REVIEW

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

Julian M. Rozenberg1*†, Svetlana Zvereva1†, Aleksandra Dalina3†, Igor Blatov1†, Ilya Zubarev†, Daniil Luppov1, Alexander Bessmertnyi5, Alexander Romanishin2,4, Lamak Alsoulaiman1, Vadim Kumeiko2, Alexander Kagansky1,2, Gerry Melino6, Carlo Ganini6 and Nikolai A. Barlev1,7*

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 its 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

© The Author(s) 2021. Open Access. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
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 |
|-----------------------|----------------------------------|---------------------------------------------------|------------|
| NSCLC                 | p73↑                             | Total p73 does not predict prognosis              | [10]       |
| NSCLC                 | DNp73↑                           | DNp73 is associated with poor prognosis           |            |
| Breast                | p73↓                             | Upregulation is associated with lower pathological grade | [11]       |
| 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]                  |                         |                                   |                    |                               |                                       |
| Hepatocellular carcinoma (HCC)        | [39]                  |                         |                                   |                    |                               |                                       |
| Cervix carcinoma                      | [40–42]               |                         |                                   |                    |                               |                                       |
| 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]               |                         |                                   |                    |                               |                                       |
| Breast cancer                         | [76–79]               |                         |                                   | [80]               | [81]                          | [82]                                  | 1.2                                   |
| Colorectal cancer                     | [25, 78, 83, 84]      | [85–87]                 | [88]                              | [84, 89]           | [94]                          | [94]                                  | 9.6                                   |
| Esophageal adenocarcinoma             | [90]                  |                         | [91–93]                           |                    |                               |                                       |
| Thyroid cancer                        | [95]                  |                         |                                   |                    |                               |                                       |
| Ovarian cancer                        | [96, 97]              |                         |                                   | [98]               |                               | 4.1                                   |
| Pancreatic cancer                     | [99, 100]             |                         |                                   | [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-terminal, 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, Nfkβ, 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.

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 TAp73a 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 γ-irradiation, therefore inhibiting cell proliferation [88].

The p73 is also involved in the DNA mismatch repair pathway, via hMLH1/c-Abi/p73a/GADD45α signaling [176]. Furthermore, MMR-dependent apoptosis is blocked by specific knockdown of the p73α isoform, while G2 arrest is p73 independent.

A remarkable example of the dual role of p73 isoforms in breast cancer is represented by oesophageal adenocarcinoma. The latter is often caused by the gastrooesophageal reflex 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 oesophageal tissue and other epithelial tissue p73 is expressed strictly in the basal cells [2]. Bile acid induces the TAp73α 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, expression 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-Abi, 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 its 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 p73β 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, Gadd45α, 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 p73 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-Abi [221] phosphorylation and YAP1 mediated corecruitment of p300 [222, 223]. Upon c-Abi-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 DNp73α and phosphorylates the latter on Ser-422, causing p73 stabilization, nuclear accumulation and
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/ Dnlp63α interaction, and TaP73 dissociation from Dnlp63α. This chain of events culminates in TaP73 translocation from the nucleus to cytoplasm [106]. TNF-α modulates genome-wide redistribution of Dnlp63α/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 demonstrated 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
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 TA7p3 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 TA7p3-deficient mouse embryonic fibroblasts (MEFs) were severely compromised in undergoing a nocodazole-induced mitotic arrest [20]. Furthermore, TA7p3−/−MEFs underwent a premature mitotic exit and passage into the G1 phase, suggesting that mitotic regulation is predominantly performed by the TA7p3 isoforms rather than DNp73 isoforms [20].

Treatment of TA7p3−/−lung fibroblasts with nocodazole for 12 h resulted in the increased polyploidy as well, whereas TA7p3−/−thymic cells showed no alternations in genomic stability [20]. This suggests that the effect of TA7p3 on the aneuploidy is tissue-specific, which could be an explanation to why TA7p3−/−mice preferentially develop lung adenocarcinomas [20].

There is multiple evidence to suggest that when overexpressed, TA7p3 interacts with SAC components Bub1, Bub3, BubR1 leading to M checkpoint activation [197, 198]. In triple-negative breast cancer MDA-MD231 cell lines, endogenous TA7p3 isoform interacts with BubR1, whereas DNp73 is not [198]. Upon overexpression, DNp73b does interact with BubR1, however, in contrast to TA7p3a, 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 led to an abnormal number of centrosomes, while TA7p3 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, TA7p3α overexpression led to a significant increase in the number of polyplloid cells, while p53, DNp73α, and TA7p3β or γ had no effect on polyploidy [197]. The effect was linked to the interaction of TA7p3α 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 TA7p3 as an activator and DNp73 as an inhibitor of SAC activity and, correspondingly, TA7p3 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.
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,
p73 promotes p73 activation and subsequent apoptosis [279]. 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, a while 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.
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

---

**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].
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, CDKNA2, 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).

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.
References

1. Wildung M, Esser TU, Grausam H, Riedel D, et al. Transcription factor TAp73 and microRNA-449 complement each other to support multilociogenesis. Cell Death Differ. 2019;26(12):2740–57.

2. Rozenberg JM, Rogovaya OS, Melino G, Barlev NA, Kagansky A. Distinct p63 and p73 protein interactions predict specific functions in mRNA splicing and polypeptide control in Euphelia. Cells. 2020;10(1).

3. Ikawa S, Nakagawa A, Ikeda Y. p53 family genes: structural comparison, expression and mutation. Cell Death Differ. 1999;6(12):1154–61.

4. Alonso ME, Bello MJ, Lomas J, Gonzalez-Gomez P, Arjona D, De Campos JM, et al. Absence of mutation of the p73 gene in astrocytic neoplasms. Int J Oncol. 2001;19(3):609–12.

5. Zaika AI, Kovalev S, Marchenko ND, Moll UM. Overexpression of the wild type p73 gene in breast cancer tissues and cell lines. Cancer Res. 1999;59(13):3257–63.

6. Yokozaki H, Shitara Y, Fujimoto J, Hiyama T, Yasui W, Tahara E. Alterations of p73 and p63 in colorectal cancers. Int J Oncol. 2001;19(3):609–12.

