K, Slade N, Fischer M, et al. Patterns of p73 N-terminal isoform expression and p53 status have prognostic value in gynecological cancers. Int J Oncol. 2006;29:889–902.

Bergamaschi D, Samuels Y, O'Neil NJ, Trigiante G, Crook T, Hsieh JK, et al. iASPP oncoprotein is a key inhibitor of p53 conserved from worm to human. Nat Genet. 2003;33:162–7.

Bergamaschi D, Samuels Y, Jin B, Duraisingham S, Crook T, Lu X. ASPP1 and ASPP2: common activators of p53 family members. Mol Cell Biol. 2004;24:1341–50.

Bernassola F, Salomoni P, Oberst A, Di Como CJ, Pagano M, Melino G, et al. Ubiquitin-dependent degradation of p73 is inhibited by PML. J Exp Med. 2004;199:1545–57.

Blandino G, Dobbelstein M. p73 and p63: why do we still need them? Cell Cycle. 2004;3:886–94.

Bork P, Sudol M. The WW domain: a signalling site in dystrophin? Trends Biochem Sci. 1994;19:531–3.

Bozzetti C, Nizzoli R, Musolino A, Martella EM, Crafa P, Lagrasta CA, Camisa, et al. p73 and p53 pathway in human breast cancers. J Clin Oncol. 2007;25:1451–3; author reply 1453–4.

Brosh R, Rotter V. When mutants gain new powers: news from the mutant p53 field. Nat Rev Cancer. 2009;9:701–13.

Cam H, Griesmann H, Beitzinger M, Hofmann L, Beinoraviciute-Kellner R, Sauer M, et al. p53 family members in myogenic differentiation and rhabdomyosarcoma development. Cancer Cell. 2006;10:281–93.

Camargo FD, Gokhale S, Johnnidis JB, Fu D, Bell GW, Jaenisch R, et al. YAP1 increases organ size and expands undifferentiated progenitor cells. Curr Biol. 2007;17:2054–60.

Casciano I, Mazzocco K, Boni L, Pagnan G, Banelli B, Allemanni G, et al. Expression of DeltaNp73 is a molecular marker for adverse outcome in neuroblastoma patients. Cell Death Differ. 2002;9:246–51.

Chan SW, Lim CJ, Guo K, Ng CP, Lee I, Hunziker W, et al. A role for TAZ in migration, invasion, and tumourigenesis of breast cancer cells. Cancer Res. 2008;68:2592–8.

Chi SW, Ayed A, Arrowsmith CH. Solution structure of a conserved C-terminal domain of p73 with structural homology to the SAM domain. EMBO J. 1999;18:4438–45.

Collavin L, Lunardi A, Del Sal G. p53-family proteins and their regulators: hubs and spokes in tumour suppression. Cell Death Differ. 2010;17:901–11.

Costanzo A, Merlo P, Pediconi N, Fulco M, Sartorelli V, Cole PA, et al. DNA damage-dependent acetylation of p73 dictates the selective activation of apoptotic target genes. Mol Cell. 2002;9:175–86.

Danovi SA, Rossi M, Gudmundsdottir K, Yuan M, Melino G, Basu S. Yes-associated protein (YAP) is a critical mediator of c-Jun-dependent apoptosis. Cell Death Differ. 2008;15:217–9.

Davison TS, Vagner C, Kaghad M, Ayed A, Caput D, Arrowsmith CH. p73 and p63 are homotetramers capable of weak heterotypic interactions with each other but not with p53. J Biol Chem. 1999;274:18709–14.

De Laurenzi V, Melino G. Evolution of functions within the p53/p63/p73 family. Ann N Y Acad Sci. 2000;926:90–100.

De Laurenzi V, Costanzo A, Barcaroli D, Terrinoni A, Falco M, Annicchiarico-Petruzzelli M, et al. Two new p73 splice variants, gamma and delta, with different transcriptional activity. J Exp Med. 1998;188:1763–8.

de Stanchina E, Querido E, Narita M, Davuluri RV, Pandolfi PP, Ferbeyre G, et al. PML is a direct p53 target that modulates p53 effector functions. Mol Cell. 2004;13:523–35.

