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## PERSPECTIVE

# The jury is in: p73 is a tumor suppressor after all

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**While p53 has been extensively characterized as a tumor suppressor, it has been more difficult to determine whether p63 and/or p73 play a similar role. Every system in which these family members have been studied, from cells to animal models to human tissues, seems to create more questions than answers. Tomasini and colleagues (pp. 2677–2691) demonstrate that one isoform of p73 is responsible for preventing tumor formation in vivo, providing critical validation of an isoform-based model of p73 function.**

## The p53 family: three genes, six promoters, 50 isoforms, and counting

Although p53, p63, and p73 share similar domain architecture and sequence identity, their differences in vivo are striking. While p53 is frequently mutated during tumorigenesis (in over 50% of human tumors), p63 and p73 are rarely mutated (Moll and Slade 2004). Instead, the p63 locus is amplified in squamous cell carcinomas (Bjorkqvist et al. 1998; Hibi et al. 2000; Massion et al. 2003), and p73 is overexpressed in many tumor types (Moll and Slade 2004). In addition, while p53-null mice develop spontaneous tumors, p63- and p73-null mice die tumor-free from developmental defects (Yang et al. 1999, 2000). Although p63 and p73 can activate apoptosis in vitro (Jost et al. 1997; Yang et al. 1998), it is clear that they are not classic Knudson-like tumor suppressors like p53.

One possibility is that p63 and p73 are tumor suppressors that are inactivated during tumorigenesis by a non-classical mechanism. Investigation of this possibility is complicated by the complexity of RNA isoforms expressed and the potential for tissue-specific expression. There are nine possible isoforms for p53, six for p63, and 35 for p73 that can arise through a combination of promoter usage and alternative splicing (Bourdon et al. 2005; Murray-Zmijewski et al. 2006). For p63 and p73, two classes of isoforms exist that either contain (TA) or

lack ( $\Delta$ N) the transactivation domain required for full activation of target genes (Fig. 1; Deyoung and Ellisen 2007).

The purported active isoform of p73, TAp73, is of particular interest because it is frequently expressed in human tumors (Deyoung and Ellisen 2007) and can be inhibited by either  $\Delta$ Np63 or  $\Delta$ Np73 (Fig. 1; Zaika et al. 2002; Deyoung and Ellisen 2007). In particular, physical  $\Delta$ Np63:TAp73 complexes that inactivate TAp73 have now been demonstrated in head and neck squamous cell carcinoma (HNSCC) and basal-like breast cancer cell lines, and evidence suggests these complexes occur in vivo in the corresponding tumor types (Deyoung et al. 2006; Rocco et al. 2006; Leong et al. 2007). In addition, tumor-specific forms of p53 have the ability to bind and inhibit p73 (Fig. 1; Di Como et al. 1999). Thus the ability of  $\Delta$ Np63,  $\Delta$ Np73, or mutant p53 to inhibit TAp73 may obviate the need for mutation of p73 during tumorigenesis. A single mutation in p53 might decrease both p53 and p73 activities. Similarly, an increase in  $\Delta$ Np63 or  $\Delta$ Np73 levels could be another means of inactivating TAp73, ultimately preventing TAp73 from engaging in tumor-suppressive activities.

Even though recently discovered p53 isoforms can inhibit p53 transcriptional activity, p53 is mutated in cancers (Ghosh et al. 2004; Bourdon et al. 2005). The p53 locus can undergo alternative splicing and contains two promoters, thus creating two classes of isoforms that also either contain or lack an N-terminal transactivation domain. Those isoforms that lack the transactivation domain have been shown to inhibit full-length p53 in co-transfection experiments (Bourdon et al. 2005), and are overexpressed in tumors (Bourdon 2007). Thus the p53, p63, and p73 genes share similar organization and can each give rise to active and inhibitory isoforms.