7. Yasui W, Yokozaki H, Fujimoto J, Naka K, Kuniyasu H, Tahara E. Genetic and epigenetic alterations in multistep carcinogenesis of the stomach. J Gastroenterol. 2000;35(Suppl 12):111–5.

8. Ganini C, Amelio I, Bertolo R, Bove P, Buonomo OC, Candi E, et al. Global mapping of cancers: the cancer genome atlas and beyond. Mol Oncol. 2011;5:352–64.

9. Mai M, Yokomizo A, Qian C, Yang P, Tindall DJ, Smith DI, et al. Activation of p73 silent allele in human NSCLC and breast cancer. Cancer Res. 1998;58(11):2347–9.

10. He Y, Fan S, Jiang Y, Chen J, Li Z, Zhang H. Study on the transcript profile of TAp73 and DeltaNp73 in human lung cancer. JAppl Clin Med. 2000;18(24):3041–54.

11. Wang B, Liu X, Liu H, Guo J, Zhang Y, Zhou N, et al. pAp73 gene and promotes the expression of TAp73. Biochem Biophys Res Commun. 2003;298(3):455–63.

12. Tomkova K, Belkhiri A, El-Rifai W, Zaika AI. p73 isoforms can induce T-cell apoptosis. Int J Oncol. 2001;18(2):199–204.

13. Inoue K, Fry EA. Alterations of p63 and p73 in human cancers. Subcell Biochem. 2008;47:385–92.

14. Engelmann D, Meier C, Alla V, Pützer BM. A balancing act: orchestrating each other to support multiciliogenesis. Cell Death Differ. 2004;11(6):564–73.

15. Gaiddon C, Lokshin M, Gross I, Levasseur D, Taya Y, Loeffler J-P, et al. Transcription factor TAp73 and microRNA-449 complement each other to support multilociogenesis. Cell Death Differ. 2019;26(12):2740–57.

16. Engelmann D, Meier C, Alla V, Pützer BM. A balancing act: orchestrating each other to support multiciliogenesis. Cell Death Differ. 2004;11(6):564–73.

17. Tanaka M, Tanaka T, Poyroux MV, Prives C. p73 induction after DNA damage is regulated by checkpoint kinases Chk1 and Chk2. Genes Dev. 2004;18(24):3041–54.

18. Yang A, Zhu Z, Kettenbach A, Kapranov P, McKeon F, Gingeras TR, et al. Genome-wide mapping indicates that p73 and p63 co-occupy target sites and have similar DNA-binding profiles in vivo. PLoS ONE. 2010;5(7):e11572.

19. Wang B, Liu X, Liu H, Guo J, Zhang Y, Zhou N, et al. Differential expression of p63 and p73 in human colorectal cancers: a comprehensive analysis using microarray and chromatin immunoprecipitation analyses. J Biol Chem. 2002;277(4):34359–68.

20. Urist M, Tanaka T, Poyroux MV, Prives C. p73 induction after DNA damage is regulated by checkpoint kinases Chk1 and Chk2. Genes Dev. 2004;18(24):3041–54.

21. Wang B, Liu X, Liu H, Guo J, Zhang Y, Zhou N, et al. Differential expression of p63 and p73 in human colorectal cancers: a comprehensive analysis using microarray and chromatin immunoprecipitation analyses. J Biol Chem. 2002;277(4):34359–68.

22. Lokeshri S, Michalopoulos I, Sideridou M, DASKALOS A, Kossida S, Spandidos DA, et al. Sp1 binds to the external promoter of the p73 gene and induces the expression of TAp73 gamma in lung cancer. FEBS Lett. 2010;527(14):3014–21.

23. Gaidd C, Lokshin M, Gross I, Levasseur D, Taya Y, Loeffler J-P, 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(30):27421–31.

24. Jia C, Guo J, Zhang Y. A critical role of glucose-6-phosphate dehydrogenase in TAp73-mediated cell proliferation. Cell Cycle. 2013;12(24):3720–6.

25. Li L, Li L, Li W, Chen T, Bin Z, Zhao L, et al. p73-induced phosphofructokinase-1 transcription promotes the Warburg effect and enhances cell proliferation. J Biol Chem. 2008;283(13):8555–63.

26. Kostecova A, Sznarkowska A, Mellier K, Acedo P, Shi Y, Mohammad Salik H, et al. JNK-NQO1 axis drives TAp73-mediated tumor suppression upon oxidative and proinflammatory stress. Cell Death Dis. 2014;5:e1484.

27. Ren C, Zhang J, Yan W, Zhang Y, Chen X. RNA-binding protein PCBP2 regulates p73 expression and p73-dependent antioxidant defense. J Biol Chem. 2016;291(18):9629–37.

28. Jiang P, Du W, Yang X. A critical role of glucose-6-phosphate dehydrogenase in TAp73-mediated cell proliferation. Cell Cycle. 2013;12(24):3720–6.

29. Li L, Li L, Li W, Chen T, Bin Z, Zhao L, et al. p73-induced phosphofructokinase-1 transcription promotes the Warburg effect and enhances cell proliferation. J Biol Chem. 2008;283(13):8555–63.

30. Vikhreva P, Petrova V, Gokbulut T, Pestlikis I, Mancini M, Di Daniele MC, et al. Loss of heterozygosity, allele silencing and decreased expression of the p73 gene in breast cancers: prevalence of alterations in inflammatory breast cancers. Oncogene. 2002;21(19):2917–22.

31. Ahomadegbe JC, Tourpin S, Kaghad M, Zelek L, Vayssade M, Mathieu MC, et al. Loss of heterozygosity, allele silencing and decreased expression of the p73 gene in breast cancers: prevalence of alterations in inflammatory breast cancers. Oncogene. 2002;21(19):2917–22.

32. Jiang P, Du W, Yang X. A critical role of glucose-6-phosphate dehydrogenase in TAp73-mediated cell proliferation. Cell Cycle. 2013;12(24):3720–6.

