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## PERSPECTIVE

# $\Delta Np73\beta$ puts the brakes on DNA repair

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**Mammalian cells are barraged with endogenous metabolic byproducts and environmental insults that can lead to nearly a million genomic lesions per cell per day. Networks of proteins that repair these lesions are essential for genome maintenance, and a compromise in these pathways propagates mutations that can cause aging and cancer. The p53 tumor suppressor plays a central role in repairing the effects of DNA damage, and has therefore earned the title of “guardian of the genome.” In this issue of *Genes & Development*, Wilhelm and colleagues (pp. 549–560) demonstrate that p73—an older sibling of p53—inhibits pathways that resolve DNA double-strand breaks.**

## p53 and its relatives

Consisting of only three members, p53 and p53-like (p63 and p73) transcription factors make up a small but influential family. p53-related proteins share three highly conserved motifs: an N-terminal transactivation (TA) domain, a core DNA-binding domain, and a C-terminal oligomerization domain (Lunghi et al. 2009). p63 and p73—the more ancient members of the family—contain a sterile  $\alpha$  motif that is not present in the more recently evolved member, p53. The *p53*, *p63*, and *p73* genes each express multiple isoforms due to usage of alternative promoters at the N terminus and various splicing events at the C terminus. The *p73* gene, for example, contains dual promoters, and use of the transcriptional start site located upstream of exon 1 produces TAp73 isoforms containing a p53-like TA domain, whereas use of an internal transcriptional start site downstream from exon 3 gives rise to the truncated  $\Delta Np73$  isoforms lacking this p53-like TA domain. Furthermore, a complex series of splicing events at the C terminus subdivides both the TAp73 and  $\Delta Np73$  classes into  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\theta$ ,  $\zeta$ , and  $\eta$  isoforms (Lunghi et al. 2009).

Despite their structural homology—which is most pronounced within the central DNA-binding domain—p53 family members have distinct biological functions. p53

plays an undisputed role as a tumor suppressor, as it is frequently lost or inactivated in human cancer. Furthermore, p53-deficient mice are highly susceptible to spontaneous tumors (Donehower et al. 1992). In contrast, the role of p63 and p73 in cancer has been more elusive. Lack of p63 is lethal, and mice are born without limbs or stratified epithelia and its associated structures (Mills et al. 1999; Yang et al. 1999). Although this severe developmental phenotype led to the discovery that *p63* mutations cause seven different developmental syndromes in humans (Rinne et al. 2007), it has hampered a direct analysis of tumor predisposition in mice completely lacking p63. Nonetheless, it is clear that *p63* heterozygous mutant mice do not have a tumor-prone phenotype comparable with that characteristic of *p53* heterozygous mutant mice (Flores et al. 2005; Perez-Losada et al. 2005; Keyes et al. 2006). p73 also functions during embryogenesis, as *p73* homozygous mutant mice have neurological and inflammatory abnormalities, and frequently succumb to an early death. Although it was reported initially that p73-deficient mice were not predisposed to spontaneous tumors (Yang et al. 2000), a later report indicated that these mice were slightly tumor-prone, and that mice heterozygous for both *p63*- and *p73*-null alleles develop tumors with decreased latency, with the wild-type alleles frequently being lost (Flores et al. 2005). While these studies lend some support for a tumor-suppressive role for these more recently discovered members of the p53 family, they were designed to completely disrupt *p63* and *p73*, and therefore are not able to address the role of individual isoforms. With the recent availability of isoform-specific  $\Delta N$  and TA mouse models—as developed by Wilhelm et al. (2010) for  $\Delta Np73$ —the function of individual family members has been further defined.

