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p53, p63 and p73 Network in Breast Cancers

Chee-Onn Leong
International Medical University,
Malaysia

1. Introduction

Inactivation of the tumor suppressor p53 is the single most common genetic defect in all human cancers. The p53 tumor suppressor is critically important in regulation of cell cycle progression, senescence, differentiation, DNA repair and apoptosis. The discovery of two closely related homologues, p63 and p73, in 1997 generated instant excitement and quick expectations about their tumor suppressor functions. However, despite a remarkable structural and partial functional similarity among p53, initial p63 and p73 mouse knockout studies revealed an unexpected functional diversity among them. p63 and p73 knockouts exhibit severe developmental abnormalities but no increased cancer susceptibility. While p53 is frequently mutated during tumorigenesis (in over 50% of human tumors), p63 and p73 are rarely mutated. Instead, the p63 locus is amplified in squamous cell carcinomas (Bjorkqvist et al., 1998; Massion et al., 2003) and p73 is overexpressed in many tumor types including breast cancers (Moll and Slade, 2004; Zaika and El-Rifai, 2006; Zaika et al., 1999). Although p63 and p73 can activate apoptosis *in vitro*, it is clear that they are not classic Knudson-like tumor suppressors like p53.

Throughout the years, impressive number of evidences has been uncovered, suggesting that the p53-family play an important role in breast cancers. The emerging picture is that of an interconnected pathway, in which all p53-family proteins are involved in the response to oncogenic stress and physiological inputs. The p53/p63/p73 family members are capable of interacting in many ways that involve direct or indirect protein interactions, regulation of same target gene promoter and regulation of each other's promoters. As such, fluctuations in the levels of selected p53 family members (or their isoforms) might change the relative availability of shared protein partners, as multiple p53-family proteins compete for interaction. Also, differential expression of selected interactors – linked with genetic variation – may distinguish the response of the p53 pathway to the same potentially oncogenic stimuli in diverse individuals.

Despite the recent advances in understanding the unique roles of p53 family protein in breast cancers, there are many outstanding questions. What are the unique functions of the TA and ΔN isoforms of p63 and p73? How is individual p53 family member mediates gene expression regulated by the interaction with mutant p53 and other family member and their splicing variants in the cell? What are the patterns of p53 family isoform expression during normal development and tumorigenesis? What are the upstream signaling pathways that regulate individual p53 family member? What are the p53, p63 and p73 target genes? Do p53, p63 and p73 regulate distinct and/or overlapping sets of genes? Understanding the

complexity of these interactions allow us to delineate the function of p53 family in human tumorigenesis and enable the development of new cancer therapeutics.

2. The origins and gene architecture of the p53 family proteins

The tumor suppressor gene, p53, was discovered in 1979 (Lane and Crawford, 1979; Linzer and Levine, 1979). Until recently, *p53* was thought to be a unique gene with no genetic paralogues. In 1997, however, Caput and coworkers serendiptiously identified a human homolog of p53 which they called p73 (Irwin and Kaelin, 2001; Kaelin, 1999; Kaghad et al., 1997). Shortly thereafter, several groups identified a third member of the family variably called Ket, p40, p51, p73L and p63 (Irwin and Kaelin, 2001; Kaelin, 1999; Osada et al., 1998; Schmale and Bamberger, 1997; Senoo et al., 1998; Trink et al., 1998; Yang et al., 1998). While p53 was discovered first, evolutionary conservation of DNA sequence suggests that p63 arose first during evolution, then p73 and finally p53 (Johnson et al., 2005).

Like many transcription factors, p53 are modular proteins with a conserved N-terminal transcriptional activation domain (TA), central DNA-binding domain (DBD) and a C-terminal oligomerization domain (OD) (Fig. 1) (Arrowsmith, 1999). The DBD has the highest degree of homology, where p63 and p73 share 65% amino-acid identity with p53, and even higher identity with each other. All three genes express many spliced isoforms — a feature that was thought to be unique for p63 and p73 but has recently found to be true for p53.

The existence of an internal promoter within the p53 family was first discovered in *p63* (Yang et al., 1998). The human and mouse *p63* genes express at least three alternatively spliced C-terminal isoforms (α, β, γ), and can be transcribed from an alternative promoter located in the intron 3 (Fig. 1). The transactivating isoforms (TAp63) are generated using the promoter upstream of exon 1 while the alternative promoter in intron 3 leads to the expression of N-terminal truncated isoforms (ΔNp63) lacking the transactivation domain. Altogether, the *p63* gene expresses at least six mRNA variants which encode for six different p63 protein isoforms (TAp63α, TAp63β, TAp63γ, ΔNp63α, ΔNp63β, and ΔNp63γ) (Murray-Zmijewski et al., 2006).

The p73 gene expresses at least seven alternatively spliced C-terminal isoforms (α, β, γ, δ, ϵ, ζ and η) and at least four alternatively spliced N-terminal isoforms (Melino et al., 2003; Moll and Slade, 2004; Stiewe et al., 2002b). Like p63, the p73 gene can be transcribed from an alternative promoter located in the intron 3 (Fig. 1). The transactivating isoforms are generated by the activity of the promoter upstream of exon 1 while the alternative promoter in intron 3 leads to the expression of the N-terminal truncated isoforms (ΔNp73) lacking the transactivation domain. Altogether, the p73 gene expresses at least 35 mRNA variants, which can encode theoretically 29 different p73 protein isoforms (Fig. 1). So far, 14 different p73 protein isoforms have been described. In contrast to p63, p73 isoforms can be initiated from different ATG and contain different part of the N-terminal domain, suggesting that they can have distinct protein interactions and specific activities (Murray-Zmijewski et al., 2006).