33. Amelio I, Inoue S, Markert EK, Levine AJ, Knight RA, Mak TW, et al. TAp73 opposes tumor angiogenesis by promoting hypoxia-inducible factor 1α degradation. Proc Natl Acad Sci USA. 2015;112(11):226–31.

34. Uramoto H, Sugio K, Oyama T, Nakata S, Ono K, Morita M, et al. Expression of the p53 family in lung cancer. Anticancer Res. 2010;30(20):6905–11.

35. Wang B, Liu X, Liu H, Guo J, Zhang Y, Zhou N, et al. Differential expression of MDM2 and TAp73 in cancer and cancer-adjacent tissues in patients with non-small-cell lung carcinoma. Pulmonology. 2018.

36. Amelio I, Inoue S, Markert EK, Levine AJ, Knight RA, Mak TW, et al. TAp73 opposes tumor angiogenesis by promoting hypoxia-inducible factor 1α degradation. Proc Natl Acad Sci USA. 2015;112(11):226–31.

37. Uramoto H, Sugio K, Oyama T, Nakata S, Ono K, Nohoe T, et al. Expression of the p53 family in lung cancer. Anticancer Res. 2010;30(20):6905–11.

38. Wang B, Liu X, Liu H, Guo J, Zhang Y, Zhou N, et al. Differential expression of MDM2 and TAp73 in cancer and cancer-adjacent tissues in patients with non-small-cell lung carcinoma. Pulmonology. 2018.
44. Mega Tiber P, Baloglu L, Ozden S, Ozgen Z, Ozyurt H, Eren M, et al. The association of apoptotic protein expressions sensitive to apoptosis gene, p73 and p53 with the prognosis of cervical carcinoma. Oncol Targets Ther. 2014;26(7):2161–8.

45. Schipper H, Alla V, Meier C, Nettelbeck DM, Herchenröder Q, Pützer BM. Eradication of metastatic melanoma through cooperative expression of RNA-based HDAC1 inhibitor and p73 by oncolytic adenovirus. Oncotarget. 2014;5(15):5893–907.

46. Steder M, Alla V, Meier C, Spitschak A, Pahnke J, Fürst K, et al. DNp73 exerts function in metastasis initiation by disconnecting the inhibitory role of EPLIN on IF1R-akt/STAT3 signaling. Cancer Cell. 2013;24(4):512–27.

47. Koeppel M, van Heeringen SJ, Kramer D, Smeenk L, Janssen-Megens E, Hartmann M, et al. Crosstalk between c-Jun and TAp73alpaha/ beta contributes to the apoptosis-survival balance. Nucl Acids Res. 2011;59(14):6069–85.

48. Zhou X, Hao Q, Zhang Q, Liao JM, Ke JW, Liao P, et al. Ribosomal proteins L11 and L5 activate TAp73 by overcoming MDM2 inhibition. Cell Death Differ. 2015;22(5):755–66.

49. Ohtsuka T, Ryu H, Minamishima YA, Ryo A, Lee SW. Modulation of p53 by interferon gamma impairs the transcriptional activity of the p73 gene. Proc Natl Acad Sci U S A. 2002;99(17):10790–5.

50. Amelio I, Markert EK, Rufini A, Antonov AV, Sayan BS, Tucci P, et al. Dormancy and drug resistance of BRCA1-mutated human mammary epithelial cells. Cancer Res. 2008;68(13):5884–94.

51. Landré V, Antonov A, Knight R, Melino G. p73 promotes glioblastoma cell survival and death through a p73-specific target element within the DeltaNP73 promoter. Mol Cell Biol. 2004;24(22):9773–86.

52. Trevisan E, Dell'Anna M, Tincani G, Cioni G, Bignami S, Allevato O, et al. Dysfunctional telomeres gene, p73 and p53 with the prognosis of cervical carcinoma. Onco Targets Ther. 2017;24(1):3823–33.

53. Kaida A, Ariumi Y, Ueda Y, Lin Y, Hjikata M, Iwakawa S, et al. Functional impairment of p73 and p53 in various cancer cell lines. Cancer Res. 2017;77(14):3823–33.

54. Steller H. The guardians of the genome (p53, TA-p73, and p63) and p73 in cancer. Cell. 2005;121(2):366–76.

55. Wang Y, Wang X, Flores ER, Yu J, Chang S. Dysfunctional telomeres are associated with triple-negative breast cancer. Aging Cell. 2016;15(4):646–60.

56. Riley MF, You MJ, Multani AS, Lozano G. Mdm2 overexpression and p73 loss exacerbate genomic instability and dappen apoptosis, resulting in Aggressive T-cell lymphoma. Oncogene. 2016;35(3):358–65.

57. Nemajerova A, Petrenko O, Trumper L, Palacios G, Moll UM. Loss of p73 promotes dissemination of Myc-induced B cell lymphomas in mice. J Clin Invest. 2010;120(6):2070–80.

58. Feeley KP, Adams CM, Mitra R, Eschen CM. Mdmd2 is required for survival and growth of p53-deficient cancer cells. Cancer Res. 2017;77(14):3823–33.

59. Wang Y, Wang X, Flores ER, Yu J, Chang S. Dysfunctional telomeres gene, p73 and p53 with the prognosis of cervical carcinoma. Onco Targets Ther. 2017;24(1):3823–33.

60. Boominathan L. The guardians of the genome (p53, TA-p73, and p63) and p73 in cancer. Cell. 2005;121(2):366–76.

61. Wang Y, Wang X, Flores ER, Yu J, Chang S. Dysfunctional telomeres gene, p73 and p53 with the prognosis of cervical carcinoma. Onco Targets Ther. 2017;24(1):3823–33.

62. Wang Y, Wang X, Flores ER, Yu J, Chang S. Dysfunctional telomeres gene, p73 and p53 with the prognosis of cervical carcinoma. Onco Targets Ther. 2017;24(1):3823–33.
126. Nakagawa T, Takahashi M, Ozaki T, Watanabe K, Hayashi S, Hosoda M, et al. Negative autoregulation of p73 and p53 by DeltaNp73 in regulating differentiation and survival of human neuroblastoma cells. Cancer Lett. 2003;197(1–2):105–9.

