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Review

The diverse oncogenic and tumour suppressor roles of p63 and p73 in cancer: a review by cancer site

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Summary. p63 and p73, the two other members of the p53 family, were identified almost 15 years ago. Here, we review their potential use for diagnosis, prognosis and prediction of response to therapy in various cancers. The two genes show distinct expression patterns in both normal and cancer tissues and each gene gives rise to multiple protein isoforms with different activities, including those with tumour-suppressor or oncogenic effects. Despite such complexity, some common themes emerge; p63 is commonly overexpressed as the ΔNp63 isoform and sometimes associated with *TP63* amplification, whereas p73 is often reduced (by methylation or gene loss), or there is an increase in the ratio of ΔNp73 to TAp73. These generalisations do not apply universally; TAp63 is overexpressed in haematological malignancies, *TP63* mis-sense mutations have been reported in squamous cancers and *TP63* translocations occur in lymphomas and some lung adenocarcinomas. There are associations with disease prognosis and response to specific therapies in individual cancer types for both p63 and p73, making their analysis of clinical relevance. We also discuss their utility for aiding in differential diagnosis, which has been demonstrated for p63, but not yet for p73. Throughout, we highlight the discrepant nature of many studies due to the variable methodologies employed, the lack of systematic evaluation of isoforms and the problems of poor antibody characterization and cross-reactions within the p63/p73 family. Finally, we emphasize the value of recently developed isoform-specific reagents that have clear advantages for the study of p63 and p73 experimentally and clinically.

Key words: p53, p63, p73, Cancer, Tumorigenesis

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Introduction

The p53 family includes three cognate proteins, p53, p63 and p73 which evolved from a common ancestor (Belyi et al., 2010). They all function as transcription factors and share the same domain organisation of an N-terminal transactivation (TA) domain, a DNA binding domain and a C-terminal tetramerization domain. The *TP63* and *TP73* genes encode several distinct protein isoforms that differ in both their C- and N-termini. We can distinguish full-length isoforms (TAp63 and TAp73) and ΔN isoforms which lack the N-terminal transactivation domain due to the use of alternative promoters. Alternative splicing of the 5'end p73 produces two more isoforms (ΔTA), which partially lack the transactivation domain (ΔEx2/3p73). Moreover, alternative splicing at the 3'-end of the transcripts produces the C-terminal isoforms p73α, β, γ, δ, ε and p63α, β, γ, δ (Deyoung and Ellisen, 2007; Nekulova et al., 2011; Costanzo et al., 2014) (Fig. 1).

The p53 protein has been called the "guardian of the genome" and terminates cell proliferation or induces cell death in response to DNA damage or other stresses.

Inactivating mutations or loss of TP53 result in tumour development (Levine and Oren, 2009). Despite homology with p53, p63 and p73 play essential roles in epidermal and neuronal development, respectively (Nekulova et al., 2011; Rufini et al., 2011) and deciphering their relevance in tumourigenesis is complex due to the existence of N-terminal isoforms that have opposing functions (TA versus ΔN), C-terminal isoforms that have different levels of transcriptional activity or even have different transcriptional targets (Ghioni et al., 2002; Holcakova et al., 2008; Boldrup et al., 2009; Logotheti et al., 2013). In addition, unlike the ubiquitous expression of p53, p73 and p63 isoforms have unique expression profiles in different tissues and cancers (Nylander et al., 2002; Nenutil et al., 2003; Nekulova et al., 2013). Thus, comprehending the roles of p63 and p73 in an individual cancer requires a careful examination of the precise isoforms that are being expressed. Although this is often achieved by the use of isoform-specific RT-PCR methods, these are likely to be misleading under many circumstances since, like p53, p63 and p73 are controlled by protein stabilization/degradation pathways and post-translational modifications. Therefore, development of isoform-specific antibodies (Nylander et al., 2002; Nenutil et al., 2003; Rosenbluth et al., 2009; Karni-Schmidt et al., 2011; Romano et al., 2012; Nekulova et al., 2013; Veselska et al., 2013; Tacha et al., 2014) and reagents for specific post-translational modifications will be needed to gain a more complete picture of the roles of p63 and p73 in human cancers. Bearing these caveats in mind, this review provides a basic insight into the roles of these two transcription factors in human cancers. We have also reviewed publicly available expression profiling, mutation and copy number variation data for these genes to provide an overview of their impact in different cancer types.

p73 and p63 – characteristic features

TAp73 and TAp63 are considered tumour suppressors due to their p53-like abilities to induce cell cycle arrest and apoptosis. On the other hand, ΔNp63/p73 isoforms form heterotetramers and/or compete for promoter binding with TA isoforms and with p53, and therefore function as oncoproteins. In addition, p53 and TAp73 induce expression of ΔNp73 and thus control p53/p73 activity by an autoregulatory feedback loop (Rufini et al., 2011). Initial studies showed that p73 and p63 knockout mice are not tumour prone, but revealed key roles for p73 in the development and maintenance of the central nervous system (Yang et al., 2000) and for p63 in limb and skin development with failure of development of mammary and prostate

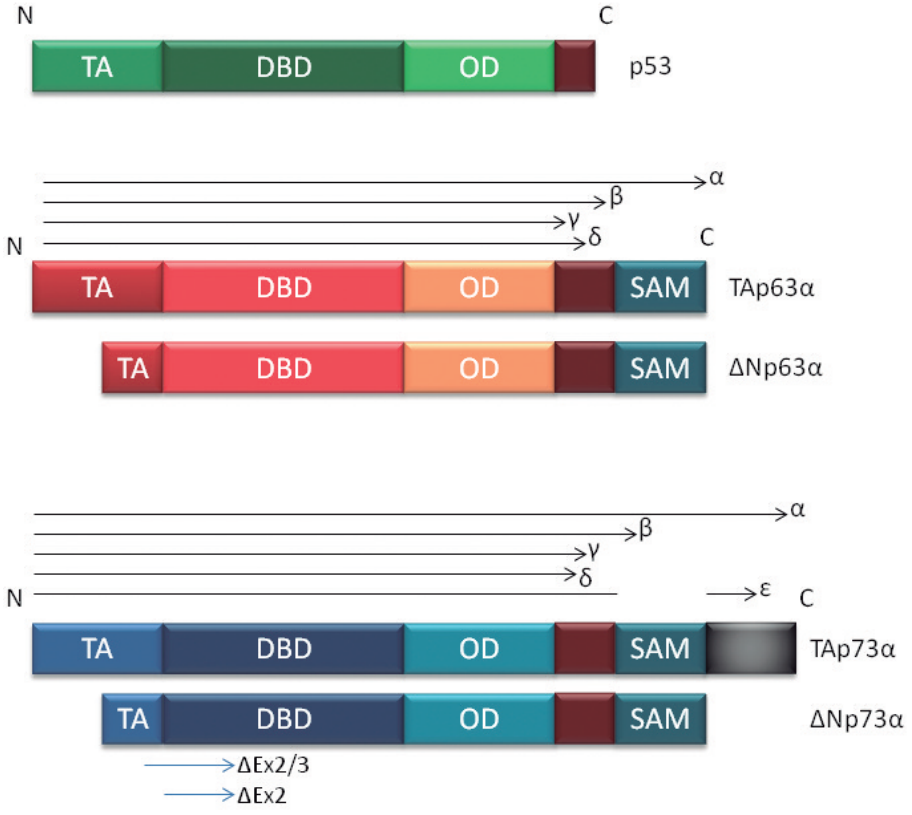

Fig. 1. Schematic structure of p53, p63 and p73 proteins. Depending on the promoter there are two distinct N-terminal isoforms: TA – full-length and ΔN – N-terminally truncated. Due to 5' alternative splicing, p73 has two more isoforms (ΔTA), which partially lack the transactivation domain (ΔEx2/3p73). Alternative splicing at the 3'-end produces different C-terminal p63/p73 isoforms. p53, p63 and p73 proteins comprise DNA binding domain (DBD), oligomerization domain (OD) and N-terminal transactivation (TA) domain (only TA isoforms), α isoforms possess a sterile alpha motif (SAM).