3. Developmental phenotypes of p53, p63 and p73 knockout mice

Since p53 is a powerful tumor suppressor gene, its loss in mice predisposes the animals to cancers of various organs (involving tissues such as blood, muscle and bone) with no visible developmental defects. Similarly, human patients with Li Fraumeni syndrome, the disease
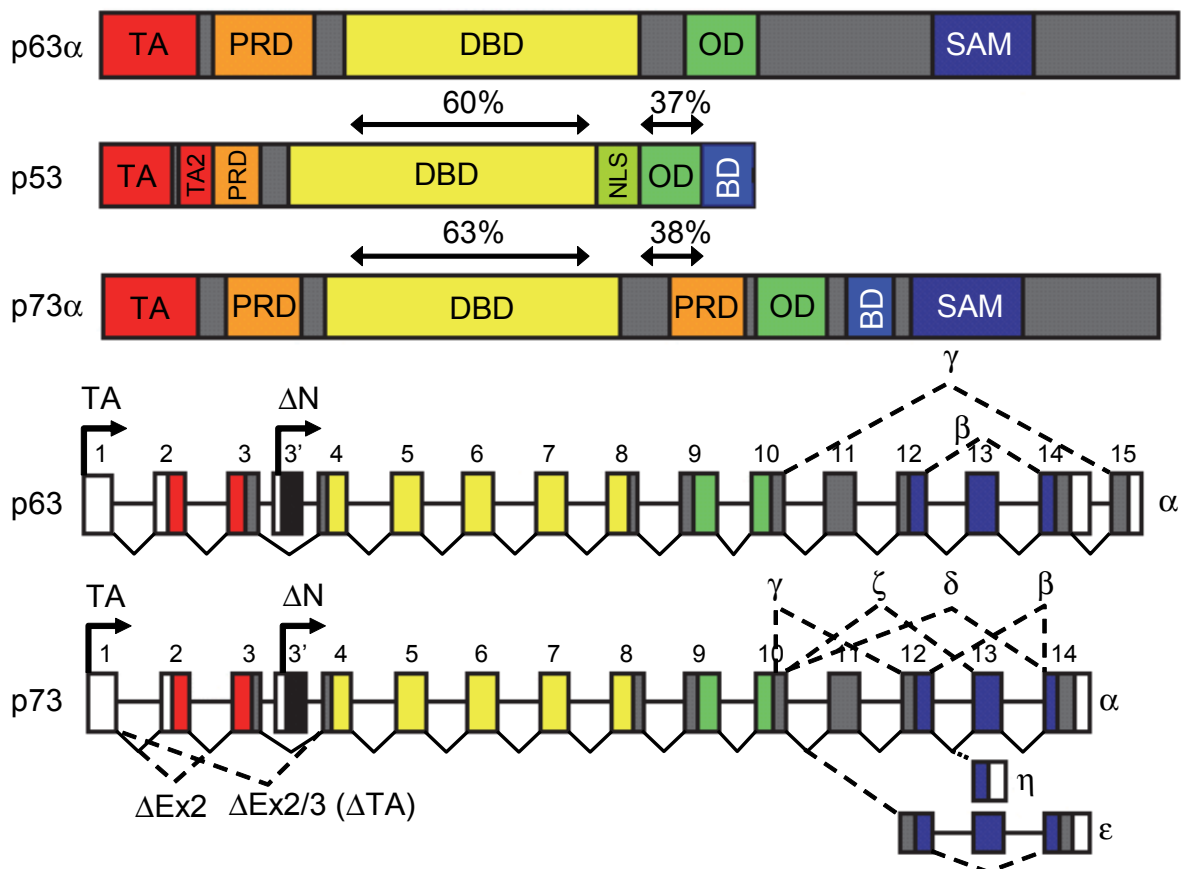
Fig. 1. **Gene architecture of the p53 family.** The p53 family includes the three genes p53, p63, and p73. Each of them has a modular structure consisting of the transactivation domain (TA), the DNA binding domain (DBD), and the oligomerization domain (OD). In addition to the 3 common domains, p63 and p73 also harbor a C-terminal sterile alpha-motif (SAM) domain in the α isoform. All p53 family genes are expressed as two major types: the full-length proteins containing the TA domain and ΔN proteins missing the TA domain. The P1 promoter in the 5'-untranslated region produces TA proteins that are transcriptionally active, whereas the P2 promoter produces ΔN proteins with dominant-negative functions toward themselves and toward wild-type p53. In addition, both p63 and p73 also undergo extensive C-terminal alternative splicing generating a myriad of isoforms with different transcriptional activity and specificity.

caused by germ line mutation of human p53, also predisposes to various cancer especially breast cancers (Johnson et al., 2005). While p53 seems to play little role in embryonic development, the p63 and p73 deficient mice have severe developmental abnormalities (Westfall and Pietenpol, 2004).

3.1 p63 in development: Role in epithelial differentiation and proliferation
p63-deficient mice are born alive but the limbs are absent or truncated owing to a malfunction of the apical ectodermal ridge (Mills et al., 1999; Yang et al., 1999). They fail to develop a stratified epidermis and most epithelial tissues (for example, hair follicles, teeth, prostate, lacrimal and salivary glands, and mammary glands), and eventually die from dehydration within hours of birth (Stiewe, 2007). Reminiscent of the knockout phenotype in

mice, heterozygous germ line point mutations of p63 in humans also cause striking autosomal dominant developmental disorders including ectrodactyly-ectodermal dysplasia (EEC) (Celli et al., 1999), ankyloblepharon-ectodermal dysplasia clefting (Hay-Wells Syndrome) (Fomenkov et al., 2003), acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome (Duijf et al., 2002), limb-mammary syndrome (LMF) (van Bokhoven et al., 2001), Rapp-Hodgkin syndrome (Chan et al., 2005), and split hand-split foot malformation syndrome (Brunner et al., 2002; Johnson et al., 2005; van Bokhoven et al., 2001).

Although the p63-deficient mice and human cases showed prominent phenotypes, the actual function of p63 in developmental processes remain controversial. The two groups that generated the p63-deficient mice reported identical phenotypes, the conclusions drawn from examination of the murine tissues differed (Westfall and Pietenpol, 2004). In one case clumps of differentiated cells were detected in the epidermis (Yang et al., 1999), whereas in the other, uncommitted ectodermal cells covered the body surface (Mills et al., 1999). This lead to two divergent points of view emerged from these analyses: one group attributed the p63-null phenotype to an absence of lineage commitment and an early block in epithelial differentiation (Mills et al., 1999); the other postulated that the phenotype was secondary to a defect in epithelial stem-cell renewal (Yang et al., 1999). It thus remained uncertain whether the primary function of p63 was in control of differentiation or self-renewal, or both (Blanpain and Fuchs, 2007).

Subsequent studies on p63 attempted to clarify this issue, but were further complicated with the discovery that the two principal isoforms of p63, ΔNp63 and TAp63, each of which have distinct roles in epithelial development. When transgenic mice expressing either TAp63 and/or ΔNp63 were bred on the p63-null background, mice expressing ΔNp63, but not TAp63, partially rescued basal epidermal gene expression, whereas only mice coexpressing both isoforms presented a significant improvement in expression of terminal differentiation marker. This data is consistent with the notion that ΔNp63 governs basal-epidermal gene expression, whereas TAp63 (possibly together with ΔNp63) promote terminal differentiation. Taken together, these studies supported a role for p63 in differentiation and not self-renewal. However, a later study by Senoo et al. (2007) demonstrated that p63 is not required for lineage commitment and differentiation of epithelial cells, as these cells present the typical markers for epithelial development and, in the case of the thymic epithelia, are fully competent to support the maturation of developing T cells in the thymus (Senoo et al., 2007). The study provides compelling evidence that p63 functions specifically to maintain the extraordinary proliferative capacity of the epithelial stem cells of the thymus and epidermis, suggesting a general function of the p63 transcription factor in maintaining the stem cells of a broad array of stratified epithelia. Thus, the question whether p63 functions in control of differentiation, self-renewal, or both remain debatable.

