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The p53 family member p73 in the regulation of cell stress response

Julian M. Rozenberg[1*], Svetlana Zvereva[1†], Aleksandra Dalina[3†], Igor Blatov[1†], Ilya Zubarev[1], Daniil Luppov[1], Alexander Bessmertnyi[5], Alexander Romanishin[2,4], Lamak Alsoulaiman[1], Vadim Kumeiko[2], Alexander Kagansky[1,2], Gerry Melino[6], Carlo Ganini[6] and Nikolai A. Barlev[1,7*]

Abstract

During oncogenesis, cells become unrestrictedly proliferative thereby altering the tissue homeostasis and resulting in subsequent hyperplasia. This process is paralleled by resumption of cell cycle, aberrant DNA repair and blunting the apoptotic program in response to DNA damage. In most human cancers these processes are associated with malfunctioning of tumor suppressor p53. Intriguingly, in some cases two other members of the p53 family of proteins, transcription factors p63 and p73, can compensate for loss of p53. Although both p63 and p73 can bind the same DNA sequences as p53 and their transcriptionally active isoforms are able to regulate the expression of p53-dependent genes, the strongest overlap with p53 functions was detected for p73. Surprisingly, unlike p53, the p73 is rarely lost or mutated in cancers. On the contrary, its inactive isoforms are often overexpressed in cancer. In this review, we discuss several lines of evidence that cancer cells develop various mechanisms to repress p73-mediated cell death. Moreover, p73 isoforms may promote cancer growth by enhancing an anti-oxidative response, the Warburg effect and by repressing senescence. Thus, we speculate that the role of p73 in tumorigenesis can be ambivalent and hence, requires new therapeutic strategies that would specifically repress the oncogenic functions of p73, while keeping its tumor suppressive properties intact.

Keywords: Cancer hallmarks, Tumor suppressor p53, p73

Background

During oncogenesis, cells typically lose their ability to repress cell cycle, repair DNA or undergo apoptosis in response to DNA damage. In the majority of human cancers this is associated with aberrant function of mutated tumor suppressor p53. Intriguingly, another member of the p53 family—transcription factor p73—binds the same DNA sequences and is able to activate transcription, which theoretically could compensate for the p53 loss. However, the p73 is rarely lost or mutated in cancers, while multiple signaling pathways can repress it's activity or stimulate the expression of transcriptionally inactive p73 isoforms. Moreover, the p73 is often overexpressed in cancers. Thus, it is not clear if p73 is a tumor suppressor or an oncogene. In this review, we address this dilemma by analyzing roles of p73 in the regulation of DNA damage response, cell cycle and apoptosis, genome stability, metabolism and senescence.

Introduction

The p53 family of transcription factors comprises three proteins: p53, p63 and p73. The p53 protein is involved in all aspects of cancer development and progression. While p63 and p73 generally overlap p53 in their functions, they also play their specific roles [1, 2]. While p53 is lost or mutated in about half of cancers, it is not so for

*Correspondence: rozenbej@gmail.com; nick.a.barlev@gmail.com
†Svetlana Zvereva, Aleksandra Dalina and Igor Blatov have contributed equally to this work
[1] Cell Signaling Regulation Laboratory, Moscow Institute of Physics and Technology, Dolgoprudny, Russia
Full list of author information is available at the end of the article

p73 [3–8]. On the other hand, specific p73 isoforms are overexpressed in a variety of malignancies and determine prognosis in various types of tumor including non-small lung cancer [9–11], breast cancer [5, 12, 13], stomach and esophagus adenocarcinomas [14], gliomas [15–17] and other solid tumor types [18, 19] (induction of expression levels are in Tables 1 and 2). This contrasts with studies in mice, demonstrating that the loss of a particular p73 isoform promotes spontaneous lung adenocarcinomas and lymphomas [20].

In humans, p73 loss does not provide cancer cells with a selective advantage (as in the p53 case) [109, 110], in

Table 1 Expression levels of p73 or p73 isoforms in various cancers

Cancer	Changes of p73 isoform expression	Conclusions	References
NSLC	p73↑	Total p73 does not predict prognosis	[10]
NSLC	DNp73↑	DNp73 is associated with poor prognosis	[11]
Breast	p73↓	Upregulation is associated with lower pathological grade	[13]
Breast	p73↑ in 27%	Upregulation is association with higher pathological grade	[12]
Breast	p73↑ in 38% alpha, gamma, delta epsilon and phi isoforms detected	p73 does not have a tumor suppressor role	[5]
Esophagus	DNp73↑ in 60%	Leads to b-catenin/TCF activation	[14]
Gliomas	p73↑ ependymomas and pilocytic astrocytomas	P73 does not influence p21 and MDM2 expression	[15]
Low grade gliomas	DNp73↑, TAp73↑, DeltaEx2-3↑	DeltaEx2-3 upregulation predicts progression	[16]
High grade gliomas	TAp73↑, DNp73↓	TAp73 is upregulated in high grade gliomas	[17]
Glioblastomas	DNp73↑, TAp73↓ by PCR	13 GBM samples examined by IB	[21]
Cervical	p73↑	Higher p73 protein is associated with better survival	[22]

Table 2 Intracellular cancer hallmarks and p73 functions in specific cancers

Cancer	Apoptosis, cell cycle	Replicative Immortality	Genomic instability, DSB response	Altered metabolism	Role of p73 isoforms in cancer	TP73 in tumor compared to normal tissue
Non-small cell lung carcinoma (NSCLC)	[24–29]	[30, 31]		[32, 33]	[34–36]	
Lung adenocarcinomas	[27]		[20]		[37, 38]	2.95
Hepatocellular carcinoma (HCC)	[39]					
Cervix carcinoma	[40–42]			[41]	[22, 43, 44]	15.2
Melanoma	[45]			[46]		
Osteosarcoma	[47–51]		[52, 53]	[54, 55]		5.4
Glioblastoma	[56, 57]				[58, 59]	5.2
Medulloblastoma				[60, 61]	[62]	–
B-cell lymphoma	[63]	[64]	[65]		[66]	33.6
T-cell lymphoma	[67, 68]					
Acute myeloid leukemia	[69–72]					
Chronic myelogenous leukemia (CML)	[73–75]			[73]		
Breast cancer	[76–79]		[80]	[81]	[82]	1.2
Colorectal cancer	[25, 78, 83, 84]	[85–87]	[88]		[84, 89]	9.6
Esophageal adenocarcinoma	[90]		[91–93]		[94]	1.1
Thyroid cancer	[95]					
Ovarian cancer	[96, 97]				[98]	4.1
Pancreatic cancer					[99, 100]	3.15
Neuroblastoma	[26, 101–103]			[104]		
Squamous carcinoma	[105, 106]				[107, 108]	1.26

The rightmost column represents the Tp73 expression in tumor tissue (Tp73Tum) in comparison to normal tissue (Tp73Norm) as a ration log2(Tp73Tum + 1)/log2(Tp73Norm + 1) [23]

contrast, the hypothesis is that for certain tumors p73 can be essential for growth [81]. In order for cancerous cells to form a malignant tumor they must develop multiple properties including unrestricted growth, evasion of the programmed cell death, sustained angiogenesis and tissue invasion, immune system evasion and altered metabolism along with the ability to later form metastases, which are collectively known as hallmarks of cancer [111]. p73 functions in many of these hallmarks are extensively reviewed [19, 112–116]. While uncontrolled cell cycle progression, accumulation of DNA damage and evasion of apoptosis require inhibition of the p73 activity, other hallmarks—alteration of metabolism, oncogene-induced senescence—depend on the p73 transcriptional activation. Finally, we attempt to categorize cancers based on the p73 roles with respect to the cancer hallmarks, providing the clues to how p73 affects progression of neoplasms.

Domain structure of p73 isoforms and their functions

All p53 protein family members, including p73, have multiple isoforms resulting from alternative transcriptional start sites and alternative splicing [18, 117, 118].

All p73 isoforms can be divided into two classes based on the resulting structure. Alternative transcription start sites generate either long transcripts containing transcriptional activator (TA) at the N- terminus, resulting in TA- isoforms (TAp73), which activate transcription [119–121] or shorter transcripts driven by the intragenic promoter to generate so called DN- isoforms (DNp73), lacking transcriptional activator domain, but retaining their DNA binding domains, so their protein products act mostly as dominant-negative repressors [122–126]. However, DN- isoforms can also activate transcription [127–130].

