Mol Neurobiol (2011) 43:139–146
DOI 10.1007/s12035-011-8172-6

p73: A Multifunctional Protein in Neurobiology

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Received: 4 February 2011 / Accepted: 22 February 2011 / Published online: 8 March 2011
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Abstract p73, a transcription factor of the p53 family, plays a key role in many biological processes including neuronal development. Indeed, mice deficient for both TAp73 and ΔNp73 isoforms display neuronal pathologies, including hydrocephalus and hippocampal dysgenesis, with defects in the CA1-CA3 pyramidal cell layers and the dentate gyrus. TAp73 expression increases in parallel with neuronal differentiation and its ectopic expression induces neurite outgrowth and expression of neuronal markers in neuroblastoma cell lines and neural stem cells, suggesting that it has a pro-differentiation role. In contrast, ΔNp73 shows a survival function in mature cortical neurons as selective ΔNp73 null mice have reduced cortical thickness. Recent evidence has also suggested that p73 isoforms are deregulated in neurodegenerative pathologies such as Alzheimer's disease, with abnormal tau phosphorylation. Thus, in addition to its increasingly accepted contribution to tumorigenesis, the p73 subfamily also plays a role in neuronal development and neurodegeneration.

Keyword p73 · Neuronal differentiation · Neural stem cells (NSC) · Neurodegeneration · Alzheimer's Disease

The Molecular Nature of p73

p73 is a member of the p53 family [1], although p73 (and p63) are more closely related to the ancestral form of the

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protein than p53. These three mammalian genes encode transcription factors that play key roles as regulators of proliferation, differentiation, cell death, stem cell renewal, and cell fate commitment [2–4]. All p53 family genes contain the same modular domain structure, including an amino-terminal transactivation domain (TA), a DNA-binding domain and a carboxy-terminal oligomerization domain. The p73 gene contains 15 exons and transcription can be initiated from two N-terminal promoters (Fig. 1). Transcription from the most upstream ATG (promoter 1) generates the transactivating (TA) isoforms, while the second promoter, situated within intron 3, yields amino-terminal truncated proteins (ΔN isoforms). In general, TA and ΔN isoforms display distinct biological activities. The TA isoforms induce cell cycle arrest and apoptosis, and are therefore candidate tumour suppressors [5, 6] while the truncated ΔN isoforms are (generally) pro-survival and favour oncogenic transformation [7]. In addition, both TAp73 and ΔNp73 transcripts undergo alternative C-terminal splicing, generating, in theory, up to seven different variants of each in normal cells, although not all these have been detected at the protein level [8–10]. This complexity has led to significant difficulties in understanding the biology of p73.

It is, however, now generally accepted that ΔN isoforms largely act as dominant negative inhibitors of the activity of TA isoforms, both by competing for consensus elements in promoter DNA and by dimerisation [7, 11]. However, this generalisation must be qualified since the longest ΔNp73α isoform contains a second C-terminal TA domain and can transactivate a set of genes distinct from that recognised by TAp73. Moreover, the α isoforms of both TA and ΔNp73 contain a C-terminal transactivation inhibitory domain, which can compromise the transcriptional activity mediated by the N-terminal TA domain as a result of intramolecular interactions. Thus, to regard the output of p73 expression as the resultant of the ratio between TA and ΔN isoform expression may be an oversimplification.

The Biology of p73: Lessons from Transgenic Mice

The human Trp73 gene was identified in 1997 when it was localised within chromosome 1p36, a region frequently deleted in tumours such as neuroblastoma and other late-stage human cancers [12, 13]. Monosomy 1p36 is also associated with developmental brain abnormalities [14]. Although genes other than p73 within the 1p36 region, such as CHD5, may also contribute to these phenotypes, these data suggest that p73 may have a role in neural development as well as in cancer.