Why might inhibitory isoforms have a differential effect on the need for mutation of p53 versus p73? Three possible answers are (1) TAp73 is not a tumor suppressor, or is a much weaker tumor suppressor than p53. (2) Tissue-specific and context-dependent upstream signals and regulators control whether p53 and/or p73 is active in tumor suppression. (3)  $\Delta$ Np73 has oncogenic properties that are separate from its ability to inhibit p53 family members. Even the first of these possibilities, whether or not TAp73 is a tumor suppressor, has been surprisingly

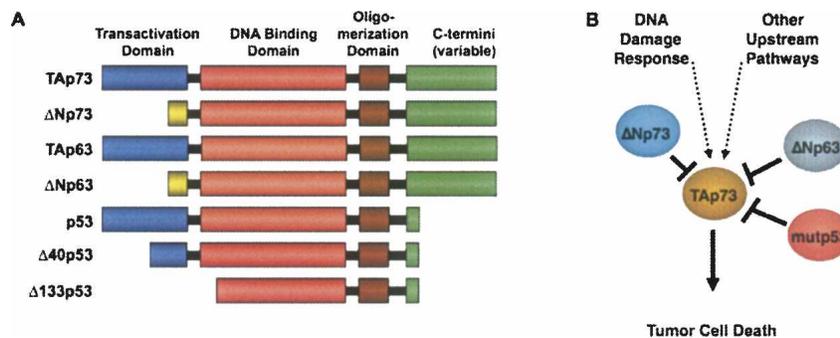
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**Figure 1.** Isoform-based model of p53 family function. (A) Active isoforms of the p53 family of transcription factors (p53, p63, and p73) contain a transactivation domain, whereas inhibitory isoforms lack a transactivation domain. (B) Other family member isoforms may inhibit TAp73 in cells, thus preventing TAp73 from engaging in tumor-suppressive functions and reducing selective pressure for mutation of p73 during tumorigenesis.



difficult to demonstrate conclusively (McKeon and Melino 2007).

Mouse models of p53 family members are an invaluable resource, providing clues as to if and when p53, p63, and p73 act as tumor suppressors in vivo. p63 transgenic mice that do and do not develop cancers have been reviewed in detail (Mills 2006). Mak and colleagues (Tomasini et al. 2008) settle the controversy for p73, using mice deficient for the TAp73 isoform of p73 to demonstrate that it is indeed a tumor suppressor.

### Cancer and infertility: manifestations of genomic instability in TAp73<sup>-/-</sup> mice

According to the isoform model of p73 function, p73-depleted animals may display complex tumor phenotypes due to the loss of both an oncogene (ΔNp73) and a tumor suppressor (TAp73) that can lead to a multitude of intermediate phenotypes. In addition, analysis of p73 deficient animals is complicated by severe developmental problems that lead to an early demise, largely attributed to loss of the ΔNp73 isoform that is expressed during development (Yang et al. 2000). Tomasini et al. (2008) circumvent these issues, using transgenic mouse techniques to delete exons that specifically encode the transactivation domain of p73. Because the *Trp73* gene contains a second promoter from which ΔNp73 can be transcribed, this approach led to a selective deficiency of all TAp73 isoforms. The developmental defects of these mice were less severe than their p73<sup>-/-</sup> counterparts. Subsequent analysis revealed an increased incidence of both spontaneous and DMBA-induced tumors in the TAp73<sup>-/-</sup> mice, showing that TAp73 is a tumor suppressor.

In part, the TAp73<sup>-/-</sup> tumors provide critical validation of previous work that demonstrated an increased rate of spontaneous tumors in p73<sup>+/-</sup> mice (Flores et al. 2005). Interestingly, this same study demonstrated that p63<sup>+/-</sup> mice develop spontaneous tumors, and that p53<sup>+/-</sup> p63<sup>+/-</sup> mice have an increased tumor burden compared with p53<sup>+/-</sup> mice (Flores et al. 2005). This is in contrast to another study using a distinct, inactivated p63 allele that demonstrated a lack of tumors in p63 heterozygous mice (Keyes et al. 2006). This second model also showed a decreased rate of tumor formation in mice heterozygous for both p53 and p63 compared with p53<sup>+/-</sup> mice

(Keyes et al. 2006). The opposing results in different p63-deficient mice heightened the need for validation and additional characterization of the p73-deficient phenotypes. Although there seem to be some differences in tumor spectrum, in general the TAp73-deficient mice recapitulate the tumor-prone phenotype of the p73<sup>+/-</sup> mice.

