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REVIEW

A double dealing tale of p63: an oncogene or a tumor suppressor

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Abstract As a member of tumor suppressor p53 family, p63, a gene encoding versatile protein variant, has been documented to correlate with cancer formation and progression, though it is rarely mutated in cancer patients. However, it has long been controversial on whether p63 is an oncogene or a tumor suppressor. Here, we comprehensively reviewed reports on roles of p63 in development, tumorigenesis and tumor progression. According to data from molecular cell biology, genetic models and clinic research, we conclude that p63 may act as either an oncogene or a tumor suppressor gene in different scenarios: TA isoforms of p63 gene are generally tumor-suppressive through repressing cell proliferation, survival and metastasis; ΔN isoforms, however, may initiate tumorigenesis via promoting cell proliferation and survival, but inhibit tumor metastasis and progression; effects of p63 on tumor formation and progression depend on the context of the whole p53 family, and either amplification or loss of p63 gene locus can break the balance to cause tumorigenesis.

Keywords TAp63 · ΔNp63 · Oncoprotein · Cell senescence · Cell migration

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p63 gene and its protein products

p63, also known as TP63 (tumor protein 63), Trp63 (transformation related protein 63), or AIS (amplified in squamous cell carcinoma), is a gene highly homologous to tumor suppressor p53. It locates on the distal long arm of human chromosome 3, 3q27 [1]. p63 gene possesses 2 promoters and 16 exons (Fig. 1a). The first promoter drives transcription of TAp63, starting at the first exon, while the second promoter triggers transcription of ΔNp63 isotypes, which starts at exon 3′ [2].

Primary transcript of either TA or ΔN isotype p63 undergoes alternative splicing. Consequently, p63 gene can generate at least 10 different protein isoforms, namely TAp63α/β/γ/δ/ε and ΔNp63α/β/γ/δ/ε (Fig. 1b). TA isoforms of p63 protein contain a longer N-terminal transactivation domain (TAD), while ΔNp63s possess a shorter region at the N-termini, which composed 14 amino acid residues and encoded by exon 3′. All isoforms share a common DNA-binding domain (DBD) and a common oligomerization domain (OD) at the middle part. α and β isoforms of p63 (p63α and p63β) contain an additional transactivation domain (TAD2) next to OD. Additionally, p63α possesses a unique sterile alpha motif (SAM) and a trans-inhibitory domain (TID) at the C-terminus, which are involved in protein–protein interaction and activity modulation [2, 3].

Activities of p63 proteins: transactivators or trans-inhibitors?

As transcription factors belonging to p53 family, p63 proteins can recognize and bind to the canonical p53 response elements (p53-REs), two or more tandem repeats of RRRCWWGYYY, in the promoter regions of various genes.

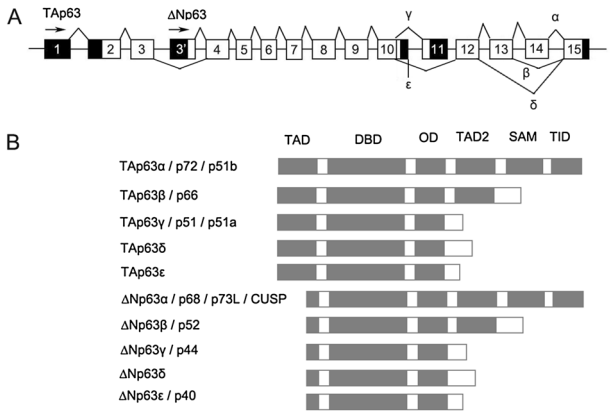

Fig. 1 Schematic presentation of p63 gene (**a**) and protein isoforms (**b**). *TAD* transactivation domain, *TAD2* additional transactivation domain, *DBD* DNA-binding domain, *OD* oligomerization domain, *SAM* sterile alpha motif, *TID* trans-inhibitory domain. All aliases of each isoforms are listed following the formal terms

Owing to the difference in the sequence of DBD, p63 and p53 exhibit different preferences for binding sequences in target promoters. Additionally, distinctions of domains else than DBDs between different p63 isoforms may lead to nuance of DNA-binding preferences [4, 5]. p63 can also positively regulate expression of genes such as Skp2 via binding to intron regions [6].