The typical domain organization of the p53 family members includes the TA- domain followed by the DNA binding domain and the tetramerization domain [131–133]. All members of the p53 family can bind the same consensus DNA to form heterotetrameric complexes between them to regulate largely overlapping gene sets [24, 120, 134, 135].

In addition, p73 also contains the sterile alpha motif (SAM) domain that is absent in p53 and responsible for the transcriptional repression by preventing interaction with p300/CBP [136]. Several isoforms (Δex2, Δex2/3) are produced as a result of alternative splicing that lack exon 2 or exons 2 and 3, which encode the transactivation domain. Therefore, they may act as dominant negatives in respect to the full-length p73. At the C- terminus, alternative splicing generates α, β, γ, δ, ε, ζ, and η isoforms [18, 137]. Thus, exon 13 deletion produces-b (TAp73b) isoform lacking the SAM domain. Moreover, the p73 C-terminus is responsible for interactions with other transcription factors such as c-Jun, Nfkb, ATF3 and many others, thereby distinguishing p73 functions from the p53 ones [42, 47, 106, 138–140].

Since the p53 and p73 DNA binding sites overlap, the p73 can bind and activate or repress the subset of the p53 target genes that regulate cell cycle and apoptosis (p21, Bax, Fas, PUMA). Moreover, p73 is regulated by the same signaling pathways as p53, such as DNA damage response pathway (ATM/ATR/CHK1 [25]) and is repressed by an E3 ligase, MDM2 [102, 141–143]. Therefore, loss of p53 functions in cancer can be, to a certain extent, compensated by TAp73 [69, 144]. At the same time, p53 target genes can be repressed by the dominant negative DNp73 isoforms [73, 145, 146]. Both TAp73 and p53 activate the DNp73 promoter, creating a negative feedback loop [53, 147, 148].

Thereby, in human carcinogenesis transcriptionally active p73 isoforms (TAp73b) are pro-apoptotic and anti-oncogenic, while transcriptional repressors (DNp73, ΔEx2-3p73) are anti-apoptotic and pro-oncogenic [16, 21, 84, 123–126, 149, 150].

In contrast to this paradigm, both TA- and DN-p73 isoforms are frequently overexpressed in cancers [16, 21, 36, 84, 98, 123–126, 149–154] (Table 2).

Thus, pro-apoptotic p73 functions must be de-activated or bypassed in the proliferating cancer cells [25–27, 49, 57, 76, 101, 155]. Therefore, a better understanding of diverse p73 repression mechanisms in different cancers should facilitate the identification of targets for future drug development [39, 41, 45, 63, 67, 74, 77, 83, 90, 102, 156–158].

Tumor-suppressor and oncogenic functions of TA- and DN-p73 isoforms in mice models

Animal models with complete ablation [122, 124, 159] and isoform-specific p73 deletions [20, 52, 159, 160] reveal interdependent, overlapping, and unique functions for p73 and other p53 family proteins. Mice lacking p73 have profound defects in pheromone sensory pathways, hippocampal dysgenesis, hydrocephalus, reproductive organs development as well as chronic infections and inflammation [122]. In contrast to p53-deficient mice, p73 knockout mice show no spontaneous tumorigenesis and most of the animals die within a month, while others could survive for up to 8 months [122]. However, mice with a knockout of pro-apoptotic TAp73 isoform live for 19 months whereas the lifespan of TAp73 ± mice is comparable with control (about 24 month). Both TAp73 ± and TAp73 −/− spontaneously develop tumors (lung adenocarcinomas and lymphomas) [20]. In contrast, spontaneous carcinogenesis was not reported

for DNp73−/− mice however, DNp73 was required for tumor formation by transformed MEFs in nude mice, highlighting the differential role of TA- and DN- p73 isoforms in carcinogenesis [52].

p73 and hallmarks of cancer

p73 in the regulation of DNA damage response

The response of the cell to DNA damage is tightly connected with the regulation of cell cycle progression. Depending on the severity of DNA damage the cell may either undergo cell cycle arrest until DNA is repaired, or senescence which permanently blocks cell cycle if DNA is unrepairable. Alternatively, cells may commit suicide by apoptosis. Importantly, cancer cells are prone to cell cycle arrest slippage and often display attenuated apoptosis. Subsequent sections will include specific p73-dependent mechanisms of the DNA damage response which regulate the decision of a cell to live to die or to senesce (Fig. 1).

Inactivating mutations or low expression of the BRCA1 gene contribute to breast and ovarian cancer development. However, BRCA1 deficient ovarian and breast tumors are sensitive to cisplatin due to induction of TAp73 [165, 166]. Mechanistically, re-expression of BRCA1 induces DNA methylation of the TAp73 promoter thereby inhibiting Zeb1 binding and Zeb1 mediated repression of the TAp73. This is in line with other investigations suggesting that DNA methylation induces tissue specific gene expression [167–169].

In contrast, the promoter of DNp73 is not methylated in the non-transformed human mammary epithelial cells (HMECs) thus permitting the inducibility of DNp73 after DNA damage and better survival after cisplatin treatment [80]. In the breast cancer cells, the level of DNp73 induction decreases with BRCA1 depletion after cisplatin treatment. Importantly, in contrast to ovarian cells, the level of TAp73 was lower in breast cancer cells [80, 165]. Interestingly, exogenous expression of DNp73 resulted in a modest, yet significant increase of cell viability after cisplatin treatment. Altogether, these findings suggest that DNp73 promotes BRCA1 deficient breast cancers [80].

Analysis of the DNA damage response (DDR) in DNp73−/− cells revealed a new role for the DNp73, as an inhibitor of the molecular signaling emanating from a DNA break to the DDR pathway [52]. Increased p53-dependent apoptosis and sensitivity to DNA damage was shown in cells from the DNp73 − / − mice [52].

Cell cycle arrest and/or apoptosis are induced by the phosphorylation of p53 by ATM [170, 171]. This process is inhibited by the DNp73, which attenuates the ATM activation. In addition, the p73 isoform DNp73b interacts with the DNA damage sensor protein 53BP1 and localizes on the sites of the DNA damage.

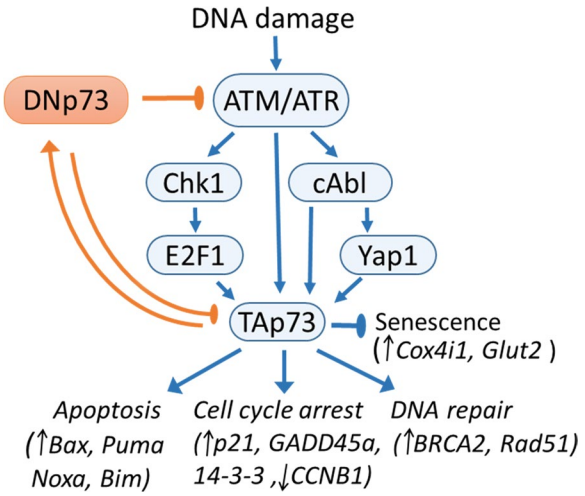

Fig. 1 DNA damage response and cell signaling pathways that regulate p73 activity. Arrows represent activation of the pathway, and brakes highlight repression of the activity. In pink are signaling that promote and in light blue are signaling that repress p73 mediated response to the DNA damage. In orange are signaling that promote and in blue are signaling that repress cell cycle progression. A DNA damage response induces ATM/ATR/c-Abl complex formation on DNA that leads to Tyr-99 phosphorylation of p73 [161–163] or ATM/ATR mediated activation of Chk1/2-E2F1 signaling cascade [25] and Yap mediated p73 activation [164]. In turn, TAp73/p53 mediated DNp73 induction repress ATM/ATR activation [52], and repress pro-apoptotic p53/p73 responsive genes [146], providing a negative feedback loop mechanism facilitating de-activation of the pathway upon DNA repair. Activation of the p73 by DNA damage halts cell cycle progression at checkpoints

Overexpression of DNp73b, but not DNp73a in the γ-irradiated U2OS cells, results in interaction between 53BP1 and DNp73b, suggesting that SAM domain inhibits the interaction [52]. Furthermore, after γ-irradiation and in the presence of excessive amount of DNp73b, authors observed decreased ATM phosphorylation, reduced p53 protein accumulation and decreased PUMA protein expression. On the contrary, DNp73 deficiency in γ-irradiated U2OS cells stimulates attraction of 53BP1, p53, and γ-H2AX to DSB sites [52].

