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News and Commentary

p73: regulator in cancer and neural development

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p73 is a member of the recently identified p53 family of genes that includes *p53*, *p73* and *p63*. Unlike p53, which in most cells is present as a single protein isoform, there are many different p73 (and p63) protein isoforms. The various p73 isoforms are the result of both alternative splicing of the C-termini and the use of two different promoters (reviewed in Irwin and Kaelin[1] and Melino *et al.*[2,3]). Interestingly, the various forms of p73 fall into two classes. First, there are the full-length, or TA, forms that are most similar to p53. Like p53, the TAp73 proteins can induce cell death, at least in part, through the activation of downstream target genes important in mediating cell cycle arrest and apoptosis. In contrast, the second class of p73 proteins, ΔNp73, or 'short forms,' lack the N-terminal transactivation domain found in TAp73 (Figure 1a). ΔNp73 proteins do not turn on the downstream target genes activated by TAp73 and p53. As a result, the ΔNp73 proteins cannot induce apoptosis, but instead appear to have antiapoptotic properties and have thus been referred to as 'survival' proteins. In fact, the ΔNp73 proteins can act as 'dominant-negative' inhibitors that block the function of the full-length forms of p73, p63 and p53. Thus, *p73* encodes both pro- and antiapoptotic proteins. Why does the *p73* gene encode these two forms of p73, each of which seem to have opposing functions? Emerging data suggest that the relative expression of the various TA and ΔNp73 forms is tightly regulated during both tumorigenesis and development. We are only beginning to understand the roles of these seemingly different proteins, and how they function within the context of the other p53 family proteins. Recent data suggest that these p73 proteins with seemingly paradoxical functions regulate specific cell death pathways that are important in cancer and the response to chemotherapy, as well as the development and maintenance of the nervous system. Specifically, in both cancer cells and neurons, the relative TAp73 : ΔNp73 ratio is crucial in the response to different types of stresses, such as DNA damage and growth factor withdrawal, respectively. Thus, in certain nonmalignant cells, changes in the expression levels of the different p73 proteins may promote tumorigenesis, while in neurons specific p73 perturbations early in life affect development, and later alterations may impair the ability of adult neurons to respond to stress or trauma, possibly leading to neurodegenerative disorders and other disease states. Importantly, manipulating the expression of the pro- and antiapoptotic forms of p73 might prove useful in therapies aimed at cancers and some neurological disorders.

p73 in the context of its family

Most of our knowledge regarding the functions of p73 and p63 comes from cellular studies in which these proteins are overexpressed. Numerous studies have demonstrated that TA-p73 (and TAp63) can, at least when overproduced, activate certain p53-responsive promoters leading to 'p53-like' effects, such as cell cycle arrest and apoptosis (reviewed in Irwin and Kaelin[1], Melino *et al.*[2,3] and Stiewe *et al.*[4]). For example, p73 and p63 can transcriptionally activate several p53-responsive genes implicated in cell-cycle control, DNA repair and apoptosis, including p21, BAX, MDM-2, GADD45, 14-3-3 σ, cyclin G, IGFBP3 and PUMA.[1–4] Interestingly, p73, p63 and p53 vary in terms of the degree to which each of the family members can transactivate these genes. Furthermore, the degree of transactivation for certain genes varies between different isoforms. It will be especially important to determine whether there are genes that are under the control of specific p53 family members rather than by all the three. Such data are being facilitated by advances in genomic technologies such as microarray comparisons between p73, p63 and p53 target genes. Understanding the unique target genes for each family member will undoubtedly lead to a better understanding of their unique functions in cancer and disease.