epithelia; inherited *TP63* mutations cause similar developmental abnormalities in humans (Mills et al., 1999; Yang et al., 1999; Rinne et al., 2007). The notion of an overall tumour suppressive function of p73 was supported by heterozygous (p73 +/-) mice – 50% developed malignant tumours by 15 months of age with increased incidence of benign lesions. Moreover, the remaining wild-type p73 allele was lost in these tumours (Flores et al., 2005). Finally Tomasini et al. deleted exons that encode the transactivation domain so that ΔNp73 isoforms were still expressed. Developmental defects were less severe but spontaneous tumour incidence increased, confirming a tumour suppressor role of TAp73 (Tomasini et al., 2008). Similarly, specific TAp63 knockout mice are tumour prone, with an apparent role for TAp63 in reducing metastasis (Su et al., 2013).

In human cancers, the *TP73* gene is often lost, notably breast, colon and kidney whilst other tumours show equal numbers of gain and loss; inactivating mutations of *TP73* are remarkably rare (Melino et al., 2002) (Figs. 2, 3; COSMIC database (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/) (Bamford et al., 2004). Whether *TP73* is the "gene of interest" of copy number changes is not clear from these data, but mRNA expression data (https://www.oncomine.org/resource/main.html; accessed October 2014) reveals that *TP73* mRNA levels are not altered in cancer compared to corresponding normal tissues (Table 1). Similarly, *TP63* mutations are very rare, but amplification is observed in many cancer types (Figs. 2, 4), adding to the original observations in squamous lung cancers (Hibi et al., 2000; Massion et al., 2003). Moreover, Oncomine data reveal a large number of tumour types with altered expression of *TP63* (Table 1) although the specific isoforms involved are not clear. Below, we summarise the evidence for the roles of p63 and p73 in the common human malignancies.

Gastrointestinal cancers

Oesophageal cancer

There are two main cancer types in the oesophagus with different pathogenesis; squamous cell carcinomas (SCC) and adenocarcinomas. According to the most

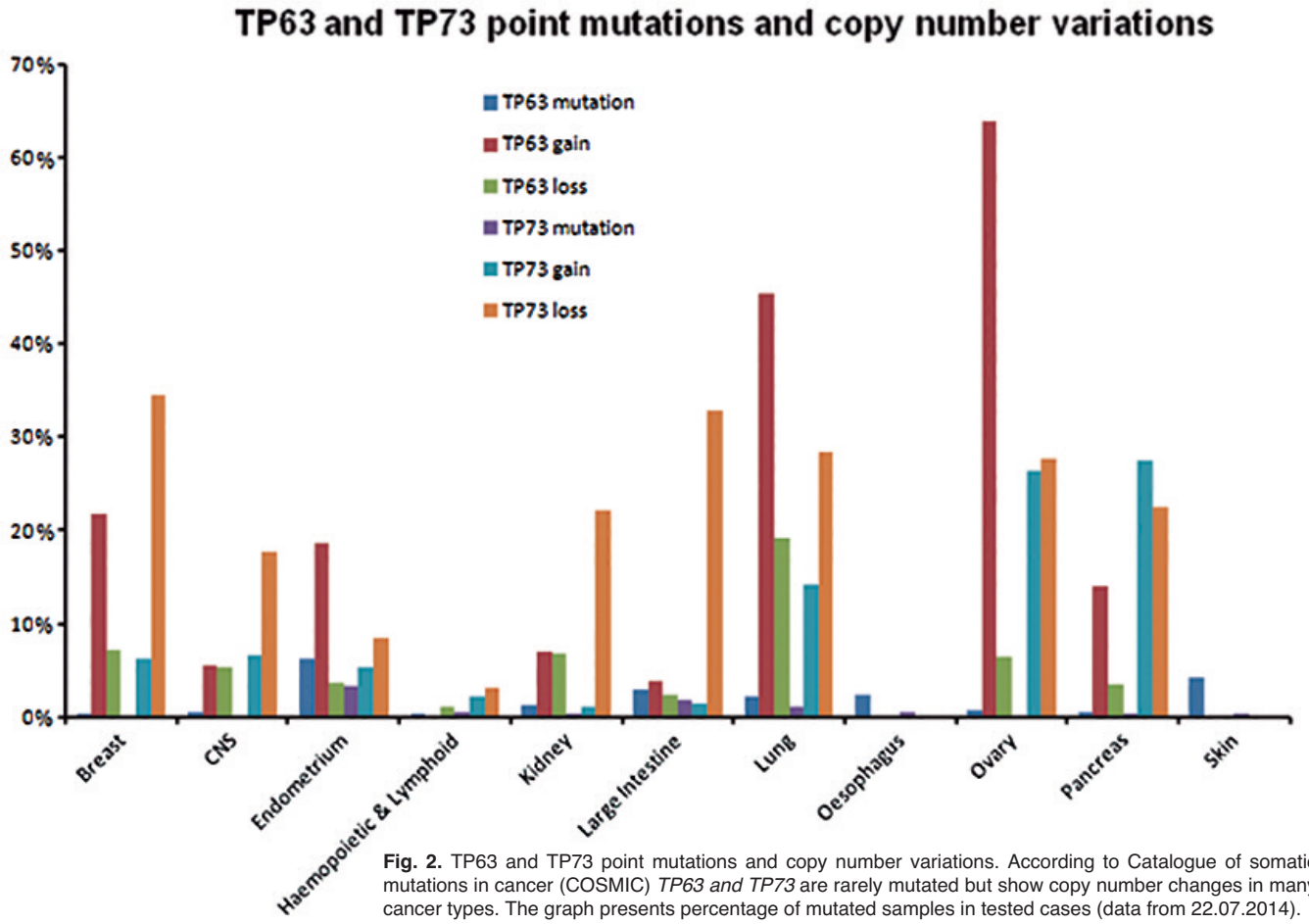

Fig. 2. TP63 and TP73 point mutations and copy number variations. According to Catalogue of somatic mutations in cancer (COSMIC) *TP63 and TP73* are rarely mutated but show copy number changes in many cancer types. The graph presents percentage of mutated samples in tested cases (data from 22.07.2014).

recent data *TP63* is not mutated or commonly amplified (Gao et al., 2014; Lin et al., 2014; Song et al., 2014) but ΔNp63 is overexpressed in oesophageal SCC but not in adenocarcinomas, making p63 a useful marker of squamous vs adenocarcinoma (Cao et al., 2009; DiMaio et al., 2012). Both TAp73 and ΔNp73 isoforms are frequently overexpressed in oesophageal adenocarcinoma (Tomkova et al., 2004), correlating with the presence of distant metastases (Ye et al., 2012). Direct exposure of oesophageal cells to bile acids in an acidic environment alters ΔNp73 phosphorylation and increases protein levels, suggesting that gastro-esophageal reflux could facilitate tumourigenic transformation of esophageal metaplastic epithelium by alteration of ΔNp73 (Zaika et al., 2013).