Downstream targets of p63 proteins are involved in a variety of essential biological processes. As mentioned above, p63 and other members of p53 family share some common downstream targets, such as $p21^{Waf1/Cip1}$, Puma, and Bax, enabling them to orchestrate to regulate cell cycle [7]. Like p53, TA isoforms of p63 can undoubtedly activate these downstream genes and consequently lead to cell cycle arrest, cell senescence and cell apoptosis. On the contrary, ΔNp63 proteins inhibit transcription of these genes, causing enhanced proliferation and cell survival. This effect of ΔNp63s is due to the lack of an intact TAD, and they can antagonize the transactivity of other p53 family proteins by means of forming inhibitory complexes with them or competitively binding to the p53-REs. Hence TAp63s enhance [3, 8–10], while ΔNp63s repress [3, 11], transcription of $p21^{Waf1/Cip1}$, which can inhibit Cyclin E/Cdk2 to mediate cell senescence and to restrain cell proliferation [12]. ΔNp63, but not TAp63, can also negatively regulate $p16^{Ink4a}$ [13], which activates Rb via inhibition of Cyclin D/CDK4/6 [14] and facilitates the formation of senescence-associated heterochromatic foci (SAHF) to keep pro-proliferative genes in an inactive sate [15, 16].

It is traditionally accepted that TAp63s are trans-activators while ΔNp63s are trans-inhibitors [3]. However, mounting evidence demonstrates that ΔNp63s can also stimulate some downstream target genes, including Caspase-1 [17], Perp [18], K14, BPAG1 [19], MKP3 [20], Hsp70 [21]. This may be because that the N-terminal fragment composed of 14 amino acid residues functions as a TAD in the ΔNp63 proteins. Of note, some genes, such as K14 and MKP3, are transactivated by only ΔNp63s, but not TAp63s [19, 20]. And genes such as Hsp70 are reported to be up-regulated by ΔNp63α but down-regulated by TAp63γ [21]. Further study indicates that the N-terminal 68 amino acids of TAp63s may function as an extra trans-inhibitory domain. So TAp63γ demonstrates to repress transcription of Hsp70. However, TAD2 in TAp63α can eliminate this repression on Hsp70 transcription [21]. These findings suggest the roles of particular domains in different p63 isoforms in modulating their specific transactivation or trans-inhibition.

p63 in development: TAp63s or ΔNp63s are the leading actors?

Vast evidence shows that p63 gene mutation leads to ectodermal defects, including ectrodactyly, ectodermal dysplasia, and facial clefting syndrome (EEC), split hand/foot malformation syndrome (SHFM), limb–mammary syndrome (LMS), acro-dermato-ungual-lacrimal-tooth syndrome (ADULT), and ankyloblepharon-ectodermal dysplasia-clefting syndrome (AEC) [22–26]. These observations demonstrate the importance of p63 in development, particularly in development of ectoderm.

Besides mutation of p63, transversion or deletion of human chromosome 7, band q21.3–q22.1, which contains SLC25A13, DSS1, DLX5 and DLX6 genes, can also lead to limb malformation [26–31]. Studies have shown that p63 can bind to a cis-acting element in this segment, thereby regulating the expression of DLX5 and DLX6 [32, 33]. And simultaneous deletion of DLX5 and DLX6 has also been shown to result in limb defects [34–36]. Therefore, it is likely that p63 regulates limb development by controlling the transcription of DLX5 and DLX6.

TAp63 proteins are barely detectable in somatic cells, but they express at a relatively higher level in oocytes, where they play key roles in quality control through turning on genes responsible for cell apoptosis upon genotoxic stress [37–39]. It was also reported that TAp63s are the first isoforms expressed during mouse embryogenesis and are pivotal to initiation of epithelial stratification program and inhibition of terminal differentiation [40].

ΔNp63s are predominant isoforms encoded by p63 gene in tissues and organs, especially epithelial basal layer in embryonic ectoderm and ectoderm-derived tissues or organs [41–43]. During development, expression of ΔNp63s is stimulated by BMP2, BMP7 and FGF10 [44]. ΔNp63s can counteract TAp63s and promote maturation of embryonic epidermis [40]. Gerry Melino group found that ΔNp63s

transactivate genes characteristic of epidermal basal layer and thymus, such as K14, FGFR2 and Jag2, while TAp63s transcribe genes characteristic of the superbasal layer, including Ets-1, K1, transglutaminases, and involucrin [19, 45, 46].