Whereas the TA forms of p73 appear to share many 'p53-like' activities, the ΔN forms, which lack the N-terminal transactivation domain, cannot activate target genes or induce apoptosis and, instead, act as 'dominant negative' inhibitors of corresponding the full-length proteins. There are two nonmutually exclusive mechanisms by which these proteins can have dominant-negative activity (Figure 1b).[5–7] First, the ΔN forms can bind to p53-DNA-binding sites and prevent the binding of the transcription-competent p53 family members (e.g. p53, TAp73 and TAp63). The second possible mechanism is that, while unbound to DNA, the ΔN forms may oligomerize with the TA forms, sequestering the TA-competent family members and thus preventing them from binding to and activating promoters of target genes. Current data suggest that both of these mechanisms can occur *in vivo* for ΔNp73, and play an important role in p73- and p53-mediated cell death in both malignant cells and developing neurons.

p73 and cancer – tumor suppressor and oncogene

Since *p73* was first identified in 1997, the question of whether it is a tumor-suppressor gene or oncogene has been the

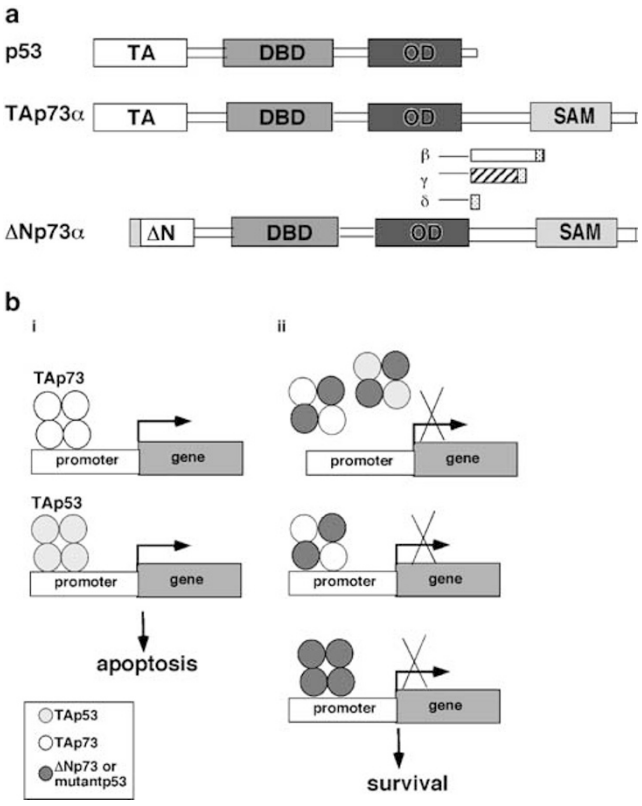

Figure 1 (**a**) Structure of p53 and p73 isoforms. The transactivation (TA), DNA binding (DBD), oligomerization (OD) and sterile-alpha motif (SAM) domains are shown for p53 and p73 protein isoforms. These domains are highly homologous (TA 30%, DBD 79% and OD 38%). Alternative splicing of p73mRNA produces different C-termini (shown are α, β, γ, δ; p73ε, ζ and η are not included in the figure). These forms are identical through the OD; alternative splicing generates different reading frames and coding sequences denoted as different spotted and striped patterns. Only the α and ζ forms contain the SAM domain, which is an important protein–protein interaction domain. ΔNp73 forms are transcribed from a cryptic promoter in intron 3 and these forms lack the TA domain and contain unique amino acids not included in the TA-containing isoforms, represented by the shaded section of the N-terminus. Additional ΔN forms are also generated as a result of alternative splicing of the N-termini. These lack the second and/or third exon, and thus also lack the transactivation domain, and are denoted Δ′Np73. *p63* also generates TA and ΔN forms. (**b**) Interactions between ΔNp73, TAp73, wild-type and mutant p53. (i) Wild-type p53 and TAp73 form oligomers that bind to the promoters of downstream target genes (such as Bax) that induce apoptosis. In certain cells, ΔNp73 acts as a dominant-negative protein by one or more of the mechanisms shown in panel (ii). ΔNp73 (shown as a black circle) can sequester TAp73 (white circle) and p53 (gray circle), preventing the formation of active TAp73 and p53 tetramers, and thus inhibiting the transcription of the 'proapoptotic' target genes. Alternatively, ΔNp73 homo-oligomers (which retain the p73DNA-binding domain) may bind the promoters, directly blocking the site normally bound by TAp73 or p53 active tetramers. Transcription of the 'proapoptotic genes would be inhibited, resulting in 'survival' instead of apoptosis. In a similar manner, in some tumors mutant forms of p53 (like ΔN) can also bind to and inhibit TAp73 (see text)