Gastric cancer

Gastric cancer is associated with *Helicobacter pylori* or Epstein–Barr virus (EBV) infections. There is limited evidence for a role of p63 in gastric cancer, with one report suggesting that increased ΔNp63α mediates cell proliferation and survival (Wang et al., 2012a). ΔNp73 is frequently overexpressed, possibly due to HIC-1 and/or TAp73 loss (Vilgelm et al., 2010), or interaction with *H. pylori* (Wei et al., 2008). In contrast, loss of *TP73* expression by methylation occurs in EBV-associated disease (Ushiku et al., 2007; Okada et al., 2013). Thus, p73 alteration is common in gastric cancer and is related to the different infectious agents.

Table 1. Summary of differential expression of TP63 and TP73 in human cancers versus corresponding normal tissues.

Cancer Type	TP63		TP73	
Bladder	2			
Brain/CNS				
Breast	1	12		
Cervical				
Colorectal		1		
Esophageal	1	2		
Gastric				
Head & Neck	3			
Kidney		2		
Leukaemia	4			
Liver				
Lung	4			
Lymphoma	4			
Melanoma	1	2		1
Myeloma		1		
Other				
Ovarian				
Pancreatic				
Prostate		6		
Sarcoma				

Data from Oncomine using default threshold values of p-value < 0.0001; Fold change >2.0; Rank Top 10%. Red shaded boxes indicate overexpression; blue shading indicates underexpression

Pancreatic cancer

Ductal adenocarcinomas of pancreas are generally aggressive, therapy resistant and have dismal prognosis. Nearly all of these cancers contain a mutant Ras protein. ΔNp63α is the predominantly expressed p63 variant in pancreatic cancer cell lines, promoting epidermal growth factor receptor (EGFR) anchorage-dependent and independent growth, motility and invasion chemoresistance (Danilov et al., 2011). p73 may play a role in apoptosis induced by mutant K-Ras by upregulation of the proapoptotic factor PUMA (Shen et al., 2012), suggesting a tumour-suppressive role. In clinical material, p63 expression was observed in 68.2% of adenocarcinomas but with no relation to clinicopathological features, and p73 was observed in 45.6% of pancreatic adenocarcinomas, inversely linked to lymph node metastasis, tumour size and proliferation (Ito et al., 2001). In contrast, other studies failed to identify p63 (Brody et al., 2009) or ΔNp63 (Basturk et al., 2005) in normal pancreatic ducts, pancreatic intraepithelial neoplasia or ordinary ductal adenocarcinomas, except in areas showing squamous differentiation, and p63 may act as a marker of squamous differentiation in pancreatic cancers.

Liver cancer

p63 is diffusely expressed in cholangiocarcinomas (derived from bile duct epithelium) while hepatocellular carcinomas do not express p63, making p63 useful in the differential diagnosis (Ramalho et al., 2006). Upregulation of ΔNp73 in hepatocellular carcinoma correlates with reduced survival and ΔNp73β negatively regulates genes encoding the death receptors CD95, TNF-R1, TRAIL-R2 and TNFRSF18, represses genes encoding caspase-2, -3, -6, -8 and -9 and inhibits

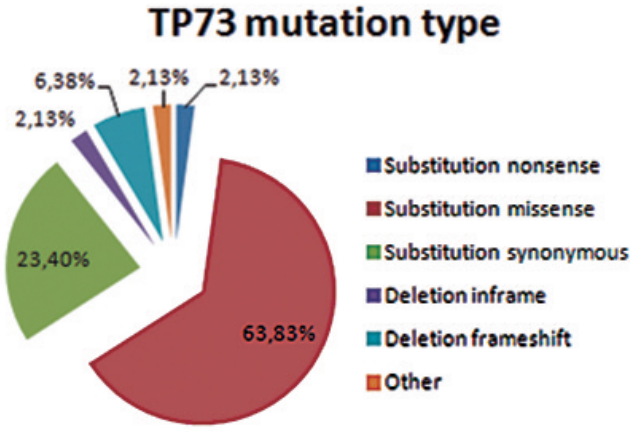

Fig. 3. TP73 mutation type. Reffering to COSMIC database, the prevailing mutations of *TP73* are substitution missense mutations with some synonymous and nonsense mutations.

apoptosis (Muller et al., 2005; Schuster et al., 2010). Thus, p63 is involved in cholangiocarcinoma but not hepatocellular carcinoma, whilst the functional status of TAp73/ΔNp73 is an important determinant of the cellular response to chemotherapeutic drugs in hepatocellular carcinoma.

Small intestine, colorectal and anal cancers

Although there are some reports of p63 expression in colorectal neoplasms associating with good or bad prognosis (Carneiro et al., 2006; Guo et al., 2012), others report that p63 is not expressed in normal small intestine or colon or in adenocarcinomas, but can distinguish anal squamous *versus* adenocarcinomas (Glickman et al., 2001; Di Como et al., 2002; Reis-Filho et al., 2003b; Owens and Greenson, 2007). The situation is clearer for p73, which is expressed in normal colon (Puig et al., 2003) and expression levels of ΔTAp73 or ΔNp73 are increased in colorectal cancers, correlating with advanced stage, decreased overall survival and drug resistance (Dominguez et al., 2006a,b; Soldevilla et al., 2011).

Haematological malignancies

Initial observations indicated that p63 is expressed in a sub-population of normal lymphocytes and in some B-cell lymphomas (Di Como et al., 2002; Nylander et al., 2002), whereas p73 is not expressed in normal lymphocytes (Puig et al., 2003). p63 is overexpressed at mRNA level (Table 1) and by immunohistochemistry in 32-53% of diffuse large B-cell lymphoma (DLBCL), 22-54% of follicular lymphoma (FL), 17% natural killer/T cell lymphoma (NK/TCL), 44% anaplastic large cell lymphoma, 25% marginal zone lymphoma and 13% T-lymphoblastic lymphoma (Di Como et al., 2002; Chilosi et al., 2003; Hedvat et al., 2005; Park and Oh, 2005; Fukushima et al., 2006; Gualco et al., 2008). Opposite to solid tumours, TAp63 is the dominant isoform in haematological malignancies (Yamaguchi et al., 2001; Nylander et al., 2002; Chilosi et al., 2003; Hedvat et al., 2005; Pruneri et al., 2005; Fukushima et al., 2006). It is therefore counter-intuitive that p63 expression correlates to higher grade of disease and poor survival in FL (Di Como et al., 2002; Pruneri et al., 2005; Fukushima et al., 2006) and to increased tumour proliferation in DLBCL (Hedvat et al., 2005), suggesting an oncogenic role for TAp63. Increased TAp63 expression is not related to *TP63* amplification (Pruneri et al., 2005) but may relate to observations that BCR signalling can reduce p63 expression (Humphries et al., 2013) whilst CD40 signalling induces TAp63 (Lewis et al., 2011). Recurrent translocations that cause expression of a truncated p63 protein have recently been reported in both B- and T-cell lymphomas and ALK-negative ALCL (Scott et al., 2012; Vasmatzis et al., 2012; Morin et al., 2013; Parrilla Castellar et al., 2014), the significance of which is unclear. Thus, p63 is a diagnostic tool to distinguish between anaplastic large cell lymphomas (44% positivity) and classical Hodgkin lymphoma (p63 negative) and may be a predictive biomarker for tumours with an intrinsically active CD40 pathway, indicative of resistance to anti-CD40 therapy (Burington et al., 2011).

