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Review Article

Mechanistic Insights into Cell Death Mediated by the P53 Family

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Abstract

Development of effective anti-cancer therapies continues to be a challenge due to genetic instability that promotes intra-tumoral molecular heterogeneity and subsequent adaptation to therapy. In this review, we briefly discuss the history of the p53 family (p53/p63/p73) and how regulatory circuits affect its function in promoting apoptotic cell death. In addition, we provide perspective on how protein-protein interactions between members of the p53 family, as well as, with other regulatory proteins can dictate response to therapy. In the future, therapies that focus on targeting the p53 family to sustain pro-apoptotic pathways in combination with cancer-specific dysregulated signaling pathways is a promising approach. With further investigation at the basic science level, improvements in efficacy and quality of life for cancer patients with diverse molecular signatures may be realized.

ABBREVIATIONS

DDR: DNA Damage Response; BAX: BCL-2-Associated X protein; PUMA: p53 Upregulated Modulator of Apoptosis; BAK: BCL-2 homologous Antagonist/killer; MOMP: Mitochondrial Outer Membrane Permeabilization; TRAIL: Tumor necrosis factor-Related Apoptosis-Inducing Ligand; PTMs: Post-Translational Modifications; ASPP: Ankirin-repeat-containing, SH3-domain-containing, and Proline-rich-region containing Protein; APID: Agile Protein Interactomes DataServer; MDM2: Mouse Double Minute protein 2; AMPK: AMP-activated Protein Kinase; NEDL2: NEDD4-like Ligase 2; NQO1: NAD(P)H Quinone oxidoreductase 1; LKB1: Liver Kinase B1; mTOR: Mammalian Target of Rapamycin; PPP: Pentose Phosphate Pathway; GLS-2: Glutaminase-2; MDMX: Murine Double Minute X; PML: Promyelocytic Leukaemia protein; IKK: I kB kinase; Plk1: Polo-like Kinase 1; Cables1: CDK5 and Abl enzyme substrate 1.

INTRODUCTION

The p53 gene was discovered in 1979 by Lionel Crawford (Imperial Cancer Research Fund, UK) [1]; Lloyd Old (Memorial Sloan-Kettering Cancer Center) [2]; as well as David P. Lane and Arnold Levine (Princeton University/University of Medicine and Dentistry of New Jersey, Cancer Institute of New Jersey) [3]. Since its discovery, p53 has undergone extensive study and is essentially positioned as a critical regulator of most aspects of cell behavior and physiology. p53 regulates cell growth, survival, differentiation, and responds to DNA damage. The capacity of p53 to regulate and maintain genomic stability largely determines whether the cell survives or undergoes cell death, senescence, or autophagy. Additionally, numerous studies suggest a critical role of p53 in longevity [4,5], metabolism [6], epigenetic modification [7], motility [8,9], and stem cell reprogramming [10]. Furthermore, p53 activation is essential for the senescence response induced by short telomeres [11]. p53 is mutated in over half of all human tumors and the emerging role of mutant p53 and gain-of-function mutations has been thoroughly reviewed by Muller and colleagues [12]. In this review, we will focus on the role of the p53 family in cancer cell apoptosis and survival. p53 suppresses tumor cell growth through multiple mechanisms. First, following DNA damage, p53 regulates the DNA Damage Response (DDR) by activating DNA repair. Second, p53 can arrest growth by holding the cell cycle at the G1/S checkpoint following DNA damage. Third, it can initiate apoptosis (i.e., programmed cell death) if DNA damage proves to be irreparable [13-16].

After the discovery of p53 in transformed cells, two additional family members, p63 and p73, were identified by McKeon's group

[13,15,17]. The three proteins have varying degrees of sequence similarity in their DNA-binding (~63%), oligomerization (~38%), and transactivation (~22%) domains. All three members can bind to the same consensus DNA-binding site [5′-Pu-Pu-Pu-C-(A/T)-(T/A)-G-Pyr-Pyr-Pyr-3′] and activate downstream target genes [15]. The structure, major functions, and knockout mouse phenotype are summarized in Figure 1. The p53 null mice are viable and largely normal in embryonic development, but can develop multiple tumor types at a young age [18]. The two major tumor types that develop are lymphomas (~75% of mice) and sarcomas (~25% of mice) [18,19]. In contrast, while p63-null and p73-null mice do not develop tumors, they exhibit major developmental defects [20-22].

Both p63 and p73 genes have two different promoter enhancer elements that are unique to each gene. p63 and p73 use their P1 promoter to yield full-length transcription activation (TA) isoforms TAp63 and TAp73, respectively, which upon translation, result in expression of the full-length proteins that contain a transactivation domain (TA) and function as tumor suppressors [23]. The P2 promoter for both TAp63 and TAp73, produces an amino-truncated (ΔN isoform), which has lost the TA domain and generally has anti-apoptotic roles since it competes with the full-length pro-apoptotic TAp63 or TAp73 proteins for the DNA binding sites of downstream target genes

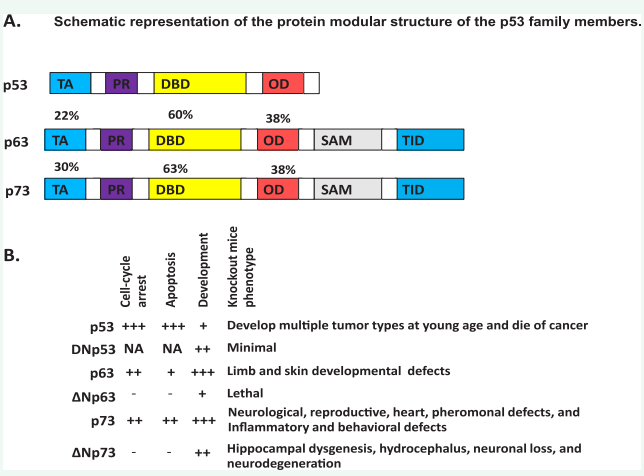

Figure 1 Schematic representation of the protein structure of the p53 family members.
(A) The p53 family includes three genes p53, p63, and p73. The overall domain structure of p53, p63, and p73 is conserved and consists of an amino-terminal transactivation domain (TA), followed by a proline-rich region (PR), a central DNA binding domain (DBD) and a carboxy-terminal oligomerization domain (OD). In p63 and p73, there is an additional sterile alpha motif (SAM), and transactional inhibitory domain (TID) in the carboxy-terminal. Identity shared by p63 and p73 with p53 is indicated.
(B) Simplified classification of the functions of the p53 family members. Members of this family have similar as well as unique cellular functions. Cell cycle arrest and apoptotic pathways are similar amongst all p53 family members. In contrast to p53, both p63 and p73 are involved in the regulation of differentiation and development. These crucial functions are well exemplified by the p63 and p73 knockout mouse phenotypes. NA= no information available
Schematic representation of the protein modular structure of the p53 family members.