However, many aspects of this phenotype were unexpected. Mak and colleagues (Tomasini et al. 2008) observed a general increase in ΔNp73 RNA levels (but not protein levels) in the TAp73<sup>-/-</sup> mice. Construction of the TA-specific deletion was a complicated affair, involving placement of a Neo cassette that terminates transcription near the 5' end of the ΔNp73 promoter in intron 3. Assuming, as evidence suggests, that the elevated ΔNp73 levels were not a consequence of the transgenic process in general, but rather a consequence of TAp73 loss, this result raises new questions about p53 family cross-talk during tumorigenesis. TAp73 is a known transcriptional inducer of ΔNp73 (Grob et al. 2001), but in TAp73-deficient mice a striking increase in ΔNp73 RNA levels was observed. TAp73 has been reported to repress the expression of several genes by interacting with other transcription factors such as Sp1 in the promoters and regulatory regions of these genes (Salimath et al. 2000; Uramoto et al. 2004; Innocente and Lee 2005; Racek et al. 2005). Many transcriptional repressors have binding sites in the ΔNp73 promoter, including Sp1 (J. Rosenbluth and J. Pietenpol, unpubl.). It is intriguing to speculate that TAp73-mediated repression of ΔNp73 acts as a positive feedback loop during tumor suppression. Indeed, in cervical squamous cell carcinomas, TAp73 and ΔNp73 are not coexpressed but rather exhibit mutually exclusive expression patterns (Liu et al. 2006).

To examine other potential p53 family interactions, Tomasini et al. (2008) tested whether the loss of TAp73 expression altered p53 function. Decreased TAp73 has been shown to inhibit p53 function in vitro in a context-dependent manner. For example, studies in E1A-transformed mouse embryonic fibroblasts (MEFs) suggested that p63 and p73 are required for p53-mediated apoptosis (Flores et al. 2002). This finding was contradicted by a second study in T cells showing that p63 and p73 are dispensable for p53-mediated apoptosis (Senoo et al. 2004). In the TAp73-null mice, E1A-transformed MEFs and T-cell precursors do not demonstrate any alteration in p53 activity, suggesting that p73 is dispensable for p53 func-

tion, or that  $\Delta Np73$  compensates for the loss of TAp73 in E1A-transformed MEFs. It would be interesting to determine the effect of TAp73 loss on p53 function in an *in vivo* model in which p53 activity is dependent on both p63 and p73, such as during ionizing radiation-induced CNS apoptosis (Flores et al. 2002). This would be particularly relevant because all three p53 family members contribute to neuron development and function, as reviewed elsewhere (Jacobs et al. 2006). Indeed, the TAp73<sup>-/-</sup> mice support a model that ascribes distinct roles for  $\Delta Np73$  in the survival of neurons after injury (Jacobs et al. 2006), and for TAp73 during hippocampal development. How this system is perturbed during genotoxic stress would provide insight into the roles of the p53 family members in the nervous system and during tumorigenesis.

Mak and colleagues (Tomasini et al. 2008) round out their tumor analyses by presenting a mechanism for TAp73 tumor-suppressive function. One clue comes from a second phenotype of TAp73-deficient mice: infertility. Unlike the p73 heterozygotes, which do not mate due to lack of pheromone sensing (Yang et al. 2000), the TAp73-null mice mate normally but are infertile. Tomasini et al. (2008) present intriguing evidence that female infertility is due to genomic instability of the oocyte. This genomic instability may lead to retention during folliculogenesis and decreased viability, and may be similar in effect to the decreased oocyte quality that occurs with natural aging.

p63 is also known to play a role in the female oocyte; TAp63 is expressed and is essential for DNA damage-induced oocyte death that does not involve p53 (Suh et al. 2006). Thus, the p53 family emerges as a central player in maintaining fidelity of the female germline. TAp73 prevents genomic stress, and loss of TAp73 during aging may contribute to the decline in oocyte viability. In contrast, TAp63 is activated by genotoxic agents to kill oocytes that have sustained genomic damage (Suh et al. 2006). Whether p73 cooperates with p63 during this process, and the roles that these family members may play in the male germline (TAp73<sup>-/-</sup> male mice are also infertile), remains unknown.

