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Editorial

p73 is critical for the persistence of memory

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Over a decade ago, the phenotype of the *p73* knockout mouse clearly indicated that *p73* is essential for appropriate brain development. *p73*-deficient mice display *ex vacuo* hydrocephalus and dysgenesis and hypoplasia of the hippocampus and caudal cortex.[1,2] p73 has been implicated in diseases of neurodegeneration, including Alzheimer's disease.[3] The prevailing view regarding the function of p73 in the brain was that the pro-survival mechanism of ΔNp73 was the key to maintaining neural stem cells in the developing and adult brain.[3,4] Four independent groups have now demonstrated that TAp73, the full-length isoform of p73, is critical to maintain neural stem cells and that an appropriate balance of both TAp73 and ΔNp73 is critical to maintain neural stem cells.[1,5–7]

p73 is a structurally complex gene with multiple isoforms.[8] These isoforms can be categorized into two main groups, the full-length TA isoforms with an acidic transactivation domain and the ΔN isoforms that lack the first three exons, including the TA domain. The structural complexity of this gene has led to confusion regarding the function of each of these isoforms in biological processes ranging from embryonic development to cancer. Recently, isoform-specific knockout mice of *p73* have been generated to shed light on the biological functions of each isoform. These mouse models are revealing the contribution of the individual isoforms in tumorigenesis and now in maintenance of stem cells in the brain.[6,9,10]

The *p73*−/− mice exhibit severe defects in the hippocampus, the part of the brain essential for memory and learning.[1,2] Importantly, the *p73*−/− mice performed poorly in multiple cognitive tests designed to assess memory, learning, and sensory motor ability.[1] Although neither TA- nor ΔN-*p73* knock-out mice display severe defects of the *p73*−/− mice, the *TAp73*−/− mice also have brain abnormalities.[1,2,6] Specifically, the lower blade of the dentate gyrus, a critical component of the hippocampus necessary for the formation of memories, is truncated or missing in *TAp73*−/− mice.[6] This phenotype implies that TAp73 is critical for neural stem cell maintenance. Indeed, the *TAp73* isoform is more highly expressed than the *ΔNp73* isoform in neural stem cells.[1,6] To further test the idea that TAp73 maintains neural stem cells, multiple groups used the *p73*−/− mouse model to isolate neural precursors and generate neurospheres.[1,5–7] The neurosphere assay was used to assess the ability of these cells to self-renew, a critical property of stem cells. The *p73*−/− neurospheres were smaller than those derived from wild-type mice, incorporated less BrdU, senesced prematurely, and were thus unable to self-renew.[1,5–7] David Kaplan's lab went one step further and showed by isolating neural precursors from *TAp73*−/− mice that TAp73 is the critical isoform in maintaining neurospheres.[6] Neurospheres derived from *TAp73*−/− mice failed to proliferate robustly and senesced prematurely. These data indicate that TAp73 is critical for the maintenance of neural stem cells. This phenotype is reminiscent of the recently identified role of TAp63 in maintaining stem cells in the dermis (skin-derived precursors, SKPs), which are necessary for wound healing and hair regeneration.[11]

Compensation within gene families has been reported in multiple contexts.[12] In such compensatory mechanisms, loss of one gene within a family of genes leads to elevated expression of another family member.[12] Owing to the well-established role of p53 in controlling cell cycle arrest and proliferation, the levels of p53 were assessed in *p73*−/− neurospheres and were found to be present at wild-type levels, indicating that loss of proliferation in neural stem cells is due to a p53-independent mechanism.[7] To more specifically test this idea, María Carmen Marín's lab generated neurospheres from *p53*−/−;*p73*−/− double-knockout mice. Interestingly, the neurospheres from double-knockout mice were smaller and less proliferative than those derived from *p53*−/− mice.[7] These results indicate that p73 has a p53-independent role in maintaining neural stem cells. This finding is reminiscent of the p53-independent function of TAp63 in maintaining epidermal stem cells and preventing premature aging in the skin.[11] These results further emphasize the complex relationship between the p53 family members, and the critical roles of the TA isoforms of *p63* and *p73* in stem-cell maintenance.

The finding showing that loss of *p53* does not rescue the proliferation defect in *p73*−/− neurospheres suggests that p73, and perhaps TAp73, transactivates novel target genes that maintain neural stem cells. The Notch pathway has been shown to be critical for the maintenance of neural stem cell number and the regulation of stem cell renewal. Indeed, Ute Moll and Gerry Melino's labs found that *Notch2* mRNA and other components of the pathway were found to be down-regulated in neural precursors derived from *p73*−/− mice.[1,5] Interestingly, Fujitani *et al.*[6] identified *Hey2*, a bHLH protein

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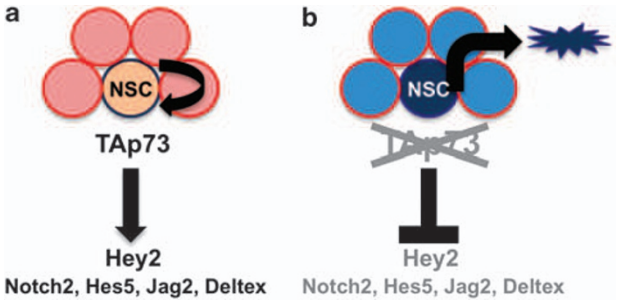

Figure 1 TAp73 maintains neural stem cells in quiescence. (**a**) TAp73 directly transactivates *Hey2* and regulates other components of the Notch pathway to regulate asymmetric cell division and self-renewal of neural stem cells (NSCs). (**b**) In the absence of *TAp73*, TAp73 target genes are not transcriptionally activated and NSCs senesce and differentiate prematurely

that promotes neural stem cell maintenance, as a novel transcriptional target of TAp73 (Figure 1).

p73 has a well-established role in the developing brain. These new findings demonstrate that TAp73 has a critical role in maintaining neural stem cells through transactivation of a novel target gene, *Hey2* (Figure 1). The findings of these four groups have important implications for the formation and maintenance of memories, neurodegeneration, and the aging process in the central nervous system. Recently, TAp63 has been shown to have a similar role in maintaining stem cells that reside in the dermis. Maintenance of these stem cells by TAp63 prevents premature aging of the skin and overall organism. These new data on TAp73 in neural stem cells further illustrate the expanding role of the p53 family in the aging process and in maintaining stem cells in various tissues in quiescence. It will be important to understand the interplay of the p53 family in other stem cell compartments to understand the relationship of the p53 family members in longevity and cancer.

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