A centrosomal view of CNS growth and disease

Embryonic development of the neural tube (NT) requires patterning and proliferation of neural progenitor cells (NPCs) to be tightly regulated, allowing the formation of the central nervous system (CNS) with the right identity, size and shape. In the ventral NT, the Sonic hedgehog (Shh) signaling pathway not only masters NPCs patterning but also controls the dynamic of motor neuron progenitor division. The Intrinsic mechanism that account for Shh signaling to maintain the symmetric proliferative division mode of NPCs relies on counteracting centrosome asymmetry. At the onset of mitosis, Shh regulates the expression of Pericentrin (PCNT) that serves as a multifunctional scaffold to anchor an equal amount of the protein kinase A (PKA) at the spindle poles. In consequence, high Shh activity maintains NPCs proliferation and the growth of embryonic CNS. A switch to asymmetric division mode of NPCs initiates the production of neurons, and a premature switch during embryonic CNS development leads to primary microcephaly, a neuro-developmental disorder characterised by a smaller brain.

Microcephaly can also arise from congenital pathogen infection, such as the Zika Virus. In this context, we unravelled the cellular mechanism underlying Zika virus-associated microcephaly. In NPCs, ZikV-NS5 protein interacts with centrosome host proteins at the base of the primary cilia, causing an atypical non-genetic ciliopathy and premature neuron delamination. In human microcephaly foetal brain tissue, ZikV-NS5 persists at the base of the motile cilia in ependymal cells, which also exhibit a severe ciliopathy. The amino acids Y25, K28, and K29 that are involved in NS5 oligomerization are essential for its localization and interaction with components of the cilium base, promoting ciliopathy and premature neurogenesis. These findings lay the foundation for therapies that target ZikV-NS5 multimerization and prevent the developmental malformations associated with congenital Zika syndrome.

Keywords: CNS growth, Neural Progenitor Cells (NPCs), Sonic hedgehog, Microcephaly, Zika virus, Centrosome, Ciliopathy.

Narrative Biosketch: Murielle Saade is a young principal investigator at the Institute de Biologia Molecular de Barcelona (IBMB-CSIC), Spain. She obtained a BSc in Cell Biology, Biochemistry and Genetics from the University Saint Joseph, Beirut, Lebanon. Following her PhD research in Immunology in Dr. Catherine Nguyen´s laboratory at the INSERM- University of Aix Marseille II in France, she undertook postdoctoral training in Development Biology at the IBMB-CSIC, with Dr. Elisa Marti. In 2020 she obtained a Ramón y Cajal position and established her research group in the same institute. Her research interests include the molecular and cellular mechanisms of embryonic development with a particular focus on diseases associated to the developing central nervous system (CNS). To address these questions, she uses a range of experimental techniques with model systems that include chick embryos as well as human embryonic stem cells.