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News and Commentary

The role of p53 protein family in gastrointestinal malignancies

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p73 and p63 (also named KET, p51, p40 and p73L) are both homologs of p53, the genes for which, TP73 and TP63, are localized at the 1p36.33 and 3q27-29 chromosomal regions, respectively. Initial studies confirmed their structural similarity to p53, while subsequent studies demonstrated functional similarity. When overexpressed, p73 and p63 mimic almost all of p53's activities.

However, despite these similarities there are a number of important differences. In contrast to p53, p73 and p63 both express as a complex variety of protein isoforms that originate from two p73 and p63 gene promoters and extensive gene splicing at the NH2- and COOH-termini. In addition, p73 and p63 genes encode a domain at the COOH-terminus that is not found in p53. This domain, termed SAM or sterile alpha motif, is responsible for protein–protein interactions and is found in a diverse range of proteins that are involved in developmental regulation. Biological function of the domain is not well understood. However, it has been implicated in lipid-membrane binding and transcriptional suppression.

The p73/p63 isoforms have a tissue-specific pattern of expression. In gastrointestinal tissues, strong expression of p63 and p73 has been detected in normal squamous epithelium of the esophagus. p73 is also expressed in the normal epithelium of the colon, pancreas and the parotid gland, primarily in the basal cells. p63 is particularly highly expressed in the progenitor or stem cell populations of a variety of epithelial tissues. Normal esophageal squamous epithelium shows strong nuclear staining for p63 in all cells of the basal and in the suprabasal cell layers. p63 has also been detected in the ducts of esophageal mucosal and submucosal glands.[1] In contrast, columnar surface and crypt epithelium in the cardia, antrum, duodenum, jejunum, ileum and colon have weaker staining or show no staining at all for p63.[1,2]

p73

Generation of p53-deficient mice conclusively demonstrated that p53 plays a role in tumor suppression, as tumor susceptibility in these animals is greatly enhanced. In contrast, an initial analysis of the p73 knockout mouse showed neurological, pheromonal and inflammatory defects, but no spontaneous tumors were found. However, the phenotype of the p73-deficient mice appears to be more multifaceted than initially thought. Flores *et al.*[3] recently reported that $p73^{+/-}$ (and $p63^{+/-}$) heterozygous animals develop malignant and benign lesions, the majority of which are thymic lymphomas, hemangiosarcomas and lung adenomas, which occur at approximately 12 months of age. Of $p63^{+/-}$ mice, 10% develop squamous cell carcinomas, and 20% developed histiocytic sarcomas. Similar to the situation in $p53^{+/-}$ mice, tumors from $p73^{+/-}$ and $p63^{+/-}$ mice undergo loss of the remaining wild-type allele (LOH). Moreover, loss of p73 and p63 can cooperate with loss of p53 function. Of the double heterozygous $p53^{+/-}$: $p73^{+/-}$ mice, 15% developed hepatocellular carcinoma, an atypical tumor for single heterozygotes.

These data are consistent with the idea that p73 and p63 act as tumor suppressors. However, current clinical data on primary human tumors imply that the role of p73 in tumorigenesis is likely more complex (see Table 1). In fact, in striking contrast to p53, which is frequently mutated, data from a substantial number of tumors, including solid and hematological ones, demonstrate that loss-of-function mutations of p73 are relatively rare. In gastric and esophageal carcinomas, only one mutation was observed in a series of 92 tumors, one mutation was found in a series of 124 hepatocellular carcinomas and no mutations in 207 colorectal cancers.

Even though LOH has been found in some gastrointestinal tumors, it is not associated with a decrease of p73 expression. By contrast, several studies, including ours, have revealed overexpression of p73 transcript and protein in multiple tumors, including carcinomas of the liver, colon, esophagus and stomach (see Table 1). These data are also consistent with an increased titer of p73 antibodies in patients with various types of cancer. It was initially thought that imprinting of the p73 locus may ease the inactivation of the p73 gene, but this is relatively uncommon in gastrointestinal tumors. In fact, the second p73 allele is specifically activated by loss of imprinting in carcinomas of the esophagus, stomach and several others. Hypermethylation of the p73 gene promoter is uncommon in esophageal and hepatocellular carcinomas, but has been reported in gastric cancer cell lines (see Table 1). However, it is important to take into account the fact that current data on alterations of p73 expression is tissue specific. Loss of expression of p73 has been demonstrated in some lymphoid and urothelial malignancies.