Consistent with evidence from human genetics, data from mouse model revealed that either pan-p63 or ΔNp63-specific knockout mice demonstrate dysplasia of limbs and epidermis. They are both deficient in ectodermal cells, leading to a lack of squamous epithelium and its derivatives, including breast, lacrimal gland and salivary glands [24, 47]. Using a transgenic mouse model, Rizzo et al. revealed that ΔNp63 overexpression results in atopic dermatitis via increasing many cytokines and chemokines, including IL-33 and IL-31 [48]. TAp63-specific knockout mice age prematurely and develop blisters, skin ulcerations, senescence of hair follicle-associated dermal and epidermal cells, and decreased hair morphogenesis, likely owing to a defect in maintenance of adult skin stem cells [49]. The similarity between pan-p63 knockout mice and ΔNp63-specific knockout mice indicates that ΔNp63s are the predominant isoforms of p63 gene regulating skin development [40].

p63 in tumor formation and progression: an oncogene or a tumor suppressor gene?

1. Amplification or loss of p63 locus causes cancers?

Although p63 gene was originally cloned as a homologue of p53 and p73, which were both well known as tumor suppressors, it is rarely mutated in tumors [3, 50]. Therefore, the link between p63 and tumorigenesis remained obscure until it was reported that p63 gene is frequently amplified in primary cell lines derived from some squamous cell carcinoma (SCC): David Sidransky group employed fluorescent in situ hybridization (FISH) analysis and detected frequent amplification of p63 locus in primary lung SCC (LSCC) and head/neck SCC (HNSCC). Moreover, amplification of the p63 locus was accompanied by RNA and protein overexpression of its gene products ΔNp63α and ΔNp63ε, whose ectopic expression in Rat 1a endowed these fibroblast cells with characteristics of malignancies, significantly enhancing their colony growth and xenograft tumor formation. They also found that most LSCC with ΔNp63α overexpression simultaneously harbored p53 mutation [51]. Another investigation in non-small cell lung cancers demonstrated a similar observation: Pierre Massion et al. found that copy number of p63 gene and protein level of ΔNp63α were significantly increased in 88% of squamous carcinomas, 42% of large cell carcinomas and adenocarcinomas of lung [1]. These results suggest that p63 may function as an oncogene, whose amplification may lead to SCC likely in combination with p53 dysfunction.

However, evidence from mouse model revealed that loss of a p63 allele increases tumor predisposition and deteriorates tumor phenotype under the background of p53 or p73 heterozygosity. To investigate whether p53 family members genetically interact each other in tumor formation, Elsa Flores et al. intercrossed mice with heterozygote of p53, p73 or p63. They found that, compared with $p53^{+/-}$ mice, $p53^{+/-}$; $p63^{+/-}$ mice spontaneously developed squamous cell carcinomas at a strikingly higher frequency. These tumors were found in multiple tissues including larynx, pharynx, cervix, and esophagus, and were more metastatic than those in $p53^{+/-}$ mice. On the other hand, compared to $p73^{+/-}$ mice, $p73^{+/-}$; $p63^{+/-}$ mice demonstrated higher predisposition to mammary adenocarcinoma, salivary adenoma, squamous cell carcinoma, osteosarcoma, transitional cell carcinoma and rhabdomyosarcoma. Their study also revealed that tumors from $p63^{+/-}$ mice underwent loss of heterozygosity (LOH), which is one of the hallmarks of tumor suppressor gene inactivation [52]. Consistent with Elsa Flores' data, analysis of tumorigenesis conducted by Alea Mills group indicated that heterozygosity of p63 significantly enhanced sarcoma development in p53-deficient mice [9]. Other independent groups reported that loss of p63 expression is associated with tumor progression and poor prognosis in human bladder carcinomas [53–55]. These investigations indicate that p63 gene has tumor-suppressive activities and loss of p63 locus may contribute to tumorigenesis.

2. ΔNp63s: oncoproteins or tumor suppressor proteins?

Since p63 can encode two classes of protein isoforms, TAp63s and ΔNp63s, which were traditionally assumed to possess contrary functions in transcription regulation, the researchers tried to identify which isoform(s) is/are the prime culprit(s) in SCC tumorigenesis. The aforesaid investigations carried out by two independent groups revealed that ΔNp63α is the predominant isoform overexpressed in different cancer types, particularly squamous carcinomas, and ectopic overexpression of ΔNp63 isoforms in cultured cells can increase soft agar growth and tumor size in mice [1, 51]. And overexpression of ΔNp63α occurs in more than 80% of SCCs arising from head/neck [56, 57], lung [1], esophagus [58], and cervix [59], as well as some cases of basal breast carcinoma [60, 61]. In keeping with these observations, we found that ΔNp63α can promote cell proliferation and tumor formation [62], as well as prevent cancer cells from apoptosis upon genotoxic stress [63, 64]. According to these findings, p63 seems to exert its oncogenic functions via expressing ΔNp63α and other ΔNp63 proteins.