This developmental role for p73 is substantiated by the phenotype of total p73 knockout mice. Unlike the tumour-susceptible p53 null mice, total p73 knockout mice do not develop tumours but show developmental defects in the central nervous system (Table 1) [15], including congenital hydrocephalus and hippocampal dysgenesis, with abnormalities in the CA1–CA3 pyramidal cell layers and the dentate gyrus. In keeping with these anatomical abnormalities, the total $p73^{-/-}$ knockout mice also have defects in both embryonal and adult neurogenesis, suggesting that p73 isoforms may be survival factors for neural stem cells [16]. $p73^{-/-}$ mice also have a reduction in cortical thickness as a consequence of loss of mature cortical neurons [17].

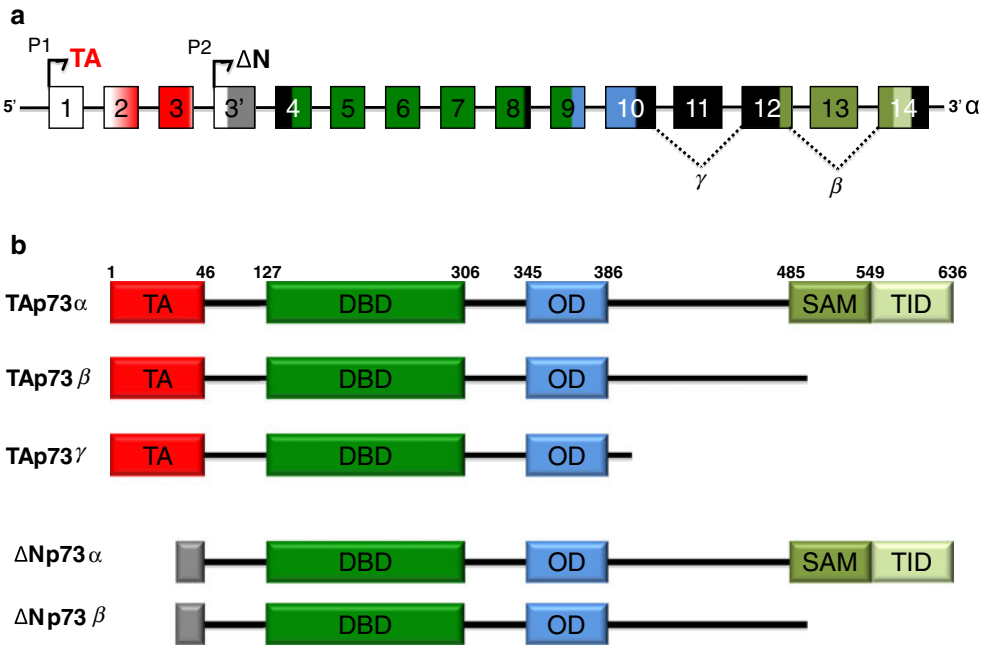

Fig. 1 p73 gene structure. **a** Genomic organisation of p73 and representation of different splicing variants that give rise to the isoforms of p73. The P1 promoter generates the TA isoforms, while the P2 promoter produces the ΔN isoforms. **b** Schematic representation of the domains encoded by the different isoforms of p73. On top, there are indicated the aminoacids included in each domain. *TA* transactivation domain, *DBD* DNA-binding domain, *OD* oligomerization domain, *SAM* SAM domain, *TID* transactivation inhibitory domain

Table 1 Neuronal defects in p73 transgenic mice

	$p73^{-/-}$ (Yang et al. [15], Pozniak et al. [17])		$TAp73^{-/-}$ (Tomasini et al. [22])		$DNp73^{-/-}$ (Wilhelm et al. [19])	
Anatomical defect						
Cortex	Hypoplasia		None		Age-dependence hypocellularity and cortex thinning	
Hippocampus	Dysgenesis		Absence lower blade of dentate gyrus		None	
Ventricular	Third ventricle enlarged and hydrocephalus		None		Enlarged ventricle	
Others	Loss of Cajal-Retzius neurons and Reelin defective. Abnormalities of the pheromone sensory pathway					
Behavioural test	(Talos et al. [16], Wetzel et al. [19])		(Personal communication)		(Personal communication)	
	Young	Aged	Young	Aged	Young	Aged
Burrowing	NT	NT	Reduced	Reduced	NT	Normal
Clasping	Positive	Reduced[a]	Positive	Positive	NT	Positive
Open field	Reduced	Reduced[a]	Reduced	Reduced	NT	Reduced
Barnes Maze	Reduced	Reduced[a]	NT	NT	NT	NT
Hind grip	Loose	Reduced[a]	NT	NT	NT	NT
Light–dark box	Positive	NT	NT	NT	NT	NT