P1 promoter methylation is the most common p73 defect in leukaemias and lymphomas and is accompanied by loss of TAp73 expression associated with relapse and poor prognosis (Corn et al., 1999; Kawano et al., 1999; Herranz et al., 2000; Garcia-Manero et al., 2002a,b; Siu et al., 2002; Gutierrez et al., 2003; Kaneko et al., 2003; Bueso-Ramos et al., 2005; Sahu and Das, 2005; van Doorn et al., 2005; Meier et al., 2006; Kondo et al., 2009). These observations indicate a widespread role for p73 as a tumour suppressor with prognostic value in haematopoietic cells and therapeutic approaches to restore p73 expression are ongoing (reviewed in (Alexandrova and Moll, 2012)). *TP73* promoter methylation is not seen in chronic lymphocytic leukaemia (CLL) cells (Corn et al., 1999) where p73 is overexpressed with no difference in levels between full-length protein and truncated isoforms (Novak et al., 2001; Leupin et al., 2004). ΔNp73 has also been found in some lymphoid and myeloid malignancies (Zaika et al., 2002; Rufini et al., 2011) suggesting that p73 dysregulation may occur through multiple mechanisms.

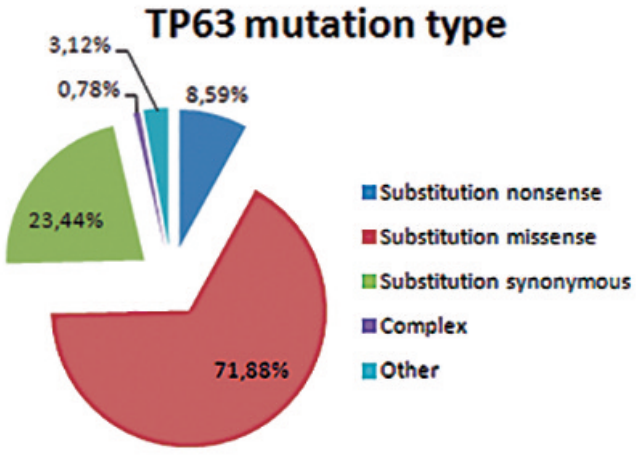

Fig. 4. TP63 mutation type. Similarly, *TP63* mutations are substitution missense mutations and many synonymous substitutions were found.

Breast cancer

P63 is essential for mammary gland development during embryogenesis. In normal adult breast, p63 and p73 are both expressed in myoepithelial cells (Barbareschi et al., 2001; Yamamoto et al., 2001). p63 (but not p73) is commonly used to distinguish invasive cancers from ductal carcinoma *in situ* and sclerosing

lesions (Lee, 2013) and is useful for distinguishing between papillomas and papillary lesions (Reisenbichler et al., 2011). High level p63 expression is seen in some metaplastic, triple-negative and basal-like tumours (Yamamoto et al., 2001; Reis-Filho et al., 2006), but roles for (ΔN)p63 in promoting cancer stem cell phenotypes and collective invasion of luminal type breast cancer have also been reported (Zucchi et al., 2008; Du et al., 2010; Kabos et al., 2011; Cheung et al., 2013; Yallowitz et al., 2014), contrasting with other reports that (TA)p63 acts as an important anti-metastatic factor in breast cancer (Adorno et al., 2009; Girardini et al., 2011; Montagner et al., 2012). Clearly, more detailed studies of TAp63 and ΔNp63 are warranted in breast cancer, although recent data indicate that TAp63 is a minor isoform and it is ΔNp63 that drives triple negative breast cancer (Chakrabarti et al., 2014).

p73 mutations are not seen in sporadic and hereditary breast cancer (Schwartz et al., 1999), but a common non-coding polymorphism of exon 2 of the *TP73* gene, G4C14-to-A4T14 (GC/AT), associates with breast cancer survival (Li et al., 2007). *TP73* methylation associates with high histological grade and high proliferation (Marzese et al., 2012) and is part of the methylation profile of triple-negative breast tumours (Branham et al., 2012). p73 expression in breast tumours has been studied mainly on mRNA level. Results are contradictory and some studies report decreased (Du et al., 2011) or increased (Zaika et al., 1999; Dominguez et al., 2001a,b, 2006a,b; Garcia et al., 2004) TP73 transcript levels. Expression of full-length TAp73 as well as N-terminally truncated ΔEx2p73, ΔEx2/3p73 and ΔNp73 isoform mRNAs have been found (Dominguez et al., 2006a).

p53 is often mutated in breast tumours, but the mutation frequency fluctuates between luminal tumours (26%) and basal tumours (88%) (Dumay et al., 2013). TAp73 may functionally replace p53 after treatment with chemotherapeutic agents (Vayssade et al., 2005; Sang et al., 2006; Tiwary et al., 2011) and inhibition of mTOR by rapamycin sensitised basal-like MDA-MB-468 cells to cisplatin treatment through the induction of p73 (Wong et al., 2011). Not only TAp73 expression but also the ΔNp63/TAp73 ratio seems to be important for chemosensitivity of breast tumour cells. ΔNp63 and TAp73 isoforms are coexpressed within a subset of triple-negative primary breast cancers that commonly exhibit mutational inactivation of p53. The ΔNp63α isoform promotes survival of breast cancer cells by binding TAp73 and thereby inhibiting its proapoptotic activity. Breast cancer cells expressing ΔNp63α and TAp73 uniquely exhibit cisplatin sensitivity dependent on TAp73 (Leong et al., 2007). In response to treatment with cisplatin, but not other chemotherapeutic agents, TAp73 undergoes c-Abl-dependent phosphorylation, which dissociates the ΔNp63α/TAp73 protein complex and induces TAp73-dependent transcription of proapoptotic Bcl-2 family members and apoptosis. These findings were confirmed *in vivo* when triple-negative tumours with high ΔNp63/TAp73 ratio were found to be more sensitive to cisplatin treatment (Silver et al., 2010). It was also shown that the sensitivity of triple negative breast cancer cells to combined PARP inhibitor/gemcitabine/cisplatin treatment is mediated by decreased p63 and increased p73-mediated apoptosis (Hastak et al., 2010). These findings define p63 and p73 as predictors of chemosensitivity in a subset of breast cancers.