127. Liu G, Nozell S, Xiao H, Chen X. DeltaNp73beta is active in transactivation and growth suppression. Mol Cell Biol. 2004;24(2):487–501.

128. Beeler JS, Marshall CB, Gonzalez-Ericsson PI, Shaver TM, Santos Guasch GL, Lea ST, et al. p73 regulates epidermal wound healing and induced keratinocyte programming. PLoS ONE. 2019;14(6):e0218458.

129. Sánchez-Carrera D, García-Puga M, Yáñez L, Romón I, Pipaon C. ΔNp73 is capable of inducing apoptosis by co-ordinately activating several BAX only proteins. Biosci Rep. 2015;35(3).

130. Nyman U, Vlachos P, Cascante A, Hermanson O, Zhivotovsky B, Joseph HO WC, Fitzgerald MX, Marmorstein R. Structure of the p53 core domain. Mol Cell. 2009;29(7):1814–25.

131. Joerger AC, Wilcken R, Andreeva A. Tracing the evolution of the p53 family. Proc Natl Acad Sci USA. 2008;105(17):6302–7.

132. Alfsäfadi S, Tournip S, André F, Vassal G, Ahomadegbe JC. p53 family: at the crossroads in cancer treatment. Curr Med Chem. 2009;16(32):4328–44.

133. Sonnemann J, Grauël D, Blümel L, Hentschel J, Marx C, Blumrich A, et al. RETRA exerts anticaner activity in Ewing's sarcoma cells independent of their TP53 status. Eur J Cancer. 2015;51(7):841–51.

134. Fernandez-Alonso R, Martinez-Martin, Gonzalez-Cano L, Garcia S, Castillo D, Diez-Prieto L, et al. p73 is required for endothelial cell differentiation, migration and the formation of vascular networks regulating VEGF and TGFβ signaling. Cell Death Differ. 2015;22(8):1287–99.

135. Nikišon-Chirou MV, Steinert JR, Agostini M, Knight RA, Dinsdale D, Cattaneo A, et al. TAp73 knockout mice show morphological and functional nervous system defects associated with loss of p75 neurotrophin receptor. Proc Natl Acad Sci USA. 2013;110(47):18982–7.

136. Gong JG, Costanzo A, Yang HQ, Melino G, Kaelin WG, Levrero M, et al. The tyrosine kinase c-Abl regulates p73 in apoptotic response to cisplatin-induced DNA damage. Nature. 1999;399(6738):806–9.

137. Wang X, Zhong L, Wang J, Chau JLF, Lai KP, Jia D, et al. A positive role for c-Abi in Atm and Atm activation in DNA damage response. Cell Death Differ. 2011;18(1):5–15.

138. Yuan ZM, Shioya H, Ishiko T, Sun X, Gu J, Huang YY, et al. p73 is regulated by tyrosine kinase c-Abi in the apoptotic response to DNA damage. Nature. 1999;399(6738):814–7.

139. Reuven N, Shaul Y. The c-Abi/TP73 apoptotic module and the HIPPO pathway. In: Oren M, Aylon Y, editors. The hippo signaling pathway and cancer. Springer, New York; 2013. p. 173–95.