Young mice: 2–4 months old. Aged mice: 15–17 months old

NT not tested

[a] The behavioural experiments were performed in $p73^{+/-}$ mice

This neurological phenotype has been attributed primarily to the loss of ΔNp73 isoforms, since these are expressed in post-mitotic neurons and act as survival factors [11]. Thus, NGF withdrawal or overexpression of p53 in sympathetic cervical ganglion cells leads to a reduction of endogenous ΔNp73 levels and apoptosis which is prevented by overexpression of ΔNp73 [18]. Recently, the generation of ΔNp73 isoform-specific KO mice has confirmed the prosurvival role of ΔNp73 in differentiated mature neurons [19]. Indeed, neuronal density in the motor cortex of $\Delta Np73^{-/-}$ mice is significantly reduced after 10 months of age and progresses with evidence of neurodegeneration [20], although there were no striking hippocampal abnormalities. The same phenotype is also evident in a second $\Delta Np73^{-/-}$ mouse model [21]. In particular, it has been observed that the number of vomeronasal neurons and Cajal-Rezius cells was profoundly reduced, and that the choroid plexuses were atrophic.

However, the severity of the neurological defects observed in the ΔNp73-specific knockout is not as dramatic as that seen in the total $p73^{-/-}$ mice, suggesting that TAp73 may also contribute to the development of the CNS. While cortical thickness in selective TAp73 null mice is normal, they show hippocampal dysgenesis with loss of the lower blade of the dentate gyrus similar to that seen in total $p73^{-/-}$ mice at P14, before the complicating effect of ventricular enlargement further distorts the hippocampal architecture in the total knockout [22]. This anatomical phenotype is reflected in the reduction in neurogenesis in the subgranular zone of the dentate gyrus (Fig. 2), suggesting that TAp73 may be required for neural stem cell proliferation [23]. Indeed, TAp73 has been shown to regulate the negative bHLH Hey2 which is known to sustain maintenance of neural precursors. Thus, the isoform-selective knockout studies suggest that TAp73 and ΔNp73 contribute to CNS development in ways that are only partially overlapping.

Differentiation or Stemness?

Both embryonic and adult neural stem cells (NSC) are primary precursors that have the ability to differentiate into different cell types (neurons, astrocytes and oligodendrocytes) while retaining the capacity to produce identical NSC progeny (self-renewal) [24], and p53 and ΔNp63 have already been implicated in NSC biology [25, 26]. Recently, four independent groups [16, 23, 27, 28] have demonstrated that p73 is also a positive regulator of embryonic and adult NSC and some of this in vivo evidence has been discussed above.

NSC can be cultured in vitro as neurospheres and subsequently differentiated into mature neurons. Neurospheres derived from $p73^{-/-}$ mice are smaller, with a reduced number of cells in S phase and an increase in the