[24-30]. For example, Wilhelm et al. used a ΔN p73-specific KO mice model and showed that primary MEFs from ΔN p73 (-/-) mice are sensitized to DNA-damaging agents which results in an increase in p53-dependent apoptosis. Moreover, human tumors with high levels of ΔNp73 expression exhibited enhanced resistance to chemotherapy. ΔNp73 localizes directly to the site of DNA damage, can interact with the DNA damage sensor protein 53BP1, and inhibit ATM activation and subsequent p53 phosphorylation and activation [24]. While p63 and p73 have tumor suppression functions similar to p53, both p63 and p73 also play central developmental roles. p63-null mice fail to develop limbs and a stratified epithelium, resulting in perinatal lethality and a severe phenotype of lacking limbs and a wide range of epithelial structures including skin, prostate, breast, and urothelial [20,21]. p73-null mice are viable but have an abnormal nervous system, hydrocephalus, and immunological problems with chronic inflammation. p73-null mice also have reproductive and behavioral defects, and generally die within several weeks after birth [22].

P53 FAMILY MEMBER-DEPENDENT APOPTOSIS

Cell death plays a vital role in tumorigenesis, growth, and progression and its induction during chemotherapy reflects its effectiveness. There are four major types of cell death mediated by the p53 family: apoptosis, necrosis, autophagy, and pyroptosis. The p53 family members play a critical role in cell cycle arrest by inducing and regulating the pivotal DDR network (e.g. Gadd45, PCNA and $p21^{Waf1/Cip1}$), cell cycle regulation (e.g. $p21^{Waf1/Cip1}$, Gadd45, Wip1, mouse double minute protein 2 (MDM2), cyclin D1, cyclin G, and 14-3-3σ), and apoptosis (BCL-2-associated X protein (BAX), Bcl-XL, Fas, IGFBP3, PAG608, p53 upregulated modulator of apoptosis (PUMA), and DR5). This review, will provide detailed discussion on the role of p53 family members in apoptosis. For insight on non-canonical cell death pathways induced by p53, refer to the review by Ranjan and Iwakuma [31].

p53 is a transcription factor that binds to the promoters and introns of target genes, leading to activation of gene expression. It plays a crucial role in maintaining organismal fitness and fidelity through two broad mechanisms: first, by facilitating the ability of cells to adapt and repair themselves following genotoxic stress and damage, and second, by eliminating cells in which damage cannot be resolved. p53 transcriptionally activates the expression of several pro-apoptotic BCL-2 family proteins, including BAX, NOXA and PUMA [32,33]. Additionally, it also directly interacts with various pro-apoptotic and anti-apoptotic proteins in the cytoplasm and at the mitochondrial membrane [34] such as BCL-2 homologous antagonist/killer (BAK), and BAX. Thus, p53 can function as both a sensitizer and an activator of apoptosis.

Apoptosis is a caspase-dependent form of programmed cell death in response to intracellular (intrinsic) and extracellular (extrinsic) stimuli. The intrinsic apoptotic cascade leads to mitochondrial outer membrane permeabilization (MOMP), which releases cytochrome c (cyto C) into the cytoplasm. Following its release, cyto C activates the caspase cascade, which leads to cell death. MOMP is regulated by the BCL-2 family of proteins, including the pro-apoptotic factors BAX and BAK that are required for forming pores in the mitochondrial membrane [35]. The extrinsic apoptotic pathway is initiated by the binding of death ligands such as FAS ligand (CD95L) or tumor necrosis

factor-related apoptosis-inducing ligand (TRAIL) to their respective receptors, leading to cell death through activation of caspase 8 [35].

It is generally assumed, although not necessarily proven, that because the functions of p53 and p63/p73 overlap, p63/p73 can substitute for the pro-apoptotic role of p53 in cells where p53 is deleted, mutated, or inactive. As noted below, however, complex regulatory interactions between p63/p73 and mutant p53 can exist. p63/p73 is activated in response to DNA damage and chemotherapeutic agents [36]. Once activated, p63/p73 can regulate the induction of apoptosis and cell cycle arrest similarly to p53. p63/p73-dependent apoptosis is primarily regulated by its ability to transcriptionally activate pro-apoptotic p53 target genes such as: the BCL-2 family members (BAX, PUMA, NOXA, BAD and BIK, the oxidoreductase PIG3, the tetraspan membrane protein PERP); the death receptors [CD95, TNF-R1, TRAIL-R1 and TRAIL-R2(DR5)]; the mitochondrial membrane protein p53 AIP1; and the caspases (caspases-3, -6 and-8) [37,38]. Induction of apoptosis by p63/p73 in response to DNA damaging agents is intimately linked not only to its transcriptional activation, but also to post-translational modifications (PTMs) of p63/p73 and interaction with transcriptional co-activators. Several PTMs including ubiquitination, acetylation, and phosphorylation, in addition to transcriptional co-activator recruitment, have been identified as regulators of p63/p73 pro-apoptotic activity. Some of the most investigated proteins that regulate p73-dependent apoptosis are c-Abl, YAP1, p300, CBP, and Ankirin-repeat-containing, SH3-domain-containing, and proline-rich-region containing protein [ASPP] family.

REGULATION 0F P53 FAMILY MEMBERS' STABILITY AND FUNCTION

A large number of PTMs and protein-protein interactions in the non-stressed and stressed conditions control the functions of proteins of the p53 family. In the Agile Protein Interactomes DataServer [APID] database, 1082 proteins interact with human p53, 152 proteins interact with human p73, and 144 proteins interact with human p63 [39]. Many of these interacting proteins could be important in determining biological effect (survival versus death) but it is important to emphasize outcome could depend on the cellular and molecular context studied. Several possible mechanisms have been discovered that regulate the stability of these p53 family members. Furthermore, Kruse et al. provides a detail review on the regulation of p53 protein activity [40,41].

As a brief overview, the major modifications and extensively studied proteins are listed in Table 1. The key features of p53 regulation are as follows

Regulation of transcription: p53 mRNA is induced during S-phase, C/EBPβ and RBP-Jκ are two major transcriptional factors that regulate transcription of the p53 gene.

Endogenous C/EBPβ binds to the p53 promoter and induces expression of p53 RNA [42], while RBP-Jκ binds to the p53 promoter and represses transcription of the p53 gene [43]. ASPP1/2 can bind to DBD domain of p53 and increases p53 transcriptional activity, while other members of ASPP family iASPP inhibit p53 activation and p53-mediated apoptosis [44,45].

Regulation by phosphorylation: Phosphorylation of p53 leads to stabilization and promotes p53 transcriptional activity to facilitate p53-mediated cell-cycle arrest and apoptosis. Phosphorylation of p53 is the first crucial step for its stabilization. p53 can be phosphorylated by a broad range of kinases, including ATM/ATR/DNA-PK, and Chk1/Chk2. Article by Thompson and colleagues provides further insight on p53 phosphorylation [46].