Ovarian cancer

According to COSMIC data, 296/462 (64.1%) ovarian epithelial cancers (OEC) show gain of *TP63*, the highest incidence of *TP63* gain of any cancer studied (Fig. 2), of which 157 have five or more copies and 28 have eight or more copies. *TP63* amplification may be a consequence of proximity to other driver genes (Hagerstrand et al., 2013), but p63 de-regulation may also contribute to the cancer phenotype in those with amplification. The correlation of p63 expression with *TP63* copy number has not yet been studied. Immunohistochemistry for total p63 showed expression in 12.9% of serous and 25% of endometrioid carcinomas (Reis-Filho et al., 2003b), and the same group reported that 11.1% of these ovarian cancers express ΔNp63 (Reis-Filho et al., 2003a). p63 was higher in benign cystadenomas than borderline tumours, with a further drop in invasive tumours (Poli Neto et al., 2006). Similarly, p63 expression was reduced in borderline compared to benign tumours, was seen in only one of six malignant Brenner tumours and was absent in ovarian transitional cell carcinoma (Liao et al., 2007), so that p63 may be useful in distinguishing between different tumour types of ovary and in distinguishing from metastatic bladder carcinomas (Liao et al., 2007; Kalebi and Hale, 2008). p63 was not detected in high stage (III or IV) ovarian cancers prior to or following neoadjuvant chemotherapy (Miller et al., 2008) or in invasive micropapillary carcinomas of ovary (Lotan et al., 2009). Taken together, loss of p63 expression is associated with increased stage and biological aggressiveness in ovarian cancer. In contrast, another immunohistochemical study found p63 expression in 67.9% of advanced ovarian carcinomas, particularly serous type, with increasing expression with higher stage (Wang et al., 2004). Similarly, ΔNp63 mRNA increased 77-fold from stage I to III whilst TAp63 mRNA remained unchanged. Patients with particularly high ΔNp63/TAp63 mRNA ratios had the poorest overall survival and poor response to platinum based therapy (Marchini et al., 2008). Using Western blotting, ΔNp63α was detected at varying levels in 49/56 EOCs, with no relation to stage, grade or histological subtype, but patients with higher p63 were more likely to progress, had higher VEGF levels and low p63 was an independent prognostic indicator of progression free survival (Jewell et al., 2009). Regarding therapeutic response, ΔNp63α was shown to impart cisplatin resistance through AKT1 and cisplatin

treatment down-regulates ΔNp63α. Analysis of patient samples revealed a good correlation between ΔNp63α and AKT1 and of ΔNp63α with cisplatin resistance (Sen et al., 2011). These data contrast with a meta-analysis indicating favourable outcome of p63 expression (Trinh et al., 2011) and with our data from KM Plotter indicating significant associations of high p63 with both progression-free and overall survival in ovarian cancers treated with platin-based chemotherapy (Fig. 5). These latter observation are similar to those made in SCCHN and breast, where p63 expression indicates a good response to cisplatin (Zangen et al., 2005; Leong et al., 2007; Silver et al., 2010). These discrepancies highlight many of the problems in the p63 field, where different methodologies are employed, ratios rather than absolute values are reported and the cut-offs used to identify "positive" samples are highly variable – for example two thirds of p63-positive samples in one study contained less than 10% positive tumour cells, with only one of 109 samples showing more than 50% positive cells (Wang et al., 2004).

Unlike *TP63,* the *TP73* gene shows gain and loss in equal proportions of ovarian cancers (Fig. 2), in keeping with a lack of functional *TP73* inactivation (Imyanitov et al., 1999). In addition, *TP73* mRNA expression does not associate with progression free survival in platin-treated ovarian cancer. On the other hand, a splice variant lacking exon 2 and producing a truncated p73 protein lacking the N-terminal TA domain was first identified in ovarian cancer tissues (Ng et al., 2000). Overexpression of dominant-negative ΔN'p73 mRNA is seen in 95% of ovarian cancers compared to normal ovary (Concin et al., 2004) and one-third of these cancers also show TAp73 up-regulation. Expression of ΔNp73 correlates with chemotherapeutic failure in ovarian carcinoma with mutated p53, and eight different p53 mutations were found to bind and inhibit TAp73 and provide a poorer outcome compared to p53 mutants with unknown effect on TAp73 (Concin et al., 2005). These data indicate cross-talk between p53 and p73 and that dominant-negative p73 isoforms are important determinants for platinum-based chemotherapy in p53 mutant cells. However, another study indicated that ovarian cancers with high ΔNp73 mRNA levels have a good prognosis (Marabese et al., 2008). Discrepancies in these studies may relate to the finding that the effect of p73 on chemosensitivity is modified by the BRCA1 pathway. In this situation, BRCA1 deficient cells show hypermethylation of *TP73* intron 1, which inhibits ZEB1 binding and increases TAp73. Thus, cisplatin induces TAp73 target genes specifically in BRCA1-deficient cancers and may serve as a response predictor (Ibrahim et al., 2010). Alternatively, co-expression of C35 and ΔNp73 reduces response to cisplatin treatment in ovarian cancer cells (Leung et al., 2013). To further complicate the issue, methylation of the CpG island in exon 1 is occasionally seen and results in *TP73* silencing (Chen et al., 2000). Finally, in support of a general role for p73, the p73 rs6695978 G>A polymorphism is a predictive factor for ovarian cancer susceptibility (Guan et al., 2012). However, an immunohistochemical study failed to identify p73 expression in 109 advanced