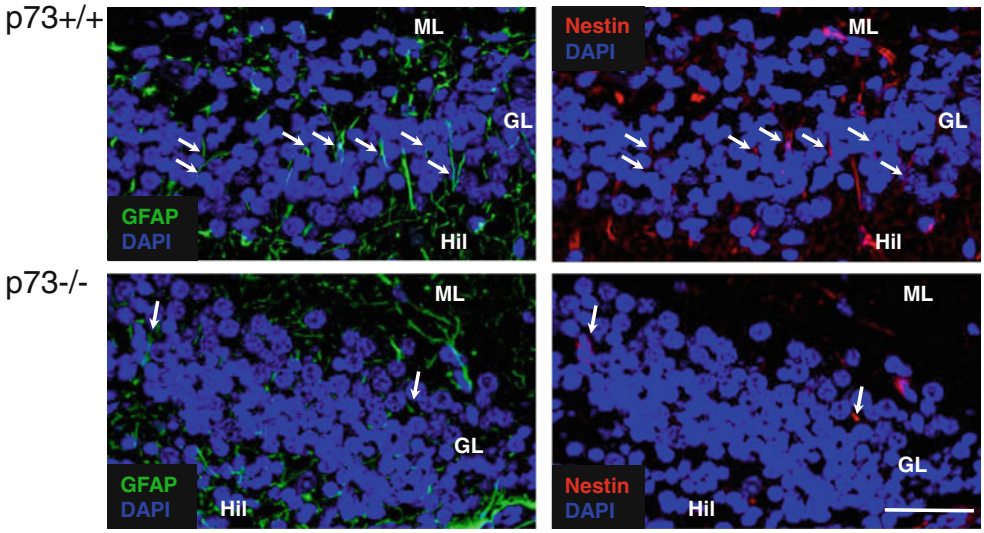

Fig. 2 Reduction of the putative stem cell in the dentate gyrus from p73$^{-/-}$ mice. The dentate gyrus from day 7 after birth (P7) of normal (p73$^{+/+}$) and knockout (p73$^{-/-}$) mice was stained with antibodies to glial fibrillary acidic protein (GFAP) and nestin. *Arrows* indicate double-positive cells. Knockout mice show nearly half of GFAP/Nestin cells, indicating a very reduced stemness potential in these mice. *GL* granular cell layer, *ML* molecular cell layer, *Hil* hilus. *Scale bars* 50 μm

senescent population [16]. At the molecular level, it has been shown that NSC from p73$^{-/-}$ mice have transcriptional dysregulation of Sox-2, Sox-3, Nanog, Notch-I, Notch-2, Hes-5, Jag2 and Deltex, which are all components of signalling pathways involved in the regulation of proliferation and/or self-renewal [29], although further studies are required to address how p73 physiologically regulates these factors. TAp73 is the predominant isoform expressed in embryonic NSC, and endogenous expression of TAp73 increases during differentiation of NSC [27]. Further studies have shown that smaller numbers of neurons can be derived from p73$^{-/-}$ NSC which do not fully differentiate, with defects in arborization of the dendritic tree and in physical connectivity. This is reflected in the anatomy of hippocampal neurons in the dentate gyrus of p73$^{-/-}$ mice in vivo, which show a reduced number of branches when compared to normal mice (Fig. 3).

p73 has also been implicated in oligodendrocyte as well as neuronal differentiation [30], and oligodendrocytic differentiation from p73$^{-/-}$ NSC is also impaired, with lower numbers and poorer quality than those derived from wild type NSC. However, dissociated p73$^{-/-}$ NSC retain the ability to differentiate into neurons, astrocytes and oligodendrocytes, indicating that loss of p73 does not affect the multipotency of NSC.

Another, though perhaps less definitive model implicating p73 in neurogenesis is the terminal differentiation of neuroblastoma cells induced by retinoic acid (RA) and which is associated with an increased expression of TAp73. In addition, ectopic expression of TAp73 itself induces terminal neuronal differentiation. During RA treatment, TAp73 isoforms regulate the N-CAM promoter, while ectopic expression of TAp73 led to a down-regulation of N-MYC and an increased expression of pRB, mimicking the RA effect on these two genes [31], which are crucial for neuroblastoma survival [32, 33].