Di Agostino S, Cortese G, Monti O, Dell'Orso S, Sacchi A, Eisenstein M, et al. The disruption of the protein complex mutantp53/p73 increases selectively the response of tumour cells to anticancer drugs. Cell Cycle. 2008;7:3440–7.

Di Como CJ, Gaiddon C, Prives C. p73 function is inhibited by tumour-derived p53 mutants in mammalian cells. Mol Cell Biol. 1999;19:1438–49.

Ding Y, Inoue T, Kamiyama J, Tamura Y, Ohtani-Fujita N, Igata E, et al. Molecular cloning and functional characterization of the upstream promoter region of the human p73 gene. DNA Res. 1999;6:347–51.

Dominguez G, Garcia JM, Pena C, Silva J, Garcia V, Martinez L, et al. DeltaTAp73 upregulation correlates with poor prognosis in human tumours: putative in vivo network involving p73 isoforms, p53, and E2F-1. J Clin Oncol. 2006a;24:805–15.

Dominguez G, Pena C, Silva J, Garcia JM, Garcia V, Rodriguez R, et al. The presence of an intronic deletion in p73 and high levels of ZEB1 alter the TAp73/DeltaTAp73 ratio in colorectal carcinomas. J Pathol. 2006b;210:390–7.

Dong J, Feldmann G, Huang J, Wu S, Zhang N, Comerford SA, et al. Elucidation of a universal size-control mechanism in Drosophila and mammals. Cell. 2007;130:1120–33.

Dupont S, Morsut L, Aragona M, Enzo E, Giulitti S, Cordenonsi M, et al. Role of YAP/TAZ in mechanotransduction. Nature. 2011;474:179–83.

Erster S, Moll UM. Stress-induced p53 runs a transcription-independent death program. Biochem Biophys Res Commun. 2005;331:843–50.

Fang L, Lee SW, Aaronson SA. Comparative analysis of p73 and p53 regulation and effector functions. J Cell Biol. 1999;147:823–30.

Ferbeyre G, de Stanchina E, Querido E, Baptiste N, Prives C, Lowe SW. PML is induced by oncogenic ras and promotes premature senescence. Genes Dev. 2000;14:2015–27.

Ferrigno O, Lallemand F, Verrecchia F, L'Hoste S, Camonis J, Atfi A, et al. Yes-associated protein (YAP65) interacts with Smad7 and potentiates its inhibitory activity against TGF-beta/Smad signaling. Oncogene. 2002;21:4879–84.

Fillippovich I, Sorokina N, Gatei M, Haupt Y, Hobson K, Moallem E, et al. Transactivation-deficient p73alpha (p73Deltaexon2) inhibits apoptosis and competes with p53. Oncogene. 2001;20:514–22.

Flinterman M, Guelen L, Ezzati-Nik S, Killick R, Melino G, Tominaga K, et al. E1A activates transcription of p73 and Noxa to induce apoptosis. J Biol Chem. 2005;280:5945–59.

Flores ER, Sengupta S, Miller JB, Newman JJ, Bronson R, Crowley D, et al. Tumour predisposition in mice mutant for p63 and p73: evidence for broader tumour suppressor functions for the p53 family. Cancer Cell. 2005;7:363–73.

Fontemaggi G, Gurtner A, Strano S, Higashi Y, Sacchi A, Piaggio G, et al. The transcriptional repressor ZEB regulates p73 expression at the crossroad between proliferation and differentiation. Mol Cell Biol. 2001;21:8461–70.