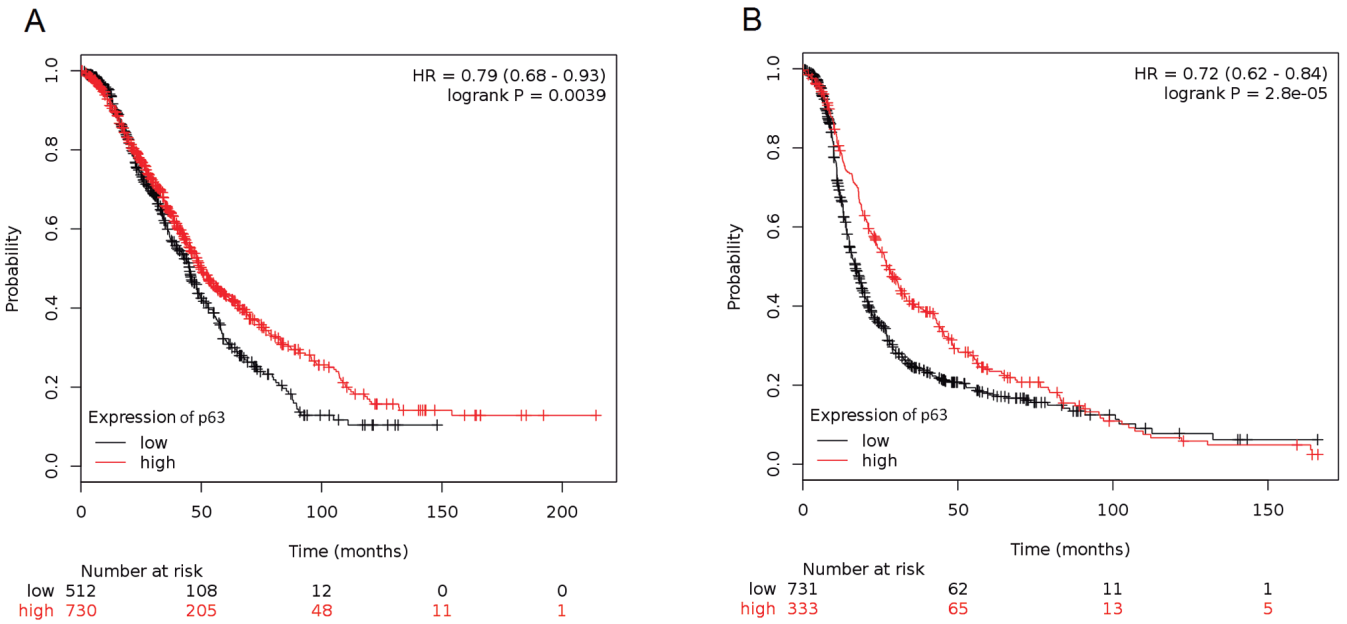

Fig. 5. P63 and cisplatin sensitivity in ovarian cancer. Kaplan Meier-plots of *TP63* expression with overall survival **(A)** and progression free survival **(B)** in ovarian cancers treated with platin-based chemotherapy (data derived from Kaplan-Meier Plotter (http://kmplot.com/analysis/).

ovarian cancers (Wang et al., 2004), once again raising the issues of different methodologies and antibody reagents in the field.

It is clear that p63 and p73 are involved in the pathogenesis of OEC. It is also evident that further investigations are warranted into the functions of p63 and p73 and it is vital to identify expression levels of individual isoforms to understand their functions in progression and response.

Squamous cell carcinomas

p63 is commonly overexpressed in squamous cell cancers (SCC) of lung, skin, cervix and head and neck (SCCHN) (Nylander et al., 2000; Wang et al., 2001), often in association with gene amplification (Hibi et al., 2000; Yamaguchi et al., 2000; Cancer Genome Atlas Research, 2012), although other genes in the amplicon may be more important tumour drivers (Redon et al., 2001, 2002). According to next generation sequencing data, 7% of SCCHN contain a *TP63* mutation in a mutually exclusive pattern with Notch and IRF6 mutations (Stransky et al., 2011), although similar studies have not identified *TP63* mutations in SCCHN (Agrawal et al., 2011), lung SCC (Cancer Genome Atlas Research, 2012) or cervical SCC (Ojesina et al., 2014). In the latter, it was suggested that the *TP63* locus is a rare site for HPV integration, leading to increased p63 levels (Ojesina et al., 2014). SCCHN has been widely studied for the effects of p63 and increased levels associate with poor prognosis (Lo Muzio et al., 2005; Loljung et al., 2014) whilst p63 knockdown sensitises to ionizing radiation and cisplatin (Thurfjell et al., 2005). Microarray analysis has identified numerous p63-regulated genes in SCCHN, many of which are involved in cell adhesion and motility in addition to proliferation, stemness and differentiation, pointing to an oncogenic role for ΔNp63 (Boldrup et al., 2007; Gu et al., 2007; Koster, 2010). One mechanism by which ΔNp63α acts as a pro-survival factor is suppression of p73-dependent apoptosis through both direct promoter binding and physical interaction with p73 (Rocco et al., 2006). Another potential mechanism involves c-REL, a member of the NFκB pathway (Lu et al., 2011). TNF-α, an inducer of c-REL, decreased TAp73 levels and enhanced the interaction between nuclear c-REL and ΔNp63α, accompanied by dissociation of TAp73 from ΔNp63α and its appearance in the cytoplasm. Overexpressed c-REL bound the p63 response sites of CDKN1A$p^{21/WAF1}$, PUMA and NOXA promoters, thereby decreasing binding of TAp73 to these sites (Lu et al., 2011). Although it is known that SCCs express a mixture of both TA- and ΔNp63 isoforms, and variably express the C-terminal isoforms (Nylander et al., 2000; Thurfjell et al., 2004), there are only a few studies that have investigated isoform-specific effects in SCC (Boldrup et al., 2009; Nekulova et al., 2013; Loljung et al., 2014), with one study showing that TAp63 expression in SCC cervix associates with improved prognosis (Nekulova et al., 2013). On the other hand, it is increasingly recognized that ΔNp63 antibodies (also called p40) are superior to measuring total p63 in SCCs, showing a higher degree of specificity for squamous versus adenocarcinomas or other tumour types (Bishop et al., 2012; Butnor and Burchette, 2013; Alomari et al., 2014). Recent data indicate that *TP63* chromosomal rearrangements or amplification occur in a small number of lung adenocarcinomas and these alterations give rise to a proportion of tumours with a $p63^{+}/p40^{-}$ phenotype (Aubry et al., 2014). It will be important in the future to determine whether these and other $p63^{+}/p40^{-}$ tumours express TAp63 or represent p63 antibody cross-reactions with p73 (Rosenbluth et al., 2009; Nekulova et al., 2013), and whether this has clinical impact, in addition to studying the impact of TAp63 co-expression with ΔNp63 (Nekulova et al., 2013).

Compared to p63, there are relatively few studies of p73 expression in SCC, which is surprising since p73 is expressed in normal basal squamous cells and is over-expressed in SCC (Choi et al., 2002; Nenutil et al., 2003; DeYoung et al., 2006). In cervical SCC, p73 mRNA levels are increased and associated with improved prognosis, whilst reduced p73 levels were seen in association with *TP73* hypermethylation (Liu et al., 2004). Using an antibody specific for p73α, these isoforms are expressed in the non-proliferative basal cells of the cervix and although total p73 levels increased during progression, p73α decreased (Nenutil et al., 2003). In another immunohistochemical study, TAp73 was paradoxically found to associate with higher grade cervical SCCs, although antibody characterization and specificity are unclear (Cheung et al., 2010). The *TP73* exon 2 G4C14-to-A4T14 polymorphism associates with risk of developing SCCHN and SCC cervix, presumably through its' effect on altering the TAp73/ΔNp73 ratio (Wang et al., 2012b; Zhang et al., 2014) and p73 expression is associated with improved radiotherapy response (Liu et al., 2004).