3.2 p73 in development: Role in neuronal and pheromonal pathways

The p73 knock-out mice have profound developmental defects including hippocampal dysgenesis, hydrocephalus, chronic infections and inflammation (Abraham and Meyer, 2003). They also exhibit abnormal reproductive and social behavior due to defects in pheromone detection, attributed to a dysfunctional nasal organ that normally expresses high levels of p73 (Johnson et al., 2005). The tissue specificity of the p73 deficient phenotype (concentrated to the brain and related structures) may be associated with variable patterns of isoforms expressed in brain vs. other tissues (Hu et al., 2000; Johnson et al., 2005).

ΔNp73 is the predominant isoform in the developing mouse brain and might act as a transcriptional repressor (Pozniak et al., 2000; Yang et al., 1998). *In situ* hybridization reveals strong ΔNp73 expression in E12.5 fetal mouse brain in the preplate layer, bed nucleus of stria terminalis, choroid plexus, vomeronasal area, and preoptic area (Yang et al., 2000). Moreover, ΔNp73 is the only form of p73 found in mouse brain and the sympathetic superior cervical ganglia in P10 neonatal mice (Pozniak et al., 2000). Functional studies and knockout mice showed ΔNp73 is required to counteract p53-mediated neuronal death during the normal development of the mouse neuronal system (Pozniak et al., 2000). Withdrawal of nerve growth factor, an obligate survival factor for mouse sympathetic neurons, leads to p53 induction and p53-dependent cell death. In pull-down assays, mixed protein complexes of p53/ΔNp73 were demonstrated, suggesting one biochemical basis for transdominance in addition to possible promoter competition. Together, these data demonstrated that ΔNp73 is downstream of nerve growth factor in the nerve growth factor survival pathway and explains why p73-deficient mice, missing all forms of p73 including protective ΔNp73, undergo accelerated neuronal death in postnatal superior cervical ganglia (Moll and Slade, 2004; Pozniak et al., 2000).

To date, there are no human developmental syndromes associated with germ line p73 mutations (Johnson et al., 2005). Unlike p53-decifiency, p73 knock-out mice show no increased susceptibility to spontaneous tumorigenesis (Stiewe and Putzer, 2002; Yang et al., 2000).

4. Role of p53 family in breast malignancy: Tumor suppressor or oncogene?

p53 is a powerful tumor suppressor, as proven by a wealth of in vivo models and dramatically confirmed by frequent mutation in human cancers. However, the role of p63 and p73 in tumor suppression is less obvious, because they are rarely deleted or mutated in cancer and the respective homozygous knockout mice die tumor-free from developmental defects in the initial studies.

4.1 p63 and cancer

p63, mainly its ΔN isoform, is highly expressed in embryonic epidermis and act as a molecular switch for initiation of an epithelial stratification program (Koster et al., 2004). In postnatal epidermis, ΔNp63 expression is restricted to the nuclei of basal cells of normal epithelia (skin, esophagus, tonsil, prostate, urothelium, ectocervix, and vagina) and to certain populations of basal cells in glandular structures of prostate, breast, and bronchi (Di Como et al., 2002; Yang et al., 1998). Specifically, p63 is expressed in myoepithelial cells of the breast that play an important role in differentiation and carcinogenesis of the breast (Davis et al., 2002; Garraway et al., 2003; Moll and Slade, 2004; Reis-Filho et al., 2003a; Ribeiro-Silva et al., 2003). p63 expression was not detected in mesenchymal, neural, endothelial, smooth muscle or adipose cells consistent with restricted p63 expression in squamous and basal epithelial tissues (Reis-Filho et al., 2003b; Westfall and Pietenpol, 2004). The initial findings showed that ΔNp63α can act antagonistically toward p53 (Yang et al., 1998). Subsequent studies found dysregulated expression of p63, sometimes in conjunction with amplification of its genomic region at 3q27-28 in a many human epithelial cancers (Crook et al., 2000; Hibi et al., 2000; Massion et al., 2003; Park et al., 2000; Yamaguchi et al., 2000). Amplification of the p63 gene frequently leads to overexpression of the ΔNp63α

variant (Hibi et al., 2000). Regardless, ΔNp63α have been reported to be frequently overexpressed in bladder, breast, cervix, head and neck, lung, prostate and nasopharyngeal carcinoma (Crook et al., 2000; Moll and Slade, 2004; Westfall and Pietenpol, 2004). Overexpression of the ΔNp63 variant in Rat 1a cells have also been shown to increase growth of these cells in soft agar and as xenograft tumors (Hibi et al., 2000). Thus, the maintenance of the ΔNp63 isoforms in squamous cancers may contribute to keeping the cells in a stem cell–like phenotype, thereby promoting tumor growth. Of note, analysis of p63 sequence isolated from various human tumors and numerous human cancer cell lines showed that p63 rarely, if ever, mutated (Hagiwara et al., 1999; Osada et al., 1998). Collectively these data suggest that p63 does not function as a tumor suppressor but rather as an oncogene (Westfall and Pietenpol, 2004).

Nevertheless, studies on the TA isoform of p63 suggest an opposite view. Transient transfection of TAp63 has been shown to induce cell cycle arrest and apoptosis (Osada et al., 1998; Westfall and Pietenpol, 2004; Yang et al., 1998). The TAp63 isoforms are able to bind to DNA through p53 response element (p53RE) and activate transcription of a subset of p53 target genes (Murray-Zmijewski et al., 2006). Interestingly, TAp63γ had the greatest transactivation activity and TAp63α had the minimal activity (Westfall and Pietenpol, 2004). The ΔNp63 isoforms can also bind DNA through p53RE and can exert dominant-negative effects over p53, p73 and p63 activities by either competing for DNA binding sites or by direct protein interaction (Benard et al., 2003). Moreover, ΔNp63 isoforms were also shown to directly activate specific gene targets not induced by TA isoforms (Dohn et al., 2001; Wu et al., 2003). Thus, p63 has the ability to regulate a number of genes with diverse roles and possesses opposing regulatory effect by expressing different amount of TAp63 and ΔNp63 isoforms. Thus, an abnormal alteration in expression of these isoforms is likely to play an important role in tumorigenesis.