Table 1: Regulation of p53 expression and its functional outcome.

	Protein	p53 region of Interaction	Function
Ubiquitination	MDM2/MDMX	TA domain	MDM2 as major p53 E3 ligase, and polyubiquitinates p53, downregulates p53 activity, MDMX stabilizes MDM2 by inhibiting MDM2 self-ubiquitylation
	Pirh2	DBD	Promotes ubiquitination of p53
Acetylation	P300 /CBP	C-terminal acetylation sites	Upregulates p53 activation
	Sirt1	DBD	Deacetylates p53, downregulates p53 activity
Transcription regulation	C/EBPβ	p53 promoter	Induces expression of p53 RNA
	RBP-Jκ	p53 promoter	Represses transcription of the p53 gene
Phosphorylation	ATM, ATR,DNAPK	Phosphorylate p53 at TA domain	Stabilizes p53 and inhibits p53 –MDM2 interaction, apoptosis
	P38 kinase	Phosphorylate p53 at ser15 & ser46	Stabilizes p53, enhances apoptosis
	CHK1/CHK2	Phosphorylate p53 at ser20	Disrupts the interaction of p53 and MDM2
Methylation	Set7/9	K372	Stabilizes p53, enhances apoptosis
ASPP family	ASPP1/2	DBD domain	Stabilizes p53, enhances apoptosis
	iASPP	DBD domain	Inhibits p53 transcription
Redox-dependent & -independent interactions	Ref-1/APE1	Not known	promotes tetramerization of p53, enhances p53 binding to target DNA

p53 is phosphorylated on Ser15 and Ser20 by ATM, ATR, DNA-PK, Chk1, and Chk2 after DNA damage and other types of stress [47-49]. The outcome of Ser15 and Ser20 phosphorylation is that p53 is stabilized since it can no longer efficiently interact with MDM2, an E3-ligase for p53. In addition, p53 can be phosphorylated by several kinases at Ser46 [50]. Smeenk and colleagues have performed genome-wide DNA-binding and expression analysis upon different chemotherapeutic treatments. They found that chromatin-associated p53 phosphorylated at Ser46 increases significantly upon apoptosis-inducing etoposide treatment, whereas, the amount of DNA-bound p53 that is phosphorylated at Ser15 remains similar following exposure to etoposide. The authors concluded that p53 phosphorylated at Ser46 is most likely involved in apoptosis induction [50].

Regulation by ubiquitin-like modifications: Cellular p53 levels are tightly controlled through its ubiquitin-mediated proteasomal degradation [51,52]. MDM2 is the principal endogenous E3-ligase with high specificity for p53 [53-55]. Multiple E3-ligases ubiquitinate p53 and lead to p53 degradation, emphasizing how critical it is to fine tune p53 levels. MDM2 independent pathways for p53 degradation include E3-ligases COP1 [56,57], Pirh2 [58], and Arf-BP1[59]. Other p53 modifications, such as acetylation, methylation, and others that are reviewed in detail by Kruse et al. [40,41].

Regulation of p53 by Ref1/APE1: The multifunctional Ref1/APE1 protein has redox and DNA repair activities. Hanson et al. showed that Ref-1 directly regulates p53 transcription factor activity. Ref1/APRE1 functions in a redox-dependent and independent manner to activate p53. Ref-1 reduces cysteine residues in p53 and via direct interaction with p53 promotes the formation of p53 tetramers *in vitro*, which collectively enhance p53 binding to target DNA [60].

As previously discussed, p63 is predominantly involved in the regulation of skin and limb development [20, 21]. p63 can mediate apoptosis and the major regulators of p63 are summarized in Table 2

Regulation of transcription: At the transcriptional level, RBM24 is an RNA-binding protein that binds to multiple regions in the p63 3' untranslated region and destabilizes the p63 transcript [61]. This leads to decreased p63 mRNA and protein. In terms of p63 activation, Bernassola et al. have demonstrated that the promyelocytic leukemia protein (PML) physically interacts with p63, thereby, resulting in accumulation of p63 in the PML nuclear-bodies (PML-NBs) and increased p63 transcriptional activity [62]. The ASPP family member ASPP1 and ASPP2 bind to the DNA binding domains of TAp63, activate the transcription of TAp63, and regulate target genes such as BAX and PIG3 in p53-mutant cells [44].

Regulation by phosphorylation: c-Abl can phosphorylate p63 at Tyr149, Tyr171, and Tyr 289 residues to enhance the transcriptional and apoptotic activity of this protein upon DNA damage [63]. I-kappa B kinase activated by radiation or TNF- can phosphorylate TAp63 which blocks p63 ubiquitylation and degradation [64]. Polo-like kinase 1 (Plk1) phosphorylates p63 at Ser52, decreases the TAp63 protein stability, and suppresses TAp63-induced cell death [65].

Regulation by ubiquitin-like modifications: The NEDD4-like ubiquitin E3 ligase Itch directly binds to the PPPY motif of p63 and polyubiquitinates p63 which triggers proteasome-dependent degradation [66]. WWP1, the homologue of Itch, can also bind to the PPPY motif of p63 and ubiquitinate it [67]. p53-

Table 2: Regulation of p63 expression and its functional outcome.

	Protein	p63 region of interaction	function
Ubiquitination and UB-like modification	WWP1	PPPY motif of SAM domain	Sequesters p63 and downregulates p63 activity
	ITCH	PPPY motif of SAM domain	Polyubiquitinates p63 proteasome degradation
	Pirh2	Not known	Polyubiquitinates p63 proteasome degradation
	NQO1	Not known	Stabilizes p63 and enhances its activity
Transcription regulation	RBM24	3'UTR	Decreases p63 mRNA and protein
	ASPP1/2	DBD domain	Upregulates p63 transcription
	PML	Not known	Stabilizes p63 and enhances its activity
Phosphorylation	c-Abl	Phosphorylate p63 at Y149,Y171 AND Y289	Stabilizes p63 and upregulate p63 transcription
	IKKB	Phosphorylate p63 at TAD	Stabilizes p63
	Plk1	Phosphorylate p63 at Ser52	Destabilizes p63
others	Mutated p53	DBD domain	Downregulates p63 activity
	Cables1	TAD and SAM domain	Stabilizes p63 and enhances its activity
	Pin1	PPPY motif of SAM domain	Stabilizes p63 and enhances its activity

induced RING-H2 (Pirh2), another E3 ubiquitin ligase, physically interacts with p63 and targets p63 for polyubiquitination and subsequently proteasomal degradation [68,69]. The p63 isoform, TAp63 can be degraded by the 20S proteasomes. NAD(P)H quinone oxidoreductase 1 (NQO1) physically interacts with, stabilizes TAp63 and protects it from ubiquitin-independent degradation by the 20S proteasome. The stabilization of TAp63 by NQO1 was especially prominent under stress induced by chemotherapy [70].