Thus the two major phenotypes of the TAp73-null mice, cancer and infertility, are both associated with genomic instability. These new data suggest that maintaining the fidelity of the genome is a key molecular function of TAp73. The possibility of functional interplay with  $\Delta Np73$ , TAp63, and p53 during this process is an intriguing question raised by the new findings of Mak and colleagues (Tomasini et al. 2008). Construction and analysis of a  $\Delta Np73$ -deficient mouse is eagerly awaited.

### **p53 family members respond to differential upstream signals**

One of the strengths of the work by Tomasini et al. (2008) is the elegant confirmation of a p53/p73 commonality; another strength comes from multiple mouse phenotypes that provide clues to the differences between p53 and p73 in human tumors. These data suggest that

different upstream signals regulate the p53 family members—temporal, tissue-specific, and context-dependent cues lead to separation of function in the p53 family. This might occur, for example, through the E3-ubiquitin ligase mdm2, which is known to degrade p53 but not p73 (Zeng et al. 1999). Or it may occur through the cofactor YAP, that binds to p73 but not p53, enhancing p73 activity as well as recruiting p73 to specific target genes during apoptosis (Strano et al. 2001, 2005). By mechanisms such as these, differential activation of p53, p63, and p73 isoforms can be achieved. Ultimately, the settings in which p53 family members are active will select for their inactivation in human tumors.

In terms of upstream signals, the DNA damage response (DDR) signaling pathway is the classic activator of p53. Initial analyses of DDR pathways were performed in the TAp73<sup>-/-</sup> mice. Intriguingly, DNA-damaging agents such as dexamethasone, irradiation, etoposide and cisplatin were all ineffective at inducing TAp73-dependent cell death in either T cells or MEFs, suggesting a clear differential response to DNA damage between p53 and p73. This is in contrast to evidence that p73 can be activated by a subset of DDR-inducing agents (Ozaki and Nakagawara 2005). Perhaps p73 responds to genotoxic stress in a tissue-specific or context-dependent manner; for example, only in the absence of p53 (Talos et al. 2007). Further inquiry *in vivo* is required to understand these conflicting data.

There is clear evidence of tissue-specific function in the TAp73<sup>-/-</sup> mice. Loss of TAp73 leads to the development of genomic instability, but only in select tissues. Tomasini et al. (2008) demonstrate that cells isolated from the lung but not the thymus are aneuploid in the absence of TAp73. This correlated with the development of lung tumors but not thymic tumors, and is highly suggestive of a causal relationship. Through such data, a model begins to emerge in which p53 is activated by environmental and/or genotoxic stress, and cells in this setting select for p53 mutations. In contrast, p73 may be activated by other types of stresses, in distinct contexts, leading to different routes of inactivation. Perhaps lessons learned from p63/p73 biology will shed further light on p53 function. p53 inhibitory isoforms are expressed in human cancer types with lower p53 mutation rates: breast cancer, AML, and HNSCC (Bourdon 2007). Because different cancers are promoted by different environmental stresses, these correlations suggest that upstream signals determine if p53 family members are inactivated by mutation or by inhibitory isoforms.

What are the alternative upstream signals, outside of classic DDR signaling? Recent work using a fibroblast model of step-wise tumorigenesis suggests that TAp73 and  $\Delta Np73$  are engaged at different stages of tumorigenesis, and that the function of TAp73 is to contribute to contact inhibition in high density cell cultures (Beitzinger et al. 2008). Loss of TAp73 enabled anchorage-independent growth, unlike p53 depletion that allows cells to escape cell cycle arrest and apoptosis. In this model, p53 and p73 perform different molecular functions that

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both lead to tumor suppression, and are activated during different stages of tumorigenesis.