4.2 p73 and cancer

Like p63, p73 is rarely, if ever mutated in cancers. Unlike p63 which is frequently amplified in epithelial cancers, p73 frequently undergoes loss of heterozygosity in breast and colon cancer, neuroblastoma, oligodendroglioma, and melanoma. This fact, in conjunction with the functional similarity to p53, originally led to the proposal that p73 is a tumor suppressor gene (Kaghad et al., 1997). Genetic data on most cancer types, however, exclude p73 as a classic Knudson-type tumor suppressor, which by definition is targeted to undergo loss of expression or function during tumorigenesis. To date, loss of function mutations in p73 are vanishingly rare (0.6%). Moreover, imprinting of the p73 locus, initially thought to be an epigenetic explanation to satisfy the two-hit hypothesis, is rather uncommon and, if present, varies from tissue to tissue and person to person and does not correlate with p73 expression levels (Kovalev et al., 1998; Moll and Slade, 2004; Nomoto et al., 1998; Tsao et al., 1999; Zaika et al., 1999).

In fact, TAp73 overexpression has been found in different tumor types including tumors of breast (Leong et al., 2007; Zaika et al., 1999), neuroblastoma (Kovalev et al., 1998), lung (Mai et al., 1998; Tokuchi et al., 1999), esophagus (Cai et al., 2000), stomach (Kang et al., 2000), colon (Sunahara et al., 1998), bladder (Chi et al., 1999; Yokomizo et al., 1999), ovarian cancer (Chen et al., 2000; Ng et al., 2000; Zwahlen et al., 2000), liver cancer (Tannapfel et al., 1999b), cholangiocellular carcinoma (Tannapfel et al., 1999a), colon carcinoma (Sun, 2002), and head and neck squamous carcinoma (Choi et al., 2002; Rocco et al., 2006; Weber et al., 2002). Of

note, primary tumors and tumor cell lines with p73 overexpression tend to simultaneously overexpress a complex profile of shorter C-terminal splice variants (p73γ, p73δ, p73δ, and p73φ), whereas the normal tissue of origin is limited to the expression of p73α and p73β (Zaika et al., 1999). Importantly, patients with high global p73 protein expression had a worse survival than patients with undetectable levels (Moll and Slade, 2004; Sun, 2002; Tannapfel et al., 1999b).

Little is known about which genes are regulated specifically by p73 under physiological conditions. When overexpressed p73 also binds to p53 DNA target sites, transactivates p53-responsive genes and is capable of inducing cell cycle arrest and apoptosis in mammalian cells in a p53-like manner (Jost et al., 1997; Kaghad et al., 1997; Stiewe and Putzer, 2002). For example, p73 can activate the promoters of several p53-responsive genes, including *p21, BAX, PUMA, MDM2, GADD45, 14-3-3σ, cyclin G, IGFBP3,* and *p53R2* (Irwin and Kaelin, 2001; Jost et al., 1997; Kaghad et al., 1997; Lee and La Thangue, 1999; Nakano et al., 2000; Ueda et al., 1999; Vikhanskaya et al., 2001; Yang et al., 1998; Yu et al., 1999; Zhu et al., 1998). Nonetheless, there is evidence that p73 can activate many other genes which are not p53 target genes. For example, aquaporin 3 (AQP3), a glycerol and water transporter, has been shown to be a specific p73-responsive gene. It is speculated, that in p73-deficient mice lack of AQP3 induction accounts for the defects in production or reabsorption of cerebrospinal fluid, resulting in hydrocephalus (Stiewe and Putzer, 2002; Zheng and Chen, 2001).

Numerous reports also indicating a quantitative difference in the transcriptional activity of the various p73 splice variants. For example, the TAp73β is a more potent transcriptional activator than TAp73α (De Laurenzi et al., 1998; Lee and La Thangue, 1999; Yu et al., 1999; Zhu et al., 1998). Likewise TAp73β is more potent than TAp73α as an inducer of apoptosis, suggesting that TAp73α contains an 'inhibitory' region not included in the β-isoform. Consistently, a C-terminal deletion mutant of TAp73α lacking the putative inhibitory region showed a significantly higher level of transcriptional activity than wild-type TAp73α (Ozaki et al., 1999; Ueda et al., 2001). Moreover, the transcriptional activity of TAp73β was reduced *in trans* by co-expression with either TAp73α or p73ε, which bears an identical C-terminal structure as TAp73α (Ueda et al., 2001). This suppression effect is most likely mediated by inter-variant associations as it depends on the presence of the oligomerization domain. These observations indicate that p73-mediated gene expression is regulated by the interaction of all p73 isoforms present in the cell. The current data therefore indicate the existence of transciptional specificity among the p53-family members with pronounced differences between p53 and p73 on the one hand and between the various p73 isoforms on the other hand (Stiewe and Putzer, 2002).

5. Regulation of p53 family functions

The p53 family proteins are entangled in a regulatory network with positive or negative modulators. Many regulatory pathways may be shared by multiple p53-family proteins, with similar or different effects (Fig. 2).