Other regulators of p63: As mentioned in the p73 section below, both p63 and p73 can be sequestered by mutated p53. In addition, CDK5 and Abl enzyme substrate 1 (Cables1) can bind to both the TA and SAM domain of TAp63 and prevent TAp63 degradation [71]. Pin1 is a ubiquitously expressed peptidyl-prolyl isomerase. Li et al. demonstrated that Pin1 binds to PPPY motif of SAM domain in TAp63α and prevents it from proteasomal-mediated degradation, and thereby increases p63-dependent apoptosis [72].

Furthermore, major regulators of p73 can occur at both the transcriptional and translational levels and are summarized in Table 3

Regulation of transcription: The E2F1 transcription factor directly binds to p73 P1 promoter E2F consensus site [TT (G/C) (G/C) CG (G/C)] to activate TAp73 transcription [73,74]. ASPP1 and ASPP2 bind to the DNA binding domains of TAp73 activate the transcription of TAp73 and regulate its target genes such as BAX and PIG3 in p53-mutant cells [44]. ASPP1/2 can increase both p73 and p63 transcriptional activity, while other members of ASPP family like iASPP inhibit p73 activation and p73-mediated apoptosis [45]. p73 is also regulated by the ribosomal protein RPL26 at both mRNA and protein levels [75]. Zhang et al reported RPL26 directly binds to p73 3' untranslated region (3'UTR) of the mRNA and regulates p73 mRNA stability. RPL26 also interacts with eIF4E and enhances the association of eIF4E with p73 mRNA, leading to increased p73 mRNA translation and p73 protein level [75].

Regulation by phosphorylation: c-Abl can phosphorylate p73 at Tyr99 and enhance the transcriptional and apoptotic activity of this protein upon DNA damage [76-79]. In contrast, when p73 is phosphorylated by cyclin/CDK complexes, its transcriptional activity is reduced [80]. p73 proteins have cyclin recognition motifs (CRM) located within the N-terminal portion of the DNA-binding domain. Cyclins regulate p73 by binding to the CRM and phosphorylating p73 at Thr86 [80]. This would be the case when cyclin/CDK complexes are activated and favor a period of cell cycle arrest instead of apoptosis following a gentoxic or metabolic stress. p73 is also involved in sensing metabolic stress via AMP-activated protein kinase (AMPK), a serine/threonine protein kinase that is a central energy sensor in the cell. AMPK has been found to directly phosphorylate p73 at Ser426. Following its phosphorylation by AMPK, p73 accumulates in the nucleus where it can escape Itch-mediated proteasomal degradation, thereby, inducing apoptosis [81]. Chk1

Table 3: Regulation of p73 expression and its functional outcome.

	Protein	p73 region of interaction	Function
Ubiquitination and UB-like modification	MDM2	TA domain	Sequesters p73 and downregulates p73 activity
	ITCH	PY motif	Polyubiquitinates p73 proteasome degradation
	YAP1	PY motif	Stabilizes p73, competes with ITCH binding to PY motif of p73
	FBXO45	SAM domain	Ubiquitination leading to p73 proteasome degradation
	UFD2a	SAM domain	Ubiquitination–independent proteasome degradation
	NEDL2	C-terminal PR domain	Stabilizes p73 and enhances its transcription
	NQO1	SAM domain	Stabilizes p73 and enhances its transcription
Transcription regulation	E2F1	TAp73 promoter region	Upregulates p73 transcription
	RPL26	3'UTR	Increases p73 mRNA and protein
ASPP family	ASPP1/2	DBD domain	Upregulates p73 transcription
	iASPP	DBD domain	Inhibits p73 transcription
Phosphorylation	c-Abl	Phosphorylate p73 at Tyr99[PY motif]	Stabilizes p73 and upregulate p73 transcription
	Cyclin/CDK	Phosphorylate p73 at Thr86	Inhibits p73 transcription
	AMPK	Phosphorylate p73 at Ser 426	Stabilizes p73
	CHK1	Phosphorylate p73 at Ser47	Stabilizes p73
others	Mutated p53	DBD and OD domain	Downregulates p73 activity

and Chk2 are the downstream effector kinases of ATM and ATR, which play a critical role in the regulation of DDR [82]. Gonzalez et al., reported that Chk1 phosphorylates p73 at Ser47 in DDR [83]. Chk1-mediated phosphorylation enhanced p73-dependent transactivation activity and its apoptotic function.

Regulation by ubiquitin-like modifications: (a) The NEDD4-like ubiquitin ligase, Itch, binds to and polyubiquitinates p73 which triggers proteasome-dependent degradation [84]. The transcriptional co-activator YAP1 prevents Itch-mediated ubiquitination of p73 by competing with Itch for the PY motif of p73 [85].

(b) MDM2, the main E3 ubiquitin ligase controlling p53 stability, also binds to p73 and interferes with p300/CBP acetylation of p73. Additionally, it blocks p73-dependent transcriptional activities [86-89]. A previous report indicates that MDM2 does not ubiquitinate p73 but rather catalyzes p73 neddylation which also inhibits p73 transcriptional activity [88]. Recently Wu et al. demonstrated that MDM2 ubiquitinates p73 under specific cell-free conditions, as well as, in p53 null Saos-2 cells. In MDM2-null MEFs, Wu and colleagues observed that overexpression of MDM2 not only promoted p73 degradation but they also noticed that this effect was dependent on Itch [89]. They further found that Itch interacts with the overexpressed MDM2 in MDM2-null cells. Further studies are needed to determine whether direct ubiquitination of p73 by MDM2 is dependent on the cell type and the molecular context.

(c) F-box protein FBXO45 binds to and promotes the ubiquitination and degradation of TA- and ΔN p73 isoforms [90].

(d) The U-box-type E3 ubiquitin ligase, UFD2a, interacts with the SAM domain of TAp73, and promotes its ubiquitination-independent proteasomal degradation [91].

(e) In contrast, NEDD4-like ligase 2 (NEDL2), a HECT-type E3 ligase, regulates p73 in a different manner. Ubiquitination of p73 by NEDL2 stabilizes p73 in a NEDL2-dependent manner. Accordingly, p73 decays at faster rates in the absence of NEDL2 than in its presence. Consistent with the NEDL2-mediated stabilization of p73, NEDL2 enhances the p73-dependent transcriptional activation [92].

(f) NQO1 physically interacts with p73 in an NADH-dependent manner and protects p73 ubiquitin-independent degradation by the 20S proteasome [93].