Frasca F, Vella V, Aloisi A, Mandarino A, Mazzon E, Vigneri R, et al. p73 tumour-suppressor activity is impaired in human thyroid cancer. Cancer Res. 2003;63:5829–37.
Gaiddon C, Lokshin M, Ahn J, Zhang T, Prives C. A subset of tumour-derived mutant forms of p53 down-regulate p63 and p73 through a direct interaction with the p53 core domain. Mol Cell Biol. 2001;21:1874–87.
Gong JG, Costanzo A, Yang HQ, Melino G, Kaelin Jr WG, Levrero M, et al. The tyrosine kinase c-Abl regulates p73 in apoptotic response to cisplatin-induced DNA damage. Nature. 1999;399:806–9.
Gonzalez S, Prives C, Cordon-Cardo C. p73alpha regulation by Chk1 in response to DNA damage. Mol Cell Biol. 2003;23:8161–71.
Grob TJ, Novak U, Maisse C, Barcaroli D, Luthi AU, Pirnia F, et al. Human delta Np73 regulates a dominant negative feedback loop for TAp73 and p53. Cell Death Differ. 2001;8:1213–23.
Guan M, Chen Y. Aberrant expression of DeltaNp73 in benign and malignant tumours of the prostate: correlation with Gleason score. J Clin Pathol. 2005;58:1175–9.
Hainaut P, Soussi T, Shomer B, Hollstein M, Greenblatt M, Hovig E, et al. Database of p53 gene somatic mutations in human tumours and cell lines: updated compilation and future prospects. Nucleic Acids Res. 1997;25:151–7.
Hao Y, Chun A, Cheung K, Rashidi B, Yang X. Tumour suppressor LATS1 is a negative regulator of oncogene YAP. J Biol Chem. 2008;283:5496–509.
Harms KL, Chen X. The C terminus of p53 family proteins is a cell fate determinant. Mol Cell Biol. 2005;25:2014–30.
Hollstein M, Soussi T, Thomas G, von Brevern MC, Bartsch. P53 gene alterations in human tumours: perspectives for cancer control. Recent Results Cancer Res. 1997;143:369–89.
Huang X, Poy F, Zhang R, Joachimiak A, Sudol M, Eck MJ. Structure of a WW domain containing fragment of dystrophin in complex with beta-dystroglycan. Nat Struct Biol. 2000;7:634–8.
Huang J, Wu S, Barrera J, Matthews K, Pan D. The Hippo signaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the Drosophila Homolog of YAP. Cell. 2005;122:421–34.
Ikawa S, Nakagawara A, Ikawa Y. p53 family genes: structural comparison, expression and mutation. Cell Death Differ. 1999;6:1154–61.
Irwin MS, Kaelin WG. p53 family update: p73 and p63 develop their own identities. Cell Growth Differ. 2001;12:337–49.
Irwin M, Marin MC, Phillips AC, Seelan RS, Smith DI, Liu W, et al. Role for the p53 homologue p73 in E2F-1-induced apoptosis. Nature. 2000;407:645–8.
Ishimoto O, Kawahara C, Enjo K, Obinata M, Nukiwa T, Ikawa S. Possible oncogenic potential of DeltaNp73: a newly identified isoform of human p73. Cancer Res. 2002;62:636–41.
Jost CA, Marin MC, Kaelin Jr WG. p73 is a simian [correction of human] p53-related protein that can induce apoptosis. Nature. 1997;389:191–4.
Kaghad M, Bonnet H, Yang A, Creancier L, Biscan JC, Valent A, et al. Monoallelically expressed gene related to p53 at 1p36, a region frequently deleted in neuroblastoma and other human cancers. Cell. 1997;90:809–19.
Kartasheva NN, Contente A, Lenz-Stoppler C, Roth J, Dobbelstein M. p53 induces the expression of its antagonist p73 Delta N, establishing an autoregulatory feedback loop. Oncogene. 2002;21:4715–27.
Komuro A, Nagai M, Navin NE, Sudol M. WW domain-containing protein YAP associates with ErbB-4 and acts as a co-transcriptional activator for the carboxyl-terminal fragment of ErbB-4 that translocates to the nucleus. J Biol Chem. 2003;278:33334–41.
Kontaki H, Talianidis I. Lysine methylation regulates E2F1-induced cell death. Mol Cell. 2010;39:152–60.
Lam-Himlin DM, Daniels JA, Gayyed MF, Dong J, Maitra A, Pan D, et al. The hippo pathway in human upper gastrointestinal dysplasia and carcinoma: a novel oncogenic pathway. Int J Gastrointest Cancer. 2006;37:103–9.
Lane DP, Crawford LV. T antigen is bound to a host protein in SV40-transformed cells. Nature. 1979;278:261–3.