5.1 Upstream regulation of p53 family members
One of the clear differences that discriminate p53 family members is the fact that they response to viral oncoproteins differently. Adenovirus E1B55, human papilloma virus E6 protein, and SV40 T antigen bind to and inactivate p53 during viral transformation (Fig. 2)
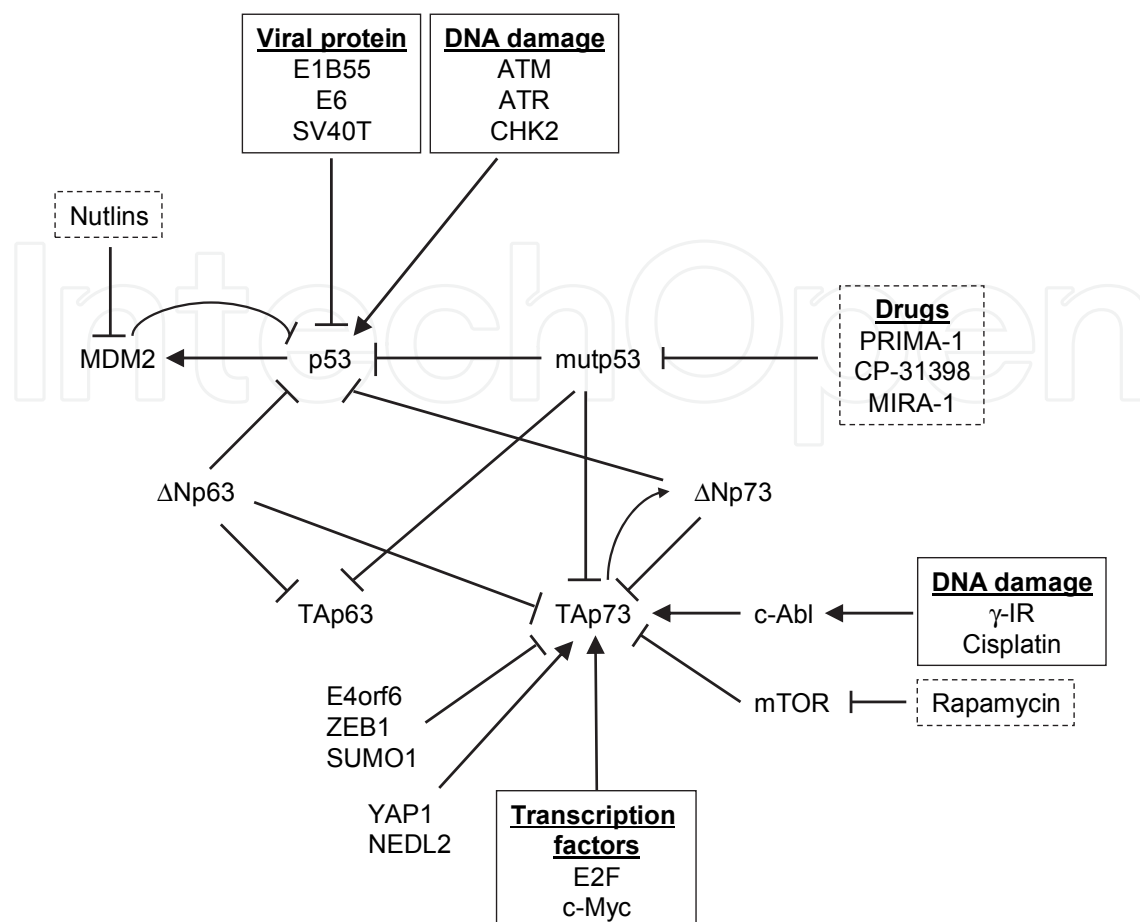
Fig. 2. The p53 family network and its regulation.

(Lechner et al., 1992; Linzer and Levine, 1979; Sarnow et al., 1982; Yew and Berk, 1992). These three proteins, however, do not bind to p73 (Dobbelstein and Roth, 1998; Marin et al., 1998; Roth et al., 1998; Steegenga et al., 1999). In fact, p73β can induce growth inhibition and apoptosis in cancer cells that produce E6 (Prabhu et al., 1998). Likewise, E6 and SV40 T antigen do not interact with p63 (Roth and Dobbelstein, 1999). The adenoviral protein E4orf6 also binds to and antagonizes p53, but there have been conflicting reports as to whether it interacts with p73. Roth *et al.* (1998) reported that E4orf6 does not affect p73 stability or the ability of p73 to activate transcription (Roth et al., 1998). Two other groups reported that E4orf6 binds to the C-terminus of p73 and blocks transcriptional activation and colony suppression by p73 (Higashino et al., 1998; Steegenga et al., 1999). Thus, certain viral oncoproteins preferentially inactivate p53 while sparing p63 and p73, despite the high degree of similarity between these three proteins (Fig. 2).

Several reports have shown that the cellular oncogenes E2F1 and c-Myc can induce and activate the endogenous TAp73α and TAp73β proteins for target gene transactivation, apoptosis, and growth suppression in p53-deficient human tumor cells (Irwin et al., 2000; Lissy et al., 2000; Stiewe and Putzer, 2000; Zaika et al., 2001). E2F1 is a specific and direct transcriptional activator of TAp73 but not p63 (Fig. 2) (Irwin et al., 2000; Stiewe and Putzer, 2000). Because oncogene deregulation of E2F1 and c-Myc are one of the most common genetic alterations in human tumors, these findings might provide a physiologic mechanism for TAp73 overexpression in tumors.

In a recent study, we showed that TAp73 is selective upregulated in BRCA1-associated ovarian tumors. Interestingly, we found that BRCA1-deficient ovarian carcinoma cells exhibit hypermethylation within a p73 regulatory region, which includes the binding site for the transcriptional repressor ZEB1. This hypermethylation leads to the abrogation of ZEB1 binding and hence increased expression of TAp73. Similarly, ZEB1 binding site methylation and TAp73 expression correlated with BRCA1 status in primary ovarian carcinomas and with clinical response to cisplatin (Fig. 2) (Ibrahim et al., 2010). Together, these data establish another important link between p73 and human cancer.

5.2 Regulation of p53 family protein stability

p53 is a short-lived protein, and its stability is very tightly regulated by ubiquitination under physiological condition (Haupt et al., 1997; Honda et al., 1997; Kubbutat et al., 1997). Polyubiquitination of p53 is carried out by the ubiquitin ligase MDM2. The polyubiquitination and degradation of p53 is influenced by a variety of factors including regulated changes in the subcellular localization of p53 and MDM2. Moreover, *MDM2* itself is a p53-inducible gene, and thus activation of p53 establishes a negative feedback loop wherein MDM2 limits p53 accumulation (Fig. 2) (Barak et al., 1993; Irwin and Kaelin, 2001).

In addition to its role in p53 degradation, MDM2 also binds to a sequence in the transactivation domain of p53 (amino acid residues 17–27) and thereby inhibits p53-dependent transactivation (Momand et al., 1992). The MDM2 binding site in p53 is well conserved in both p63 and p73. Several groups have shown that MDM2 bind to p73 and prevent it from binding to the transcriptional coactivators p300 and CBP (Balint et al., 1999; Ongkeko et al., 1999; Zeng et al., 1999; Zeng et al., 2000). This leads to impaired p73-dependent transcriptional activation and diminished apoptosis. Of note, like p53, p73 can activate the *MDM2* promoter (Wang et al., 2001b; Zeng et al., 1999; Zhu et al., 1998). Although MDM2 does not target p73 for polyubiquitination, p73 stability is indirectly dependent upon the activity of the proteasome. Specifically, many proteosome inhibitors have been shown to increase p73 levels (Balint et al., 1999; Irwin and Kaelin, 2001; Ongkeko et al., 1999). Thus, it is possible that p73 is polyubiquitinated in cells by a yet unknown E3 ligase.