Recent studies of large patient groups with hepatocellular carcinomas and colorectal carcinomas have found a statistically significant correlation between high global expression of the p73 protein and poor clinical outcome. Moreover, significantly greater vascularization and VEGF expression was observed in colorectal tumors, which express p73, than in p73 negative tumors, suggesting a potential role for p73 in tumor angiogenesis.[4] This is consistent with the reduced

Table 1 Incidence of alterations in p73 and p63 in gastrointestinal tumors

Publication	Method of analysis	p73/p63 expression, (%) (case number)	LOH, (%) (case number)	Mutations
p73				
Gastric carcinoma				
Multiple simultaneous gastric cancer Tannapfel A *et al.* (*J. Pathol.*, 2001)[19]	*In situ* hybridization Sequencing Western blotting IHC	45% (23/51) transcripts; 49% (33/68) protein; $<1\%$ in non-neoplastic mucosa; Tumor-specific upregulation of p73	—	0
Kang M *et al.* (*Clin. Cancer Res.*, 2000)[23]	RT-PCR	94.9% (37/39); 87.5% (14/16) in matched tissues (T/N); Tumor-specific upregulation of p73; Loss of imprinting in a subset of tumors	—	—
Pilozzi E *et al.* (*Mol. Pathol.*, 2003)[24]	RT-PCR SSCP	—	—	1/13
Huang and Xie (*Zhejiang Da Xue Xue Bao Yi Xue Ban*, 2002)[25]	RT-PCR	53% (17/32); 14/16 (87.5%) matched T/N; Tumor-specific upregulation	—	—
Yokozaki H *et al.* (*Int. J. Cancer*, 1999)[26]	PCR-RFLP RT-PCR SSCP Sequencing	—	37.5% (12/32); LOH occurs preferentially in foreolar type of tumor	0
Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA)				
Masuda N *et al.* (*Cancer Sci.*, 2003)[27]	IHC	Tumor-specific upregulation of p73	—	—
ESCC Nimura Y *et al.* (*Int. J. Cancer*, 1998)[28]	RT-PCR SSCP	8/8 (100%) $p73\alpha > p73\beta$	8% (2/25)	0/48
ESCC Cai Y *et al.* (*Carcinogenesis*, 2000)[29]	RT-PCR IHC	9/15 (60%); Loss of imprinting; Tumor-specific upregulation of p73	9/14 (64%)	0
ESCC and EA Ryan B *et al.* (*Br. J. Cancer*, 2001)[7]	PCR	—	37.8% (14/37) Polymorphism (pos. 4, 14) is associated with a reduced incidence of esophageal carcinoma	—
Cui R *et al.* (*Biochem. Biophys. Res. Commun.*, 2005)[30]	RT-PCR Westerm blotting	Overexpression of TAp73 and ΔNp73 in ESCC and EA	—	—
Pancreatic carcinoma				
Ito Y *et al.* (*Int. J. Mol. Med.*, 2001)[31]	IHC	45.6% Tumor-specific upregulation of p73; More in cystic than in ductal carcinomas	—	—
Colorectal carcinoma				
Sun XF (*Clin. Cancer Res.*, 2002)[32]	IHC	67% (147/221); 95% (55/58) in metastases; Elevated p73 expression predicts poor prognosis	—	—
Liu L *et al.* (*J. Int. Med. Res.*, 2001)[33]	IHC	$T = 92$; Elevated expression correlates with poor survival	—	—
Guan M *et al.* (*Jpn. J. Clin. Oncol.*, 2003)[4]	IHC Western blotting	73% (41/56) by IHC; 82% (46/56) by Western blotting; Elevated expression of p73 positively correlates with angiogenesis	—	—
Sunahara M *et al.* (*Int. J. Oncol.*, 1998)[34]	RT-PCR SSCP	Elevated p73 expression	17%	0
Pfeifer D *et al.* (*Carcinogenesis*, 2005)[8]	PCR PCR-RFLP IHC	41% (17/41) moderate+strong IHC staining	0% (0/50)	—
Hepatocellular carcinoma (HCC)				
Tannapfel A *et al.* (*J. Natl. Cancer Inst.*, 1999)[35]	*In situ* hybridization IHC	34% (25/74) mRNA; 32% (61/193) protein; Tumor-specific upregulation; Elevated expression correlates with poor prognosis	—	—
Stiewe T *et al.* (*Clin. Cancer Res.*, 2004)[12]	PCR-RFLP RT-PCR	Strong tumor-specific upregulation of TAp73 and ΔN'p73 mRNA	0% (0/4)	—

