New molecular insight into vertebrate brain development

November 17 2008

In the December 1st issue of *G&D*, Dr. Fred H. Gage (The Salk Institute for Biological Studies) and colleagues reveal a role for the Hippo signaling pathway in the regulation of vertebrate neural development, identifying new factors – and potential therapeutic targets – that may be involved in congenital brain size disorders and neurological tumor formation.

Establishing the basic embryonic brain requires the formation of a hollow neural tube, which serves as the rudimentary central nervous system, as well as the controlled proliferation and differentiation of neural progenitor cells into various specialized cell types.

The Hippo pathway is an ancient conserved signaling cascade that is known to regulate organ size in the fly and mouse. Previous research has demonstrated that Hippo signaling serves as a brake on cell growth and proliferation by preventing another protein, YAP, from entering the nucleus and activating pro-growth genes.

Drs. Xinwei Cao, Samuel Pfaff and Fred Gage now report that Hippo signaling is a critical master regulator of bran size in vertebrates that functions by restricting instructing the survival, proliferation and differentiation of neural precursor cells. In addition, the researchers identified the TEA domain (TEAD) transcription factor protein as the long-sought-after cognate DNA-binding partner of YAP in the nucleus.

Using genetic manipulation of chick embryos, the scientists

demonstrated the consequences of altered Hippo signaling on vertebrate neural tube development. Increased YAP/TEAD activity induced neural progenitor cell overproliferation and the formation of an expanded neural progenitor cell population. Decreased YAP/TEAD activity led to increased cell death, while repression of YAP/TEAD target genes induced premature neuronal differentiation.

Owing to the evolutionary conservation of the Hippo signaling pathway, Dr. Gage states that "understanding the HIPPO path may bring insights to human brain malformations. There are a number of brain size defects for which we are considering a follow up, including microcephaly and Autism, where the overall brain size is affected but structures retain the proportionality. The function of the HIPPO pathway also has implications for brain size evolution, which is of great interested to us."

Their paper will be made available online ahead of print on 11/17 at http://genesdev.org.

Source: Cold Spring Harbor Laboratory