Unlike p73 and p53, p63 does not bind to either MDM2 (Wang et al., 2001a). Although there are no data implicating ubiquitination pathways in p63 degradation, Ratovitski *et al.* (2001) showed that p63 abundance could be regulated by caspase-dependent proteolysis due to the presence of a caspase recognition site, YVED, in the amino acid sequence (Irwin and Kaelin, 2001; Ratovitski et al., 2001).

Besides MDM2, the degradation and protein stability of p53 family proteins might be regulated by small ubiquitin-related modifier-1 (SUMO-1) (Minty et al., 2000; Moll and Slade, 2004). Conjugation to SUMO-1 has been shown to affect p53 transcriptional activity but does not appear to influence p53 stability (Fig. 2) (Gostissa et al., 1999; Irwin and Kaelin, 2001; Rodriguez et al., 2001). Nevertheless, modification of p73α by SUMO-1 has been reported to alter p73 subcellular localization and increased the rate of p73 degradation. On the other hand, the novel Hect domain containing NEDD4-like E3 ubiquitin ligase, NEDL2, binds to p73 via its PY motif in the C-terminal region (Miyazaki et al., 2003). p53, which lacks the PY motif, does not bind to NEDL2. Overexpression of NEDL2 results in the ubiquitination of p73. However, rather than mediating degradation, ubiquitination by NEDL2 enhances the stability of p73 and its ability to transactivate p53/p73-responsive

promoters (Fig. 2). The differential binding of NEDL2 to p53 family members is thus another factor that might contribute to their functional divergence. Likewise, the NAD(P)H:quinone oxidoreductase-1 (NQO1) stabilizes p73α (as well as p53) but not p73β by binding to the SAM domain of p73α and protect p73α from 20S proteasomal degradation.. This NQO1-mediated stabilization of p73α and p53 might explan why NQO1 knockout mice and human with inactive NQO1 polymorphisms are susceptible to cancer (Asher et al., 2002; Moll and Slade, 2004).

5.3 Regulation of p53 family protein transcriptional activity

The ankyrin-rich, Src holomogy 3 domain, proline-rich proteins, ASPP1 and ASPP2, stimulate the apoptotic function of p53, p63, and p73 (Bergamaschi et al., 2004; Samuels-Lev et al., 2001). By binding to the DBD of p53, p63, and p73, ASPP1 and ASPP2 stimulate the transactivation function of all three proteins on the promoters of *BAX*, *PIG3*, and *PUMA* but not *MDM2* or *p21^{WAF-1/CIP1}*. Hence, ASPP1 and ASPP2 are the first two identified common activators of all p53 family members.

The transcriptional coactivator Yes-associated protein (YAP) has also been shown to potentiate TAp73-mediated transactivation of BAX after DNA damage. Conversely, Akt phosphorylates YAP, which induces interaction with 14-3-3, relocation of YAP to the cytoplasm, and attenuation of p73-mediated apoptosis (Basu et al., 2003; Moll and Slade, 2004).

5.4 DNA damage response and postranslational modification

p53 stabilization and activation by genotoxic stress is associated with multiple post-translational modifications at the N- and C-termini of p53. Under genotoxic stress, activation of stress kinases such ATM, ATR, and Chk2 lead to phosphorylation of p53 at multiple residues at Ser15, Ser20, Ser33, Ser37, Ser46, Thr18, Thr81, Ser315 and Ser392 to stabilize the protein by interfering with MDM2 binding (Fig. 2). In addition, acetylation at Lys320, Lys373, and Lys382, and sumoylation at Lys386 have also been reported to activate the transcriptional activity of p53 (Appella, 2001).

p73 is also activated for apoptosis in response to various genotoxix agents including cisplatin, taxol, and γ-irradiation. The activation of p73 is highly dependent on the non-receptor tyrosine kinase c-abl (Agami et al., 1999; Gong et al., 1999; Moll and Slade, 2004; Yuan et al., 1999). In response to γ-irradiation and cisplatin, TAp73 undergoes phosphorylation at Tyr99 by c-abl (Fig. 2). This, in turn, lead to the stabilization of the protein and dissociation of TAp73 from the TAp73/ΔNp63 inhibitory complex followed by apoptosis (Agami et al., 1999; Leong et al., 2007; Tsai and Yuan, 2003; Yuan et al., 1999).

The activation and phosphorylation of p73 is mainly through the direct interaction between the PXXP motifs of p73 and the Src homology 3 domain of c-abl (Moll and Slade, 2004). Because c-abl is itself phosphorylated and activated by the ATM, ATM may also be involved in the pathway leading to c-abl-dependent p73 activation (Shaul, 2000). These findings suggest that p73 might participate in a mismatch-repair signaling pathway. Recent microarray gene expression profiles further support a role for p73 in response to and repair of DNA damage (Vikhanskaya et al., 2001). In addition to cisplatin, Taxol also increases p73 accumulation, but UV irradiation, actinomycin D, and methylmethane sulfonate do not (Irwin and Kaelin, 2001; Levrero et al., 1999). As p63 does not have the PXXP motifs, it is unlikely that c-abl will phosphorylate p63 (Moll and Slade, 2004).

In addition to c-abl, p73 proteins may also be regulated by cyclin-CDK complexes and play a role in the regulation of cell cycle. p73 physically interacts with various cyclins and certain cyclin-CDK complexes including cyclin A-CDK1/2, cyclin B-CDK1/ 2, and cyclin E-CDK2, which can phosphorylate various p73 isoforms in vitro at Thr86. This cell cycle–dependent phosphorylation inhibits p73 to induce endogenous p21 expression (Gaiddon et al., 2003). p73 is a physiologic target of the cyclin B-CDK1 mitotic kinase complex in vivo, which results in a decreased ability of p73 to bind DNA and activate transcription in mitotic cells. Thus, both p73α and p73β isoforms have been shown to be hyperphosphorylated in normal mitotic cells (Fulco et al., 2003).

DNA damage also induces acetylation of p73 at Lys321, Lys327, and Lys331 by the acetyltransferase p300/cAMP-responsive element binding protein. Non-acetylated p73 is defective in inducing proapoptotic genes such as p53AIP1 but retains the ability to activate other target genes such as p21. This indicates that DNA damage-dependent p73 acetylation, like in p53, potentiates the apoptotic function of p73 by selectively increasing its ability to induce the transcription of proapoptotic target genes (Costanzo et al., 2002; Moll and Slade, 2004).