Table 1 (Continued)

Publication	Method of analysis	p73/p63 expression, (%) (case number)	LOH, (%) (case number)	Mutations
Sayan A *et al.* (*Oncogene*, 2001)[15]	RT-PCR	100% (7/7) ΔNp73 mRNAs; 29% (2/7) p73 mRNA; Lack of the p73 mRNA in the normal liver	—	—
Mihara M *et al.* (*Br. J. Cancer*, 1999)[36]	RT-PCR	43/43 p73 mRNA; P73α > p73β; Equal p73 mRNA expression in tumor and normal tissues	20% (5/25)	0/48
Pan H *et al.* (*Acta Oncol.*, 2002)[37]	RT-PCR PCR-RFLP PCR-SSCP Methylation analysis	100% (8/8); T > N; Lack of hypermethylation; Biallelic expression in tumor and normal tissues	0% (0/8)	0/18
Aoki T *et al.* (*Int. J. Oncol.*, 2004)[38]	PCR-RFLP	—	33%; LOH correlates with poor disease-free survival	0
Herath N *et al.* (*Hepatology*, 2000)[39]	RT-PCR IHC	33.3% (8/24); p73α (8/8) > p73β (5/8) Lack of the p73 mRNA in the normal liver; Tumor-specific p73 mRNA upregulation	40% (14/35) at 1p35-36; Elevated p73 expression occurs despite LOH	—
Peng C *et al.* (*Anticancer Res.*, 2000)[40]	Mutational analysis	biallelic expression in normal and tumor tissues	18% (2/18)	1/22
Fukushima K *et al.* (*Hepatol. Res.*, 2001)[41]	PCR Sequencing	100% (23/23)	11% (1/9)	0/36
Qin *et al.* (*World J. Gastrointerol.*, 2005)[42]	IHC	36.2% (17/47); p73 overexpressed in tumors; p73 expression correlates with lymph node metastasis	—	—
p63				
Squamous cell carcinoma of the esophagus (ESCC), esophageal adenocarcinoma (EA), and Barrett's esophagus (BE)				
Glickman J *et al.* (*Hum. Pathol.*, 2001)[1]	IHC	0% (0/12) in BE; 69% (9/13) in BE-associated multilayered epithelium; 100% (4/4) in ESS dysplasia; 100% (7/7) in ESCC; 0% (0/12) in BE-associated dysplasia; 0% (0/7) in EA; ΔNp63 is expresses in all benign and neoplastic squamous tissues	—	—
Hara *et al.* (*Int. J. Mol. Med.*, 2004)[43]	IHC	96.9% (63/65) in ESCC	—	—
Hall T *et al.* (*Gut*, 2001)[2]	IHC	50% (10/20) in BE; 70% (7/10) in high-grade dysplasia; 60% (6/10) in EA; Nuclear p63 expression increases with the severity of neoplastic changes in BE	—	—
Geddert H *et al.* (*Hum. Pathol.*, 2003)[44]	IHC PCR	100% (4/4) – p63, 50% (2/4) – ΔNp63 in squamous low-grade neoplasia; 94.4% (17/18) – p63, 100% (18/18) – ΔNp63 in squamous high-grade neoplasia; 88% (44/50) – p63, 76% (38/50) – ΔNp63 in ESCC; 7.3% (3/41) – p63, 0% (0/41) – ΔNp63 in BE-associated specialized epithelium; 14.3% (3/21) – p63, 0% (0/21) – ΔNp63 in BE-associated high-grade neoplasia; 16% (8/50) – p63, 6% (3/50) – ΔNp63 in EA	20% (2/10) p63 gene amplification in ESCC; 10% (1/10) in EA	—
Hu H *et al.* (*Int. J, Cancer*, 2002)[45]	IHC RT-PCR	90% (10/11) in ESC dysplasia; 98% (50/51) in ESCC; T = N ΔNp63 mRNA ΔNp63 mRNA is a predominant species	—	—