An approach to identify upstream regulators of transcription factors using downstream gene signatures has recently been reported (Rosenbluth et al. 2008). Using this approach, mammalian target of rapamycin (mTOR) was identified as a negative regulator of p73. Notably, pharmacologic inhibition of mTOR in primary human mammary epithelial cells resulted in differential regulation of p53 family members. Cells exhibited selective up-regulation of TAp73, whereas  $\Delta$ Np63 and p53 levels both decreased (Rosenbluth et al. 2008). 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.

Initial analyses of TAp73<sup>-/-</sup> mice both confirm that p73 is a tumor suppressor, and provide intriguing evidence of differences between members of the p53 family. Additional studies with these mice, involving modulation of upstream pathways and alteration of  $\Delta$ Np73, p53, or p63 levels, will continue to yield insight into the coordinate and diverse functions of this family of transcription factors. In addition, the identification of upstream activators of p53 homologs may yield new therapeutic approaches for cancer. The validation of TAp73 as a tumor suppressor that is not lost or mutated in cancers makes it an intriguing therapeutic target—one that can engage p53-associated tumor suppressor signaling pathways in the absence of p53.

### Acknowledgments

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### References

- Beitzinger, M., Hofmann, L., Oswald, C., Beinoraviciute-Kellner, R., Sauer, M., Griesmann, H., Bretz, A.C., Burek, C., Rosenwald, A., and Stiewe, T. 2008. p73 poses a barrier to malignant transformation by limiting anchorage-independent growth. *EMBO J.* **27**: 792–803.
- Bjorkqvist, A.M., Husgafvel-Pursiainen, K., Anttila, S., Karjalainen, A., Tammilehto, L., Mattson, K., Vainio, H., and Knuutila, S. 1998. DNA gains in 3q occur frequently in squamous cell carcinoma of the lung, but not in adenocarcinoma. *Genes Chromosomes Cancer* **22**: 79–82.
- Bourdon, J.C. 2007. p53 and its isoforms in cancer. *Br. J. Cancer* **97**: 277–282.
- Bourdon, J.C., Fernandes, K., Murray-Zmijewski, F., Liu, G., Diot, A., Xirodimas, D.P., Saville, M.K., and Lane, D.P. 2005. p53 isoforms can regulate p53 transcriptional activity. *Genes & Dev.* **19**: 2122–2137.
- Deyoung, M.P. and Ellisen, L.W. 2007. p63 and p73 in human cancer: Defining the network. *Oncogene* **26**: 5169–5183.
- Deyoung, M.P., Johannessen, C.M., Leong, C.O., Faquin, W., Rocco, J.W., and Ellisen, L.W. 2006. Tumor-specific p73 up-regulation mediates p63 dependence in squamous cell carcinoma. *Cancer Res.* **66**: 9362–9368.
- Di Como, C.J., Gaiddon, C., and Prives, C. 1999. p73 function is inhibited by tumor-derived p53 mutants in mammalian cells. *Mol. Cell. Biol.* **19**: 1438–1449.
- Flores, E.R., Tsai, K.Y., Crowley, D., Sengupta, S., Yang, A., McKeon, F., and Jacks, T. 2002. p63 and p73 are required for p53-dependent apoptosis in response to DNA damage. *Nature* **416**: 560–564.