In the cases of ΔNp63s promoting tumorigenesis, ΔNp63s may antagonize p53 and TAp73 transactivities,

consequently increasing transcription of the abovementioned genes involved in cell cycle arrest and apoptosis. As a result, cell proliferation and cell survival are enhanced, while cell senescence and cell apoptosis are inhibited [63, 65–67]. It was also documented that ΔNp63α may up-regulate transcription of Hsp70, which is a stress response protein and a determinant of cell death and cell transformation, to prime HNSCC [21], as well as that ΔNp63α can target transcription of chromatin remodeler Lsh to bypass oncogene-induced senescence (OIS) and drive tumorigenesis in vivo [68]. It was also reported that ΔNp63α positively regulates cell matrix adhesion molecules, including integrins α6, β1 and β4, as well as matrix protein Laminin-γ2. Ablation of ΔNp63α can cause a significant down-regulation of these proteins, resulting in cell death by anoikis, which can be perfectly rescued by restoring expression of ΔNp63α. This mechanism may interpret roles of ΔNp63α in tumorigenesis and tumor cell survival from another perspective [69]. On the other hand, Dennis McCance group found that in primary human foreskin keratinocytes expressing HPV16 E6/E7 genes, expression of pan p63 promotes cell migration, extracellular matrix (ECM) remodelling and cell invasion via inducing Src–FAK complex expression/activation [70]. In one of our recent work, we found that metformin, a drug for type II diabetes, promoted WWP1-mediated proteasomal degradation of ΔNp63α, resulting in disruption of cell matrix adhesion and subsequent apoptosis in human squamous carcinoma cells [71]. In addition, data from our group and other labs revealed that ΔNp63α activates c-Myc via several mechanisms, likely promoting cell cycle progression and tumorigenesis [72, 73].

As mentioned above, loss of p63 expression or locus is reported to associate with tumorigenesis or progression, particularly metastasis, in a variety of cancers. Among these cancer types, ΔNp63s are the predominant p63 isoforms in some of their normal tissues, such as breast [74–76], urothelium [53, 77], prostate [78, 79], and cervix [80]. These observations indicate that ΔNp63s may possess anti-metastasis activities. Further research using an intravenous injection assay proved that ectopic expression of ΔNp63α significantly inhibited metastasis of malignant spindle carcinoma D3S2 cells to the lungs [81].

During the initiation of metastasis for cancer progression, epithelial cells have to lose their cell polarity and cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells. This process is termed epithelial–mesenchymal transition (EMT). A reverse process termed mesenchymal–epithelial transition (MET) is believed to participate in the establishment and stabilization of distant metastases by allowing cancerous cells to regain epithelial properties and integrate into distant organs [82]. Investigations on the molecular mechanism demonstrated that ΔNp63s inhibit cell metastasis via regulating genes involved in cell adhesion, motility and migration. As has been noted previously, positive regulation of molecules involved in cell matrix adhesion may contribute to tumor repressive activities of ΔNp63s [69]. Additionally, this mechanism may also prevent tumor cells from detaching the matrix. Cell–cell adhesion is another aspect of epithelial properties, in which the transmembrane protein Perp is an important factor to maintain proper desmosome structure and function. Perp is a direct downstream target of various p53-family proteins including ΔNp63s [18]. Logically, ΔNp63s may inhibit EMT via facilitating cell matrix and cell–cell adhesion. On the other hand, ablation or reduced expression of ΔNp63s were reported to result in up-regulation of other proteins involved in cell adhesion, motility and migration, such as N-cadherin, L1 cell adhesion molecule (L1CAM), Periostin, and Wnt-5a [83]. It was also documented that ΔNp63α inhibits cell invasion via up-regulating inhibitor of differentiation-3 (Id-3), which can down-regulate expression of matrix metallopeptidase 2 (MMP2) to prevent from cleaving components of the extracellular matrix [84]. We recently reported that activation of oncogenic phosphatidylinositol 3 kinase (PI3K), Ras, and Her2 signaling can down-regulate ΔNp63α in cancer development via activating Akt, which in turn phosphorates Foxo3a to prevent it from binding to p63 promoter region. This decrease in ΔNp63α leads to down-regulation of its downstream targets including E-cadherin, Desmoplakin and Par3, resulting in enhanced cell motility and tumor metastasis [85]. In some of our other studies, we identified the metastasis suppressor CD82 (cluster of differentiation 82) and mitogen-activated protein kinase phosphatase 3 (MKP3) as direct ΔNp63*α* transcriptional targets, and found that ΔNp63*α* up-regulates CD82 or MKP3 to inhibit caner metastasis [20, 86]. It was also reported that ΔNp63s are involved in regulation of crucial players of EMT such as Snails and TGF-β [87–89], as well as p53-, particularly mutant p53-, mediated regulation of metastasis [81, 90, 91]. It remains unclear whether p63 is involved in MET process during the colonization and formation of a metastatic nodule [92].