Table 1 (Continued)

Publication	Method of analysis	p73/p63 expression, (%) (case number)	LOH, (%) (case number)	Mutations
Cui R *et al*. (*Biochem. Biophys. Res. Commun.*, 2005)[30]	RT-PCR Westerm blotting	Both TAp63 and ΔNp63 is overexpressed in ESCC but not in EA	—	—
Gastric carcinoma				
Multiple simultaneous gastric cancer Tannapfel A *et al*. (*J. Pathol*., 2001)[19]	*In situ* hybridization IHC	22/46 (48%) p63 mRNA; 25/68 (37%) p63 and ΔNp63 protein; Tumor-specific upregulation of p63 and ΔNp63 mRNAs and proteins	—	0
Huang and Xie (*Zhejiang Da Xue Xue Bao Yi Xue Ban*, 2002)[25]	RT-PCR	Tumor-specific upregulation of p63γ	—	—
Hepatocellular carcinoma				
Hamada K *et al*. (*Cancer Lett*., 2000)[46]	PCR-SSCP DNA sequencing	—	—	0/51
Fukushima K *et al*. (*Hepatol. Res*., 2001)[41]	RT-PCR	No detectable mRNA expression	—	—
Pancreatic carcinoma				
Ito Y *et al*. (*Int. J. Mol. Med*., 2001)[31]	IHC	68.2% Tumor-specific upregulation	—	—
Hornick J *et al*. (*Am. J. Surg. Pathol*., 2005)[47]	IHC	8% (2/25) in metastatic pancreatic adenocarcinoma; 0% (0/25) in bile duct adenoma; 0% (0/10) in bile duct hamartoma	—	—

IHC = immunohistochemistry; SSCP = single-strand conformation polymorphism analysis; RFLP = restriction fragment length polymorphism analysis; T = tumor; N = normal

expression of antiangiogenic factor thrombospondin-1 and the increased levels of the VEGF protein that is observed both *in vitro* and *in vivo* in ovarian cells that stably overexpress TAp73α.[5] However, when TAp73α is transiently expressed, VEGF mRNA and protein are suppressed.[6]

The p73 gene polymorphism in the 5′-untranslated region at positions 4 (G>A) and 14 (C>T) was implicated in gastrointestinal tumorigenesis. AT/AT homozygotes appear to be protected against the development of esophageal cancer in an Irish population,[7] but have a greater risk of developing colorectal cancer in a Swedish population.[8] In contrary, Hamajima *et al*.[9] did not find any relationship between this polymorphism and the risk of esophageal, stomach and colorectal cancer patients in a Japanese population suggesting that genotypic variations in different populations might play a role.

The discrepancy between the properties of the p73 protein along with the clinical and genetic data led to an investigation of the oncogenic potential of p73. To date, several studies have demonstrated tumor-specific upregulation of ΔNp73, the inhibitory isoform of p73, in a number of tumors including cancer of the liver, esophagus and stomach.