140. Ibrahim N, He L, Leon-C O, Xing D, Karlan BY, Swisher EM, et al. BRCA1-associated epithelial regulation of p73 mediates an effecttor pathway for chemosensitivity in ovarian carcinoma. Cancer Res. 2010;70(18):7155–65.
171. Cannam CE, Lim DS, Cimprich KA, Taya Y, Tamai K, Sakaguchi K, et al. Activation of the Akt/kinase by ionizing radiation and phosphorylation of p53. Science. 1998;281(5383):1677–9.
172. Zhang Y-X, Pan W-Y, Chen J. p53 and its isoforms in DNA double-stranded break repair. J Zhejiang Univ Sci B. 2019;20(6):457–66.
173. Lin Y-L, Sengupta S, Gurdziel K, Bell GW, Jacks T, Flores ER. p63 and p73 transcriptionally regulate genes involved in DNA repair. PLoS Genet. 2009;5(10):e1000680.
174. Wakasugi T, Izumi H, Uchiimi T, Suzuki H, Aota T, Nishio K, et al. ZNF143 interacts with p73 and is involved in cisplatin resistance through the transcriptional regulation of DNA repair genes. Oncogene. 2007;26(25):3194–203.
175. Gong L, Pan X, Abali GK, Little JB, Yuan Z-M. Functional interplay between p53 and Δ133p53 in adaptive stress response. Cell Death Differ. 2020;27(5):1618–32.
176. Li LS, Morales JC, Hwang A, Wagner MW, Boothman DA. DNA mismatch repair-dependent activation of c-Abp/p73alpha/GADD45alpha-mediated apoptosis. J Biol Chem. 2002;278(31):23194–403.
177. Jackson JG, Pereira-Smith OM. p53 is preferentially recruited to the promoters of growth arrest genes p21 and GADD45 during replicative senescence of normal human fibroblasts. Cancer Res. 2006;66(17):8755–60.
178. Engeland K. Cell cycle arrest through indirect transcriptional repression by p53. I have a DREAM. Cell Death Differ. 2018;25(11):114–32.
179. Vanço R, Bartkova J, Merchet-May JM, Hall A, Bouchal J, Dryskjæt L, et al. Autophagy roles in response to oncogenes and DNA replication stress. Cell Death Differ. 2020;27(3):1134–53.
180. Li L, Yang G, Ren C, Tanimoto R, Hirayama T, Wang J, et al. Glioma pathogenesis-related protein 1 induces prostate cancer cell death through Hsc70-mediated suppression of AURKA and TPX2. Mol Oncol. 2013;7(3):484–96.
181. Liu H, Weng W, Guo R, Zhou J, Xue J, Zhong S, et al. p53 transcriptionally regulate genes involved in DNA repair. PLoS Genet. 2007;3(6):5194–203.
182. Tozluoğlu M, Karaca E, Haliloglu T, Nussinov R. Cataloging and organification of the p73 pathway. Oncogene. 2004;23(28):4807–17.
183. Marrazzo E, Marchini S, Tavecchio M, Alberio T, Previdi S, Erba E, et al. The expression of the DeltaNP73beta isoform of p73 leads to tetraploidy. Eur J Cancer. 2009;45(3):443–53.
184. Engeland K. Cell cycle arrest through indirect transcriptional repression by p53. Science. 1998;281(5383):1677–9.
185. Lin Y-L, Sengupta S, Gurdziel K, Bell GW, Jacks T, Flores ER. p63 and p73 transcriptionally regulate genes involved in DNA repair. PLoS Genet. 2009;5(10):e1000680.
186. Veronese P, Neale MH, Barcaroli D, Munariz E, Kiraly RT, Tomasini R, et al. TAp73alpha inhibits the kinaseactivity of p73 and blocks Bub3 function in polyploidy. Cell Cycle. 2009;8(3):421–9.
187. Tomasini R, Tsuchihara K, Tsuda C, Lau SK, Wilhelm M, Rufini A, et al. TAp73 regulates the spindle assembly checkpoint by modulating Bub1 activity. Proc Natl Acad Sci USA. 2009;106(3):797–802.
188. Veronese P, Neale MH, Barcaroli D, Munariz E, Kiraly RT, Tomasini R, et al. TAp73alpha binds the kinaseactivity of p73 and blocks Bub3 function in polyploidy. Cell Cycle. 2009;8(3):421–9.
189. Merlo P, Fulco M, Costanzo A, Mangiacasale R, Strano S, Blandino G, et al. Aurora kinase A reduces DNA damage-induced apoptosis and spindle assembly checkpoint response functions of p73. Cancer Cell. 2012;21(2):196–211.
190. Sayan BS, Yang AL, Conforti F, Tucci P, Piro MC, Browne GJ, et al. Differential control of TAp73 and DeltaNp73 protein stability by the ring finger ubiquitin ligase PIR2. Proc Natl Acad Sci USA. 2010;107(29):12877–82.
191. Munarriz E, Marchini S, Tavecchio M, Alberio T, Previdi S, Erba E, et al. The expression of the DeltaNP73beta isoform of p73 leads to tetraploidy. Eur J Cancer. 2009;45(3):443–53.
192. Mulkensova E, Neradil J, Zitterbart K, Sterba J, Veselska R. Overexpression of the ΔNp73 isoform is associated with centrosome amplification in brain tumor cell lines. Tumour Biol. 2015;36(10):7483–91.
193. Katayama H, Wang J, Tsuchihara K, Tsuda C, Lau SK, Wilhelm M, Rufini A, et al. Aurora kinase A inactivates DNA damage-induced apoptosis and spindle assembly checkpoint response functions of p73. Cancer Cell. 2012;21(2):196–211.
194. Sasai K, Tsuchihara K, Tsuda C, Lau SK, Wilhelm M, Rufini A, et al. Aurora kinase A inactivates DNA damage-induced apoptosis and spindle assembly checkpoint response functions of p73. Cancer Cell. 2012;21(2):196–211.
195. Wang XQ, Ongkeko WM, Lau AW, Leung KM, Poon RY. A possible role for p73 in the regulation of cyclin B1, GADD45A, and BTG2. Breast Cancer Res Treat. 2011;129(3):777–84.
196. 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(48):78255–68.
197. Yan W, Zhang J, Zhang Y, Jung Y-S, Chen X. p73 expression is regulated by RNPC1, a target of the p53 family, via mRNA stability. Mol Cell Biol. 2012;32(13):3336–48.
198. Salama M, Benitez-Riquelme D, Elabd S, Munoz L, Zhang P, Glenammann M, et al. Fam83 induces p53 stabilisation and promotes its activity. Cell Death Differ. 2019;26(10):1215–38.
199. Zhu T, Tsui J, Chen C. Roles of PCC isoforms in the induction of apoptosis elicited by aberrant Ras. Oncogene. 2010;29(7):1050–61.
200. Sayan BS, Yang AL, Conforti F, Tucci P, Piro MC, Browne GJ, et al. Differential control of TAp73 and DeltaNp73 protein stability by the ring finger ubiquitin ligase PIR2. Proc Natl Acad Sci USA. 2010;107(29):12877–82.
201. Sun G, Jin S, Baskaran R. MMR/c-Ab1-dependent activation of INIG2/p73alpha signaling regulates the cell death response to N-methyl-N’-nitro-N-nitrosoguanidine. Exp Cell Res. 2009;315(18):3163–71.
202. Jones EV, Dickman MJ, Whitmarsh AJ. Regulation of p73-mediated apoptosis by c-Jun N-terminal kinase. Biochem J. 2007;405(3):617–23.
203. Berensof F, Salomoni P, Osterb A, Di Como CJ, Pagano M, Melino G, et al. Ubiquitin-dependent degradation of p73 is inhibited by PML. J Exp Med. 2004;199(11):1545–57.
204. Shimodaira H, Yoshioka-Yamashita A, Kolodner RD, Wang JY. Interaction of mismatch repair protein PM22 and the p53-related transcription factor p73 in apoptosis response to cisplatin. Proc Natl Acad Sci USA. 2003;100(5):2420–5.
205. Kubo N, Okoshi R, Nakashima K, Shimozato O, Nakagawa A, Ozaki T. MDM2 promotes the proapoptotic degradation of p73 through the interaction with Itch in HeLa cells. Biochem Biophys Res Commun. 2010;403(3–4):405–11.
206. Wu H, Zeinab RA, Flores ER, Leng RP, Pirh2, a ubiquitin E3 ligase, inhibits p73 transcriptional activity by promoting its ubiquitination. Mol Cancer Res. 2011;9(12):1780–90.
207. Peschirolli A, Scalpi F, Berensof F, Pagano M, Melino G, et al. Ubiquitin-dependent degradation of p73 is inhibited by PML. J Exp Med. 2004;199(11):1545–57.
208. Shimodaira H, Yoshioka-Yamashita A, Kolodner RD, Wang JY. Interaction of mismatch repair protein PM22 and the p53-related transcription factor p73 in apoptosis response to cisplatin. Proc Natl Acad Sci USA. 2003;100(5):2420–5.
metabolite of aminolevulinic acid, induces apoptosis in TP53-deficient cancer cells. Cell Div. 2018;26(13):10.