3. TAp63α: simply as a tumor suppressor?

Since a great deal of evidence demonstrates that TAp63s transactivate various genes to promote cell cycle arrest and cell apoptosis [8, 38, 93, 94], it is almost indisputably accepted that TAp63 isoforms have tumor-suppressive activity [95]. Using a TAp63-specific knockout mouse model, Alea Mills group found that TAp63 deficiency compromises Ras-induced senescence, enhances proliferation and promotes tumorigenesis in the context of p53 deficiency. Exogenous expression of TAp63s, including TAp63α, TAp63β and TAp63γ, can induce cell senescence in cultured cells and inhibit tumor formation upon xenograft implantation in nude

mice [9]. Elsa Flores groups employed another conditional knockout mouse model and found that TAp63s suppress cancer metastasis through up-regulating miR-130b and Dicer [96]. TAp63s can directly bind to and transactivate the promoter of endoribonuclease Dicer, which was responsible for processing of mcroRNAs and involved in cancer metastasis [97, 98]. Deficiency of TAp63s leads to down-regulation of Dicer and a decrease in spontaneous development of highly metastatic tumors. Processing of various metastasis-related microRNAs, including miR-10b, miR-200b, miR-200c, miR-34a and miR-130b, is deficient in TAp63$^{-/-}$ mice. TAp63s can also directly bind to and transactivate miR-130b promoter. Most importantly, restore of either Dicer or miR-130b partially rescues invasive phenotype in TAp63$^{-/-}$ MEFs, while simultaneous restore of both molecules perfectly reverses invasion induced by TAp63 deficiency [96]. In addition, TAp63s can also potently activate transcription of Perp to inhibit metastasis [18].

Though TA isoforms of p63 are once assumed to induce cell senescence, which contributes to tumor-suppressive activities of TAp63s [9], TAp63-specific conditional knockout mice employed by Elsa Flores group demonstrate enhanced cell senescence [49]. This is likely due to genomic instability and increased DNA damage resulted from TAp63 deficiency. And this senescence induced by TAp63 deficiency occurs not only in dermal precursor cells [49], but also in osteosarcomas and rhabdomyosarcomas in TAp63$^{-/-}$; p53$^{+/-}$ mice [96]. This observation is in conflict with above-mentioned data from Alea Mills group that TAp63s induce cell senescence [9].

Additionally, despite the widespread concept of TAp63s as tumor suppressors, Roberta Malaguarnera et al. reported that TAp63α protein is in a high percentage of thyroid carcinomas, but not in normal thyroid cells or benign thyroid adenomas [99]. In these thyroid cancer cells, the tumor-suppressive activities of TAp63α are absent, because either endogenous or exogenous TAp63α fails to transactivate its downstream genes. On the contrary, TAp63α seems to antagonize effects of p53 on its target genes, cell viability and foci formation in these cells. Moreover, transactivity of p53 in thyroid cancer cells can be strikingly elevated by TAp63α silencing. These oncogenic effects of TAp63α likely depend on its C-terminus, which contains a unique sterile alpha motif (SAM) and a trans-inhibitory domain (TID), since neither TAp63β nor TAp63γ are still able to induce the target genes and to exert tumor-restraining effects in thyroid cancer cells [99]. Another investigation demonstrated that mRNA levels of TAp63s, but not ΔNp63s, are higher in high-grade follicular lymphomas compared to non-neoplastic lymphocytes. This overexpression of p63 is independent of gene amplification [100]. Whether and how up-regulated TAp63s are involved in formation and progression of lymphomas in these cases requires further investigation.