ΔNp73α lacks the N-terminal transactivation domain of p73 and inhibits the expression of p53-inducible genes such as p21/Waf1, Bax, MDM2 and 14-3-3σ. Thus, ΔNp73α can exert a dominant-negative effect on wild-type p53 and p73. An inhibitory function of ΔNp73α may suggest a tumor-promoting role. Indeed, Petrenko *et al*.[10] found that ΔNp73α can facilitate immortalization of primary cells. ΔNp73α cooperates with oncogenic Ras in the transformation of mouse embryonic fibroblasts *in vitro* and the induction of tumors *in vivo* in immunocompromised mice. Wild-type p53 is likely a major target of ΔNp73α inhibition in these cells, although a growing body of experimental data indicates that ΔNp73α has an additional p53-independent function. Overexpression of ΔNp73α in the p53 null cell line H1299 reduced the levels of p21/Waf1 mRNA but did not affect other p53-responsive genes. It also affected the expression of several other cancer-related genes, including EGR1, cMyc, CDC6 and NF-κB.[11]

Taken together, these data suggest that ΔNp73α may play an oncogenic role in at least a subset of human tumors. They can also partially explain the tumor-associated transcriptional upregulation of p73 gene. However, a number of studies, including ours, have found that proapoptotic TAp73 transcripts and proteins are also overexpressed in tumors. This has been demonstrated by RT-PCR and Western Blotting or immunohistochemistry with N-terminally reactive antibodies, in primary cancers and cancer-derived cell lines. Comprehensive analysis of p73 isoforms in hepatocellular carcinomas demonstrated that TAp73 mRNAs are the most abundant (absolute copy number) among all the transcripts for p73 isoforms.[12] A similar trend has been observed in gastric and esophageal tumors.[13]

Given the proapoptotic and tumor-suppressor properties of TAp73, it is conceivable that TAp73 is inactivated in tumors or may acquire tumor-associated gain-of-function properties. Indeed, it has been demonstrated that certain tumor-derived p53 mutants can physically associate with and inhibit transcriptional activation of p73 and/or p63. Moreover, a correlation exists between the efficiency of p53 binding and inhibition of p73 and p63. Interestingly, the interaction between p73 and mutant p53 depends on the presence of a common p53 polymorphism, arginine versus proline, at amino

acid 72, in which arginine 72 favors binding to p73.[14] Besides mutant p53, ΔNp73α may also inhibit p73 and p53 *in vivo* in cancer tissues. Indeed, several studies have demonstrated concomitant upregulation of p73 and ΔNp73 in gastrointestinal tumors.[12,13,15] Interestingly, ΔNp73 and mutant p53 can cooperate with TAp73 to induce the upregulation of β-catenin in gastric cancer cell lines.[13]

p63

p63 is highly expressed in progenitor or stem cell populations of a variety of epithelial tissues. Mice deficient in p63 die soon after birth and display a number of striking developmental defects, including the absence of epidermis, teeth, salivary and lachrymal glands, as well as severe abnormalities in limb development. In these mice, the normal stratified squamous epithelium of the esophagus and forestomach is replaced by an unusual array of columnar ciliated and goblet-like cells. A deficiency in basal cells has also been demonstrated.

Recent data suggest that the p63 isoforms, TAp63 and ΔNp63, play distinct roles in epithelial differentiation. Koster *et al*.[16] demonstrated that TAp63 is the first isoform to be expressed during mouse embryogenesis and initiates the epithelial stratification. Once the mature epithelia are formed, this isoform is required for maintenance of the proliferative potential and suppression of the differentiation of committed progenitor basal cells. Ectopic expression of TAp63 in the mouse simple epithelium *in vivo* induced squamous metaplasia.[16] By contrast, ΔNp63 promotes terminal differentiation of basal cells, presumably by counteracting p63 function.[16]

The TP63 gene is located in a region on chromosome 3q27-ter, which is amplified in various cancers making it more similar to an oncogene than a tumor suppressor. Amplification of the p63 gene has been detected in approximately 20% of esophageal squamous cell carcinomas and in 10% of esophageal adenocarcinomas (see Table 1). Given that the total frequency of tumors in which p63 is upregulated is higher, gene amplification is unlikely to be the main mechanism underlying the increased levels of p63. Rather, currently unknown transcriptional or post-transcriptional changes are involved. Increases in the levels of mRNA and protein increase occur in the absence of mutations in the TP63 gene. Thus, in tumors, the behavior of p63 is similar to that of p73.