- Flores, E.R., Sengupta, S., Miller, J.B., Newman, J.J., Bronson, R., Crowley, D., Yang, A., McKeon, F., and Jacks, T. 2005. Tumor predisposition in mice mutant for p63 and p73: Evidence for broader tumor suppressor functions for the p53 family. *Cancer Cell* **7**: 363–373.
- Ghosh, A., Stewart, D., and Matlashewski, G. 2004. Regulation of human p53 activity and cell localization by alternative splicing. *Mol. Cell. Biol.* **24**: 7987–7997.
- Grob, T.J., Novak, U., Maise, C., Barcaroli, D., Luthi, A.U., Pirmia, F., Hugli, B., Graber, H.U., De Laurenzi, V., Fey, M.F., et al. 2001. Human  $\Delta$ Np73 regulates a dominant negative feedback loop for TAp73 and p53. *Cell Death Differ.* **8**: 1213–1223.
- Guertin, D.A. and Sabatini, D.M. 2007. Defining the role of mTOR in cancer. *Cancer Cell* **12**: 9–22.
- Hibi, K., Trink, B., Patturajan, M., Westra, W.H., Caballero, O.L., Hill, D.E., Ratovitski, E.A., Jen, J., and Sidransky, D. 2000. AIS is an oncogene amplified in squamous cell carcinoma. *Proc. Natl. Acad. Sci.* **97**: 5462–5467.
- Innocente, S.A. and Lee, J.M. 2005. p73 is a p53-independent, Sp1-dependent repressor of cyclin B1 transcription. *Biochem. Biophys. Res. Commun.* **329**: 713–718.
- Jacobs, W.B., Kaplan, D.R., and Miller, F.D. 2006. The p53 family in nervous system development and disease. *J. Neurochem.* **97**: 1571–1584.
- Jost, C.A., Marin, M.C., and Kaelin Jr., W.G. 1997. p73 is a simian [correction of human] p53-related protein that can induce apoptosis. *Nature* **389**: 191–194.
- Keyes, W.M., Vogel, H., Koster, M.I., Guo, X., Qi, Y., Petherbridge, K.M., Roop, D.R., Bradley, A., and Mills, A.A. 2006. p63 heterozygous mutant mice are not prone to spontaneous or chemically induced tumors. *Proc. Natl. Acad. Sci.* **103**: 8435–8440.
- Leong, C.O., Vidnovic, N., DeYoung, M.P., Sgroi, D., and Ellisen, L.W. 2007. The p63/p73 network mediates chemosensitivity to cisplatin in a biologically defined subset of primary breast cancers. *J. Clin. Invest.* **117**: 1370–1380.
- Liu, S.S., Chan, K.Y., Cheung, A.N., Liao, X.Y., Leung, T.W., and Ngan, H.Y. 2006. Expression of  $\Delta$ Np73 and TAp73 $\alpha$  independently associated with radiosensitivities and prognosis in cervical squamous cell carcinoma. *Clin. Cancer Res.* **12**: 3922–3927.
- Massion, P.P., Taflan, P.M., Jamshedur Rahman, S.M., Yildiz, P., Shyr, Y., Edgerton, M.E., Westfall, M.D., Roberts, J.R., Pietenpol, J.A., Carbone, D.P., et al. 2003. Significance of p63 amplification and overexpression in lung cancer development and prognosis. *Cancer Res.* **63**: 7113–7121.
- McKeon, F. and Melino, G. 2007. Fog of war: The emerging p53 family. *Cell Cycle* **6**: 229–232.
- Mills, A.A. 2006. p63: Oncogene or tumor suppressor? *Curr. Opin. Genet. Dev.* **16**: 38–44.
- Moll, U.M. and Slade, N. 2004. p63 and p73: Roles in development and tumor formation. *Mol. Cancer Res.* **2**: 371–386.
- Murray-Zmijewski, F., Lane, D.P., and Bourdon, J.C. 2006. p53/p63/p73 isoforms: An orchestra of isoforms to harmonize cell differentiation and response to stress. *Cell Death Differ.*