subject of a great deal of speculation.[4] *p53* is a classical tumor-suppressor gene. It is mutated in more than 50% of human cancers and patients with *p53* germline mutations develop the Li-Fraumeni hereditary cancer syndrome, characterized by an increased risk of developing a spectrum of tumors, including sarcomas, brain tumors and breast cancers. Furthermore, mice lacking one or two copies of p53 (*p53*−/− or *p53*−/+) develop tumors. *p73* is located at chromosome 1p36, a region that is frequently deleted in a variety of human tumors including neuroblastoma, melanoma, breast and colon cancer. The chromosomal location of *p73* together with its similarities to *p53* led to initial speculation that *p73* was a tumor-suppressor gene. However, *p73* does not conform to Knudson's two-hit model because, despite the fact that there is loss of heterozygosity (LOH) of *p73* in a variety of tumors, very extensive studies have revealed only rare *p73* mutations in human tumors and cell lines.[1,2]

Although *p73* gene mutations are rare, the expression and function of different p73 isoforms are clearly altered in certain cancers. Many groups have reported that the levels of p73mRNA and protein are higher in tumor tissue compared with the normal surrounding tissue.[1] Unfortunately, only a subset of these early studies used reagents that would be expected to discriminate between the TA full-length forms of p73 and the shorter ΔN forms. More recent reports have addressed the specific role of ΔNp73. These studies have demonstrated convincingly that ΔNp73 is overexpressed in a subset of tumors, including breast cancer, ovarian cancer, vulval cancer and neuroblastoma.[2,4] Moreover, higher levels of ΔNp73 may be associated with an overall worse clinical outcome, presumably due to the 'antiapoptotic' properties of ΔNp73, and its ability to inactivate both TAp73 and p53.[7,8]

p73 overexpression is not the only abnormality reported in tumors. There are also reports that describe both decreased levels of p73 and inactivation of p73 function in certain cancers. For example, decreased expression of p73 occurs in certain some hematological malignancies. There is LOH for the *p73* gene locus and inactivation of p73 by methylation or deletion in some leukemias and lymphomas (reviewed in Irwin and Kaelin[1]). An additional mechanism by which p73 function is diminished includes the formation of hetero-oligomers (Figure 1b). Some p53 mutant proteins, including some of the mutants most commonly found in human tumors, can inactivate p73. These p53 mutant proteins can bind to TA-p73, sequestering TA-p73 in a transcriptionally inactive complex, and thus, inhibiting its proapoptotic functions.[9,10] Interestingly, the strength of this interaction between p73 and mutant p53 is further influenced by the presence of a polymorphism at p53 codon 72.[10] p53 mutant proteins with an arginine at residue 72 (R72), as opposed to a proline (P72), more strongly bind to and inactivate p73. The stronger p73 binding by p53 R72 mutant proteins may explain the clinical finding that, in patients who are heterozygous in their germline for the p53 R/P polymorphism at residue 72, there is preferential mutation and retention of the p53 R72 allele in tumors, including non-melanoma skin cancers, squamous cell cancers of the head and neck and vulva and bladder cancers (reviewed in Irwin[11]). These findings suggest that inactivation of p73 by certain p53 mutants may provide a selective advantage in promoting tumorigenesis. Thus, under certain circumstances, p73 loss leads to cancer, while, in other cases, activation of p73 expression seems to promote tumorigenesis. This paradox is likely explained by the fact that *p73* encodes both putative tumor suppressor (TA) and putative oncogene (ΔN) p73 isoforms. However, many of the earliest studies of p73 expression in cancer will need to be re-interpreted, since the available reagents at that time used to quantitate p73 expression did not discriminate between the TA and ΔN forms.