Finally, the mammalian target of rapamycin (mTOR) was recently identified as a negative regulator of p73 (Fig. 2). Notably, pharmacologic inhibition of mTOR in primary human mammary epithelial cells resulted in differential regulation of p53 family members (Rosenbluth et al., 2008). Cells exhibited selective up-regulation of TAp73, whereas ΔNp63 and p53 levels were both decreased. Interestingly, inhibition of mTOR by rapamycin synergizes cisplatin sensitivity in breast cancer cells through upregulation of TAp73 (Wong et al., 2010). Since mTOR is a master regulator of energy homeostasis and cell growth, and is often active in tumors (Guertin and Sabatini, 2007), this suggests that mTOR may inhibit TAp73 in tumors. In general, cancer cells may use upstream kinases or cofactors to inhibit p53 family members in different cellular contexts, ultimately maintaining proliferation and survival (Rosenbluth and Pietenpol, 2008).

6. The p53 pathway as a network

The significance interplay between p53 family and their isoforms in tumor is demonstrated by the fact that p53 cannot induce apoptosis in response to DNA damage, without the presence of p63 and p73 (Flores et al., 2002). Various mechanisms by which p53/p63/p73 proteins and their isoforms determine the cell fate through formation of transdominant heterocomplex, promoter competition and autoregulatory feedback loop have been proposed. These mechanisms are likely to play an important role in the transition between normal cell cycling and the onset of tumor formation.

6.1 Homotypic and heterotypic interactions among p53 family members

Physical interaction between oncogenic and antioncogenic p53 family members have been demonstrated to interfere with the tumor suppressor functions of wild-type p53 and TAp73 (Nakagawa et al., 2002; Stiewe et al., 2003; Stiewe et al., 2002a; Zaika et al., 2002). Mixed protein complexes were found between endogenous ΔNp73α or ΔNp73β on the one hand and either wild-type p53, TAp73α, or TAp73β on the other hand in primary human tumors, cultured human tumor cells, and mouse neurons (Moll and Slade, 2004). In human head and neck suqamous cell carcinoma and triple-negative breast cancer, endogenous ΔNp63 was shown to physically interact with TAp73 and suppresses TAp73 tumor suppressor activities (Fig. 2) (Leong et al., 2007; Rocco et al., 2006).

In addition, physical interactions between certain human p53 mutants and TAp73 or TAp63 proteins have been reported in coimmunoprecipitation assays, and these interactions correlate with functional transdominance. In contrast, complexes between wild-type p53 and p73 are not observed in mammalian cells (Di Como et al., 1999; Marin et al., 2000; Pozniak et al., 2000; Vikhanskaya et al., 2000). Unexpectedly, protein contact occurs between the DBD of mutant p53 and the DBD and oligomerization domain of p73 rather than between the respective oligomerization domains (Davison et al., 1999; Gaiddon et al., 2001; Strano et al., 2000; Vikhanskaya et al., 2000). In cotransfection experiments, mixed heterocomplexes were shown between p53 mutants p53Ala143, p53Leu173, p53His175, p53Cys220, p53Trp248, or p53Gly281 and TAp73α, TAp73γ, TAp73δ and TAp63 (Di Como et al., 1999; Gaiddon et al., 2001; Marin et al., 2000; Strano et al., 2000). Physiologic complexes were found in five tumor cell lines between endogenous mutant p53 and p73 (Marin et al., 2000; Strano et al., 2000). Functionally, formation of such stable complexes leads to a loss of p73- and p63-mediated transactivation and proapoptotic abilities. Moreover, E2F1-induced p73 transactivation, apoptosis, and colony suppression was inhibited by coexpressed p53His175 (Stiewe and Putzer, 2000). Interestingly, the Arg/Pro polymorphism at codon 72 of mutant p53 is a biological determinant for binding and inactivation of p73, with 72R mutants of p53 being inhibitory, whereas 72P mutants are not (Fig. 2) (Bergamaschi et al., 2003; Marin et al., 2000; Moll and Slade, 2004).

This functional inhibition of TAp73 or TAp63 by some p53 mutants mirrors the ability of many transdominant missense p53 mutants to abrogate wild-type p53 function (Kern et al., 1992; Unger et al., 1992). It suggests that in tumors that express both TAp73 and mutant p53 (typically at very high levels due to deficient MDM2-mediated degradation), the function of TAp73 and TAp63 might be inactivated. If this occurs in primary human tumors, it might have far-reaching consequences because (a) it argues for a transdominant inhibition of the tumor suppressor function of TAp73 isoforms during tumor development, (b) it could be the underlying mechanism for the gain-of-function activity of certain p53 mutants, and (c) it might further increase chemoresistance in cancer therapy of established tumors.

p53 is exceptional among tumor suppressors in that it selects for the overexpression of missense mutants rather than for loss of expression as most other suppressor genes do. This gain-of function increased tumorigenicity compared with p53-null parental cells, increased resistance to cancer agents, and increased genomic instability due to abrogation of the mitotic spindle checkpoint (Dittmer et al., 1993; Halevy et al., 1990; Shaulsky et al., 1991). Conceivably, p63 might also participates in this network. A recent study shown that mutant p53His273 is required for survival of breast cancer cells as knock-down of endogenous mutant p53His273 in breast cancer cells induces massive apoptosis. Surprisingly, the survival effects of p53His273 is independent of TAp73 or TAp63 function as depletion of both isoforms did not rescue the cells from apoptosis following p53His273 knock-down (Lim et al., 2009). Therefore, it is important to note that not all p53 mutants have transdominant effects against TAp73 or TAp63. Some p53 mutants are clearly recessive toward TAp73 (e.g., p53His283, p53Tyr277 and p53His273) and do not interfere with its action (Gaiddon et al., 2001; Lim et al., 2009; Moll and Slade, 2004).

6.2 Promoter competition

Promoter competition by ΔNp73 and ΔNp63 at TAp73/p53 response elements has been reported previously (Kartasheva et al., 2002; Rocco et al., 2006; Stiewe et al., 2002a). It is conceivable that ΔNp73 or ΔNp63 homo-oligomers might have a stronger affinity to certain

target gene promoters than wild-type p53 or TAp73. In those cases, p53 or TAp73 inhibition could occur due to competition at the level of target gene access. In the wild-type p53-containing ovarian carcinoma cell line A2780, coexpression of increasing amounts of either TAp73α, TAp73β, TAp73γ, or TAp73ε inhibits specific DNA binding and transcriptional activity of p53 in the absence of hetero-oligomer formation (Moll and Slade, 2004; Ueda et al., 1999; Vikhanskaya et al., 2000). These results suggest that promoter competition could be another mechanism for transdominance between p53 family proteins.