- 13:** 962–972.
- Ozaki, T. and Nakagawara, A. 2005. p73, a sophisticated p53 family member in the cancer world. *Cancer Sci.* **96:** 729–737.
- Racek, T., Mise, N., Li, Z., Stoll, A., and Putzer, B.M. 2005. C-terminal p73 isoforms repress transcriptional activity of the human telomerase reverse transcriptase (hTERT) promoter. *J. Biol. Chem.* **280:** 40402–40405.
- Rocco, J.W., Leong, C.O., Kuperwasser, N., DeYoung, M.P., and Ellisen, L.W. 2006. p63 mediates survival in squamous cell carcinoma by suppression of p73-dependent apoptosis. *Cancer Cell* **9:** 45–56.
- Rosenbluth, J.M., Mays, D.J., Pino, M.F., Tang, L.J., and Pietenpol, J.A. 2008. A gene signature-based approach identifies mTOR as a regulator of p73. *Mol. Cell. Biol.* doi: 10.1128/MCB.00305-8.
- Salimath, B., Marme, D., and Finkenzeller, G. 2000. Expression of the vascular endothelial growth factor gene is inhibited by p73. *Oncogene* **19:** 3470–3476.
- Senoo, M., Manis, J.P., Alt, F.W., and McKeon, F. 2004. p63 and p73 are not required for the development and p53-dependent apoptosis of T cells. *Cancer Cell* **6:** 85–89.
- Strano, S., Munarriz, E., Rossi, M., Castagnoli, L., Shaul, Y., Sacchi, A., Oren, M., Sudol, M., Cesareni, G., and Blandino, G. 2001. Physical interaction with Yes-associated protein enhances p73 transcriptional activity. *J. Biol. Chem.* **276:** 15164–15173.
- Strano, S., Monti, O., Pediconi, N., Baccharini, A., Fontemaggi, G., Lapi, E., Mantovani, F., Damalas, A., Citro, G., Sacchi, A., et al. 2005. The transcriptional coactivator Yes-associated protein drives p73 gene-target specificity in response to DNA damage. *Mol. Cell* **18:** 447–459.
- Suh, E.K., Yang, A., Kettenbach, A., Bamberger, C., Michaelis, A.H., Zhu, Z., Elvin, J.A., Bronson, R.T., Crum, C.P., and McKeon, F. 2006. p63 protects the female germ line during meiotic arrest. *Nature* **444:** 624–628.
- Talos, F., Nemaierova, A., Flores, E.R., Petrenko, O., and Moll, U.M. 2007. p73 suppresses polyploidy and aneuploidy in the absence of functional p53. *Mol. Cell* **27:** 647–659.
- Tomasini, R., Tsuchihara, K., Wilhelm, M., Fujitani, M., Rufini, A., Cheung, C.C., Khan, F., Itie-Youten, A., Wakeham, A., Tsao, M.-S., et al. 2008. TAp73 knockout shows genomic instability with infertility and tumor suppressor functions. *Genes & Dev.* (this issue). doi: 10.1101/gad.1695308.
- Uramoto, H., Wetterskog, D., Hackzell, A., Matsumoto, Y., and Funahashi, K. 2004. p73 competes with co-activators and recruits histone deacetylase to NF-Y in the repression of PDGF  $\beta$ -receptor. *J. Cell Sci.* **117:** 5323–5331.
- Yang, A., Kaghad, M., Wang, Y., Gillett, E., Fleming, M.D., Dotsch, V., Andrews, N.C., Caput, D., and McKeon, F. 1998. p63, a p53 homolog at 3q27-29, encodes multiple products with transactivating, death-inducing, and dominant-negative activities. *Mol. Cell* **2:** 305–316.
- Yang, A., Schweitzer, R., Sun, D., Kaghad, M., Walker, N., Bronson, R.T., Tabin, C., Sharpe, A., Caput, D., Crum, C., et al. 1999. p63 is essential for regenerative proliferation in limb, craniofacial and epithelial development. *Nature* **398:** 714–718.
- Yang, A., Walker, N., Bronson, R., Kaghad, M., Oosterwegel, M., Bonnin, J., Vagner, C., Bonnet, H., Dikkes, P., Sharpe, A., et al. 2000. p73-deficient mice have neurological, pheromonal and inflammatory defects but lack spontaneous tumours. *Nature* **404:** 99–103.
- Zaika, A.I., Slade, N., Erster, S.H., Sansome, C., Joseph, T.W., Pearl, M., Chalas, E., and Moll, U.M. 2002.  $\Delta$ Np73, a dominant-negative inhibitor of wild-type p53 and TAp73, is up-regulated in human tumors. *J. Exp. Med.* **196:** 765–780.
- Zeng, X., Chen, L., Jost, C.A., Maya, R., Keller, D., Wang, X., Kaelin Jr., W.G., Oren, M., Chen, J., and Lu, H. 1999. MDM2 suppresses p73 function without promoting p73 degradation. *Mol. Cell. Biol.* **19:** 3257–3266.