The mouse knockout model for p73 might have helped in better defining the role for p73 in tumor development; however, unlike *p53−/−* mice, *p73−/−* mice do not get tumors. Furthermore, since these mice lack all forms of p73, specific questions related to the unique roles of the TA and ΔNp73 isoforms in tumor formation cannot be completely addressed. Ultimately, studies of mice in which specific isoforms of p73 are knocked out or overexpressed as a transgene might provide more insight into the unique roles of TA p73 and ΔNp73 in tumor development. Recent cell-based studies do support a role for ΔNp73 in cellular transformation since overexpression of ΔNp73 leads to malignant transformation of primary fibroblasts (both alone and cooperatively with the oncogene RAS).[12,13] Furthermore, cells that overproduce ΔNp73 form tumors when injected into nude mice. These studies argue that the ΔN form of p73 has oncogenic properties. Thus, current data suggest that TAp73 has many 'p53-like' properties and thus behaves more like a 'tumor suppressor,' while high levels of ΔNp73 promote cellular transformation in a similar manner to many classic oncogenes. How the balance between the TA and ΔN forms is regulated, and perhaps dysregulated, during tumorigenesis is an area of active research. Some oncogenes such as myc and the transcription factor E2F, which is also dysregulated in tumors, directly activate p73; however, clearly, other signals must influence the relative balance between the TA and ΔN proteins.[14–17] Given the complexity of the different p73 isoforms and their opposing functions, future studies of human tumors will need to assess both the specific expression levels and the ratio of the TA : ΔN p73 proteins. In addition, the status of the p53 polymorphism at residue 72 may also influence the relative function of p73 in certain tumor types. These are some of the issues that will need to be addressed before devising therapeutic strategies aimed at increasing or decreasing the relative levels of the pro- and antiapoptotic p73 proteins, respectively.

Role of p73 in chemotherapy sensitivity: p73 and apoptosis

The importance of p53 in chemotherapy-induced apoptosis of cancer cells has been extensively studied and reviewed in detail.[18] Recent studies show that the p53 homologues p73 and p63 are also activated by DNA-damaging agents, including commonly used chemotherapies (reviewed in Irwin[11]). In fact, TAp73 is activated in response to a subset of DNA-damaging drugs, including drugs from numerous classes of anticancer agents, including anthracyclines, topoisomerase I and II inhibitors, microtubule inhibitors and alkylating agents.[11] Many of these drugs appear to activate TA-p73 by inducing post-translational modifications, including phosphorylation (following cisplatin and gamma irradiation treatment) and acetylation (following doxorubicin treatment). These modifications affect both the stability of the TA-p73 protein and its ability to bind to downstream target genes and induce apoptosis. The mechanisms whereby p73 induces apoptosis following chemotherapy treatment include both transcriptional activation of proapoptotic genes such as AIP1, Bax and PUMA (reviewed in Irwin[11]), and activation of the mitochondrial pathway.[19] Importantly, not all cells demonstrate activation of p73 in response to each of these DNA-damaging agents, and thus the p73-dependent response to chemotherapy is likely to be both dependent on the cellular context and the relative abundance of other pro- and antiapoptotic proteins, including the other p53 family proteins.

Several different experimental techniques have been used to demonstrate that the activation of p73 following chemotherapy treatment leads to induction of apoptosis. Jacks and colleagues demonstrated that mouse embryo fibroblasts (MEFs) created from knockout mice lacking either *p73* or *p63* were more resistant to chemotherapy than wild-type cells, and that MEFs in which both *p73* and *p63* were deleted were as resistant to chemotherapy as those lacking *p53*.[20] They further demonstrate that the binding of p53 to the promoters of proapoptotic gene targets such as PERP and BAX requires the cooperative binding of p73 and/or p63 (either at the same site in the promoter or another yet undefined site). Thus, the p53 family proteins must collaborate to activate target genes involved in apoptosis following chemotherapy treatment.

More recent reports using tumor cell lines have more clearly defined the contribution of different p73 isoforms to chemotherapy-induced killing of cells. Specific inactivation of the TA-p73 isoforms in tumor cells leads to chemoresistance. In studies by Irwin *et al.* and Bergamaschi *et al.*, short interfering RNA (siRNA) was used to selectively 'knock out' TA p73 in tumor cells.[21,22] Importantly, the ΔNp73 isoform levels were not affected. These cells with 'knocked out' TAp73 were more resistant to chemotherapy than cells that expressed TAp73. Additional assays using dominant-negative p73 proteins that inhibit TAp73 function likewise made tumor cells more resistant to chemotherapy.[21,22] In contrast, as expected, overproduction of the ΔN isoforms of p73 in tumor cells can block chemotherapy-induced apoptosis.[7] This finding suggests that the reason that tumors with high levels of ΔN p73 have a poor clinical prognosis is that they may inherently be more resistant to anticancer therapies because the 'antiapoptotic' ΔNp73 proteins can inhibit the 'proapoptotic' TAp73 and p53 proteins (as shown in Figure 1b). Therefore, once again, the balance between the pro- and antiapoptotic forms of p73 is important, this time in determining the response to chemotherapy.