In conclusion, while recent work indicates a clear requirement for p73, and particularly TAp73 in the maintenance of stemness via a yet not fully identified mechanism both in vivo and in vitro [16, 23, 27, 28], other data suggest an involvement of p73 in neuronal [31] and oligodendrocyte [30] differentiation. These multiple biological activities in the nervous system may reflect the

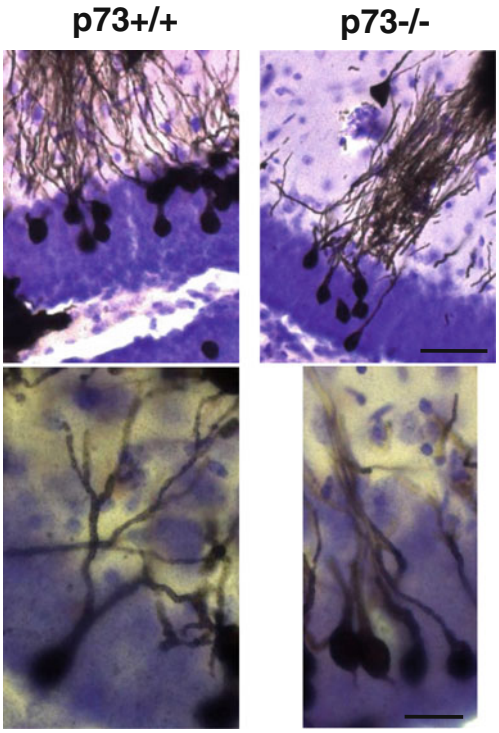

Fig. 3 Hippocampal neuron morphology is altered in the dentate gyrus of knockout (p73$^{-/-}$) mice. Golgi staining of dentate gyrus from normal (p73$^{+/+}$) and p73$^{-/-}$ mice (age=18 days after birth). Knockout mice show reduced branching and connectivity of neurons. A representative photomicrograph is shown. *Scale bars* 100 μm (*top panel*) and 50 μm (*low panel*)

molecular complexity of the 14 protein isoforms of p73, their interactions with each other as well as their interplay with other p53/p63 family members, which are themselves expressed as multiple isoforms. Alternatively, since p73 appears to regulate between 1,000 and 2,000 genes, including 100–200 transcription factors, several apparently divergent pathways could be simultaneously activated.

p73 and Neurodegeneration

During the last 15 years, it has emerged that the p53 family has an important role in several neurodegenerative diseases. Of special interest to us, and on which we will focus, is their role in the most (and increasingly) prevalent form of neurodegeneration, Alzheimer's disease (AD).

AD exists as both familial and sporadic forms. The familial early onset (EOAD) form, accounting for only a small percentage of cases, is inherited via mutations in either the β-amyloid precursor protein (APP) or one of the two presenilins (PS), PS1 and PS2. In contrast, the greatest genetic risk for the sporadic, late onset (LOAD) form is the ε4 allele of apolipoprotein E (APOE) [34]. Recently, genome-wide association studies have identified three additional risk genes, albeit with much weaker effects than APOE; ApoJ/CLU, PICALM and CR1 [35, 36]

Both sporadic and familial forms of the disease are characterised by two brain lesions: senile plaques—extracellular deposits of the β-amyloid (Aβ) peptide; and neurofibrillary tangles (NFTs)—intracellular aggregates of paired helical filaments (PHF) composed of hyperphosphorylated forms of the microtubule associated protein, tau [37]. The appearance of senile plaques precedes that of NFTs. Aβ is derived by proteolytic processing from the APP, with the presenilins being a necessary component of the γ-secretase complex responsible for the final stage of this process [37]. The phosphorylation state of tau regulates its ability to bind microtubules; in its hyperphosphorylated state tau is unbound and eventually polymerises into paired helical filaments, which then aggregate into NFTs. It is emerging that it is not these insoluble aggregates of tau, but rather some soluble form that is the toxic species responsible for neuronal dysfunction and eventually neuronal death [38]. That mutations in APP give rise to increased Aβ production (as do mutations in the presenilins, as subsequently observed), and as senile plaque appearance precedes that of NFTs, the amyloid cascade hypothesis was formulated [39]. This hypothesis, which has not yet been refuted, holds that increased levels of Aβ lead to the hyperphosphorylation of tau which then leads to neuronal dysfunction and eventually neurodegeneration. Attempts to model this cascade of events in mice has for the most part failed, as even when mutant transgenic forms of both APP and PS1 are introduced, despite high levels of Aβ production leading to extensive plaque formation, the aggregation of tau is not observed. It is only when APP, PS1 and human tau are concomitantly over expressed in triple transgenic mice that both plaques and tangles are observed.

