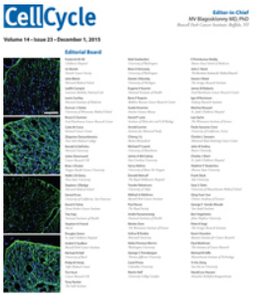

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P73 and P63: The siblings that work together in neurodevelopment

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P73 and P63: The siblings that work together in neurodevelopment

News and Views: Cancino GI, et al. Conditional ablation of p63 indicates that it is essential for embryonic development of the central nervous system. Cell Cycle 2015; 14(20):3270-81; PMID: 26359534. DOI: 10.1080/15384101.2015.1087618.

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The members of the p53 gene family, p73 and p63, participate in multiple biological functions and are key regulators of development. p63 was recognized early on as a master regulator of epidermal development. The deletion of p63 results in the absence of skin, truncated limbs and craniofacial malformations. p73, the p63 sibling, is considered a main player controlling neural development.

However, the role of p63 in brain development has been harder to decipher. Although p63 and p73 are highly similar in structure, function and posttranslational regulation, and both proteins have the ability to control cell cycle and apoptosis, p63 functions during the development of the brain have remained controversial. In this issue of Cell Cycle, Cancino and colleagues induced the conditional and tissue specific ablation of p63 in embryonic neuronal precursors.[1] They obtained convincing data that supports a key function of p63 promoting the survival of cortical precursors and neurons. The authors also show that, in the absence of p63, the truncated ΔNp73 isoform takes a compensatory function, allowing the normal brain development and masking the importance of p63 in brain development.

p63 and p73 are expressed as 2 main isoforms; i) the full length proteins, called TA isoforms which have transactivation domains (TA) essential for their function as transcription factors and ii) the N-terminally truncated (ΔN) isoforms, that lack of a TA domain and can act as dominant negative inhibitors of p53 and TA isoforms. Thus, TA and ΔN isoforms have pro- and anti-apoptotic properties respectively.

Mice deficient in all isoforms of p73 show severe developmental defects, including hippocampal dysgenesis and hydrocephalus, confirmed early on the main role of p73 in controlling neural development.[2] By contrast, p63 null mice, although inviable postnatally, do not have deficits in neural development, showing normal forebrain and embryo cortices,[3] which questions the importance of p63 in the developing brain.

Although the role of p73 in neurodevelopment is complex, the emerging view is that the TAp73 isoforms are involved in hippocampal development, in the maintenance and self-renewal of neural stem/progenitors cells and neuronal differentiation.[4] The ΔNp73 isoforms are essential for survival of neural progenitor cells during nervous system development as well as of postmitotic neurons both embryonic[5] and adult.[2]

In a similar way, while examining the role of p63 protein in during neuronal development, the Kaplan and Miller group found that TAp63 expression mediates apoptosis of sympathetic neurons, and the ΔNp63 expression rescues cortical precursors and newly born cortical neurons from the apoptosis induced by the silencing of p63.[5] In addition, haploinsufficiency as well as conditional acute ablation of p63 induce the death of adult neural precursors, via activation of p53-PUMA pro-apoptotic signaling. Moreover, p63 and p73 functionally interact regulating apoptosis and senescence of neural precursors in a p53-dependent manner. Thus, the coordinated work of the p53 family establishes a correct balance between survival, cell death, senescence and adult neurogenesis.[6] In the adult neural precursors, ΔNp63 acts as a pro-survival protein and its acute deletion impairs cognitive functions.[7] Therefore, by analogy to p73 it was assumed that ΔNp63 was a key isoform in promoting the survival of embryonic cortical precursors, an idea that seemed contradictory with the normal brain of p63 deficient embryos.

In this scenario, the work of Cancino and colleagues is relevant and timely. In agreement with previous results it supports the crucial function of p63 in the survival of neural precursors. It also explains why the absence of p63 from the start of development does not have considerable consequences in brain morphology. A ΔNp73 compensatory increase allows the survival of cortical precursors, while acute ablation of p63 during embryonic development causes apoptosis of cortical precursors and neurons and thinner cortices.

Neuronal developmental death is essential for the correct formation of neuronal networks, and the complex work of p53 family members determines the correct balance between maintenance and self-renewal of neural stem cells, as well as the survival, differentiation and cell death of neuronal precursors and neurons. Although the truncated isoforms ΔNp73 and ΔNp63 have different functions during neuronal development, ΔNp73 can compensate the early loss of ΔNp63. If the system does not have p63 since the beginning, it is perfectly capable of supplying the missing piece and to continue forward. However, when the system is already organized and suddenly suffers the loss of a piece, the consequences are tragic.

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