In addition to the complex inter-relationship between the TA and ΔN p73 proteins in chemotherapy-induced apoptosis, interactions between tumor-derived p53 mutant proteins and TA-p73 also modulate chemosensitivity (reviewed in Irwin[11]). A subset of p53 mutants known as 'gain of function' mutants not only lose the ability to bind DNA of target genes and induce apoptosis, but also acquire additional activities, including an increased resistance to chemotherapy. At least some of this resistance is likely due to the fact that these mutant p53 proteins can bind to and render TAp73 inactive. As a result, cells are less sensitive to p73-mediated apoptosis following chemotherapy. Thus, certain cancers that express the p53 mutants known to interact with TA-p73 might be expected to be more resistant to chemotherapy due to inactivation of the p73 apoptotic pathway.

Since the status of TAp73, ΔNp73 and p53 clearly affects the relative chemosensitivity or resistance of a tumor cell, therapeutic modulation of these proteins might prove effective

in targeting cancer cells. Specifically, increasing the relative amounts of the 'proapoptotic' p73 isoforms and decreasing the antiapoptotic p73 isoforms and/or the mutant p53 proteins that inactivate p73 might be expected to improve the efficacy of concomitant chemotherapy that requires an intact TAp73-dependent pathway to induce apoptosis. There are numerous junctions in this pathway that might serve as targets. First, screens aimed at identifying small molecule agonists or other drugs that are able to increase the expression of TA-p73 in cancer cells directly or through increasing the activity of upstream activators would be expected to increase chemosensitivity. In tumors that express high levels of ΔNp73, strategies would be aimed at decreasing the levels or activity of the ΔN proteins. Several studies have already shown that the new technique of siRNA can effectively be used to inhibit the expression of numerous genes in the mouse and is far more effective than traditional anti-sense methods. Numerous siRNA delivery systems are currently being developed for use in the clinical setting. Thus, adaptations of siRNA technology may be useful in overcoming chemoresistance attributed to high levels of ΔNp73. In addition, one might consider screening for drugs that can inhibit the expression of ΔNp73 and/or its physical interaction with as yet undetermined regulatory proteins.

Another option to affect the p73-chemosensitivity pathway, specifically in tumors that harbor p53 mutations, would be to target specific p53 mutant genes and/or proteins. Inactivation of these p53 mutant proteins would in theory 'free' TAp73 proteins from mutant p53, allowing TA-p73 to activate target genes and induce apoptosis. At least two alternative methods have been used in cellular assays and might prove useful in future clinical therapies. First, siRNA could be used to downregulate the expression of mutant p53 in human tumors. Martinez *et al.*[23] have demonstrated that siRNA targeted against specific point mutant forms of p53 can be used *in vitro* to 'knock out' mutant p53, while not affecting the expression of wild-type p53. SiRNA could then be tailored to a patient's specific tumor mutation, and in combination with traditional chemotherapy would be predicted to improve the response to treatment by increasing the amount of 'free' TAp73. Another alternative method to target the p73-mutant p53 complex would take advantage of the recently discovered small molecules and compounds that can induce mutant forms of p53 to adopt a wild-type conformation.[24,25] These drugs have been used *in vitro* to restore wild-type function in cell lines expressing mutant proteins. Since the conformation of p53 mutants is the most important determinant of its interaction with and inactivation of p73, rescuing the abnormal conformation of p53 would result in it being unable to bind to p73, and ultimately allowing for a higher level of p73-induced apoptosis following chemotherapy treatment. These therapies would be limited to patients whose tumors expressed one of the mutant forms of p53 known to interact with TAp73.