## The DNA damage response (DDR)

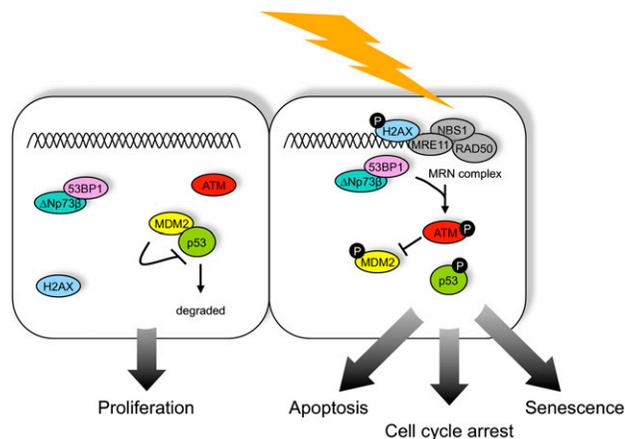
p53's tumor-suppressive function is attributed in large part to its role in the DDR (Fig. 1). Under normal cellular conditions, p53 levels are kept in check by MDM2-mediated degradation (Momand et al. 1992; Jones et al. 1995; Montes de Oca Luna et al. 1995). In response to dsDNA breaks induced by DNA-damaging agents such as anti-cancer therapeutic compounds and ionizing radiation, the MRN (MRE11–RAD50–NBS1) complex localizes to damaged sites and mediates activation of the protein kinase ataxia telangiectasia mutated (ATM). Activated ATM phosphorylates MDM2, thereby targeting it

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**Figure 1.** Model for the role of  $\Delta Np73\beta$  in the DDR. The data presented by Wilhelm et al. (2010) support a model in which  $\Delta Np73\beta$  inhibits ATM-p53 signaling. (Left) In normal cells,  $\Delta Np73\beta$  interacts with 53BP1, and p53 activity is kept in check via MDM2-mediated degradation. (Right) In response to dsDNA breaks triggered by DNA damage, the  $\Delta Np73\beta$ :53BP1 complex is recruited to sites of DNA damage, ATM is activated, and MDM2's inhibitory effect on p53 is alleviated; in the absence of  $\Delta Np73\beta$ , this pathway is enhanced. Although p53 is localized to DNA damage-induced foci under physiological conditions, this association is clearly not needed for 53BP1 localization, as 53BP1 localizes to sites of DNA damage even in the absence of  $\Delta Np73\beta$ .

for degradation and releasing its constraints on p53. ATM also directly modulates p53 via phosphorylation of Ser 15, priming p53 for further modifications and activation (Meek 2009). Efficient activation of ATM requires the DNA damage checkpoint protein 53BP1. When 53BP1 is depleted, ATM can no longer undergo efficient autophosphorylation and activation (Wilson and Stern 2008). Indeed, deficiency of 53BP1 sensitizes cells to ionizing radiation and enhances tumorigenesis in vivo (Ward et al. 2003).

In the study in this issue of *Genes & Development*, Wilhelm et al. (2010) generated mice that are specifically lacking the  $\Delta Np73$  class of p73 proteins. They demonstrate a neuroprotective role for  $\Delta Np73$ , in agreement with previous reports (Pozniak et al. 2000; Tissir et al. 2009). Furthermore, Wilhelm et al. (2010) discovered that  $\Delta Np73\beta$  inhibits p53 activation via a direct interaction with 53BP1, thus incorporating  $\Delta Np73\beta$  in the growing network of proteins regulating the p53-dependent DDR.

A role for p73 in the DDR has long been recognized. Flores et al. (2002) demonstrated that, in response to DNA damage, mouse embryonic fibroblasts (MEFs) deficient for p73 are partially resistant to apoptosis, and that the combined lack of both p63 and p73 impairs p53-dependent apoptosis in cultured cells and in vivo. Conversely, Senoo et al. (2004) found that, in the context of T cells in vivo, p53-mediated apoptosis was unaffected by depletion of p63 and/or p73. These findings suggest that the role of p73 and p63 in modulating p53-mediated apoptosis might not be a generalized feature, but rather is highly influenced by the cellular context. The above work, although elegant, does not address the extent to which individual p73 isoforms affect p53-mediated responses.

