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p73 and p63: Estranged relatives?

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Genes p73 and p63 are close relatives. They are very similar in their genomic organization and sequence and encode proteins related to the oncosuppressor gene p53. p73 and p63 use at least two different promoters that direct synthesis of full-length proteins with transactivation potential (TA) and N-terminally truncated (ΔN) proteins. Each group has several members generated by alternative splicing and polyadenylation. TA isoforms can bind and activate p53-responsive genes and promote apoptosis. In contrast, ΔN isoforms are not transcriptionally competent. They are believed to act as dominant negatives, thus promoting cell survival. Unlike p53, p63 and p73 are not mutated in tumors; however, their truncated forms are upregulated.[1] Global p73 knockout mice develop spontaneous tumors, and both TAp73 and ΔNp73 specific knockouts display impaired susceptibilities to DMBA- and MCA-induced carcinogenesis, albeit with a gender bias.[2,3] These data validate a role of p73 as modulator of tumorigenesis. In contrast, the perinatal death of global p63 knockout mice and the lack of isoform-specific mutants have thus far precluded such a validation for p63.

Whereas p73 isoforms are heavily expressed in the developing central nervous system, p63 proteins are detected only at very low levels. Analyses of knockout mice that lack all p73 forms,[4] only TAp73[3] or only ΔNp73[5] have shown that p73 proteins play crucial roles in brain development. Similarly, studies of p63 knockout mice and rare human syndromes such as Ectrodactyly, Ectodermal Dysplasia and Cleft Lip/Palate Syndrome 3 (OMIM 604292) demonstrated that TAp63 and ΔNp63 have powerful pro- and anti-apoptotic effects in non neural tissues, such as skin and limbs.

Despite the weak expression of p63 in the nervous system, reports from the groups of David Kaplan and Freda Miller have implicated p63 in survival of neural stem cells and sympathetic neurons and proposed that, like p73, p63 is a major regulator of neural development.[6,7] To assess the physiological role of p63 in the nervous system, Lena Holembowski et al.,[8] analyzed thoroughly the brain and spinal cord of global p63 knockout mice. By comparing p63 mutants and littermate controls at different developmental stages, they did not find any anatomical abnormality in the CNS of the mutants. p63 deficiency does not increase neuronal death nor does it affect the number of neural stem cells, their proliferation or their ability to differentiate and give rise to neurons, astrocytes or oligodendrocytes. Furthermore, phenotypes of double p63 and p73 mutant animals were simple additions of single mutant phenotypes, with no indication of any genetic interaction or redundancy between p63 and p73. Although negative results are rarely definitive, this battery of new data argues against a significant role for p63 in the CNS. The discrepancy between this study and previous ones could reflect artifacts inherent to experimental systems (i.e., transfections of cultured cells and shRNA knockdown) used in the Kaplan/Miller work.

Intriguingly, a widely acclaimed publication from the same team[9] reported an incidence of hyperphosphorylated Tau-positive profiles reminiscent of neurofibrillary tangles, a hallmark of Alzheimer disease, in aged p73 mutant mice and attributed this neuropathology to loss of ΔNp73. On the other hand, using a ΔNp73-specific knockout together with other models, we and others failed to confirm any link/association between p73 and Tau pathology.

The present work is important in that it clarifies the physiological role of p63 as compared to that of p73. Consistent with their expression patterns, p63 is involved in the development of skin and limbs, whereas p73 is essential to brain development.

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