Prostate cancer

Most prostate cancers are adenocarcinomas and recent data suggest that both luminal and basal stem/progenitor cells can give rise to prostate adenocarcinomas (Xin, 2013). Prostate basal cells express p63, mainly as the ΔNp63α isoform (Yang et al., 1998), which is required for prostate development (Signoretti et al., 2000) and p63 plays a critical role in maintaining a prostate stem cell population (Signoretti et al., 2005; Pignon et al., 2013). p63 is rarely expressed in mouse and human prostate adenocarcinoma tumour cells (Signoretti et al., 2000; Dabir et al., 2012; Pignon et al., 2013) and is consistently downregulated at the mRNA level in cancer *versus* normal prostate (Table 1). Thus, p63 immunohistochemistry is useful for identifying normal basal myoepithelial cells, which are maintained surrounding benign lesions but are lost in cancers, and is widely used as part of an antibody cocktail that includes

the cancer expressed antigen AMACR (Humphrey, 2007; Dabir et al., 2012). Given that prostate basal cells express ΔNp63, detecting these isoforms rather than pan-p63 staining shows higher specificity, although there are potential problems with antibody quality and background staining of the currently employed polyclonal reagents (Sailer et al., 2013). It should also be borne in mind that the rare form of basal-type prostate cancer may show p63 staining in tumour cells (Ali and Epstein, 2007). Immunohistochemistry for p63 is also valuable for distinguishing between urothelial and prostate carcinoma; p63 is absent in prostate adenocarcinoma and positive in urothelial carcinoma, opposite to P501S (prostein), especially useful where diagnostic tissue is limited (Srinivasan and Parwani, 2011). Mechanistically, via miR-205, p63 down-regulates ZEB1 expression, a marker of EMT (epithelial-mesenchymal transition). Loss of both TP63 mRNA and miR-205 correlates with higher levels of prostate-specific antigen and higher Gleason scores. Additionally, mutant p53 interacts with and inhibits p63 (Tucci et al., 2012). Several studies suggest altered expression of p73 (Takahashi et al., 2001; Konishi et al., 2002), although others do not (Yokomizo et al., 1999a; He et al., 2013). In particular, upregulation of ΔNp73 in prostate carcinoma and hyperplasia has been reported and positively correlated with Gleason score (Guan and Chen, 2005). In keeping with an oncogenic role for ΔNp73, altered TAp73/ΔNp73 ratios due to the *TP73* exon 2 polymorphism acts to increases tumour aggressiveness (Carastro et al., 2014). In contrast, down-regulation of p73 together with miR-200b-3p has been reported in androgen-independent prostate cancer. It was suggested that low expression of p73 downregulates miR-200b-3p, resulting in increased proliferation of tumour cells (He et al., 2013). Similarly, Wang et al. reported a correlation between KLLN and p73, with KLLN showing reduced expression in prostate cancer compared to normal prostate. KLLN binds to p73 and p53 promoters to induce apoptosis in an androgen-independent manner (Wang et al., 2013). It is clear that further studies will be required to delineate the role of p73 isoforms in this disease.

Brain/CNS

p73 is essential for brain development, neuronal differentiation and neural stem cell maintenance (Yang et al., 2000; Agostini et al., 2010; Talos et al., 2010). The role of p63 is controversial (Dugani et al., 2009; Holembowski et al., 2011), but cooperation between p53, p63 and p73 seems necessary for maintaining neural precursor cells (Fatt et al., 2014). Elevated *TP73* mRNA has been detected in glioblastomas, medulloblastomas and ependymomas (Loiseau et al., 1999). In medulloblastoma and medulloblastoma-derived cell lines both TA- and ΔNp73 isoforms were detected (Castellino et al., 2007; Zitterbart et al., 2007; Nekulova et al., 2010), the latter protein being found in the nucleus and Golgi apparatus (Veselska et al., 2013), with positive associations of TAp73 and negative associations of ΔNp73 mRNA levels with patient outcomes. In contrast, *TP73* hypermethylation and loss of expression is common in gliomas (Palani et al., 2011) and linked to reduced progression-free and overall survival (Kuo et al., 2009). High levels of TAp63 mRNA and p63 protein, but not TAp73 mRNA, associate with prolonged survival in these tumours (Yamaki et al., 2013). ΔNp73 is highly expressed in undifferentiated human neuroblastic tumours (Douc-Rasy et al., 2002) and associates with reduced apoptosis and reduced survival (Casciano et al., 2002). A direct cytoprotective role of ΔNp73 in neuroblastoma cells was demonstrated *in vitro* using antisense oligonucleotide (Simoes-Wust et al., 2005) and cyclooxygenase inhibitors induce apoptosis independently of p53 through downregulation of ΔNp73 and induction of TAp73β (Lau et al., 2009), whereas TAp73 induces differentiation of neuroblastoma cells by regulation of miRNAs (Agostini et al., 2011) and glutaminase (Velletri et al., 2013). On the other hand, TAp73α and ΔNp73α have the same effect of reducing MYCN expression in neuroblastoma cells (Horvilleur et al., 2008). ΔNp63α overexpression in neuroblastomas induces VEGF and promotes angiogenesis through IL-6 and IL-8 (Bid et al., 2014). In retinoblastomas, p63 and p73 were detected by immunohistochemical staining in 59% and 93%, respectively, with high risk tumours showing significantly increased p73 (Adithi et al., 2008).

Melanoma

Although p63 is not expressed in primary melanocytes, upregulation of p63 mRNA and protein was reported in melanoma cell lines and clinical samples (Matin et al., 2013). Genotoxic stress stabilized both nuclear and mitochondrial p63 and a mitochondrial interaction between p63 and p53 prevented p53 nuclear translocation. TAp63 and ΔNp63 each conferred chemoresistance *in vitro* and expression of p63 in clinical samples correlated with poor outcome (Matin et al., 2013). These observations provide a possible explanation for abrogation of the p53-mediated apoptotic pathway in melanoma, implicating novel approaches aimed at sensitizing melanoma to therapeutic agents. On the other hand, immunohistochemical expression of p63 and/or ΔNp63 is rare in human melanomas (Reis-Filho et al., 2003a,b), casting doubt on the generality of the observations for a role of ΔNp63 in inhibiting wild-type p53 in this disease. For p73, initial studies showed no *TP73* mutations or differential expression in human melanomas (Schittek et al., 1999; Tsao et al., 1999). Enhanced expression of p73 in metastatic versus primary melanoma was subsequently reported *in vitro* and *in vivo* (Zhang and Rosdahl, 2001; Zhang et al., 2002), although this was not seen in a different cell line model of melanoma metastasis (Gutgemann et al., 2001). More detailed analysis of p73 isoforms revealed upregulation

of p73Δex2 and Δex2/3 isoforms in metastatic lesions, correlating with high levels of TAp73 and E2F1 (Tuve et al., 2004). Mechanistically, ΔNp73 may drive metastasis through induction of an EMT-like phenotype and IGF1R-AKT/STAT3 activation (Steder et al., 2013). Inhibiting p73 increased sensitivity to commonly used therapeutics *in vitro* (Shen et al., 2007), whilst a p73/miR-205 pathway influenced drug resistance (Alla et al., 2012).

Urothelial carcinoma

Bladder cancer is another striking example of the discrepancies that have been observed in the study of p63 and p73 in cancer. Initial findings showed that p73 is increased (Chi et al., 1999; Yokomizo et al., 1999b), whereas other studies demonstrated p63 and p73 expression is lost in bladder cancer and associates with tumour progression (Di Como et al., 2002; Urist et al., 2002; Koga et al., 2003; Puig et al., 2003; Fukushima et al., 2009). Subsequently, newly developed isoform-specific antibodies revealed that ΔNp63 identifies basal (rather than luminal) bladder cancer (Karni-Schmidt et al., 2011) and p63 expression in muscle invasive cancers indicates very poor prognosis (Choi et al., 2012, 2014). The latest data from the Cancer Genome Atlas did not identify genetic alterations in TP63 or TP73 in bladder cancer (Cancer Genome Atlas Research, 2014).