Having engineered a mouse model lacking  $\Delta Np73$  isoforms, and observing neuronal phenotypes suggestive of cellular depletion, Wilhelm et al. (2010) found that  $\Delta Np73^{-/-}$  MEFs were indistinguishable from wild-type controls. However, treatment with DNA-damaging agents that induce double-strand breaks revealed that cells lacking  $\Delta Np73$  had enhanced sensitivity; this result was recapitulated in  $\gamma$ -irradiated  $\Delta Np73^{-/-}$  thymocytes, and further via siRNA knockdown of  $\Delta Np73$  in U2OS cells, a human osteosarcoma cell line with wild-type p53. The enhanced sensitivity to DNA damage was reversed in a  $p53^{-/-}$  background, indicating that  $\Delta Np73$  functions as a negative regulator of p53-dependent apoptosis. The augmented apoptotic response was accompanied by increased ATM phosphorylation. Wilhelm et al. (2010) demonstrated that endogenous  $\Delta Np73\beta$  binds 53BP1, and furthermore found that, upon  $\Delta Np73$  depletion, localization of 53BP1 to foci of double-stranded breaks is enhanced. The ability of  $\Delta Np73$  to compromise p53-dependent apoptosis in MEFs had been demonstrated earlier (Petrenko et al. 2003). However, the relationship between  $\Delta Np73$  and 53BP1 is intriguing and suggests a deeper involvement of  $\Delta Np73$  in the DDR than previously appreciated. Furthermore, since  $\Delta Np73$  transcription is activated via p53 and TAp73 (Kartasheva et al. 2002; Nakagawa et al. 2003), a reasonable conclusion from the findings of the Mak group (Wilhelm et al. 2010) is that there is a negative feedback loop between p73 and p53: Activated p53 initiates transcription of  $\Delta Np73$ ;  $\Delta Np73$  binds 53BP1, thereby reducing levels of phosphorylated ATM and stabilizing MDM2, and, ultimately, inactivating p53.

By overexpressing  $\Delta Np73$ , Pozniak et al. (2000) were able to rescue neuronal cells from p53-induced apoptosis. This implies that  $\Delta Np73$  exerts its neuroprotective role via its ability to inhibit p53-dependent apoptosis. However, Pozniak et al. (2000) also showed that, in cultured cells,  $\Delta Np73\beta$  can interact directly with p53, and therefore they attributed the rescued phenotype to this interaction. In the current study, Wilhelm et al. (2010) show an interaction between  $\Delta Np73\beta$  and 53BP1. Since it has been shown that p53 can interact directly with 53BP1 (Iwabuchi et al. 1994; Derbyshire et al. 2002), the relationship between these three partners—including ATM and MDM2—might not be as straightforward as  $\Delta Np73\beta \rightarrow 53BP1 \rightarrow ATM \rightarrow MDM2 \rightarrow p53$ , but rather, these players might function as dynamic complexes in which the stoichiometry dictates the various outcomes of the DDR. It would be interesting to determine whether TAp73, as well as TAp63 and  $\Delta Np63$  isoforms, also interacts with 53BP1, since they share the 53BP1-interacting region found in p53 and  $\Delta Np73$ , as well as to assess whether mutation of this region—for example, as found in patients with split-hand-foot malformation (SHFM) caused by p63 mutations—precludes its interaction with 53BP1.

### Senescence as a tumor-suppressive mechanism

When Wilhelm et al. (2010) transformed  $\Delta Np73^{-/-}$  MEFs by expressing E1A and RAS<sup>V12</sup>, they noted a significant

delay in tumor initiation, as well as a decrease in tumor size compared with wild-type controls. Surprisingly, the reduced capacity of  $\Delta$ Np73<sup>-/-</sup> MEFs to form tumors was not attributed to a higher level of apoptosis, but instead to enhanced cellular senescence, as demonstrated by increased expression of the senescence markers p16<sup>Ink4a</sup>, senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -gal), and DcR2. Cellular senescence provides a potent tumor-suppressive mechanism in vivo (Collado and Serrano 2006). Senescent cells are observed in premalignant lesions in humans, and escape from this tumor-protective barrier (in response to activation of oncogenes or inactivation of tumor suppressors) is a prerequisite for malignancy.

