Lhx2 Functions as a Key Regulator of Brain Size Control

A research group led by Dr. Shen-Ju Chou, an Assistant Research Fellow at the Institute of Cellular and Organismic Biology, Academia Sinica, in cooperation with Dr. Jonathan Touboul from Collège de France, has recently identified a novel function of protein Lhx2 (a homeodomain containing transcription factor) in controlling the size of the cerebral cortex. This study contributes to the understanding of molecular mechanisms leading to neurodevelopmental diseases, such as microcephaly. The article was published online on September 14, 2015 in *The Proceedings of the National Academy of Sciences (PNAS)*.

The cerebral cortex is the most highly evolved brain structure and is responsible for the perception of sensory stimuli, the execution of motor actions, cognition, and consciousness. During embryonic development, cortical progenitors generate these neurons. Tight regulatory mechanisms ensure the correct number and types of neurons are generated to achieve brain functions. Microcephaly patients usually show learning defects that are likely due to the decreased number of neurons in their brain. Dr. Chou's group found once Lhx2 is deleted in cortical progenitors during embryonic development, cortical neurons are generated earlier and it leads to a much smaller cortex, about 50% of the normal brain size, with decreased number of neurons.

Dr. Chou's research group found that Lhx2 is required for the Wnt/β-catenin pathway to maintain cortical progenitor proliferation. The Wnt/β-catenin signaling pathway was previously shown to be a key regulator for controlling brain size. Forcing Wnt/β-catenin pathway activation in mouse cortical progenitors results in a very big cortex with furrows, similar to a human brain. Dr. Chou's group demonstrated that without Lhx2, the Wnt/β-catenin pathway fails to function. They further demonstrated that Lhx2 and the Wnt/β-catenin pathway can collaboratively regulate the expression of downstream genes.

Cortical size expansion and the increase in cortical neuronal number suggest that regulation of neurogenesis has changed over evolution. This study provides insights about how the timing of different phases of neurogenesis impacts the size and composition of the cortex. The findings from Dr. Chou's group suggested that the intricate interplay between Lhx2 and the Wnt/β-Cat signaling pathway that modify the timing of neurogenesis appears to be a key regulatory mechanism in cortical development. In the future, Dr. Chou's group plans to further understand how different types of neurons are generated during cortical development.

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The full article, entitled “Lhx2 regulates the timing of β-catenin-dependent cortical neurogenesis”, is available at the PNAS website at:
http://www.pnas.org/content/early/2015/09/10/1507145112.full.pdf