One of the best-characterized tumors that overexpresses p63 is esophageal squamous cell carcinoma in which p63 transcript and protein upregulation is extremely frequent. p63 isoforms are upregulated not only in carcinomas but also in squamous low- and high-grade displasias (see Table 1). ΔNp63 is the predominant variant that is found in these neoplastic tissues. In Barrett's esophagus (BE), a disorder in which the stratified epithelium is replaced by a simple columnar epithelium that consists of mucosecretory cells, p63 gene expression is not highly prominent. There is some controversy regarding the expression of p63 in BE-associated adenocarcinomas. Glickman *et al*.[1] and Daniely *et al*.[17] reported that Barrett's metaplasia and adenocarcinoma are mostly p63 negative, but Hall *et al*.[18] found strong staining in adenocarcinomas and weak staining in Barrett's metaplasia.

Upregulation of the TAp63 and ΔNp63 proteins has been found in 37% of multiple simultaneous gastric cancers.[19] Significant association of p63 staining with histological tumor type and cellular differentiation was found in high-grade poorly differentiated and diffuse type of carcinomas. In intestinal metaplasia, atrophic gastritis, and in the presence of Helicobacter pylori, increased p63 staining was also observed.[19] Of the other types of gastrointestinal tumors, p63 overexpression has been reported in carcinomas of the pancreas (see Table 1).

Based on the aforementioned data, it is unlikely that p63 acts as a tumor suppressor in gastrointestinal tissues. Rather, p63 isoforms may have tumor-promoting properties that are related to its intrinsic role in epithelial differentiation. This is consistent with the data demonstrating that overexpression of ΔNp63 in Rat-1A cells led to a significant increase in colony growth in soft agar and xenograft tumor formation in nude mice.[20] Recently, ΔNp63 has been identified as a downstream target of the phosphoinositide 3-kinase (PI3K) pathway, a cell survival and proliferation pathway in cancer.[21] At least two mechanisms may contribute to the oncogenic properties of the TP63 gene. Overexpression of ΔNp63 may have an inhibitory effect on p53, p73 or p63. In this context, ΔNp63 behaves in a similar manner to ΔNp73. In addition, it was recently demonstrated that ΔNp63 induces accumulation of intracellular β-catenin by inhibiting the glycogen synthase kinase GSK3β.[22] Accordingly, β-catenin, which is a well-known oncogene, may be a downstream effector for the biological effects of p63.

Conclusion

p53 acts as 'the guardian of genome,' protecting higher multicellular organisms against aberrant cell growth and tumor development. The recent identification of the p53–p63–p73 axis has undoubtedly opened a new chapter in cancer research. In particular, it emphasizes that there is a tight link between developmental processes and tumorigenesis. Indeed, p63 and p73 play important roles in normal development, but are also clearly implicated in human tumorigenesis. Our understanding of these processes is still preliminary as many issues are still unclear or the subject of debate. It is therefore likely that conclusions drawn at this stage will have to be revised in the future.

What is clear is that p73 and p63 share substantial functional similarities with p53 under experimental conditions. However, despite these similarities, p73 and p63 have been found to behave differently in many human tumors, including gastrointestinal malignancies. A large number of studies have demonstrated that p73 and p63 are specifically overexpressed in tumor tissues compared with their normal counterparts. In particular, this occurs in the absence of mutations in the TP73 or TP63 genes. Moreover, in some tumors, upregulation of p73 correlates with a poor prognosis. These apparently contradictory findings are difficult to explain using only a simple oncogene/tumor-suppressor paradigm. In this situation, two issues have to be taken into consideration: first, the existence of extensive gene splicing that produces many isoforms with diametrically opposed properties and, second, tissue specific effects.

To advance our understanding of the role of p53 homologs in tumorigenesis, we need to describe the dynamic changes that occur in the network of interactions between the multiple isoforms of p73 and p63, as well as wild-type and mutant p53 in normal and tumor tissues. Although this task will be challenging, the potential benefits with respect to novel diagnostic and therapeutic approaches outweigh the costs.

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