Mutated p53: Di Como et al., demonstrated that mutant p53 could sequester p73 and inhibit its transcription and proapoptotic activity [94]. Surface plasmon resonance and atomic force spectroscopy revealed that a stable complex is formed between mutant p53 and p73 protein, but not between p73 and wild type p53 [95]. The mutant p53 DBD domain interacts with the DBD and oligomerization domain (OD) of p73 proteins [96]. p53 mutants, most of which have mutations in the DBD domain, exhibit an increased aggregation propensity and can induce misfolding and coaggregation of wild-type p53, p63, and p73. Inactivation of p63 and p73 by mutant p53 results in blockade of p63-and p73-mediated downstream target genes and promotes cancer cell survival [23,97]. The precise role for the association between mutant p53 and p63/p73 warrants further investigation to uncover if blocking these interactions or potential interactions with heat shock proteins such as HSP90 [98] could be a useful option for anti-cancer treatment in mutant p53 cancers.

p53/p63/p73 and cancer cell metabolism

Cancer cells proliferate rapidly due to metabolic changes or metabolic reprograming. Nutrients, particularly glucose and glutamine, are used by cancer cells to produce energy through the Warburg effect which increases survival in low-oxygen environments. Oncogenic pathways (Ras, PI3K or Myc) promote glycolysis, while tumor suppressors like p53 and liver kinase B1 (LKB1) inhibit it. p53 and its family members, p63 and p73, have been implicated in many aspects of cellular metabolism, including AMPK and mTOR signaling, carbohydrate and lipid metabolism, the regulation of autophagy, and the maintenance of mitochondrial integrity and redox balance [99-102].

p53/p63/p73 inhibit mTOR signaling

Akeno et al. demonstrated that p53 can suppress carcinogenesis by inhibiting mammalian target of rapamycin (mTOR) signaling. They used mouse models ($Rb^{+/-}$ vs $Rb^{+/-}p53^{+/-}$) to demonstrate that mTOR activity was markedly increased in p53-deficient tumors and rapamycin treatment suppressed tumor cell growth, identifying mTOR inhibition as a critical p53 tumor suppressive function. p53 transcriptionally induces expression of multiple genes that repress mTOR pathway signaling such as Sesn2, Tsc2, plk2 [102]. The mTOR protein is an important positive regulator of cell growth and proliferation that can influence the development of diabetes, aging, and cancer [101]. mTOR forms two multimeric protein complexes, each with distinct functions [103,104]. The mTORC1 complex plays multiple roles in the regulation of protein translation and synthesis, mitochondrial biogenesis, lipid synthesis, and autophagy [99]. The mTORC2 complex has not been studied as extensively, but clearly functions in regulating cytoskeletal assembly [104] and cell survival [105]. Activation of p53 in response to nutrient stress is essential for tumor suppression. Although previous studies have emphasized the importance of p53-dependent cell cycle arrest and apoptosis for tumor suppression, recent studies have suggested that other areas of p53 regulation, such as metabolism and DNA damage repair, are also essential for p53-dependent tumor suppression. However, the intrinsic connections between p53-mediated DNA damage repair and metabolic regulation remain unclear. Franklin et al. reported a rate-limiting enzyme that promotes glycolysis called PFKFB3 [105]. The suppression of PFKFB3 increases the flux of glucose through the pentose phosphate pathway (PPP), which increases nucleotide production. Subsequently, this results in more efficient DNA damage repair and increased cell survival [105]. Interestingly, PFKFB3 suppression by p53 could increase the two major PPP products, NADPH and nucleotides, but only nucleotide production is essential to promote DNA damage repair [105]. In this study, they reported that metabolic stresses activate AMPK, which phosphorylates and inactivates murine double minute X (MDMX), a homolog of MDM2 [106]. This results in p53 stabilization and activation [106]. TAp73 transcriptionally activates the expression of glutaminase-2 (GLS-2) which favors conversion of glutamine into glutamate, thus, providing cancer cells an energy resource to help maintain cellular redox homeostasis [107].

FUTURE DIRECTIONS

A significant hurdle for treating cancer is not only the molecular heterogeneity associated with cancer, but also the development of small molecule inhibitors to pertinent signaling pathways that are delivered to the site(s) of the tumor at adequate levels as to engage the target(s) for sufficient duration. Effective target modulation that has a significant inhibitory impact on tumor growth without major debilitating toxicities will be essential to the development of anti-cancer therapies. To this end, multiple phases of combination therapy, each tailored for the molecular signature of the relapsed tumor, will most likely be required to stabilize and/or cure various cancers. Therapies that exploit the DNA damage response by sustaining p53/p63/p73-mediated apoptosis in combination with those that target multiple signaling pathways require further investigation. In wildtype p53 and in some mutated p53 cancers, combination frontline therapy with MDM2 protein-protein interaction inhibitors (PPI) that block binding of p53 [108-111] and p73 [112-114] to MDM2 and sustain p53- or p73-mediated cell death can increase tumor cell kill in vitro and in some human xenograft models. It is important to note that not all MDM2 PPIs can block binding of p73 to MDM2 in mutant p53 cells and that the molecular context of the cell type may dictate response to MDM2 PPIs in mutant p53 cells [112-114]. For example, early generation MDM2 PPIs Nutlin3a and RG7112, but not third generation RG7388, can block binding of p73 to MDM2 (Ding and Pollok, unpublished observations) [112]. In contrast to p53, p73 is rarely mutated in cancer and appropriate pharmacological manipulation of the p73 pathway for cancer therapy is underexplored.

There are three major areas of investigation that should be considered to increase our understanding of p73 mechanism of action, as well as, identifying new therapeutic targets for cancer: (1) Increase TAp73 levels, for instance, by stimulating its transcription or by inhibiting degradation of the protein; (2) Modulate the expression or function of TAp73 upstream regulators such as kinases; and (3) Release p73 from inhibitory interactions with other cellular proteins, such as ΔN p73 isoforms, mutant p53, or E3 Ligases such as MDM2.

Initial clinical trials that utilize MDM2 PPI report evidence of therapeutic responses in relapsed leukemia [115] and liposarcoma [108]. For detailed information regarding clinical trials of MDM2/MDMX inhibitors, refer to the review by Burgess et al. [116]. In summary, investigations to date have uncovered multiple mechanisms that regulate the ability of the p53 family members to effectively promote death of cancer cells. Continued studies focused on p53/p63/p73-mediated cell death will contribute to uncovering further mechanistic insights that can be exploited therapeutically and lead to improved stabilization of disease and, ultimately, curing cancers with wildtype or mutant p53 backgrounds.