Isoforms of p73 control DNA damage response not only through protein–protein interactions but also via transcription of the DNA DSB repair genes [88, 93, 172–174]. For example, γ-irradiation of the HCT116 cells showed strong induction of the TAp73α isoform [88]. Similar to p53, the TAp73a isoform binds simultaneously with Δ133p53 to the dedicated responsive elements in the promoters of RAD51, LIG4, and RAD52 repair genes, thereby stimulating their expression [88, 175]. Furthermore, the TAp73a and Δ133p53 co-expression stimulates DNA DSB repair mechanisms, including homologous recombination (HR), non-homologous

end joining (NHEJ) and single-strand annealing (SSA). Importantly, p73 knockdown results in G2 phase cell cycle arrest upon ɣ-irradiation, therefore inhibiting cell proliferation [88].

The p73 is also involved in the DNA mismatch repair pathway, via hMLH1/c-Abl/p73a/GADD45a signaling [176]. Furthermore, MMR-dependent apoptosis is blocked by specific knockdown of the p73a isoform, while G2 arrest is p73 independent.

A remarkable example of the dual role of p73 isoforms in cancer is represented by oesophageal adenocarcinoma. The latter is often caused by the gastroesophageal reflux disease (GERD). GERD is caused by the bile acid salts flux from the stomach, generating acidification, ROS and DNA damage [92]. DNA repair in the oesophageal cells is promoted by the p73. Notably, in the oesophagus, and other epithelial tissue p73 is expressed strictly in the basal cells [2]. Bile acid induces the TAp73a isoform that transcriptionally upregulates SMUG1 and MUTYH, two glycosylases which are involved in base excision repair [93]. In these conditions, TAp73α acts as a pro-survival factor that induces DNA repair enzymes and inhibits apoptosis [93], contradictory to the established pro- apoptotic functions of the wild-type TAp73 isoform discussed above [53, 147]. In turn, exposure of p53 null esophageal adenocarcinoma SK-GT-4 cells to the bile acid and pro-inflammatory cytokines IL-1β and TNFα induced DNp73α. The DNp73α induction was dependent on c-Abl, IKK, and p38 MAPK kinases [91]. In addition, the SK-GT-4 cells that exogenously expressed DNp73α showed increased survival upon bile acid exposure.

Altogether, these data highlight the pro-survival role of DN- and TA- p73 isoforms facilitating DNA repair.

p73 in the regulation of cell cycle

Regulation of the G1 checkpoint

Upon DNA damage, p53 is phosphorylated by ATM/ATR/Chk1,2 and MDM2 mediated proteasomal degradation of 53 is inhibited. Alternatively, upon oxidative or oncogenic stress, p14ARF interacts with MDM2, thereby also stabilizing p53. As a result, p53 now binds DNA [177] and activates a set of genes that inhibits cell cycle progression (p21, 14–3-3σ, Gadd45). p21 inhibits CyclinD/CDK4,6 complex formation leading to Rb hypo-phosphorylation and interaction with transcription factor E2F, inhibiting cell cycle related E2F target genes leading to the growth arrest. In addition, expression of the distinct set of cell cycle related genes regulated by the p53-p21-DREAM-E2F/CHR is inhibited [178, 179].

However, even in the absence of p53, cancer cells are still able to halt cell cycle in response to genotoxic stimuli [180, 181]. It was shown that in response to chemotherapeutic agents, cell cycle arrest and apoptosis are p73 dependent [71, 156, 157, 182]. Accordingly, p63 and p73 are required for the p53 dependent apoptosis in mouse embryonic fibroblasts [183].

Mechanisms of the G1 checkpoint sensing by p73 and p53 are similar [184] (Fig. 2). Specifically, expression and stability of the transcriptionally active p73 is induced by the DNA damage via ATM/ATR/Chk1 pathway [25, 105, 145, 185]. Importantly, p73 is phosphorylated at Thr-86 during cell cycle progression by Cyclin E/CDK2, Cyclin A/CDK1/2, and Cyclin B/CDK1/2 complexes leading to repression of the p73b transcriptional activity [28, 186]. On the contrary, PKC dependent phosphorylation of Ser-388 [130] induces transcriptional activity of p73 towards the cell cycle regulatory genes p21, Gadd45a, Wee, 14–3–3σ causing cell cycle arrest [70, 76, 90, 187] (Fig. 2).

What are the mechanisms that inhibit p73 mediated cell cycle arrest in normal and cancer cells? Numerous signaling pathways regulate p73 transcription, translation, stability and cell cycle progression [56, 130, 184, 203–205] and apoptosis [25, 29, 42, 50, 51, 75, 206–211] (Fig. 3a).

Specifically, negative regulators include E3 ubiquitin ligases Itch, Pirh2, FBXO45, WWP2 and SUMO ligase PIAS1 which promote p73 degradation in 26 proteasomes [212–217] (Fig. 3a).

Binding p73 to ATF3 prevents the ubiquitination and degradation of p73 [42]. Unlike the other E3 ubiquitin ligases, ubiquitinylation by NEDL2 enhances p73α stability, while the interaction with NQO1 protects p73α from the ubiquitin-independent degradation in 20S proteasome. Notably, NEDL2 regulates metaphase to anaphase transition [218, 219] (Fig. 3a).

The p73 transcriptional activity is induced by PKC [130, 220] and c-Abl [221] phosphorylation and YAP1 mediated corecruitment of p300 [222, 223]. Upon c-Abl-mediated phosphorylation, the prolyl isomerase Pin1 induces conformational changes of p73 required for its acetylation by p300 [224] (Fig. 3a).

SIRT2, a NAD-dependent histone deacetylase, is required for glioblastoma stem cells proliferation and tumorigenicity [56]. Furthermore, SIRT2 regulates p73 transcriptional activity by deacetylating its C-terminal lysines 620, 623, and 627. Importantly p73 inactivation (in the absence of p53) by SIRT2 is critical for glioblastoma cells proliferation and tumorigenicity [56]. In HEK293 cells, SIRT1 binds p73 in vivo and in vitro, deacetylates it, and suppresses p73-dependent transcriptional activity thereby partially inhibiting p73-dependent apoptosis [225].

The IKKβ protein kinase, which regulates NFkB, also binds DNp73a and phosphorylates the latter on Ser-422, causing p73 stabilization, nuclear accumulation and