Role of p73 in the nervous system: p73 and survival

p73 plays a critical role in the pathways that determine cell death in the developing and mature nervous system (reviewed in Jacobs *et al.*[26]). In particular, examination of the *p73−/−* mouse revealed that it does not develop tumors, but instead has significant neurological abnormalities including enlarged ventricles, hippocampal dysgenesis, abnormalities in pheromone-sensory pathways[27] and loss of peripheral sympathetic neurons.[28] Interestingly, most of these phenotypes can be explained by either the absence or loss of neurons; the hippocampal phenotype was associated with the absence of neurons (Cajal–Retzius cells) important for development, the olfactory/pheromone phenotype was associated with the coincident absence of peripheral olfactory neurons,[27] and the *p73−/−* animals displayed enhanced loss of both PNS and CNS neurons postnatally.[28,29] Somewhat unexpectedly, ΔNp73 was the predominant isoform of p73 expressed in the murine fetal nervous system, leading to the conclusion that the neurological abnormalities in the *p73−/−* mice must be due to loss of the antiapoptotic form of p73.

How does the loss of ΔNp73 lead to these abnormalities? A careful analysis of some of these *p73−/−* phenotypes provided possible explanations. Pozniak *et al.*[28,29] examined the sympathetic ganglia and cortex of the *p73−/−* animals, and demonstrated that in both of these systems the loss of ΔNp73, the predominant isoform, led to enhanced neuronal apoptosis, leading them to conclude that this antiapoptotic p73 isoform is necessary for survival and long-term maintenance of both CNS and PNS neurons. Clues as to the underlying mechanism(s) came largely from their studies of peripheral sympathetic neurons, where the enhanced neuronal apoptosis was largely developmental. During nervous system development, neurons are overproduced, and those cells that do not make appropriate connections are 'weeded out' during a process known as naturally occurring cell death. During this period, neurons compete for their required growth factors in order to survive, and die by apoptosis if unsuccessful. For sympathetic neurons, this developmental apoptosis is partially dependent upon p53, and the same process will occur in a culture dish if these neurons are deprived of nerve growth factor or NGF. What Pozniak *et al.*[28] found in this system was that neurons that would normally survive the developmental apoptosis period instead died in the *p73−/−* mice. In cultured wild-type sympathetic neurons, NGF caused a dramatic increase in ΔNp73 levels, which presumably antagonized the apoptotic actions of p53 and promoted survival. In the absence of NGF, the levels of ΔNp73 decreased rapidly and cells died by apoptosis. This apoptosis could be rescued by the introduction of exogenous ΔNp73, arguing that the enhanced sympathetic neuron death seen *in vivo* in *p73−/−* mice was directly due to the loss of this important antiapoptotic protein. A similar direct mechanism likely explains the gradual loss of *p73−/−* CNS cortical neurons in the weeks and months after birth 28. Thus, the expression of different p73 and ΔNp73 isoforms modulates apoptosis and as a result regulates the number of neurons during development.

The mechanism by which ΔNp73 mediates its 'antiapoptotic' or 'survival' function in neurons appears to be, at least in part, similar to how it works in tumor cells as described above. It is likely that ΔNp73 blocks p53-dependent transcriptional activation of proapoptotic genes in neurons potentially by preventing the binding of p53 to these promoters (Figure 1b).

In that regard, Bax, a direct p53 target gene, is required for sympathetic neuron apoptosis.[30] In addition, preliminary evidence suggests that ΔNp73 may also promote survival in a p53-independent manner by acting upstream of the mitochondrial pathways (Lee and Miller, unpublished data). Finally, the proapoptotic TAp63 isoforms may also play an essential role in these apoptotic pathways in the developing nervous system (Jacobs and Miller, unpublished data). Therefore, the balance between p53 and the TA and ΔN forms of p73 and p63 modulate the level of apoptosis in neurons during development.

The role of ΔNp73 in neuronal survival is not limited to developing neurons. *p73*−/− mice exhibit continued neuron loss throughout life.[29] By adulthood, the *p73*−/− mice had developed enlarged ventricles and significant thinning of the cortical hemispheres as well as decreases in other neuronal populations including facial motor neurons. Thus, ΔNp73 appears to be important for the long-term maintenance of adult neurons in both the PNS and CNS. Interestingly, the ventricular enlargement and overall decrease in tissue mass that occurs in the *p73*−/− mouse is reminiscent of human neurodegenerative disorders, raising the possibility that abnormalities in ΔNp73 may predispose to the accelerated loss of neurons that is characteristic of neurodegenerative disorders. Intriguingly, one histopathological study of brain tissue from patients with Alzheimer Disease revealed that the subcellular distribution of p73 in hippocampal neurons was altered in patients with Alzheimer Disease when compared to control samples.[31] In the Alzheimer Disease neurons, p73 immunoreactivity was seen in the nucleus, while normal control neurons appeared to demonstrate more predominant cytoplasmic distribution.