REFERENCES

1. Crawford LV, O'Farrell PZ. Effect of alkylation on the physical properties of simian virus 40 T-antigen species. J Virol. 1979; 29: 587-596.
2. DeLeo AB, Jay G, Appella E, Dubois GC, Law LW, Old LJ. Detection of a transformation-related antigen in chemically induced sarcomas and other transformed cells of the mouse. Proc Natl Acad Sci U S A. 1979; 76: 2420-2424.
3. Lane DP, Crawford LV. T antigen is bound to a host protein in SV40-transformed cells. Nature. 1979; 278: 261-263.
4. Feng Z, Lin M, Wu R. The Regulation of Aging and Longevity: A New and Complex Role of p53. Genes Cancer. 2011; 2: 443-452.
5. Donehower LA. Longevity regulation in flies: a role for p53. Aging (Albany NY). 2009; 1: 6-8.
6. Napoli M, Flores ER. The p53 family orchestrates the regulation of metabolism: physiological regulation and implications for cancer therapy. Br J Cancer. 2017; 116: 149-155.
7. Iwamoto KS, Mizuno T, Seyama T, Kyoizumi S. Mutant p53: epigenetic mutator of the T-cell receptor via induction of methylation. Mol Carcinog. 1999; 25: 113-121.
8. Hwang CI, Matoso A, Corney DC, Flesken-Nikitin A, Körner S, Wang W, et al. Wild-type p53 controls cell motility and invasion by dual regulation of MET expression. Proc Natl Acad Sci U S A. 2011; 108: 14240-14245.
9. Yeudall WA, Wrighton KH, Deb S. Mutant p53 in cell adhesion and motility. Methods Mol Biol. 2013; 962: 135-146.
10. Yamashita M, Nitta E, Suda T. Regulation of hematopoietic stem cell integrity through p53 and its related factors. Ann N Y Acad Sci. 2016; 1370: 45-54.
11. Artandi SE, Attardi LD. Pathways connecting telomeres and p53 in senescence apoptosis and cancer. Biochem Biophys Res Commun. 2005; 331: 881-890.
12. Muller PA, Vousden KH. p53 mutations in cancer. Nat Cell Biol. 2013; 15: 2-8.
13. Yang A, Kaghad M, Wang Y, Gillett E, Fleming MD, Dötsch 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: 305-316.
14. Lakin ND, Jackson SP. Regulation of p53 in response to DNA damage. Oncogene. 1999; 18: 7644-7655.
15. 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: 1661-1670.
16. Speidel D. The role of DNA damage responses in p53 biology. Arch Toxicol. 2015; 89: 501-517.
17. 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: 809-819.
18. Donehower LA, Harvey M, Slagle BL, McArthur MJ, Montgomery CA Jr, Butel JS. Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. Nature. 1992; 356: 215-221.
19. Tsukada T, Tomooka Y, Takai S, Ueda Y, Nishikawa S, Yagi T, et al. Enhanced proliferative potential in culture of cells from p53-deficient mice. Oncogene. 1993; 8: 3313-3322.
20. Mills AA, Zheng B, Wang XJ, Vogel H, Roop DR, Bradley A. p63 is a p53 homologue required for limb and epidermal morphogenesis. Nature. 1999; 398: 708-713.
21. 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: 714-718.
22. 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.

23. Flores ER, Sengupta S, Miller JB, Newman JJ, Bronson R, Crowley D, et al. Tumor predisposition in mice mutant for p63 and p73: evidence for broader tumor suppressor functions for the p53 family. Cancer Cell. 2005; 7: 363-373.

24. Wilhelm MT, Rufini A, Wetzel MK, Tsuchihara K, Inoue S, Tomasini R, et al. Isoform-specific p73 knockout mice reveal a novel role for delta Np73 in the DNA damage response pathway. Genes Dev. 2010; 24: 549-560.

25. Ravni A, Tissir F, Goffinet AM. DeltaNp73 transcription factors modulate cell survival and tumor development. Cell Cycle. 2010; 9: 1523-1527.

26. Romano RA, Solomon LW, Sinha S. Tp63 in oral development neoplasia and autoimmunity. J Dent Res. 2012; 91: 125-132.

27. Romano RA, Sinha S. Dynamic life of a skin keratinocyte: an intimate tryst with the master regulator p63. Indian J Exp Biol. 2011; 49: 721-731.

28. 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: 304-306.

29. Grob TJ, Novak U, Maisse C, Barcaroli D, Lüthi AU, Pirnia F, et al. Human delta Np73 regulates a dominant negative feedback loop for TAp73 and p53. Cell Death Differ. 2001; 8: 1213-1223.

30. Stiewe T, Theseling CC, Pützer BM. Transactivation-deficient Delta TA-p73 inhibits p53 by direct competition for DNA binding: implications for tumorigenesis. J Biol Chem. 2002; 277: 14177-14185.

31. Ranjan A, Iwakuma T2. Non-Canonical Cell Death Induced by p53. Int J Mol Sci. 2016; 17: 2068.

32. Chipuk JE, Green DR. Dissecting p53-dependent apoptosis. Cell Death Differ. 2006; 13: 994-1002.

33. Yu J, Wang Z, Kinzler KW, Vogelstein B, Zhang L. PUMA mediates the apoptotic response to p53 in colorectal cancer cells. Proc Natl Acad Sci U S A. 2003; 100: 1931-1936.

34. Green DR, Kroemer G. Cytoplasmic functions of the tumour suppressor p53. Nature. 2009; 458: 1127-1130.

35. Shamas-Din A, Kale J, Leber B, Andrews DW. Mechanisms of action of Bcl-2 family proteins. Cold Spring Harb Perspect Biol. 2013; 5: a008714.

36. Irwin MS, Kondo K, Marin MC, Cheng LS, Hahn WC, Kaelin WG Jr. Chemosensitivity linked to p73 function. Cancer Cell. 2003; 3: 403-410.

37. Melino G, De Laurenzi V, Vousden KH. p73: Friend or foe in tumorigenesis. Nat Rev Cancer. 2002; 2: 605-15.

38. Müller M, Schleithoff ES, Stremmel W, Melino G, Krammer PH, Schilling T. One two three--p53 p63 p73 and chemosensitivity. Drug Resist Updat. 2006; 9: 288-306.

39. Alonso-López D, Gutiérrez MA, Lopes KP, Prieto C, Santamaria R, De Las Rivas J. APID interactomes: providing proteome-based interactomes with controlled quality for multiple species and derived networks. Nucleic Acids Res. 2016; 44: 529-535.

40. Kruse JP, Gu W. Modes of p53 regulation. Cell. 2009; 137: 609-622.

41. Kruse JP, Gu W. SnapShot: p53 posttranslational modifications. Cell. 2008; 133: 930-930.

42. Boggs K, Reisman D. Increased p53 transcription prior to DNA synthesis is regulated through a novel regulatory element within the p53 promoter. Oncogene. 2006; 25: 555-565.

43. Boggs K, Henderson B, Reisman D. RBP-Jkappa binds to and represses transcription of the p53 tumor suppressor gene. Cell Biol Int. 2009; 33: 318-324.

44. 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: 1341-1350.

45. 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: 259-268.

46. Thompson T, Tovar C, Yang H, Carvajal D, Vu BT, Xu Q, et al. Phosphorylation of p53 on key serines is dispensable for transcriptional activation and apoptosis. J Biol Chem. 2004; 279: 53015-53022.

47. Shieh SY, Ikeda M, Taya Y, Prives C. DNA damage-induced phosphorylation of p53 alleviates inhibition by MDM2. Cell. 1997; 91: 325-334.