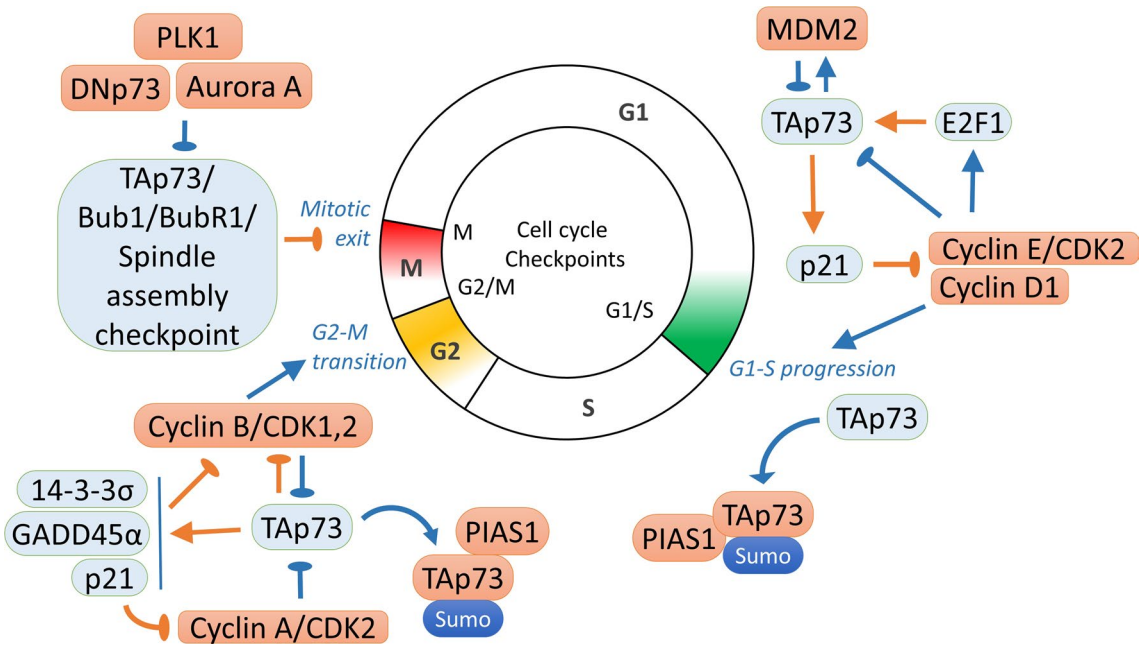

Fig. 2 Cell cycle regulation by p73. In blue are molecules and signalling that promote cell cycle and in orange are signaling that repress cell cycle progression. Colors on the cell cycle diagram represent p73 activity that decreases at checkpoint exit [81, 186, 188]. G1/S checkpoint. Active TAp73 induces p21 leading to repression of the cell cycle related genes [70]. In turn, TAp73 transcriptional activity is inhibited by phosphorylation at Thr-86 by CyclinE/CDK2 complexes [28], or by inhibition of E2F1 transcriptional activity by the E2F1/Rb complex [189–191]. G2-S checkpoint: TAp73 inhibits Cyclin B transcription [192] or via induction of GADD45a [193], Wee, p21 and 14–3–3σ [76, 90], that represses CyclinB/CDK1 [194, 195]. To facilitate G2-M transition, p73 activity is inhibited by CyclinB/CDK1 [188], by MDM2 negative feedback loop [196] or by PLK2 [76]. Mitotic checkpoint: overexpressed TAp73 interacts with SAC components Bub1, Bub3, BubR1 leading to checkpoint activation [197, 198]. DNp73 was shown to bind to SAC proteins but have no activity in M- checkpoint [198] or to inhibit checkpoint functions [199, 200]. Phosphorylation of the p73 S235 by Aurora-A kinase results in inactivation of its DNA damage and spindle assembly checkpoint activation functions and mitotic exit due to release of the Mad2-Cdc20 from the SAC spindle assembly checkpoint complex [201, 202]

repression of the p53-regulated genes in several cancer cell lines [226, 227].

In contrast, in p53-null squamous cell carcinoma cells, TNF-α promoted c-REL nuclear translocation, c-REL/DNp63α interaction, and TAp73 dissociation from DNp63α. This chain of events culminates in TAp73 translocation from the nucleus to cytoplasm [106]. TNF-α modulates genome-wide redistribution of DNp63α/TAp73 and NF-κB c-REL cumulative binding at the TP53 and AP-1 DNA binding sites to induce an oncogenic gene expression program in squamous cancer [140] (Fig. 3c).

On the related note, the TAp73 can inhibit wild type p53 activity and induction of apoptosis [97, 228]. Similarly, the complex of p53 with chaperones and MDM2 deactivates TAp73 [229] (Fig. 3b). In contrast, p53/TAp73 can activate each other's functions in different cells by MDM2 quenching [95] or co-recruitment upon p53 Thr-81 phosphorylation [88, 230] while other demonstraetd that Mdm2 and MdmX binding represses p73 masking its transcription [217].

Viral infection causes development of cancers such as cervical and Kaposi sarcoma [231]. The activity of p53 family members in viral oncogenesis has been established [232, 233]. Viral onco-proteins were shown to fine-tune the p73 activity. For example, interaction of p53 and p73 with CBP can be inhibited by the human T-cell leukemia virus type1 Tax protein [68] as well as by adenovirus E1A protein [234].

Thus, the effects of p73 isoforms on the cell cycle and apoptosis are highly diverse and different mechanisms in turn are utilized in cancers to repress the p73 activity.

p73 mediated regulation of replicative G2-M checkpoint

Upon completion of the DNA synthesis, cells execute G2/M replicative checkpoint. During this stage, DNA integrity is verified and repaired as well as the levels of proteins required for the mitosis are evaluated.

The p73 is involved in the regulation of the DNA damage response during G2-M and M checkpoints [28, 41, 81, 88, 90, 188, 216, 239] (Fig. 2). The ability of cells to activate p73 correlates with the specific stage of the cell cycle. Specifically, the activity of p73 is high at the checkpoints and low upon checkpoints exit, regulating the key cell cycle related genes [81, 186, 188] (Fig. 2). For

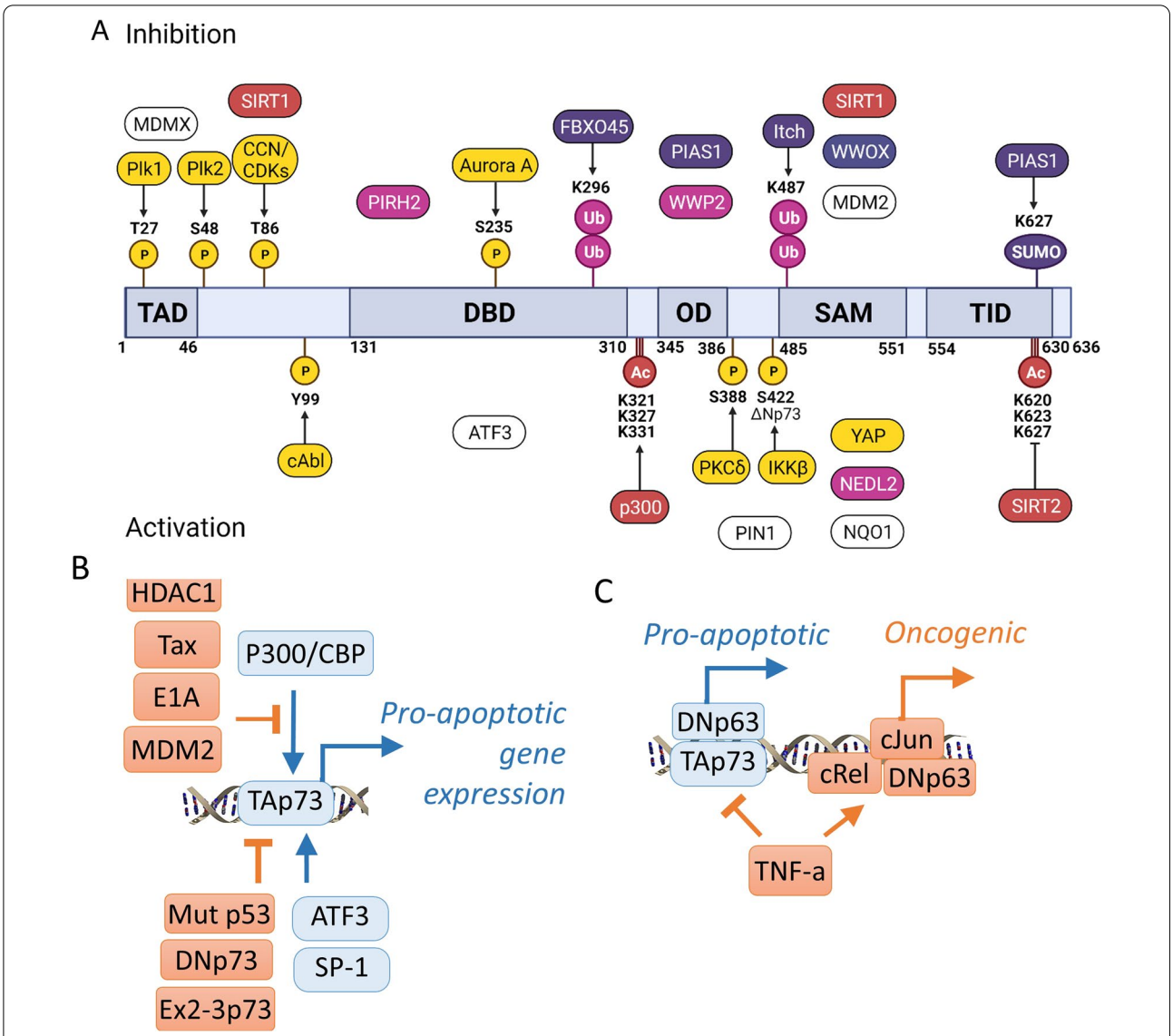

Fig. 3 Signaling pathways that regulate p73 activity. **a** The diagram shows the TAp73α isoform domain structure and known phosphorylation sites and kinases (yellow), ubiquitinylation sites and ubiquitin ligases (purple), acetylation sites (red), and the sumoylation site (violet). The positions of PTM sites correspond to the TAp73α isoform unless indicated otherwise. TAD, transactivation domain; DBD, DNA binding domain; OD, oligomerization domain; SAM, sterile alpha motif; TID, transcription inhibition domain. See text for the literature. **b** Regulation of transcriptional activation. In red are denoted proteins and signalling that inhibit transcriptional activation of TAp73 [56, 79, 102, 123, 126, 235, 236] and in blue are signalling pathways and proteins that promote TAp73 regulated pro-apoptotic gene expression [42, 237, 238]. **c** In squamous carcinoma, TNFa induces nuclear translocation of cREL and induces re-localization of TAp73 binding sites from pro-apoptotic to pro-oncogenic [140]