Finally, in addition to an ongoing role in maintenance, ΔNp73 also appears to be required as a survival factor in the response of adult neurons to certain stresses, such as DNA damage and trauma. Many previous reports have demonstrated that p53 is activated in neurons as a result of numerous stresses (reviewed in Jacobs *et al*.[26]); however, until recently, the role of p73 has not been well studied. With regard to DNA damage, overexpression of ΔNp73 rescues cortical neurons from cell death induced by the chemotherapeutic drug campthothecin,[29] and *p73*+/− adult sensory neurons are more sensitive to camptothecin-induced apoptosis than *p73*+/+ neurons (unpublished data, Walsh and Miller). Furthermore, excitotoxicity induced by ischemia or seizures, which is associated with DNA damage, causes apoptosis through pathways involving p53 (reviewed in Jacobs *et al*.[26]), and preliminary data indicate that such excitotoxicity can be rescued by overexpression of ΔNp73 (Zanassi and Miller, unpublished data). As was the case in tumor cells, the upstream pathways involved in p73 DNA damage-induced apoptosis in neurons may include the E2F/Rb and ATM pathways (reviewed in Jacobs *et al*.[26]). With regard to trauma, interactions between ΔNp73 and p53 have also been implicated in the survival of neurons following axonal injury. First, adult dorsal root ganglion neurons from *p73*+/− mice are more sensitive than wild-type littermate neurons to axotomy-induced death (Walsh and Miller, unpublished data). Conversely, loss of p53 in neonatal motor neurons results in a rescue from axotomy-induced death, making the neurons more 'adult-like' in their relative insensitivity to this apoptotic stimuli (reviewed in Jacobs *et al*.[26]) These findings, together with the above data demonstrating the importance of p73 in maintenance of adult neuron number, suggest that ΔNp73 may act to modulate or 'buffer' the level of apoptosis in adult neurons depending on the amount and/or type of cellular damage encountered by a neuron. Thus, these findings support a model where the relative levels or ratio of p53 and ΔNp73 modulate the sensitivity of neurons to different traumatic stimuli throughout life, and perhaps account for the relative invulnerability of neonatal neurons that progressively diminishes throughout aging.

In the nervous system, ΔNp73 is the predominant p73 isoform expressed and clearly plays the role of 'survival' protein. However, as in other cell types, it is the balance between this p73 isoform and the remaining proapoptotic p53 family proteins (p53, TAp63 and to a lesser extent TAp73) and other antiapoptotic family proteins (ΔNp63) that determines the relative apoptotic response during development and later in life to certain stresses. Thus, further elucidation of these pathways may provide a clinical correlation by which p73 levels that determine the vulnerability of neurons to injury and stress may also play active roles in human diseases in which the brain sustains injury such as stroke, neurotrauma, treatment with certain DNA-damaging agents (such as chemotherapy), aging and neurodegenerative disorders.

Conclusion

In summary, although the TAp73 and ΔNp73 proteins have seemingly opposite functions in cells, it is their balance, or ratio, that is most important in determining the apoptotic fate of both cancer cells and neurons. The balance between p53 (wild-type or mutant) and TA and ΔNp73 (and p63) is especially important in cancer and the response to chemotherapy, as well as the pathways controlling neuronal survival and death during development and throughout life. Ultimately, a better understanding of these pathways may lead to the development of therapies targeting p73. For cancers, increasing the levels and/or function of TAp73 may be used to enhance tumor chemosensitivity. In contrast, in the brain enhancing the expression or activity of ΔNp73 in adult neurons may improve their ability to respond to stresses such as trauma and aging. Why *p73* encodes these two seemingly opposite proteins is still somewhat of a mystery. However, the regulation of ΔNp73 and TAp73 in different cells at various points during life is clearly important in determining whether cancer cells or neurons, and perhaps many other types of cells, survive or undergo apoptosis.

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