48. Shieh SY, Ahn J, Tamai K, Taya Y, Prives C. The human homologs of checkpoint kinases Chk1 and Cds1 (Chk2) phosphorylate p53 at multiple DNA damage-inducible sites. Genes Dev. 2000; 14: 289-300.

49. Appella E, Anderson CW. Post-translational modifications and activation of p53 by genotoxic stresses. Eur J Biochem. 2001; 268: 2764-2772.

50. Smeenk L, van Heeringen SJ, Koeppel M, Gilbert B, Janssen-Megens E, Stunnenberg HG, et al. Role of p53 serine 46 in p53 target gene regulation. PLoS One. 2011; 6: e17574.

51. Michael D, Oren M. The p53-Mdm2 module and the ubiquitin system. Semin Cancer Biol. 2003; 13: 49-58.

52. Brooks CL, Gu W. p53 ubiquitination: Mdm2 and beyond. Mol Cell. 2006; 21: 307-315.

53. Haupt Y, Maya R, Kazaz A ,Oren M. Mdm2 promotes the rapid degradation of p53. Nature. 1997; 387: 296-299.

54. Honda R, Tanaka H, Yasuda H. Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressor p53. FEBS Lett. 1997; 420: 25-27.

55. Kubbutat MH, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. Nature. 1997; 387: 299-303.

56. Dornan D, Bheddah S, Newton K, Ince W, Frantz GD, Dowd P, et al. COP1 the negative regulator of p53 is overexpressed in breast and ovarian adenocarcinomas. Cancer Res. 2004; 64: 7226-7230.

57. Dornan D, Wertz I, Shimizu H, Arnott D, Frantz GD, Dowd P, et al. The ubiquitin ligase COP1 is a critical negative regulator of p53. Nature. 2004; 429: 86-92.

58. Leng RP, Lin Y, Ma W, Wu H, Lemmers B, Chung S, et al. Pirh2 a p53-induced ubiquitin-protein ligase promotes p53 degradation. Cell. 2003; 112: 779-791.

59. Chen D, Kon N, Li M, Zhang W, Qin J, Gu W. ARF-BP1/Mule is a critical mediator of the ARF tumor suppressor. Cell. 2005; 121: 1071-1083.

60. Hanson S, Kim E, Deppert W. Redox factor 1 (Ref-1) enhances specific DNA binding of p53 by promoting p53 tetramerization. Oncogene. 2005; 24: 1641-1647.

61. Xu E, Zhang J, Zhang M, Jiang Y, Cho SJ, Chen X. RNA-binding protein RBM24 regulates p63 expression via mRNA stability. Mol Cancer Res. 2014; 12: 359-369.

62. Bernassola F, Oberst A, Melino G, Pandolfi PP. The promyelocytic leukaemia protein tumour suppressor functions as a transcriptional regulator of p63. Oncogene. 2005; 24: 6982-6986.

63. Gonfloni S, Di Tella L, Caldarola S, Cannata SM, Klinger FG, Di Bartolomeo C, et al. Inhibition of the c-Abl-TAp63 pathway protects mouse oocytes from chemotherapy-induced death. Nat Med. 2009; 15: 1179-1185.

64. MacPartlin M, Zeng SX, Lu H. Phosphorylation and stabilization of TAp63gamma by IkappaB kinase-beta. J Biol Chem. 2008; 283: 15754-15761.

65. Komatsu S, Takenobu H, Ozaki T, Ando K, Koida N, Suenaga Y, et al. Plk1 regulates liver tumor cell death by phosphorylation of TAp63. Oncogene. 2009; 28: 3631-3641.

66. Rossi M, De Simone M, Pollice A, Santoro R, La Mantia G, Guerrini L, et al. Itch/AIP4 associates with and promotes p63 protein degradation. Cell Cycle. 2006; 5: 1816-1822.

67. Li Y, Zhou Z, Chen C. WW domain-containing E3 ubiquitin protein ligase 1 targets p63 transcription factor for ubiquitin-mediated proteasomal degradation and regulates apoptosis. Cell Death Differ. 2008; 15: 1941-1951.

68. Jung YS, Qian Y, Yan W, Chen X. Pirh2 E3 ubiquitin ligase modulates keratinocyte differentiation through p63. J Invest Dermatol. 2013; 133: 1178-1187.

69. Yan W, Chen X, Zhang Y, Zhang J, Jung YS, Chen X. Arsenic suppresses cell survival via Pirh2-mediated proteasomal degradation of DeltaNp63 protein. J Biol Chem. 2013; 288: 2907-2913.

70. Hershkovitz Rokah O, Shpilberg O, Granot G. NAD(P)H quinone oxidoreductase protects TAp63gamma from proteasomal degradation and regulates TAp63gamma-dependent growth arrest. PLoS One. 2010; 5: 11401.

71. Wang N, Guo L, Rueda BR, Tilly JL. Cables1 protects p63 from proteasomal degradation to ensure deletion of cells after genotoxic stress. EMBO Rep. 2010; 11: 633-639.

72. Li C, Chang DL, Yang Z, Qi J, Liu R, He H, et al. Pin1 modulates p63alpha protein stability in regulation of cell survival proliferation and tumor formation. Cell Death Dis. 2013; 4: 943.

73. 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: 645-648.

74. Seelan RS, Irwin M, van der Stoop P, Qian C, Kaelin WG Jr, Liu W. The human p73 promoter: characterization and identification of functional E2F binding sites. Neoplasia. 2002; 4: 195-203.

75. Zhang M, Zhang J, Yan W, Chen X. p73 expression is regulated by ribosomal protein RPL26 through mRNA translation and protein stability. Oncotarget. 2016; 7: 78255-78268.

76. Agami R, Blandino G, Oren M, Shaul Y. Interaction of c-Abl and p73alpha and their collaboration to induce apoptosis. Nature. 1999; 399: 809-813.

77. Gong JG, Costanzo A, Yang HQ, Melino G, Kaelin WG Jr, Levrero M, et al. The tyrosine kinase c-Abl regulates p73 in apoptotic response to cisplatin-induced DNA damage. Nature. 1999; 399: 806-809.

78. 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: 814-817.

79. Satija YK, Das S. Tyr99 phosphorylation determines the regulatory milieu of tumor suppressor p73. Oncogene. 2016; 35: 513-527.

80. Gaiddon C, Lokshin M, Gross I, Levasseur D, Taya Y, Loeffler JP, et al. Cyclin-dependent kinases phosphorylate p73 at threonine 86 in a cell cycle-dependent manner and negatively regulate p73. J Biol Chem. 2003; 278: 27421-27431.

81. Adamovich Y, Adler J, Meltser V, Reuven N, Shaul Y. AMPK couples p73 with p53 in cell fate decision. Cell Death Differ. 2014; 21: 1451-1459.