Lapi E, Di Agostino S, Donzelli S, Gal H, Domany E, Rechavi G, et al. PML, YAP, and p73 are components of a proapoptotic autoregulatory feedback loop. Mol Cell. 2008;32:803–14.
Lee CW, La Thangue NB. Promoter specificity and stability control of the p53-related protein p73. Oncogene. 1999;18:4171–81.
Lei QY, Zhang H, Zhao B, Zha ZY, Bai F, Pei XH, et al. TAZ promotes cell proliferation and epithelial-mesenchymal transition and is inhibited by the hippo pathway. Mol Cell Biol. 2008;28:2426–36.
Levrero M, De Laurenzi V, Costanzo A, Gong J, Wang JY, Melino G. The p53/p63/p73 family of transcription factors: overlapping and distinct functions. J Cell Sci. 2000;113(Pt 10):1661–70.
Levy D, Adamovich Y, Reuven N, Shaul Y. Yap1 phosphorylation by c-Abl is a critical step in selective activation of proapoptotic genes in response to DNA damage. Mol Cell. 2008;29:350–61.
Linzer DI, Levine AJ. Characterization of a 54K dalton cellular SV40 tumour antigen present in SV40-transformed cells and uninfected embryonal carcinoma cells. Cell. 1979;17:43–52.
Lissy NA, Davis PK, Irwin M, Kaelin WG, Dowdy SF. A common E2F-1 and p73 pathway mediates cell death induced by TCR activation. Nature. 2000;407:642–5.
Marabese M, Vikhanskaya F, Rainelli C, Sakai T, Broggini M. DNA damage induces transcriptional activation of p73 by removing C-EBPalpha repression on E2F1. Nucleic Acids Res. 2003;31:6624–32.
Marabese M, Vikhanskaya F, Broggini M. p73: a chiaroscuro gene in cancer. Eur J Cancer. 2007;43:1361–72.
Marin MC, Kaelin Jr WG. p63 and p73: old members of a new family. Biochim Biophys Acta. 2000;1470:M93–100.
Marin MC, Jost CA, Brooks LA, Irwin MS, O'Nions J, Tidy JA, et al. A common polymorphism acts as an intragenic modifier of mutant p53 behaviour. Nat Genet. 2000;25:47–54.
Matallanas D, Romano D, Yee K, Meissl K, Kucerova L, Piazzolla D, et al. RASSF1A elicits apoptosis through an MST2 pathway directing proapoptotic transcription by the p73 tumour suppressor protein. Mol Cell. 2007;27:962–75.
Melino G. p73, the "assistant" guardian of the genome? Ann N Y Acad Sci. 2003;1010:9–15.
Melino G, De Laurenzi V, Vousden KH. p73: friend or foe in tumourigenesis. Nat Rev Cancer. 2002;2:605–15.
Melino G, Bernassola F, Ranalli M, Yee K, Zong WX, Corazzari M, et al. p73 Induces apoptosis via PUMA transactivation and Bax mitochondrial translocation. J Biol Chem. 2004;279:8076–83.
Mills AA. p53: link to the past, bridge to the future. Genes Dev. 2005;19:2091–9.
Minty A, Dumont X, Kaghad M, Caput D. Covalent modification of p73alpha by SUMO-1. Two-hybrid screening with p73 identifies novel SUMO-1-interacting proteins and a SUMO-1 interaction motif. J Biol Chem. 2000;275:36316–23.
Miyazaki K, Ozaki T, Kato C, Hanamoto T, Fujita T, Irino S, et al. A novel HECT-type E3 ubiquitin ligase, NEDL2, stabilizes p73 and enhances its transcriptional activity. Biochem Biophys Res Commun. 2003;308:106–13.
Moll UM, Slade N. p63 and p73: roles in development and tumour formation. Mol Cancer Res. 2004;2:371–86.
Morin-Kensicki EM, Boone BN, Howell M, Stonebraker JR, Teed J, Alb JG, et al. Defects in yolk sac vasculogenesis, chorioallantoic fusion, and embryonic axis elongation in mice with targeted disruption of Yap65. Mol Cell Biol. 2006;26:77–87.
Muller M, Schilling T, Sayan AE, Kairat A, Lorenz K, Schulze-Bergkamen H, et al. TAp73/Delta Np73 influences apoptotic response, chemosensitivity and prognosis in hepatocellular carcinoma. Cell Death Differ. 2005;12:1564–77.
Murray-Zmijewski F, Lane DP, Bourdon JC. p53/p63/p73 isoforms: an orchestra of isoforms to harmonise cell differentiation and response to stress. Cell Death Differ. 2006;13:962–72.
Naka M, Ozaki T, Takada N, Takahashi M, Shishikura T, Sakiyama S, et al. Functional characterization of naturally occurring mutants (P405R and P425L) of p73alpha and p73beta found in neuroblastoma and lung cancer. Oncogene. 2001;20:3568–72.

