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CIPF Lecture Series

Brain development: microtubule organization at the transition from proliferation to differentiation

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IRB Barcelona, Spain
04/10/19- 12:30 h
Location: Salón de Actos CIPF (Eduardo Primo Yúfera, 3, 46012 Valencia)

Regulating microtubule nucleation in space and time is crucial for cell proliferation and differentiation. Specific targeting of the microtubule nucleator gamma-TuRC spatially restricts formation of new microtubules to microtubule organizing centers such as the centrosome. Alternatively, gamma-TuRC can be recruited by augmin to nucleate microtubule branches from the lattice of preexisting microtubules. In cycling cells both nucleation pathways contribute to robust spindle assembly, whereas in post-mitotic neurons, as we could recently show, microtubules are nucleated by the augmin pathway, but not centrosomes. Augmin knockout in mice is lethal as a result of mitotic defects at early embryonic stages. However, since the early mouse embryo also lacks centrosomes, the relative contributions of centrosomal and augmin-mediated nucleation to spindle assembly, proliferation and organismal development remain unclear. Moreover, the embryonic lethality also prevented analysis of augmin-mediated nucleation in post-mitotic neurons. Here we have explored the roles of augmin in brain development by conditional knockout (cKO) of the augmin subunit *Haus6* in mice. Strikingly, loss of augmin in neuroprogenitors, contrary to the loss of centrioles as shown in previous studies, completely aborts cortical development and is lethal. This involves mitotic defects, p53 induction, and massive apoptosis in the subventricular zone of the developing cortex. Augmin deficiency delays mitotic spindle assembly, entry into anaphase and causes spindle pole fragmentation, resembling mitotic defects described for augmin depletion in cell lines. While we have only started analyzing augmin cKO in post-mitotic neurons, our preliminary data suggest important roles also in this cell type. Together this ongoing study not only reveals that microtubule nucleation mediated by augmin is essential for proliferation and survival of neuroprogenitors and thus brain development, but also suggests additional roles of augmin in proper brain function.

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