82. Walworth N, Davey S, Beach D. Fission yeast chk1 protein kinase links the rad checkpoint pathway to cdc2. Nature. 1993; 363: 368-371.

83. Gonzalez S, Prives C, Cordon-Cardo C. p73alpha regulation by Chk1 in response to DNA damage. Mol Cell Biol. 2003; 23: 8161-8171.

84. 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: 836-848.

85. Levy D, Adamovich Y, Reuven N, Shaul Y. The Yes-associated protein 1 stabilizes p73 by preventing Itch-mediated ubiquitination of p73. Cell Death Differ. 2007; 14: 743-751.

86. Dobbelstein M, Wienzek S, König C, Roth J. Inactivation of the p53-homologue p73 by the mdm2-oncoprotein. Oncogene. 1999; 18: 2101-2106.

87. 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: 3257-3266.

88. Watson IR, Blanch A, Lin DC, Ohh M, Irwin MS. Mdm2-mediated NEDD8 modification of TAp73 regulates its transactivation function. J Biol Chem. 2006; 281: 34096-34103.

89. Wu H, Leng RP. MDM2 mediates p73 ubiquitination: a new molecular mechanism for suppression of p73 function. Oncotarget. 2015; 6: 21479-21492.

90. Peschiaroli A, Scialpi F, Bernassola F, Pagano M, Melino G. The F-box protein FBXO45 promotes the proteasome-dependent degradation of p73. Oncogene. 2009; 28: 3157-3166.

91. Hosoda M, Ozaki T, Miyazaki K, Hayashi S, Furuya K, Watanabe K, et al. UFD2a mediates the proteasomal turnover of p73 without promoting p73 ubiquitination. Oncogene. 2005; 24: 7156-7169.

92. 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: 106-113.

93. Asher G, Lotem J, Sachs L, Kahana C, Shaul Y. Mdm-2 and ubiquitin-independent p53 proteasomal degradation regulated by NQO1. Proc Natl Acad Sci U S A. 2002; 99: 13125-13130.

94. Di Como CJ, Gaiddon C, Prives C. p73 function is inhibited by tumor-derived p53 mutants in mammalian cells. Mol Cell Biol. 1999; 19: 1438-1449.

95. Santini S, Di Agostino S, Coppari E, Bizzarri AR, Blandino G, Cannistraro S. Interaction of mutant p53 with p73: a Surface Plasmon Resonance and Atomic Force Spectroscopy study. Biochim Biophys Acta. 2014; 1840: 1958-1964.

96. 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: 29503-29512.

97. Xu J, Reumers J, Couceiro JR, De Smet F, Gallardo R, Rudyak S, et al. Gain of function of mutant p53 by coaggregation with multiple tumor suppressors. Nat Chem Biol. 2011; 7: 285-295.

98. Whitesell L, Lindquist SL. HSP90 and the chaperoning of cancer. Nat Rev Cancer. 2005; 5: 761-772.

99. Berkers CR, Maddocks OD, Cheung EC, Mor I, Vousden KH. Metabolic regulation by p53 family members. Cell Metab. 2013; 18: 617-633.

100. Howell JJ, Manning BD. mTOR couples cellular nutrient sensing to organismal metabolic homeostasis. Trends Endocrinol Metab. 2011; 22: 94-102.

101. Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer diabetes and ageing. Nat Rev Mol Cell Biol. 2011; 12: 21-35.

102. Akeno N, Miller AL, Ma X, Wikenheiser-Brokamp KA. p53 suppresses carcinoma progression by inhibiting mTOR pathway activation. Oncogene. 2015; 34: 589-599.

103. Laplante M, Sabatini DM. An emerging role of mTOR in lipid biosynthesis. Curr Biol. 2009; 19: 1046-1052.

104. Laplante M, Sabatini DM. mTOR signaling at a glance. J Cell Sci. 2009; 122: 3589-3594.

105. Franklin DA, He Y, Leslie PL, Tikunov AP, Fenger N, Macdonald JM, et al. p53 coordinates DNA repair with nucleotide synthesis by suppressing PFKFB3 expression and promoting the pentose phosphate pathway. Sci Rep. 2016; 6: 38067.

106. He G, Zhang YW, Lee JH, Zeng SX, Wang YV, Luo Z, et al. AMP-activated protein kinase induces p53 by phosphorylating MDMX and inhibiting its activity. Mol Cell Biol. 2014; 34: 148-157.

107. Amelio I, Markert EK, Rufini A, Antonov AV, Sayan BS, Tucci P, et al. p73 regulates serine biosynthesis in cancer. Oncogene. 2014; 33: 5039-5046.

108. Ray-Coquard I, Blay JY, Italiano A, Le Cesne A, Penel N, Zhi J, et al. Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study. Lancet Oncol. 2012; 13: 1133-1140.

109. Wang H, Cai S, Bailey BJ, Reza Saadatzadeh M, Ding J, Tonsing-Carter E, et al. Combination therapy in a xenograft model of glioblastoma: enhancement of the antitumor activity of temozolomide by an MDM2 antagonist. J Neurosurg. 2017; 126: 446-459.

110. Hai J, Sakashita S, Allo G, Ludkovski O, Ng C, Shepherd FA, et al. Inhibiting MDM2-p53 Interaction Suppresses Tumor Growth in Patient-Derived Non-Small Cell Lung Cancer Xenograft Models. J Thorac Oncol. 2015; 10: 1172-1180.

111. Lakoma A, Barbieri E, Agarwal S, Jackson J, Chen Z, Kim Y, et al. The MDM2 small-molecule inhibitor RG7388 leads to potent tumor inhibition in p53 wild-type neuroblastoma. Cell Death Discov. 2015; 1: 15026.

112. Lau LM, Nugent JK, Zhao X, Irwin MS. HDM2 antagonist Nutlin-3 disrupts p73-HDM2 binding and enhances p73 function. Oncogene. 2008; 27: 997-1003.

113. Supiot S, Hill RP, Bristow RG. Nutlin-3 radiosensitizes hypoxic prostate cancer cells independent of p53. Mol Cancer Ther. 2008; 7: 993-999.

114. Tonsing-Carter E, Bailey BJ, Saadatzadeh MR, Ding J, Wang H, Sinn AL, et al. Potentiation of Carboplatin-Mediated DNA Damage by the Mdm2 Modulator Nutlin-3a in a Humanized Orthotopic Breast-to-Lung Metastatic Model. Mol Cancer Ther. 2015; 14: 2850-2863.

115. Andreeff M, Kelly KR, Yee K, Assouline S, Strair R, Popplewell L, et al. Results of the Phase I Trial of RG7112 a Small-Molecule MDM2 Antagonist in Leukemia. Clin Cancer Res. 2016; 22: 868-876.

116. Burgess A, Chia KM, Haupt S, Thomas D, Haupt Y, Lim E. Clinical Overview of MDM2/X-Targeted Therapies. Front Oncol. 2016; 6: 7.

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