Nakagawa T, Takahashi M, Ozaki T, Watanabe Ki K, Todo S, Mizuguchi H, et al. Autoinhibitory regulation of p73 by delta Np73 to modulate cell survival and death through a p73-specific target element within the Delta Np73 promoter. Mol Cell Biol. 2002;22:2575–85.

Nimura Y, Mihara M, Ichimiya S, Sakiyama S, Seki N, Ohira M, et al. p73, a gene related to p53, is not mutated in esophageal carcinomas. Int J Cancer. 1998;78:437–40.

Nomoto S, Haruki N, Kondo M, Konishi H, Takahashi T. Search for mutations and examination of allelic expression imbalance of the p73 gene at 1p36.33 in human lung cancers. Cancer Res. 1998;58:1380–3.

Ohtsuka T, Ryu H, Minamishima YA, Ryo A, Lee SW. Modulation of p53 and p73 levels by cyclin G: implication of a negative feedback regulation. Oncogene. 2003;22:1678–87.

Oka T, Mazack V, Sudol M. Mst2 and Lats kinases regulate apoptotic function of Yes kinase-associated protein (YAP). J Biol Chem. 2008;283:27534–46.

Omerovic J, Puggioni EM, Napoletano S, Visco V, Fraioli R, Frati L, et al. Ligand-regulated association of ErbB-4 to the transcriptional co-activator YAP65 controls transcription at the nuclear level. Exp Cell Res. 2004;294:469–79.

Ory K, Legros Y, Auguin C, Soussi T. Analysis of the most representative tumour-derived p53 mutants reveals that changes in protein conformation are not correlated with loss of transactivation or inhibition of cell proliferation. EMBO J. 1994;13:3496–504.

Overholtzer M, Zhang J, Smolen GA, Muir B, Li W, Sgroi DC, et al. Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. Proc Natl Acad Sci U S A. 2006;103:12405–10.

Ozaki T, Nakagawara A. p73, a sophisticated p53 family member in the cancer world. Cancer Sci. 2005;96:729–37.

Ozaki T, Naka M, Takada N, Tada M, Sakiyama S, Nakagawara A. Deletion of the COOH-terminal region of p73alpha enhances both its transactivation function and DNA-binding activity but inhibits induction of apoptosis in mammalian cells. Cancer Res. 1999;59:5902–7.

Ozaki T, Okoshi R, Sang M, Kubo N, Nakagawara A. Acetylation status of E2F-1 has an important role in the regulation of E2F-1-mediated transactivation of tumour suppressor p73. Biochem Biophys Res Commun. 2009;386:207–11.

Pan D. Hippo signaling in organ size control. Genes Dev. 2007;21:886–97.

Pearson M, Carbone R, Sebastiani C, Cioce M, Fagioli M, Saito S, et al. PML regulates p53 acetylation and premature senescence induced by oncogenic Ras. Nature. 2000;406:207–10.

Pediconi N, Ianari A, Costanzo A, Belloni L, Gallo R, Cimino L, et al. Differential regulation of E2F1 apoptotic target genes in response to DNA damage. Nat Cell Biol. 2003;5:552–8.