The first indication that the p53 family may play a role in AD came in 1996 with the demonstration that intracellular Aβ upregulates p53 in the brains of transgenic mice overexpressing just the Aβ fragment of APP [40]. That same year, the Kosik group examined neurons from a $p53^{-/-}$ mouse, observing that p53 has a role in neuronal differentiation and in tau phosphorylation [41]. In 2001 use of pifithrin-α, an inhibitor of p53-dependent gene transcription was shown to protect neurons against Aβ-induced apoptosis [42]. The p53 protein was also found to be upregulated in the brain of AD sufferers [43], a finding which we later confirmed [44]. In 2004, Caricasole et al. [45] showed that Aβ activates the expression of the p53 target gene encoding the soluble wnt antagonist, Dickkopf-1 (Dkk1) [46], and that knock-down of Dkk1 in primary neurons almost completely blocked Aβ-induced tau phosphorylation, implicating the p53 family in the "amyloid cascade" pathway. In the same year, it was also reported [47] that the p73 protein exhibits an altered subcellular distribution in AD brain. In hippocampal pyramidal neurons of control subjects, p73 immunoreactivity was predominately cytoplasmic, while in AD samples increased levels of p73 were found in the nuclei of pyramidal neurons and in dystrophic neurites.

We employed a simple cell model to show that transcriptionally active forms of p53 are able to induce tau phosphorylation at specifc phosphoepitopes, particularly the AT8/Tau-1 (S199, S202 and S205) and PHF-1 (S396 and S404) sites [44]. We found that this also holds true for p73, with the TA forms increasing tau phosphorylation, while the ΔN forms do not [48]. In this system, we also found that transcriptionally active forms of p63 activate tau phosphorylation, while ΔNp63 forms do not (unpublished observations).

In 2008, the Miller/Kaplan group [49] reported that in brains of aged (16–18 months) heterozygous $p73^{+/-}$ mice, there were substantial increases in tau phosphorylation levels together with filamentous aggregates of hyperphosphorylated tau with similarities to NFTs. When they crossed these haploinsufficent p73 mice with mice harbouring a double mutant form of APP (the TgCRND8 mouse), tau phosphorylation and tau filament formation occurred as early as 1.5 months. This finding is especially remarkable given that Aβ-based mouse models of AD do

not manifest overt tau pathology. It also lends yet further support to the amyloid cascade hypothesis, showing that Aβ lies upstream of tau pathology and also that the cascade of events that Aβ must set into motion, leading to the hyperphosphorylation of tau and subsequent neurodegeneration, involves the p53 family, and in particular p73.

The Miller/Kaplan group went on to show [49] that in primary cortical neurons generated from p73 KO mice the activity of c-jun N-terminal kinase (JNK) increased as the number of WT p73 alleles decreased, and that JNK inhibition decreased tau phosphorylation in these neurons. They propose that, since ΔNp73 can bind and inhibit JNK, which the TA forms of p73 cannot, it is the loss of the ΔN forms of p73 that brings about tau phosphorylation and neurodegeneration. The same group has previously demonstrated that ΔNp73 plays a neuroprotective role in the CNS [17, 50] and also claim that ΔN forms of p73 predominate, at least in the postnatal mouse brain. The loss of one copy of the entire p73 gene results in a reduction in ΔNp73 isoforms leading to an increase in JNK activity.

In support of this claim, there is an extensive literature implicating JNK in AD pathology, e.g. [51–53]. Our group has shown that JNK directly targets tau [54] and also plays a role in the regulation of APP processing [55]. Inhibiting JNK has also been shown to protect against Aβ toxicity in an APP/PS1 brain slice model of AD [56].

