The role of centrosomal proteins in neurogenesis

During corticogenesis, apical progenitor cells either undergo proliferative symmetrical divisions or neurogenic asymmetric divisions. The balance between these two types of divisions determines the size of the progenitor cell pool and ultimately the number of neurons generated in the brain. One hypothesis proposes that centrosomes are required for proper neural progenitor cell fate specification through the regulation of mitotic spindle orientation such that vertical cleavage correlates with asymmetrical divisions and horizontal cleavage favors symmetrical divisions. Another model, supported by live imaging data, argues that the angle of the cleavage plane has little correlation with daughter cell fates[4]. Instead, proper spindle orientation is proposed to be required for the maintenance of adherent junctions[5]. Thus the importance of spindle orientation in mammalian corticogenesis and the consequence of randomized spindle orientation are still under debate.

Our studies on microcephaly mutants have begun to provide insight into this controversial issue by showing that multiple microcephaly mutants cause abnormal spindle orientation in neural progenitor cells. CDK5RAP2 is a centrosomal protein implicated in human microcephaly[1]. Our lab has shown that mice harboring mutations in *Cdk5rap2* also develop microcephaly and exhibit defects in neurogenesis[2] (Figure 1). Consistent with the role of Cdk5rap2 in the centrosome, the mutant progenitor cells show randomized spindle orientation and mitotic arrest, presumably as a consequence of centrosome and spindle dysfunction (Figure 2). Additionally, mice deficient for Nde1, another centrosomal protein, exhibit a very similar phenotype including severe microcephaly, premature neural progenitor cell depletion, multipolar spindles and randomized spindle orientation[3]. This provides further support for the role of the centrosome in the regulation of neurogenesis and evidence that centrosomal dysfunction could be a common mechanism underlying the pathogenesis of microcephaly.

In addition to randomized spindle orientation, other centrosome-related defects such as multipolar spindle and cell cycle aberration are currently under investigation in our lab in an effort to clarify the role of the centrosome in neurogenesis and better understand disorders of human microcephaly.

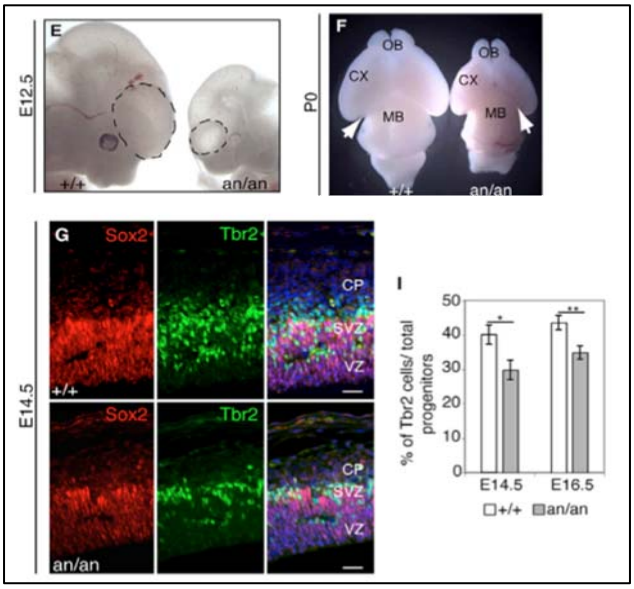

Figure 1. *Cdk5rap2*$^{an/an}$ embryos have reduced brain size due to loss of neural progenitor cells. Adapted from Lizarraga *et al.*[2]

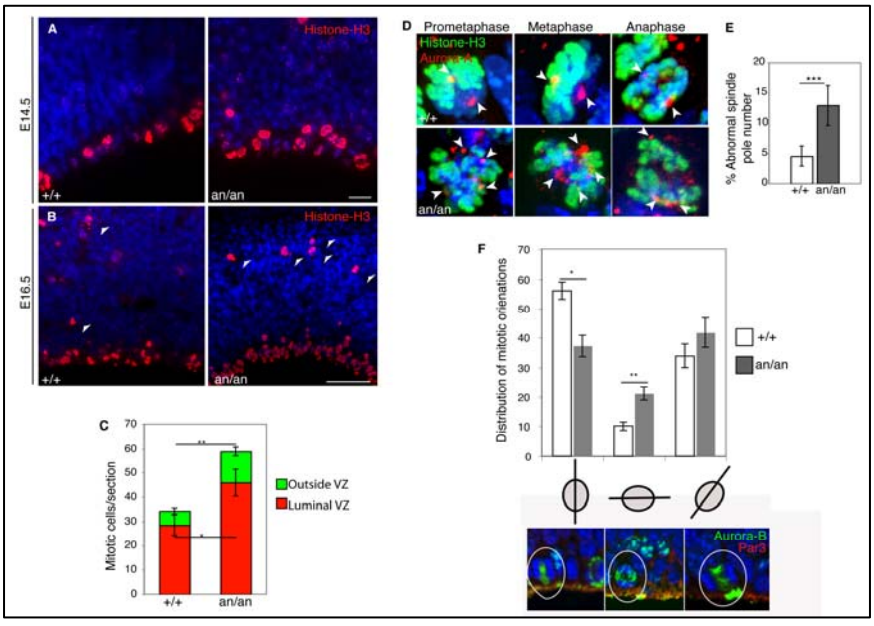

Figure 2. Centrosome and spindle abnormalities in Cdk5rap2$^{an/an}$ brain. (A, B, C) Elevated mitotic index in mutant brain, presumably due to mitotic arrest. (D, E) More mutant progenitor cells have abnormal spindles, demonstrated by disorganized chromosomes and mono/multi-polar spindle poles. (F) Abnormal spindle orientation of mutant progenitor cells, with significant decrease in horizontal divisions and increase in vertical divisions. Adapted from Lizarraga *et al.*[2]

~ Xuyu Cai, PhD Candidate

References:

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