example, a p73/SP1 heterodimer represses CyclinB1 transcription [192]. In turn, there is a negative regulation of p73 by CyclinB1/CDK1 complex that associates with and phosphorylates p73 at Thr-86 resulting in the inhibition of DNA binding and transcriptional activity of p73 upon progression from the G2 phase to mitosis [188]. c-Abl kinase interacts with ATM/ATR participating in DNA damage Chk1 phosphorylation, p53 and p73 activation [161–163]. c-Abl phosphorylates p73 at Tyr99 leading to inhibition of p73 degradation by TRIM28 E3 ligase, subsequent p73 stabilization and activation of the anti-oncogenic program [221] A similar stabilization mechanism has also been described in the context of pharmacological stabilization of p53 [240]. It has been suggested that c-Abl/p73 pathway is active during G2/S checkpoint because at G1 checkpoint hypophosphorylated Rb inhibits E2F1 and c-Abl [190, 241]. Another mechanism of G1/S and G2/M exit is mediated via inactivation of p73

by PIAS-1 binding that stabilises and symoylates p73-alpha isoforms inhibiting transcriptional activity. Importantly, PIAS-1 is expressed exclusively in the S-phase and PIAS-1 knockdown leads to accumulation of cells in the G2 phase of cell cycle [216].

Genome stability and p73 in regulation of mitosis. M checkpoint

Errors in the molecular mechanisms responsible for regulation of the chromosome segregation during meiosis and mitosis decrease the genomic stability, which leads to aneuploidy. The M checkpoint occurs between metaphase and anaphase, right before the onset of chromosomal separation to ensure their proper alignment. To execute the "M" checkpoint, cells assemble a so-called spindle assembly checkpoint complex (SAC) that is localized at the kinetochores and measures correct attachment of microtubules to the spindle poles [242, 243]. This complex activates the mitotic checkpoint complex (MCC) that in turn binds to and inhibits activity of the Anaphase promoting complex (APC/Cdc20) which activation leads to the cohesin cleavage, segregation of chromosomes (mitotic exit) and degradation of the CyclinB1 [244–247].

A role of the p73 in regulation of genomic stability during mitosis has been extensively characterized [20, 28, 104, 186, 188, 198, 199, 201, 202, 248] (Fig. 2).

During the drug induced M-phase arrest of Hct116(3) cells, the TAp73 is phosphorylated by the Cdc2-CyclinB, losing the DNA binding capacity and transcriptional activity [188]. During mitosis, the p73 was not associated with the centromeres and was excluded from the condensed chromosomes in H1299 cells [188]. However, the TAp73-deficient mouse embryonic fibroblasts (MEFs) were severely compromised in undergoing a nocodazole-induced mitotic arrest [20]. Furthermore, TAp73 −/− MEFs underwent a premature mitotic exit and passage into the G1 phase, suggesting that mitotic regulation is predominantly performed by the TAp73 isoforms rather than DNp73 isoforms [20].

Treatment of TAp73 −/− lung fibroblasts with nocodazole for 12 h resulted in the increased polyploidy as well, whereas TAp73 −/− thymic cells showed no alternations in genomic stability [20]. This suggests that the effect of TAp73 on the aneuploidy is tissue-specific, which could be an explanation to why TAp73 −/− mice preferentially develop lung adenocarcinomas [20].

There is multiple evidence to suggest that when overexpressed, TAp73 interacts with SAC components Bub1, Bub3, BubR1 leading to M checkpoint activation [197, 198]. In triple-negative breast cancer MDA-MD231 cell lines, endogenous TAp73 isoform interacts with BubR1, whereas DNp73 is not [198]. Upon overexpression, DNp73b does interact with BubR1, however, in contrast to TAp73a, its binding does not affect the interaction of BubR1 with phosphorylated histone H1 suggesting that DNp73 does not have a role in SAC function [198]. In contrast, overexpression of DNp73b leads to tetraploidy in human lung carcinoma H1299 cells [199] suggesting that DNp73 affects genomic stability as well. Accordingly, in glioblastoma cells DNp73 isoform overexpression leaded to an abnormal number of centrosomes, while TAp73 overexpressing cells showed normal centromeres count with no association with BubR1, suggesting that DNp73 can inhibit checkpoint activation [200].

In contrast, in Saos2 osteosarcoma cell line, TAp73α overexpression led to a significant increase in the number of polyploid cells, while p53, DNp73α, and TAp73β or γ had no effect on polyploidy [197]. The effect was linked to the interaction of TAp73α with Bub1 and Bub3 that were also overexpressed in these cells whereas neither p53 nor any of the other p73 isoforms interacted with Bub1 or Bub3.

Phosphorylation of the p73 S235 by Aurora-A kinase results in inactivation of its DNA damage and spindle assembly checkpoint activation functions and mitotic exit is accelerated due to release of the Mad2-Cdc20 from the SAC spindle assembly checkpoint complex [201, 202]. In addition, inhibitor of Aurora kinase B AZD1152-HQPA induces apoptosis in p53/p73 wild type U87MG glioblastoma cell line, whereas in p53/p73 double null SK-N-MC cells inhibition of Aurora kinase B leads to induction of cell cycle related genes, endoreplication and polyploidy, highlighting the role of p53/p73 [104, 201].

All together, these publications reveal the roles of TAp73 as an activator and DNp73 as an inhibitor of SAC activity and, correspondingly, TAp73 as an inhibitor and DNp73 as an activator of early mitotic exit and chromosomal abnormalities.

DNA damage can occur at any stage of the cell cycle and p73-activated checkpoints are utilised by cells for DNA repair and maintaining genome stability. If DNA damage or SAC signals persist, the p53/p73 activates transcription of pro-apoptotic genes, whose products ultimately trigger apoptosis [249].

Regulation of apoptosis by p73

Apoptosis is mediated by dynamic equilibrium of activating and repressing signals. A key event of triggering apoptosis is accumulation of the cytoplasmic protein Bax on the outer mitochondrial membrane [250]. Bax oligomerization and formation of pores on the outer mitochondrial membrane leads to the release of cytochrome C in the cytoplasm, apoptosome assembly and subsequent caspase-mediated cleavage of cellular proteins

[251]. At the late stages, apoptosis culminates in DNA fragmentation [252] and induction of phagocytosis [253].

On the other hand, Bax mediated release of the cytochrome C is repressed by Bcl-2 protein family (Bcl-2, Bcl-XL, Mcl-1, Bcl-w, A1, Bcl-L10, Bcl-G and Bcl-Rambo) whereas, so called BH3-only family of proteins (such as Puma, Noxa, Bad, Bid, Bim, Hrk, Bik and Bmf) bind to and inhibit the Bcl-2 anti-apoptotic functions [254].

Specifically, p73 is required for induction of apoptosis by regulating transcription of key pro-apoptotic genes (Fig. 4). Transcriptional induction of Bax by p73 leads to apoptosis in different settings [41, 255–259]. In addition, mechanisms of p73 induction of apoptosis involve transcriptional activation of PUMA which, in turn, induces Bax mitochondrial accumulation and release of cytochrome C [228, 260–262]. The p73 phosphorylated by Aurora-A at S235 loses the chromatin binding affinity, and is exported from the nucleus to cytoplasm [201], thereby halting the expression of its transcriptional targets such as p21 [201] and pro-apoptotic BH3-only protein Bim. This affects cytochrome C release and caspase activation [248].