There exists one other knock-out mouse with a phenotype that includes neurodegeneration with accompanying aggregates of hyperphosphorylated tau filaments [57]. The deleted gene is Prolylisomerase-1, which is associated with Aβ production and aggregation through its binding with phospho-Thr688 of APP, and tau phosphorylation through interaction with phospho-Thr231 of tau. Of interest, Pin1 also stabilises TAp73 via the c-Abl pathway [58].

Aβ has been shown to activate c-Abl and increase p73 levels [59], while the Swedish mutant form of APP increases expression from both the TA and ΔN promoters of the p73 gene, but results in an overall increase in the TA forms [60]. It appears then that p73 plays a key role in AD and, in particular, that the balance between the TA and ΔN forms is crucial. However, from the above, and other observations such as the fact that p53 transcriptional activity is regulated by the presenilins and that many of the components of the γ-secretase complex are themselves regulated by p53 [61], it would seem unlikely that p73 acts alone. Further investigations into p73 interactions with other p53 family members, in particular p53 itself, within nervous tissues will undoubtedly aid our understanding of its roles in both normal adult brain and in the pathogenic processes underlying Alzheimer's disease.

Conclusion

From these studies, it emerges that p73 is the p53 family member with a fundamental role in central nervous system development and maintenance, and even in its degeneration. Indeed, as shown in Fig. 4, the p73 gene plays a role throughout the neurogenesis process, from neural stem cells to mature postmitotic neurons. Although perhaps simplistic at this stage, these new findings suggest that TAp73 is the isoform essential for neuronal differentiation and maintenance of neural stem cells. In contrast, ΔNp73 seems to play a major role in neuronal survival. However, the phenotype observed in isoform specific knock-out mice is milder than that in the full knock-out mice, indicating that, as in cancer, it is the interaction between p73 isoforms, which ultimately determines the phenotype.

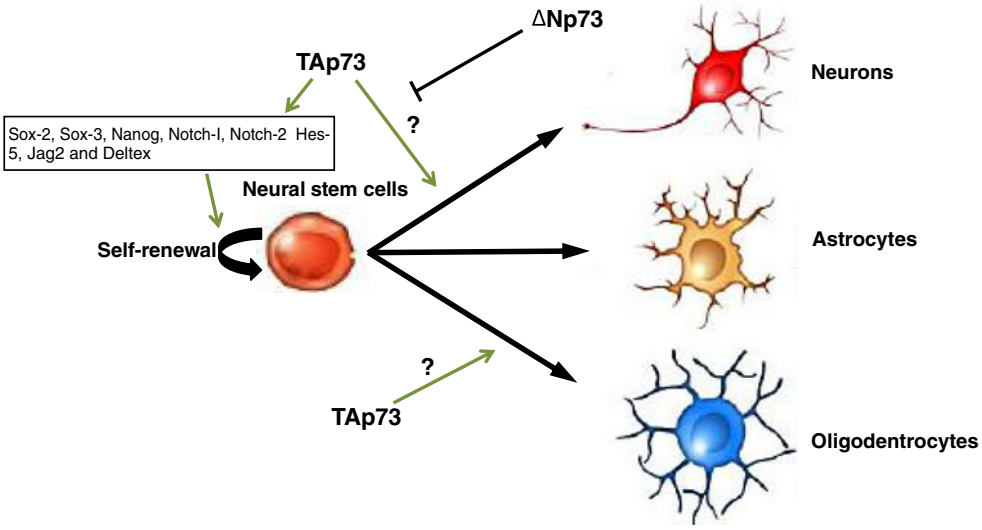

Fig. 4 Role of p73 in neurogenesis. Functional neurons are generated from neural stem cells and then after maturation, integrated in neuronal circuits. TAp73 is essential for neuronal differentiation and maintenance of neural stem cells. ΔNp73 plays a major role both as a survival mechanism as well as yet unknown pathways. *Question marks* indicate that molecular mechanism has not been fully investigated yet

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