Previous studies have also implicated p53 family members in cellular senescence. Senescent cells express robust levels of p53, and p53 deficiency compromises senescence, leading to cellular transformation and tumorigenesis. It was also shown that deficiency of p63 induces a program of cellular senescence, and that conditional ablation of p63 in proliferative cells of the epidermis leads to accelerated aging in vivo (Keyes et al. 2005). As cellular senescence protects from malignancy, perhaps this explains the observation that mice with haploid levels of p63 are not prone to spontaneous or chemically induced carcinogenesis (Keyes et al. 2006). It has been shown recently which p63 isoforms mediate the senescence response. By engineering a TAp63 conditional mouse model, Guo et al. (2009) discovered that TAp63 isoforms are both necessary and sufficient for inducing senescence in MEFs. Yet, in a distinct cellular context, TAp63 is essential for primary oocyte death in response to DNA damage (Suh et al. 2006). DeYoung et al. (2006) brought p73 into the picture, as they found that depletion of  $\Delta$ Np63 in primary keratinocytes induced cellular senescence in a TAp73-dependent manner, yet in squamous cell carcinoma cells, depletion of  $\Delta$ Np63 induced apoptosis independently of TAp73. These results suggested that p53-related proteins affect distinct pathways modulating both cellular senescence and apoptosis, consistent with the findings of Wilhelm et al. (2010) in different settings. In light of these earlier studies, it would be interesting to determine whether loss of  $\Delta$ Np73 affects the balance between apoptosis and senescence in an in vivo setting.

The p53 gene is lost in the majority of human cancers, yet the p63 and p73 loci are typically intact. This suggests that modulation of p63 and/or p73 activities may be promising in the clinic. Inducible expression of TAp63 induces p21-mediated cellular senescence that causes abrupt tumor regression in vivo (Guo et al. 2009). Importantly, TAp63-mediated cellular senescence in this setting is completely independent of p53. The study by Wilhelm et al. (2010) suggests that  $\Delta$ Np73 $\beta$  works against ATM-p53-mediated tumor suppression. It would be interesting to determine whether depletion of  $\Delta$ Np73 using an inducible RNAi strategy could inhibit progression of tumors that were already established, as well as to assess whether depletion of  $\Delta$ Np73 could inhibit the growth of tumors lacking p53, as was demonstrated for TAp63 (Guo et al. 2009).

TAp73<sup>-/-</sup> and TAp73<sup>+/-</sup> mice are tumor-prone, and the wild-type allele is typically lost in the heterozygotes (Tomasini et al. 2008). This and other findings have established TAp73 as a tumor suppressor. In contrast, a predisposition to spontaneous tumors has not been reported for  $\Delta$ Np73<sup>-/-</sup> mice (Tissir et al. 2009; Wilhelm et al. 2010). Rather,  $\Delta$ Np73 seems to function as an oncogene. Several observations support this claim.  $\Delta$ Np73 is overexpressed in human cancers (Buhlmann and Putzer 2008). In lung cancer and neuroblastoma,  $\Delta$ Np73 is correlated with poor prognosis (Casciano et al. 2002; Uramoto et al. 2004), and recurrence of cervical cancer is more frequent in  $\Delta$ Np73-positive patients (Liu et al. 2006). By targeting  $\Delta$ Np73 to the liver, Tannapfel et al. (2008) developed a model for hepatic cell carcinoma. In contrast,  $\Delta$ Np73 ablation was found to inhibit proliferation of cancer cells in vivo (Emmrich et al. 2009). The current study by Wilhelm et al. (2010) further strengthens an oncogenic role for  $\Delta$ Np73. Additionally, they provide a mechanistic basis for this potential with the finding that  $\Delta$ Np73 acts as a negative regulator of p53-mediated apoptosis via the DNA damage checkpoint protein 53BP1.

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## Vernersson-Lindahl and Mills

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