Similarly, p73 binds to the promoter and transcriptionally activates GRAMD4. As a result, apoptosis is induced via GRAMD4 translocation from nucleus to mitochondria and interaction with Bcl-2 [264].

It was shown that p73 could mediate cell death independently of other p53 family members. In the p53 deficient cells, p73 is induced upon DNA damage by E2F1 transcriptional activation downstream of Chk1/2 [25, 269–271] (Fig. 1). However, as it is discussed in the previous section, effects of p73 are dependent on other p53 family members' activity. For example, the loss of p63 in normal keratinocytes causes p21 induction, inhibition of cell cycle and senescence independent of p53 and p73, whereas in squamous cell carcinoma the loss of p63 induces p73-dependent cell death [272]. Accordingly, in head and neck squamous cell carcinoma cells, the p63 knockdown induces pro-apoptotic Puma and Noxa and cell death in p53 independent and p73-dependent manner [273]. Similarly, in triple negative breast cancer cells,

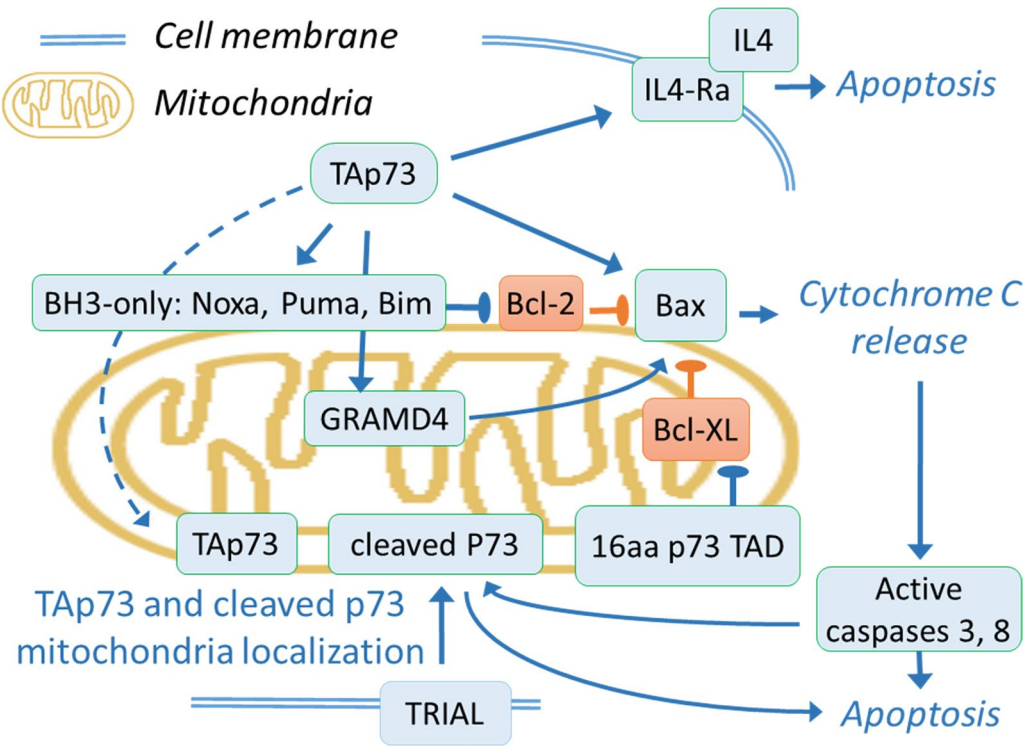

Fig. 4 Schematic representation of p73 involvement in the regulation of apoptosis. In blue, molecules that promote and in orange—molecules that repress apoptosis. Arrows and bars in green—signalling that promote and in red—repress apoptosis and senescence. A. p73 mediated regulation of apoptosis. Transcriptional activation of p73 promotes expression of Bax [41, 255–259] and BH3-only family members PUMA [228, 260–263], Noxa [238], Bim [248] and GRAMD4 [264] that repress Bcl-2 and induces Bax activity. The p73 regulated induction of IL4R sensitize cells to IL-4-induced apoptosis [265]. In turn, p73 repressing pathways inhibit apoptosis [266]. Alternatively, p73 or p73 fragments can localize to mitochondria during TRIAL induced apoptosis [267] and 16 aa peptide from the transactivation domain of p73 can interact with and inhibit Bcl-x [268]

p63 inhibits p73 activity and apoptosis mediated by PUMA and NOXA [274]. In several human cancer cell lines, interleukin 4 receptor alpha is up-regulated by p73 but not significantly by p53, sensitizing cells to IL-4-induced apoptosis [265]. FBXO45 binds specifically to, and ubiquitylates p73 triggering its proteasome-dependent degradation. When FBXO45 is downregulated, p73 is stabilized and it consequently induces cell death in the p53 independent manner [214].

In addition, p73 apparently regulates apoptosis in a transcription-independent manner (Fig. 4). Intriguingly, caspase cleaved p73 fragments augment TRAIL induced apoptosis of HCT116 cells independently of p73-mediated transcription [267]. Accordingly, in lung adenocarcinoma cells, a peptide from the p73 transactivation domain interacts with Bcl-XL and mediates transcription-independent apoptosis [268]. In turn, scaffolding protein RanBP9 interacts with, and stabilises p73a, inducing mitochondrial dysfunction and apoptosis in the primary hippocampal neurons by transcriptional effects and likely directly at mitochondria [275].

An important aspect of cancer cells is their ability to switch between cell cycle arrest and apoptosis in the cases of irreparable damage. Interestingly, p73 differentially activates cell cycle related and pro-apoptotic genes [130, 190, 228, 257, 276, 277].

Differential p73 effects on cell proliferation and apoptosis upon doxorubicin treatment were dependent on specific post-translational modifications. For example, in osteosarcoma cancer cells and mouse embryonic fibroblasts p300 in cooperation with c-Abl enhanced p73 acetylation at lysines 321, 327, and 331 [276, 278]. Accordingly, in the chronic myeloid leukemia cells, forced nuclear localization of the Bcr-Abl fusion protein promotes p73 activation and subsequent apoptosis [279].

In p53-/- lung adenocarcinoma cells, overexpression of TAp73a increases apoptosis induced by the cisplatin treatment, which was inhibited by E3 ubiquitin ligase CHIP overexpression. This effect was determined by the binding of CHIP to the C-terminus of p73a isoforms and targeting of the p73 to proteasomal degradation [280]. Notably, overexpression of CHIP has no effect on p73b isoforms [280].

In contrast, in colon cancer cells with functional p53, TAp73 restrained p53 mediated activation of apoptosis after low levels of DNA damage by forming a protein complex with p53 that is incapable of DNA binding at Puma, p21 and Bax promoters [228]. Interestingly, the p73 was induced and complexed with the p53 in cells treated with small doses of cisplatin, awhile after higher cisplatin doses, p73 induction and high molecular weight p53 complex were not observed, facilitating activation of the pro- apoptotic genes [228].

Although there are no publications describing the direct effect of p73 on necroptosis and ferroptosis, as opposed to p53 and p63, it is tempting to speculate that p73 acts as a repressor of ferroptosis since p73 regulates genes such as glucose-6-phosphate dehydrogenase, a rate-limiting enzyme of the pentose phosphate pathway [32, 55, 281–283]. The product of this gene is pivotal for glutathione biosynthesis and anti-oxidative cellular response [284].

Thus, p73 functions as a part of the p53 signaling pathway and its overall effects are modulated by the p53 status and cell type [285]. Also, p73 plays a unique role in the regulation of cell cycle and apoptosis [286, 287].

p73 dependent regulation of metabolism

Consistent with the hallmarks of cancer defined by Weinberg [111] the metabolic alterations in cancer include:

1. Utilization of glycolysis for energy production in hypoxia or in the presence of oxygen (so called Warburg effect) with lactate production and acidification of extracellular environment and enhanced biosynthesis [288, 289].
2. Increase of the reduced glutathione production leads to chemoresistance and lower sensitivity to superoxide radicals produced by immune cells [116, 290].

In general, metabolic alterations can be traced back to crucial molecular events such as mutations in critical genes, building gene associated gene signatures [291, 292].