218. Miyazaki K, Ozaki T, Kato C, Hanamoto T, Fujita T, Ino S, et al. A novel HECT-type E3 ubiquitin ligase, NEDL2, stabilizes p73 and enhances its transcriptional activity. Biochem Biophys Res Commun. 2003;308(1):106–13.

219. Lu L, Hu S, Wei R, Qu X, Lu K, Fu Y, et al. The HECT type ubiquitin ligase NEDL2 is degraded by anaplast-361promoting complex/cycloosome (APC/C-Cdh1), and its tight regulation maintains the metaphase to anaphase transition. J Biol Chem. 2013;288(50):35637–50.

220. Ganapathy S, Peng B, Shen L, Yu T, Li P. Suppression of p73A causes oncogenic stress for triggering apoptosis in cancer cells. Oncotarget. 2017;8(19):30992–1002.

221. Satija YK, Das S. Tyr99 phosphorylation determines the regulatory milieu of tumor suppressor p73. Oncogene. 2016;35(4):513–27.

222. Strano S, Monti O, Pediconi N, Baccarini A, Fornettaghi G, Lapi E, et al. The transcriptional coactivator Yes-associated protein drives p73 gene-target specificity in response to DNA damage. Mol Cell. 2005;18(4):447–59.

223. Raj N, Bam R. Reciprocal crosstalk between yap1/hippo pathway and p73 function. Cell Dev Biol. 2019;9(7):159.

224. Mantovani F, Piazza S, Gostissa M, Strano S, Zacchi P, Mantovani R, et al. The antimalarial drug amodiaquine stabilizes p73 through ribosome biogenesis stress, independently of its autophagy-inhibitory activity. Cell Death Differ. 2020;27(2):773–89.

225. Wang JY. Regulation of cell death by the Abl tyrosine kinase. Oncogene. 2000;19(49):5643–50.

226. Chen C, Whitney IP, Banejee A, Sacristan C, Sekhri P, Kern DM, et al. Ectopic activation of the spindle assembly checkpoint signaling cascade reveals its biochemical chemical. Curr Biol. 2019;29(1):104-119.e10.

227. Dick AE, Gerlich DW. Kinetic framework of spindle assembly checkpoint signaling. Nat Cell Biol. 2013;15(1):1370–7.

228. Musacchio A. The molecular biology of spindle assembly checkpoint signaling dynamics. Curr Biol. 2015;25(20):R1002–18.

229. Lischetti T, Nilsson J. Regulation of mitotic progression by the spindle assembly checkpoint. Mol Cell Oncol. 2015;2(1):e970484.

230. Frank T, Tsuppi M, Hugle M, Dotsch V, van Wijk S, Fulda S. Cell cycle arrest in mitosis promotes interferon-induced necroptosis. Cell Death Differ. 2019;26(10):2046–60.

231. Chen J, Li J, Song L, Bai D, Huang MSY, Liu Y, et al. S3BP1 loss rescues embryonic lethality but not genomic instability of BRCA1 total knockout mice. Cell Death Diff. 2020;27(9):2552–67.

232. Toh WH, Narn SY, Sabapathy K. An essential role for p73 in regulating mitotic cell death. Cell Death Differ. 2010;17(5):787–800.

233. Saadatzadeh MR, Elfvi AN, Pandya PH, Bhajji-Vishelskarae K, Ding J, Starmatkin CW, et al. The role of MDM2 in promoting genome stability versus instability. Int J Mol Sci. 2017;18(10).

234. Wei MC, Zong WX, Cheng EH, Lindtsten T, Panoutsokopoulou V, Ross AJ, et al. Proapoptotic BAX and BAK: a requisite gateway to mitochondrial dysfunction and death. Science. 2001;292(5517):727–30.

235. Julien O, Wells JA. Caspases and their substrates. Cell Death Differ. 2017;24(8):1380–9.

236. Li LY, Luo X, Wang X. Endonuclease G is an apoptotic DNAse when released from mitochondria. Nature. 2001;412(6842):95–9.

237. Asare PF, Roscioni E, Hurtado PR, Tran BH, Mah CY, Hodge S. LC3-associated phagocytosis (LAP): a potentially influential mediator of efferocytosis-related tumor progression and aggressiveness. Front Oncol. 2020;5(10):1298.

238. Wang C, Youle RJ. The role of mitochondria in apoptosis*. Annu Rev Genet. 2009;43:95–118.

239. Soond SM, Carroll C, Townsend PA, Sayan E, Melino G, Behrmann I, et al. STAT1 regulates p73-mediated Bax gene expression. FEBS Lett. 2007;581(6):1217–26.

240. Canficozza R, Muscillo M, Marzano V, Annibaldi A, Marinari B, Levrero D, et al. The antimalarial drug amodiaquine stabilizes p73 through regulation of mitochondrial genome stability and apoptosis. Cell Death Differ. 2012;19(8):1298.

241. Wang C, Youle RJ. The role of mitochondria in apoptosis*. Annu Rev Genet. 2009;43:95–118.

242. Soond SM, Carroll C, Townsend PA, Sayan E, Melino G, Behrmann I, et al. STAT1 regulates p73-mediated Bax gene expression. FEBS Lett. 2007;581(6):1217–26.

243. Canficozza R, Muscillo M, Marzano V, Annibaldi A, Marinari B, Levrero D, et al. The antimalarial drug amodiaquine stabilizes p73 through regulation of mitochondrial genome stability and apoptosis. Cell Death Differ. 2012;19(8):1298.
263. Ming L, Sakaida T, Yue W, Jha A, Zhang L, Yu J. Sp1 and p73 activate PUMA following serum starvation. Carcinogenesis. 2008;29(10):1878–84.

264. John K, Alfa V, Meier C, Pützer BM. GRAMD4 mimics p53 and mediates the apoptotic function of p73 at mitochondria. Cell Death Differ. 2011;18(5):874–86.

265. Sasaki Y, Mita H, Toyota M, Ishida S, Morimoto I, Yamashita T, et al. Identification of the interleukin 4 receptor alpha gene as a direct target for p73. Cancer Res. 2003;63(23):8145–52.