Concluding remarks: a double dealer depending on context

p63 gene can encode two groups of proteins, namely TA and ΔN isoforms [2]. Increasing evidence demonstrates that transactivities of p63 proteins are much complicated: besides their trans-repressive activities [3, 11, 13], ΔNp63s also possess transactivities for some downstream genes [19, 21]; TAp63s are generally transactivators [3, 9, 96], but they may lose their transactivities even act as trans-inhibitors in certain scenarios [21, 99]. Evidence from human genetics and mouse model reveals that p63 gene is essential for organism development [19, 24, 40, 41, 47, 49]: TAp63s are expressed at a relatively high level in oocytes and during early stage of embryogenesis to maintain certain progenitor cells, particularly of skin stem cells; expression of ΔNp63s gathers along with the differentiation of ectoderm layer to promote its maturation and stratification of epithelium.

TA and ΔN isoforms of p63 regulate tumor formation, growth and metastasis via multiple mechanisms (Fig. 2). TAp63s are generally assumed to function as tumor suppressor proteins, because they can transactivate a batch of genes to induce cell cycle arrest and cell apoptosis [8, 38, 93, 94]. Evidence from mouse models also reveals that TAp63s repress tumorigenesis and metastasis [9, 96]. Tumor-suppressive activity of TAp63s seems to depend on genetic background or cell type: TAp63 deficiency induces cell senescence in normal epidermal cells and epithelium-derived cancer cells [49, 96], but increases proliferation and enhances Ras-mediated oncogenesis in the context of p53 deficiency in vivo [9]; in some thyroid carcinomas, TAp63α loses its tumor-suppressive activity and even exhibits its oncogenic effects via antagonizing p53 transactivity [99]. ΔNp63s also have dual effects on cancers: in various types

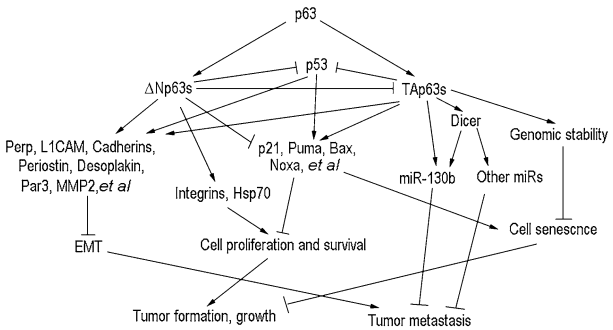

Fig. 2 Roles of p63 in tumor formation, growth and metastasis. TAp63s mainly act as tumor suppressors by inhibiting cell proliferation, survival and tumor metastasis, and occasionally exert oncogenic activity via repressing p53 trans-activity. ΔNp63s promote formation and growth of some epithelium-derived tumors through enhanced cell proliferation and survival. On the other hand, ΔNp63s repress tumor metastasis via inhibition of EMT. A full arrow means a positive regulation, while a blunt arrow represents an inhibition

of squamous cell carcinomas, they are overexpressed as a consequence of p63 gene amplification and function as oncoproteins to initiate tumor formation [1, 51]. Oncogenic effects of ΔNp63s may be due to their activities on cell proliferation and cell survival [63, 65–69]. On the other hand, ΔNp63s can also transactivate a vast body of genes involved in EMT [18, 20, 65, 69, 82, 84]. This may account for the observation that ΔNp63s can suppress metastasis during the progress of some cancer types [81, 85], though some evidence indicates that p63, including ΔNp63 isoforms, can drive cell invasion under some circumstances [70].

Since ΔN and TA isoforms of p63 can, respectively, promote or inhibit tumor initiation, effects of p63 gene on tumorigenesis are delicate. In normal somatic cells, oncogenic ΔNp63s are balanced with tumor-suppressive TAp63s, TAp73s and p53. Under certain scenarios, particularly in the absence of sufficient functional p53 or p73, either amplification or loss of p63 gene locus may exacerbate this subtle imbalance, leading to predisposition to cancer.

Owing to dual roles of p63s in cancer formation and progression, future investigations are required to elucidate how p63 isoforms are regulated at either transcriptional or post-transcriptional levels, and how they are regulated to exert their oncogenic or tumor-suppressive activities in different cell types, as well as how they switch their different activities at different stage of tumor development. With these questions addressed, it would be possible to explore some small molecule drugs targeting specific p63 isoforms, their regulators or downstream genes for cancer therapy according to different scenarios.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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