In this context, the role of p73 in metabolism was recently reviewed in an excellent publication [116] and here we will discuss only the cancer-related findings.

The p73 is known to regulate several key enzymes of glycolysis and energy production [33, 293], anabolism of amino acids and detoxification [54, 294–296] (Fig. 5). Importantly, p73 influences expression of glucose-6-phosphate dehydrogenase (G6PD), a rate-limiting enzyme of the pentose phosphate pathway (PPP) [32, 55, 281, 282]. The fraction of PPP in glucose consumption is about 10% and is rapidly increasing upon oxidative stress to produce NADPH—a metabolite necessary for generation of the reduced glutathione—the main ROS and xenobiotics scavenger of the cell [32, 33, 55, 297–302]. Altogether, this increasing amount of evidence is also showing the potential role of oxidative stress as a candidate therapy target [303].

TAp73 overexpression in Saos-2 cells was shown to enhance the Warburg effect by inducing the level of lactate produced during glycolysis. Concomitantly, these cells exhibited a decreased level of pyruvate but increased levels of acetyl-CoA, S-adenosylmethionine, and cysteine

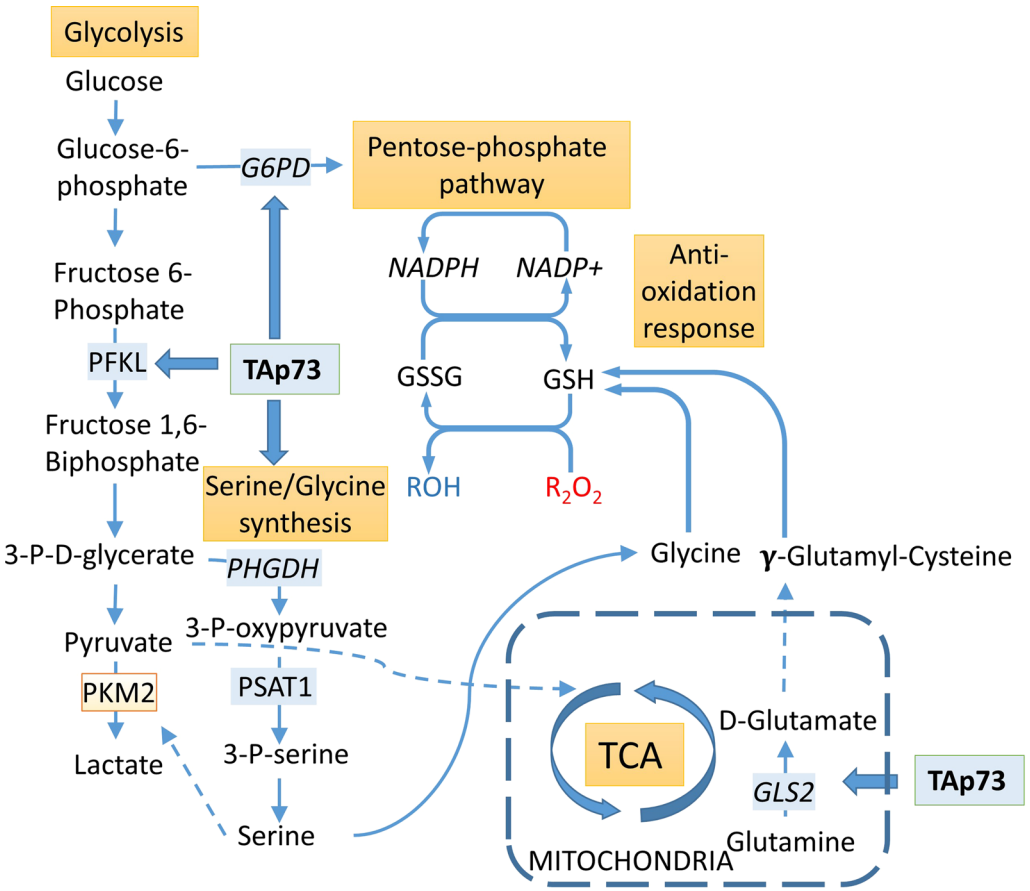

Fig. 5 Metabolic signaling regulated by p73. The p73 regulates expression of glucose-6-phosphate dehydrogenase, inducing pentose phosphate pathway and anaerobic glycolysis [32, 55, 281, 282] glutathione production and response to oxidative stress and xenobiotics [297–300]. Further down the glycolysis pathway, TAp73 transcriptionally regulates liver type phosphofructokinase-1 (PFKL) that enhances glycolysis rate [33] and enzymes of the serine/glycine biosynthesis [54] necessary for cell growth in serine deprivation and regulation of pyruvate kinase (PMK2) which activity is associated with lactate production and cancerogenesis [304, 305]. Further, p73 regulates expression of the glutaminase-2, which converts glutamine to glutamate influencing glutathione synthesis [54]

[294]. Cellular anabolism is also influenced by the ability of TAp73 to stimulate transcription of serine biosynthesis enzymes and glutaminase-2, which converts glutamine to glutamate [54]. Importantly, lung cancer patients with coordinately increased p73 and GLS-2 were characterized by significantly worse prognosis [54]. In addition, enhanced serine production activates PMK2 and promotes conversion of pyruvate to lactate [304].

Thus, TAp73 overexpression promotes production of metabolic intermediates cysteine and glutamate that are converted by glutamate-cysteine ligase to glutathione, thereby enhancing the antioxidant defense.

In E1A/H-RasV12-transformed mouse embryonic fibroblasts, TAp73 is crucial for the G6PD transcription, and consequently for PPP functioning, NADPH homeostasis, cellular growth and tumor formation [55]. Notably, depletion of TAp73 was rescued by G6PD expression or supplementation with nucleosides and ROS scavenger in MEFs [55]. Similarly, experiments on H1299 non-small lung carcinoma cells showed that p73-depleted H1299 cells overexpressing G6PD grew the same as control, proving that G6PD expression is vital for TAp73-mediated H1299 cells proliferation [32].

Similarly, in E1A/H-RasV12-transformed mouse embryonic fibroblasts, osteosarcoma U2OS, and lung cancer H1299 cell lines TAp73 transcriptionally regulates phosphofructokinase-1, liver type (PFKL) and promotes glycolysis [33]. Notably, decreased proliferation of TAp73$^{-/-}$ MEFs or tumorigenicity of HCT116 cells was rescued by PFKL and PFKL/G6PD overexpression respectively [33].

The p73 is often overexpressed in medulloblastomas. Furthermore, TAp73 appears to be critical for the medulloblastoma cells proliferation as its expression correlates with glutamine level. Accordingly, it was shown that glutamine starvation along with injections of cisplatin led to

increased apoptosis in both in vitro and in vivo experiments on medulloblastoma xenograft mice [60, 61].

To summarize, TAp73 promotes cancerous metabolism, oxidative and xenobiotic stress response, and the Warburg effect both in in vitro experiments and mice models, all together supporting tumor growth.

Senescence and replicative immortality

Telomerase is a ribonucleoprotein that synthesizes telomere repeats at the DNA ends in embryonic tissue, in germline tissue and in the immortalized cancer cell lines. In the normal somatic tissue, telomerase is not active [306] and hence, with increasing number of cellular divisions the telomeres repeats are gradually lost. This mechanism limits the replicative potential of the cell, thereby preventing replicative immortality.

Senescence is defined as a permanent growth arrest of the metabolically active cell without cell death associated with the telomere shortening after about 40 cellular divisions [307–310].

In addition, normal cells preferentially undergo senescence rather than cell death in response to various forms of stresses including the oncogene activation [311, 312], DNA damage [313] and oxidative stress [314–317].

Senescence is deemed as an anti-cancer cellular response that compliments apoptosis [318] in response to sub-lethal doses of stress [319, 320].

The senescence signaling pathways are frequently altered in cancers [321, 322]. This is exemplified by the mutations in key senescence genes such as p53, CDKN2A, CDKN2B, TERT promoter [321].

On the molecular level, senescence is mediated by activation of p14ARF that interacts with MDM2, hence preventing p53 degradation and eliciting the growth arrest. Independently, p16INK inhibits the CyclinD1/CDK4/6 complex leading to the RB hypo-phosphorylation and sequestering the transcription factor E2F. The latter event results in transcriptional inactivation of cell cycle-related E2F target genes and subsequent growth arrest, which can be rescued by the alteration of other molecular events in specific cancer contexts [323].