266. Schuster A, Schilling T, De Laurenzi V, Koch AF, Seitz S, Staib F, et al. ΔNp73β is oncogenic in hepatocellular carcinoma by blocking apoptosis signaling via death receptors and mitochondria. Cell Cycle. 2010;9(3):2629–39.

267. Sayan AE, Sayan BS, Gogvadze V, Dinsdale D, Nyman U, Hansen TM, et al. P73 and caspase-cleaved p73 fragments localize to mitochondria and augment TRAIL-induced apoptosis. Oncogene. 2008;27(31):4363–72.

268. Yoon M-K, Kim B-Y, Lee J-Y, Ha J-H, Kim SA, Lee D-H, et al. Cytoplasmic p73 activates the apoptotic function of p73 at mitochondria. Cell Death Differ. 2010;17(13):2629–39.

269. Agosti M, Annicchiarico-Petruzzelli M, Melino G, Rufini A. Metabolic pathways regulated by TAp73 in response to oxidative stress. Oncotarget. 2016;7(21):29881–900.

270. Dobon B, Montanucci L, Peretó J, Bertranpess J, Laayouni H. Gene connectivity and enzyme evolution in the human metabolic network. Biol Direct. 2019;14(1):17.

271. Costanzo A, Merlo P, Pediconi N, Fulco M, Sartorelli V, Cole PA, et al. DNA damage-induced transcription. PLoS ONE. 2012;7(8):e43564.

272. He H, Wang C, Dai Q, Li F, Bergholz J, Li Z, et al. p53 and p73 regulate mitochondrial network mediates chemosensitivity to cisplatin in a biologically defined subset of primary breast cancers. J Clin Invest. 2013;125(6):2001–17.

273. Mullarky E, Cantley LC. Diverting glycolysis to combat oxidative stress. In: Nakao K, Minato N, Uemoto S, editors. Innovative medicine: basic research and development. Springer, Tokyo; 2015.

274. Kuehne A, Emmert H, Soehlie J, Winnefeld M, Fischer F, Wench K, et al. Acute activation of oxidative pentose phosphate pathway as first line response to oxidative stress in human skin cells. Mol Cell. 2015;59(3):559–71.

275. Ben-Yoseph O, Boxer PA, Ross BD. Assessment of the role of the glutathione and pentose phosphate pathways in the protection of primary cerebrocortical cultures from oxidative stress. J Neurochem. 1996;66(6):2359–37.

276. Ataulakhanov FI, Buratovsky VN, Zhabotinskii AM, nonna SB, Pichugin AV. Interaction of the Embden-Meyerhof pathway and hexose monophosphate shunt in erythrocytes. Biochimia. 1981;46(4):723–31.

277. Pallucca R, Visconti S, Camoni L, Cesareni G, Melino S, Panni S, et al. Specificity of ε and non-ε isoforms of arabinodigest 14–3–3 proteins towards the H4–ATFase and other targets. PLoS ONE. 2014;9(6):e90764.

278. Lamasra FR, De Angelis R, Antonucci A, Salvatori D, Procopio P, Casabianca M, et al. Polymer composite random lasers based on diatom frustules as scatterers. RSC Adv. 2014;4(106):61809–16.

279. Mauretti A, Neri A, Kossower O, Seliktar D, Wench K, et al. Design and functionality in human germline and embryonic tissues and cells. Dev Genet. 2007;117(5):1370–80.

280. Liu T, Roh SE, Woo JA, Ryu H, Kang DE. Cooperative role of RanBP9 and P73 in mitochondria-mediated apoptosis. Cell Death Dis. 2013;4:e476.

281. Kostanze A, Menlo P, Pediconi N, Fulco M, Santorelli V, Cole PA, et al. DNA damage-dependent acetylation of p73 dictates the selective activation of apoptotic target genes. Mol Cell. 2002;9(1):175–86.

282. He H, Wang C, Dai Q, Li F, Bergholz J, Li Z, et al. p53 and p73 regulate apoptosis but not cell-cycle progression in mouse embryonic stem cells upon DNA damage and differentiation. Stem Cell Rep. 2016;7(6):1087–98.

283. Agami R, Bianco G, Oren M. Shaul Y. Interaction of c-Abl and p73alpha and their collaboration to induce apoptosis. Nature. 1999;399(6738):809–13.

284. Li Q, Huang Z, Gao M, Cao W, Xiao Q, Luo H, et al. Blockade of Y177 and nuclear translocation of Bcr-Abl inhibits proliferation and promotes apoptosis in chronic myeloid leukemia cells. Int J Mol Sci. 2017;18(3).

285. Tanwar K, Pati U. Inhibition of apoptosis via CHAP-mediated proteosomal degradation of TAp73α. J Cell Biochem. 2019.

286. Deponte M. Glutathione catalysis and the reaction mechanisms of glutathione-dependent enzymes. Biochim Biophys Acta. 2013;1830(5):3217–66.

287. Geiger A. Rôle of glutathione in anaerobic tissue glycolysis. Biochem J. 1935;29(4):811–23.

288. Li Y, Cao Y, Xiao J, Shang J, Tan Q, Ping F, et al. Inhibitor of apoptosis stimulating protein of p53 inhibits ferropoasis and alleviates intestinal ischemia/reperfusion-induced acute lung injury. Cell Death Differ. 2020;27(9):2635–50.

289. Vance JE. Inter-organelle membrane contact sites: implications for lipid metabolism. Biol Direct. 2020;15(1):1.

290. Celardo I, Melino G, Melino AM. Commensal microbes and p53 in cancer. Biol Direct. 2020;15(1):25.

291. Schmelz K, Wagner M, Dörken B, Tamm I. S-Aza-2′-deoxycytidine induces p21WAF expression by demethylation of p73 leading to p53-independent apoptosis in myeloid leukemia. Int J Cancer. 2005;114(5):683–95.