Pediconi N, Guerrieri F, Vossio S, Bruno T, Belloni L, Schinzari V, et al. hSirT1-dependent regulation of the PCAF-E2F1-p73 apoptotic pathway in response to DNA damage. Mol Cell Biol. 2009;29:1989–98.

Petrenko O, Zaika A, Moll UM. deltaNp73 facilitates cell immortalization and cooperates with oncogenic Ras in cellular transformation in vivo. Mol Cell Biol. 2003;23:5540–55.

Pozniak CD, Radinovic S, Yang A, McKeon F, Kaplan DR, Miller FD. An anti-apoptotic role for the p53 family member, p73, during developmental neuron death. Science. 2000;289:304–6.

Pozniak CD, Barnabe-Heider F, Rymar VV, Lee AF, Sadikot AF, Miller FD. p73 is required for survival and maintenance of CNS neurons. J Neurosci. 2002;22:9800–9.

Ramadan S, Terrinoni A, Catani MV, Sayan AE, Knight RA, Mueller M, et al. p73 induces apoptosis by different mechanisms. Biochem Biophys Res Commun. 2005;331:713–7.

Ren J, Datta R, Shioya H, Li Y, Oki E, Biedermann V, et al. p73beta is regulated by protein kinase Cdelta catalytic fragment generated in the apoptotic response to DNA damage. J Biol Chem. 2002;277:33758–65.

Robinson RA, Lu X, Jones EY, Siebold C. Biochemical and structural studies of ASPP proteins reveal differential binding to p53, p63, and p73. Structure. 2008;16:259–68.

Rodriguez MS, Desterro JM, Lain S, Midgley CA, Lane DP, Hay RT. SUMO-1 modification activates the transcriptional response of p53. EMBO J. 1999;18:6455–61.

Rossi M, Sayan AE, Terrinoni A, Melino G, Knight RA. Mechanism of induction of apoptosis by p73 and its relevance to neuroblastoma biology. Ann N Y Acad Sci. 2004;1028:143–9.