Notably, senescence regulation differs in mice and humans [324, 325]. While mice fibroblasts require p14ARF-p53 for oncogene induced senescence [324, 326, 327], human cells are p53 independent and in turn require p16INK-CyclinD/CDK4/6 signal transduction [324, 325]. Of note, p53 mutations in cancer cells contribute to bypassing senescence in response to oxidative stress [315].

As it is discussed in the corresponding sections of our review, p73 is involved in the regulation of the DNA damage response, metabolism and oxidative stress responses [30, 31, 290, 328] thereby influencing senescence (Fig. 6).

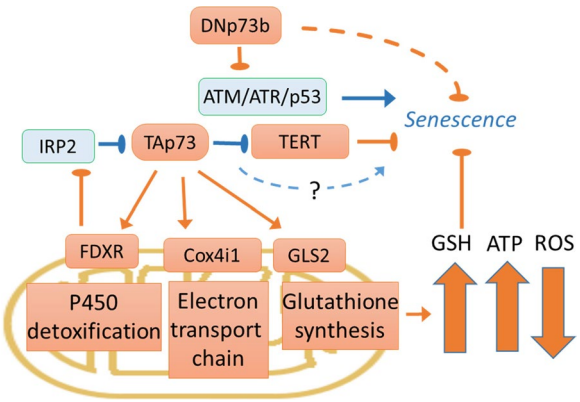

Fig. 6 Schematic representation of p73 involvement in the regulation of senescence. In blue, molecules that promote and in orange—molecules that repress senescence. TAp73 inhibits TERT activity, however, the effect on senescence is not established [329]. In contrast, DNp73 represses p53/p73 activating signalling emanating from the DNA double stranded breaks by the ATM/ATR signalling also repressing senescence [52]. TAp73 induced transcription of the mitochondrial enzymes Cox4i1 regulating ROS, ATP levels and oxygen consumption is critical for senescence repression in MEFs [87]. Similarly p73 target genes GLS2 is a key enzyme in glutathione biosynthesis to reduce ROS level [330, 331] and FDXR has roles in electron transfer to p450 and p73 mRNA stability by IRP2 regulation [332]. Altogether, these processes lead to higher oxidation rate and ATP generation, glutathione biosynthesis, lower ROS levels and inhibition of senescence

While the role of the p53 family proteins in regulation of cellular senescence is firmly established [85, 322, 333–338], several publications also demonstrate the role of p73 in this process [52, 64, 87, 329, 333, 339–341] (Fig. 6).

Telomeres are protected from the DNA damage by a protein complex called shelterin [86, 342]. If the shelterin component Pot1b is depleted in p63 knockout mice, telomeres activate ATR-Chk1 DNA damage response and p73 dependent apoptosis [64].

It was shown that overexpression of the TAp73a or TAp73b isoforms represses TERT transcription and TERT activity in the HEK cell line [329]. Using luciferase reporter assays, it was shown that p73-mediated TERT reporter repression was rescued by the NF-YB depletion. The TERT transcription and TERT activity were also repressed by the overexpression of TAp63g and p53 [329]. Even though senescence was not examined, the TAp73 overexpression-mediated repression of the TERT might promote senescence of the HEK cell line [329].

However, direct experiments revealed that both TA- and DN-p73 isoforms repress senescence. Such as, E1A/RasV12 transformed MEFs generated from the DNp73 knockout mice formed smaller xenograft tumors with higher b-gal staining and higher expression of senescence markers p16 and DcR2 [52].

When TAp73 knockout mice were examined, MEFs grew slowly, and 3.5 times higher senescence levels were observed [87]. Accordingly, the p16 and p19 senescence markers were induced. Mechanistically, the effect was attributable to the inhibition of the mitochondrial complex IV activity, specifically due to the depletion of the direct TAp73 target, Cox4i1. Authors observed higher ROS level, lower ATP and oxygen consumption and higher oxidative stress sensitivity. Depletion and restoration of the Cox4i1 level mimics and inhibits effects of the TAp73 depletion, respectively [87].

Reduction of TAp73 is responsible for ROS accumulation upon depletion or knockout of the RNA-binding protein PCBP2 in H1299 cells [31], presumably through regulation of the p73—induced gene, glutaminase 2 [330], which is involved in the anti- oxidative response [331]. Although senescence was not reported in the human cell lines in that study, about the 24-fold induction of b-gal staining was observed in PCBP2 − / − MEF cells [31].

Depletion of both p73 and ferredoxin reductase (FDXR, the mitochondrial electron transfer protein) induces senescence of MEFs [332]. The p73 is reduced upon the loss of the FDXR due to induction of the iron-regulatory protein 2 (IRP2) which binds to and destabilises p73 mRNA [332]. Interestingly, FDXR is a p73 transcriptional target [343], suggesting a possible positive feedback loop between FDXR and p73. It would be interesting to compare the effect of p73 and p53 on IRP2 since restoration of decreased p53 in FDXR KO cells reduces IRP2 [344].

Consistently, induction of senescence was observed in the neural precursor cells of the p63 and p73 haplo-insufficient mice [341]. Increased DNA damage and p53 activation were responsible for the phenotype since genetic ablation of the p53 completely inhibited this effect.

To summarize, in most cases, either TA- or DN-isoforms of p73 act as senescence inhibitors. Thus, induction of p73 activity will presumably lead to either cell cycle arrest or apoptosis but not senescence, because of p73 being a positive regulator of the antioxidation metabolism.

Conclusions

The p53 protein family members, p53 and p73, share the same DNA binding site, have similar domain structure and overlapping signaling pathways that regulate their activity. Hence, it is a long-standing question: why p73 is rarely mutated or lost in cancer while p53 aberrations are found in the vast majority of cancers and considered to be fundamental for cancer development? Evidence presented in this review suggests a dual role of the p73 in cancer. First, it is involved in the cell cycle arrest and anti-oxidative response thereby promoting cell survival. On the other hand, being a homolog of p53, it promotes DNA damage induced cell death. Finally, it can also serve as biomarker, as p53, in many cancer contexts [345, 346]. Consequently, cancer cells seem to develop mechanisms that favor pro- oncogenic and repress anti- oncogenic functions of the p73, especially in the absence of functional p53. However, understanding of signaling pathways that fine tune the balance is very limited. Hence, the exact role of TAp73 in tumorigenesis and aggressiveness remains debated, highlighting the need for further and more precise investigations. New findings on the molecular mechanisms that define the exact outcome of p73 activity in tumour cells will help to develop treatments that will specifically induce pro-apoptotic functions of the p73 in cancer.

Abbreviations

HMECs: Human mammary epithelial cells; DDR: DNA damage response; TAD: Transactivation domain; DBD: DNA binding domain; OD: Oligomerization domain; SAM: Sterile alpha motif; TID: Transcription inhibition domain; SAC: Spindle assembly checkpoint; MCC: Mitotic checkpoint complex; APC: Anaphase promoting complex; MEFs: Mouse embryonic fibroblasts; PPP: Pentose phosphate pathway; ROS: Reactive oxygen species.

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Authors' contributions

Conceptualization, J.M.R, I.B., A.K.; resources, G.M., N.A.B. A.K, V.K.; data curation, J.M.R., A.D., writing—original draft preparation J.M.R., A.K., I.Z, D.L., A.B., L.A., A.R.; writing—review and editing, J.M.R., I.B., N.A.B., A.K., C.G., A.D., GM; visualization, J.M.R., S.Z., A.R.; funding acquisition, N.A.B., All authors have read and agreed to the published version of the manuscript.

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Competing interests

The authors declare no competing interests.

Author details

[1]Cell Signaling Regulation Laboratory, Moscow Institute of Physics and Technology, Dolgoprudny, Russia. [2]School of Biomedicine, Far Eastern Federal University, Vladivostok, Russia. [3]The Engelhardt Institute of Molecular Biology, Russian Academy of Science, Moscow, Russia. [4]School of Life Sciences, Immanuel Kant Baltic Federal University, Kaliningrad, Russia. [5]HSE University, Moscow, Russia. [6]Department of Medicine, University of Rome Tor Vergata, Rome, Italy. [7]Institute of Cytology, Russian Academy of Science, Saint-Petersburg, Russia.

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