292. Muscoli M, Cianfranca R, Sajeva A, Mazzotti S, Ferrandina G, Costanzo A, et al. Trichostatin A up-regulates p73 and induces Bax-dependent apoptosis in cisplatin-resistant ovarian cancer cells. Mol Cancer Ther. 2008;7(6):1410–9.

293. Warburg O, Wind F, Negelein E. Über den stoffwechsel von tumoren im körper. Klin Wochenschr. 1926;5(18):829–32.

294. Liberati MV, Locasale JW. The warburg effect: how does it benefit cancer cells? Trends Biochem Sci. 2016;41(13):211–8.

295. Xu Y, Chen X. Glyoxalase II, a detoxifying enzyme of glycolysis byproduct methylglyoxal and a target of p65 and p73, is a pro-survival factor of the p53 family. J Biol Chem. 2006;281(36):26702–13.

296. Shahid T, Dai C, Martell E, Ghassemi-Rad MS, Hanes MR, Murphy PJ, et al. TAp73 modifies metabolism and positively regulates growth of cancer stem-like cells in a redox-sensitive manner. Clin Cancer Res. 2019;25(6):2001–17.

297. Mullarky E, Cantley LC. Diverting glycolysis to combat oxidative stress. In: Nakao K, Minato N, Uemoto S, editors. Innovative medicine: basic research and development. Springer, Tokyo; 2015.

298. Ataulakhanov F, Buratovsky VN, Zhabotinskii AM, Nonna SB, Pichugin AV. Interaction of the Embden-Meyerhof pathway and hexose monophosphate shunt in erythrocytes. Biokhimia. 1981;46(4):723–31.

299. Pallucca R, Visconti S, Camoni L, Cesareni G, Melino S, Panni S, et al. Specificity of ε and non-ε isoforms of arabinodigest 14–3–3 proteins towards the H4–ATFase and other targets. PLoS ONE. 2014;9(6):e90764.
310. Shahbandi A, Rao SG, Anderson AY, Frey WD, Olaiwola JO, Ungerleider NA, et al. BH3 mimetics selectively eliminate chemotherapy-induced senescent cells and improve response in TP53 wild-type breast cancer. Cell Death Differ. 2020;27(11):3097–116.

311. Di Micco R, Sulli G, Dobreva M, Liontos M, Botrugno OA, Gargiulo G, et al. Interplay between oncogene-induced DNA damage response and heterochromatin in senescence and cancer. Nat Cell Biol. 2011;13(3):292–302.

312. Sati S, Bonev B, Szabo Q, Jost D, Bensadoun P, Serra F, et al. 4D genome rewiring during oncogene-induced and replicative senescence. Mol Cell. 2020;78(3):522–38.

313. Van Nguyen T, Puebla-Osorio N, Pang H, Djuka ME, Zhu C. DNA damage-induced cellular senescence is sufficient to suppress tumorigenesis: a mouse model. J Exp Med. 2007;204(6):1453–61.

314. Davalli P, Mitic T, Caporali A, Lauriola A, D’Arca D. ROS, cell senescence, and novel molecular mechanisms in aging and age-related diseases. Oxid Med Cell Longev. 2016;10(2016):3565127.

315. Macip S, Kosey A, Lee SW, D’Onofrio MJ, Aaronson SA. Oxidative stress induces a prolonged but reversible arrest in p53-null cancer cells, involving a Chk1-dependent G2 checkpoint. Oncogene. 2006;25(45):6037–47.

316. Sabelli R, Iorio E, De Martino A, Podo F, Ricci A, Vitociè G, et al. Rhodanese-thioredoxin system and alky sulfur compounds. FEBS J. 2008;275(15):3884–90.

317. Nepravishta R, Sabelli R, Iorio E, Micheli L, Paci M, Melino S. Oxidative damage-induced cellular senescence is sufficient to suppress tumorigenesis. J Biol Chem. 2012;287(24):20737–47.

318. Velletri T, Romeo F, Tucci P, Peschiaroli A, Annicchiarico-Petruzzelli M, et al. Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. Proc Natl Acad Sci USA. 2010;107(16):7455–60.

319. Zhang J, Kong X, Zhang Y, Sun W, Wang J, Chen M, et al. FDXR regulates TP73 tumor suppressor via IRP2 to modulate aging and tumor suppression. J Pathol. 2020;251(3):294–96.

320. Fujita K. p53 isoforms in cellular senescence- and ageing-associated biological and physiological functions. Int J Mol Sci. 2019;20(23).

321. Yao Y, Bellon M, Shelton SN, Nicot C. Tumor suppressors p53, p63TAα, p63TAy, p73α, and p73β use distinct pathways to repress telomerase expression. J Biol Chem. 2012;287(24):20737–47.

322. Vellenti T, Romeo F, Fucci P, Peschiaroli A, Annicchiarico-Petruzzelli M, Niklison-Chirou MV, et al. GLS2 is transcriptionally regulated by p73 and contributes to neuronal differentiation. Cell Cycle. 2013;12(22):3564–73.

323. Hu W, Zhang C, Wu R, Sun Y, Levine A, Feng Z. Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. Proc Natl Acad Sci USA. 2010;107(16):7455–60.

324. Jiang K, Kong X, Zhang Y, Sun W, Wang J, Chen M, et al. ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes. Nature. 2020;578(7793):82–93.

325. Takaoka M, Harada H, Deramaudt TB, Oyama K, Andl CD, Johnstone CN, et al. Ha-Ras(G12V) induces senescence in primary and immortalized human fibroblasts. Oncogene. 2001;98(9):5025–30.

326. Lin AW, Lowe SW. Oncogenic ras activates the ARF-p53 pathway to suppress epithelial cell transformation. Proc Natl Acad Sci USA. 2001;98(8):5025–30.

327. Li T, Kon N, Jiang L, Tan M, Ludwig T, Zhao Y, et al. Tumor suppression in the absence of p53-mediated cell-cycle arrest, apoptosis, and senescence. Cell. 2012;149(6):1269–83.

328. Marini A, Rotblat B, Stabroto T, Niklison-Chiuw MV, Knight JRP, Dudek K, et al. Tap73 contributes to the oxidative stress response by regulating protein synthesis. Proc Natl Acad Sci USA. 2018;115(24):6219–24.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.