Concluding remarks

The p53 family functions as an interacting network

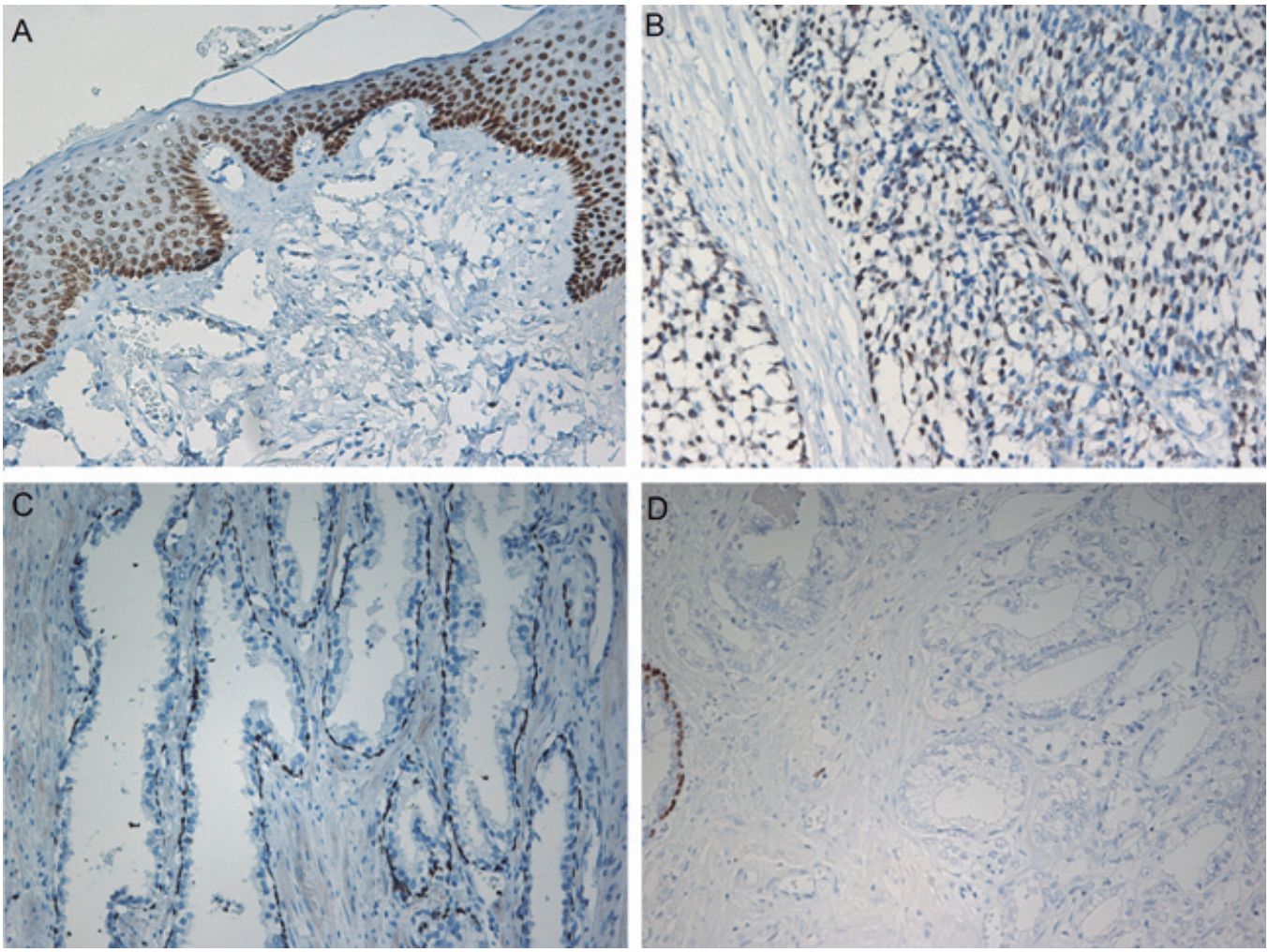

Fig. 6. Immunostaining of ΔNp63 with ΔNp63 1.1 antibody. The specific expression patterns of ΔNp63 in human tissues are shown using a novel monoclonal antibody. **A.** Stratified epithelium shows nuclear staining in basal and suprabasal epithelial cells. **B. T**riple negative breast cancer showing widespread ΔNp63 expression in tumour nuclei. **C**. Non-neoplastic prostate shows nuclear ΔNp63 expression in basal cells but not luminal cell nuclei. **D.** Prostate carcinoma shows a lack of ΔNp63 in tumour cells, although basal cells surrounding an area of normal prostate are seen to the left of the photomicrograph.

of proteins that in combination determine cellular responses to chemotherapeutic drug treatment. Unlike p53, p63 and p73 are rarely mutated but are often aberrantly expressed in specific cancers. Of the two, p63 has been more widely studied in clinical material and has shown utility for differential diagnosis in a number of situations, whereas this has yet to be demonstrated for p73. One major roadblock has been the lack of consistency of data, where the results of different studies are often contradictory in terms of levels of expression and clinical effect. These apparent contradictions are due in large part to different methodologies, measurement of total or specific isoforms, the reporting of ratios rather than absolute values and the use of arbitrary cut-off values to identify "positive" samples. Added to this is the use of antibodies that are poorly characterized (it is often uncertain which isoforms are recognized and which not) and that may even show cross-reaction with other family members, such as the cross-reactivity of 4A4 (by far the most widely used anti-p63 antibody) and other p63 antibodies with p73, and of anti-p73 antibodies with p63 (Rosenbluth et al., 2009; Nekulova et al., 2013). Fortunately, novel antibodies with improved selectivity and/or isoform-specificity are beginning to become available (Nenutil et al., 2003; Rosenbluth et al., 2009; Karni-Schmidt et al., 2011; Romano et al., 2012; Nekulova et al., 2013; Veselska et al., 2013; Tacha et al., 2014) (Fig. 6) and are being more widely used for both research and clinical studies as they demonstrate the improved data they provide (Karni-Schmidt et al., 2011; Bishop et al., 2012; Butnor and Burchette, 2013; Gailey and Bellizzi, 2013; Nekulova et al., 2013; Rossi et al., 2013; Sailer et al., 2013; Alomari et al., 2014; Vogt et al., 2014). We can also expect that the more detailed analysis of tumour material for p63 and p73 isoforms will lead to a better understanding of their roles in tumour progression and their ability to act as predictive biomarkers and will be a step further in the targeted therapy of cancer. For instance, ΔNp63 is a pro-survival factor that is targeted by cisplatin (Fomenkov et al., 2004), thereby acting as an Achilles heel for those specific tumours of breast and SCCHN that rely on ΔNp63 expression (Zangen et al., 2005; Leong et al., 2007). Ultimately, therapeutic modulation of ΔNp63 and/or TAp73 expression might be used to target various cancers, including those with p53 mutations.

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