Rossi M, De Laurenzi V, Munarriz E, Green DR, Liu YC, Vousden KH, et al. The ubiquitin-protein ligase Itch regulates p73 stability. EMBO J. 2005;24:836–48.
Salomoni P, Pandolfi PP. The role of PML in tumour suppression. Cell. 2002;108:165–70.
Samuels-Lev Y, O'Connor DJ, Bergamaschi D, Trigiante G, Hsieh JK, Zhong S, et al. ASPP proteins specifically stimulate the apoptotic function of p53. Mol Cell. 2001;8:781–94.
Sanchez-Prieto R, Sanchez-Arevalo VJ, Servitja JM, Gutkind JS. Regulation of p73 by c-Abl through the p38 MAP kinase pathway. Oncogene. 2002;21:974–9.
Sawada A, Kiyonari H, Ukita K, Nishioka N, Imuta Y, Sasaki H. Redundant roles of Tead1 and Tead2 in notochord development and the regulation of cell proliferation and survival. Mol Cell Biol. 2008;28:3177–89.
Sayan AE, Sayan BS, Gogvadze V, Dinsdale D, Nyman U, Hansen TM, et al. P73 and caspase-cleaved p73 fragments localize to mitochondria and augment TRAIL-induced apoptosis. Oncogene. 2008;27:4363–72.
Shishikura T, Ichimiya S, Ozaki T, Nimura Y, Kageyama H, Nakamura Y, et al. Mutational analysis of the p73 gene in human breast cancers. Int J Cancer. 1999;84:321–5.
Slade N, Zaika AI, Erster S, Moll UM. DeltaNp73 stabilises TAp73 proteins but compromises their function due to inhibitory hetero-oligomer formation. Cell Death Differ. 2004;11:357–60.
Stiewe T, Putzer BM. Role of the p53-homologue p73 in E2F1-induced apoptosis. Nat Genet. 2000;26:464–9.
Stiewe T, Putzer BM. Role of p73 in malignancy: tumour suppressor or oncogene? Cell Death Differ. 2002;9:237–45.
Stiewe T, Theseling CC, Putzer BM. Transactivation-deficient Delta TA-p73 inhibits p53 by direct competition for DNA binding: implications for tumourigenesis. J Biol Chem. 2002;277:14177–85.
Strano S, Blandino G. p73-mediated chemosensitivity: a preferential target of oncogenic mutant p53. Cell Cycle. 2003;2:348–9.
Strano S, Munarriz E, Rossi M, Cristofanelli B, Shaul Y, Castagnoli L, et al. Physical and functional interaction between p53 mutants and different isoforms of p73. J Biol Chem. 2000;275:29503–12.
Strano S, Munarriz E, Rossi M, Castagnoli L, Shaul Y, Sacchi A, et al. Physical interaction with Yes-associated protein enhances p73 transcriptional activity. J Biol Chem. 2001;276:15164–73.
Strano S, Monti O, Pediconi N, Baccarini A, Fontemaggi G, Lapi E, et al. The transcriptional coactivator Yes-associated protein drives p73 gene-target specificity in response to DNA damage. Mol Cell. 2005;18:447–59.
Sudol M. Yes-associated protein (YAP65) is a proline-rich phosphoprotein that binds to the SH3 domain of the Yes proto-oncogene product. Oncogene. 1994;9:2145–52.
Sudol M, Hunter T. NeW wrinkles for an old domain. Cell. 2000;103:1001–4.
Sudol M, Bork P, Einbond A, Kastury K, Druck T, Negrini M, et al. Characterization of the mammalian YAP (Yes-associated protein) gene and its role in defining a novel protein module, the WW domain. J Biol Chem. 1995;270:14733–41.
Takahashi H, Ichimiya S, Nimura Y, Watanabe M, Furusato M, Wakui S, et al. Mutation, allelotyping, and transcription analyses of the p73 gene in prostatic carcinoma. Cancer Res. 1998;58:2076–7.
Tanaka Y, Kameoka M, Itaya A, Ota K, Yoshihara K. Regulation of HSF1-responsive gene expression by N-terminal truncated form of p73alpha. Biochem Biophys Res Commun. 2004;317:865–72.
Tannapfel A, Wasner M, Krause K, Geissler F, Katalinic A, Hauss J, et al. Expression of p73 and its relation to histopathology and prognosis in hepatocellular carcinoma. J Natl Cancer Inst. 1999;91:1154–8.
Tannapfel A, John K, Mise N, Schmidt A, Buhlmann S, Ibrahim SM, et al. Autonomous growth and hepatocarcinogenesis in transgenic mice expressing the p53 family inhibitor DNp73. Carcinogenesis. 2008;29:211–8.