6.3 Autoregulatory feedback loop among p53, TAp73, and ΔNp73

p53 and TAp73 regulate ΔNp73 but not ΔNp63 levels by binding to the p73 P2 promoter and inducing its transcription (Fig. 2). A p73-specific responsive element was mapped within the P2 region (Nakagawa et al., 2002). This generates a negative feedback loop analogous negatively regulates the activity of p53 and p73 (Grob et al., 2001; Kartasheva et al., 2002; Nakagawa et al., 2002; Vossio et al., 2002). As mentioned earlier, ΔNp73 blocks p53 and TAp73 activity through heterocomplex formation (Nakagawa et al., 2002; Stiewe et al., 2002a; Zaika et al., 2002) or through promoter competition (Kartasheva et al., 2002; Stiewe et al., 2002a) and thus contributes to the termination of the p53/p73 response in cells. In contrast to ΔNp73, ΔNp63 expression is transcriptionally repressed by p53 (Moll and Slade, 2004; Waltermann et al., 2003).

7. Targeting the p53 family for treatment of breast cancers

As described above, activation of wild-type TAp73 (or TAp63) lead to cell death in cancer cells. This hypothesis is intriguing given the fact that p73 and p63 are rarely mutated in cancer. Instead, overexpression of TAp73 has been reported in many tumor types including breast cancers and head and neck squamous carcinoma (Leong et al., 2007; Rocco et al., 2006). As such, selective activaton of TAp73 (or TAp63) might induce tumor specific cell death. In principle, activation of the p53 family tumor suppressive pathways might be achieved in several ways (Kaelin, 1999).

First, induction and activation of TAp73 have been reported in response to wide variety of chemotherapeutic agents including Adriamycin, cisplatin, taxol, and etoposide in different tumor cell lines (Bergamaschi et al., 2003; Irwin et al., 2003; Moll and Slade, 2004). In particular, cisplatin treatment has been shown to induce c-abl dependent phosphorylation of TAp73 and lead to its dissociation from the TAp73/ΔNp63 inhibitory complex in head and neck squamous cell carcinoma and breast cancer cells (Fig. 2) (Leong et al., 2007; Rocco et al., 2006). Similarly, a recent clinical study also shown that cells that co-overexpressed TAp73 and ΔNp63 is more likely to response to cisplatin compare to tumors that have no TAp73 expression. These results suggest that certain chemotherapeutic agents can activate TAp73 even in the presence of high level of ΔN isoforms.

Second, a more detailed understanding of the upstream signals that impinge upon p73 and p63 might allow for the design of drugs that would activate the transcription of these genes or stabilize their protein products. For example, the mammalian target of rapamycin (mTOR) was recently identified as a negative regulator of p73 (Rosenbluth et al., 2008). Inhibition of mTOR in primary human mammary epithelial cells selectively up-regulate TAp73 (Rosenbluth et al., 2008; Rosenbluth and Pietenpol, 2008). Combination of cisplatin and mTOR inhibitor, rapamycin, has also been shown to synergizes cisplatin sensitivity in basal-like breast cancer cells through up-regulation of TAp73 recently (Fig. 2) (Wong et al.,

2010). Of note, a phase II neo-adjuvant clinical trial of cisplatin and mTOR inhibitor, everolimus, in patients with triple-negative breast cancer has recently opened for recruitment (ClinicalTrials.gov Identifier: NCT00930930) and will be able to directly address whether targeting these pathways will increase the sensitivity of tumors towards cisplatin chemotherapy.

Finally, it might be possible to design or discover drugs that block the interaction of mutant p53 with p73 or intreraction of MDM2 with p73 which has been shown to inhibit p73 transcription activity (Kaelin, 1999). In theory, molecules already in development that block the interaction of MDM2 with p53 or molecules that restore mutant p53 function might also function in this setting. For example, PRIMA-1, CP-31398 and MIRA-1 are molecules that have been shown to restore wild-type conformation and transcriptional transactivation to mutant p53 (Fig. 2) (Wiman, 2006). Similarly, MDM2 inhibitor such as Nutlins, might interfere MDM2-p73 binding and hence restore the tumor suppressor function of p73 (Ambrosini et al., 2007; Shangary and Wang, 2008). Whether these molecules will selectively activate TAp73 remain to be investigated.

8. Concluding remarks

In concludion, studies of the newly identified p53 family members, p63 and p73, have revealed several structural and functional similarities. The p53 transactivation, DNA binding, and oligomerization domains are highly conserved among all family members. Like p53, p63 and p73 can form oligomers, bind DNA, and transactivate the promoters of a subset of p53 target genes and induce apoptosis. In addition, certain cellular and viral proteins known to bind and regulate p53 activity likewise can bind to p63 and p73.

Despite the fact that p63 and p73 mimic many p53 activities, more recent studies highlight significant differences between the family members. In contrast to *p53*, *p63* and *p73* give rise to multiple functionally distinct protein isoforms due to alternative promoter utilization and alternative mRNA splicing. The ΔN isoforms, which lack the N-terminal transactivation domain, can function as "dominant-negative" proteins, blocking certain activities of the corresponding full-length proteins.

Differences in the upstream signaling pathways involved in activation of each of the family members are also becoming apparent. Only a subset of the DNA-damaging agents that induce p53 also induce p73. Many cellular and viral oncoproteins also discriminate between p53 and the newer family members. Finally, it is becoming apparent that *p63* and *p73* are not classical Knudson-type tumor suppressor genes. In particular, these genes are not frequently mutated in tumors, and germ-line mutations in these genes do not cause tumors in mice. Instead, mice with deletions in *p63* and *p73* have significant developmental abnormalities.

Despite the significant advances in understanding the unique roles of p53, p63 and p73, there are still several outstanding questions. Understanding the complexity of p53 family members interactions may allow us to to delineate the function of the p53 family network in human tumorigenesis and facilitate the development of anticancer therapeutics that seek to induce the activation of "p53-responsive" genes in cells lacking wild-type p53.

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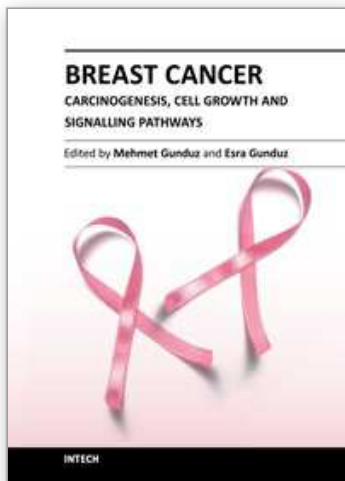
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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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