Terrinoni A, Ranalli M, Cadot B, Leta A, Bagetta G, Vousden KH, et al. p73-alpha is capable of inducing scotin and ER stress. Oncogene. 2004;23:3721–5.
Tomasini R, Tsuchihara K, Tsuda C, Lau SK, Wilhelm M, Ruffini A, et al. TAp73 regulates the spindle assembly checkpoint by modulating BubR1 activity. Proc Natl Acad Sci U S A. 2009;106:797–802.
Ueda Y, Hijikata M, Takagi S, Chiba T, Shimotohno K. New p73 variants with altered C-terminal structures have varied transcriptional activities. Oncogene. 1999;18:4993–8.
Uramoto H, Sugio K, Oyama T, Nakata S, Ono K, Morita M, et al. Expression of deltaNp73 predicts poor prognosis in lung cancer. Clin Cancer Res. 2004;10:6905–11.
Uramoto H, Sugio K, Oyama T, Nakata S, Ono K, Nozoe T, et al. Expression of the p53 family in lung cancer. Anticancer Res. 2006;26:1785–90.
Urist M, Tanaka T, Poyurovsky MV, Prives C. p73 induction after DNA damage is regulated by checkpoint kinases Chk1 and Chk2. Genes Dev. 2004;18:3041–54.
Vassilev A, Kaneko KJ, Shu H, Zhao Y, DePamphilis ML. TEAD/TEF transcription factors utilize the activation domain of YAP65, a Src/Yes-associated protein localized in the cytoplasm. Genes Dev. 2001;15:1229–41.
Vermeulen K, Berneman ZN, Van Bockstaele DR. Cell cycle and apoptosis. Cell Prolif. 2003;36:165–75.
Vossio S, Palescandolo E, Pediconi N, Moretti F, Balsano C, Levrero M, et al. DN-p73 is activated after DNA damage in a p53-dependent manner to regulate p53-induced cell cycle arrest. Oncogene. 2002;21:3796–803.
Wager M, Guilhot J, Blanc JL, Ferrand S, Milin S, Bataille B, et al. Prognostic value of increase in transcript levels of Tp73 DeltaEx2-3 isoforms in low-grade glioma patients. Br J Cancer. 2006;95:1062–9.
Wang P, Yu W, Hu Z, Jia L, Iyer VR, Sanders BG, et al. Involvement of JNK/p73/NOXA in vitamin E analog-induced apoptosis of human breast cancer cells. Mol Carcinog. 2008;47:436–45.
Wu S, Murai S, Kataoka K, Miyagishi M. Yin Yang 1 induces transcriptional activity of p73 through cooperation with E2F1. Biochem Biophys Res Commun. 2008;365:75–81.
Yaffe MB, Elia AE. Phosphoserine/threonine-binding domains. Curr Opin Cell Biol. 2001;13:131–8.
Yagi R, Chen LF, Shigesada K, Murakami Y, Ito Y. A WW domain-containing yes-associated protein (YAP) is a novel transcriptional co-activator. EMBO J. 1999;18:2551–62.
Yang A, Kaghad M, Wang Y, Gillett E, Fleming MD, Dotsch V, et al. p63, a p53 homolog at 3q27-29, encodes multiple products with transactivating, death-inducing, and dominant-negative activities. Mol Cell. 1998;2:305–16.
Yang A, Schweitzer R, Sun D, Kaghad M, Walker N, Bronson RT, et al. p63 is essential for regenerative proliferation in limb, craniofacial and epithelial development. Nature. 1999;398:714–8.
Yang A, Walker N, Bronson R, Kaghad M, Oosterwegel M, Bonnin J, et al. p73-deficient mice have neurological, pheromonal and inflammatory defects but lack spontaneous tumours. Nature. 2000;404:99–103.
Yuan ZM, Shioya H, Ishiko T, Sun X, Gu J, Huang YY, et al. p73 is regulated by tyrosine kinase c-Abl in the apoptotic response to DNA damage. Nature. 1999;399:814–7.
Yuan M, Tomlinson V, Lara R, Holliday D, Chelala C, Harada T, et al. Yes-associated protein (YAP) functions as a tumour suppressor in breast. Cell Death Differ. 2008;15:1752–9.
Zaidi SK, Sullivan AJ, Medina R, Ito Y, van Wijnen AJ, Stein JL, et al. Tyrosine phosphorylation controls Runx2-mediated subnuclear targeting of YAP to repress transcription. EMBO J. 2004;23:790–9.
Zender L, Spector MS, Xue W, Flemming P, Cordon-Cardo C, Silke J, et al. Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. Cell. 2006;125:1253–67.
Zeng X, Chen L, Jost CA, Maya R, Keller D, Wang X, et al. MDM2 suppresses p73 function without promoting p73 degradation. Mol Cell Biol. 1999;19:3257–66.

Zeng X, Li X, Miller A, Yuan Z, Yuan W, Kwok RP, et al. The N-terminal domain of p73 interacts with the CH1 domain of p300/CREB binding protein and mediates transcriptional activation and apoptosis. Mol Cell Biol. 2000;20:1299–310.

Zhang J, Smolen GA, Haber DA. Negative regulation of YAP by LATS1 underscores evolutionary conservation of the Drosophila Hippo pathway. Cancer Res. 2008;68:2789–94.

Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, et al. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes Dev. 2007;21:2747–61.

Zhu J, Jiang J, Zhou W, Chen X. The potential tumour suppressor p73 differentially regulates cellular p53 target genes. Cancer Res. 1998;58:5061–5.