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“We believe that identifying the mechanisms regulating developmental events is requisite for understanding the basis of most biological disorders and is essential both for prevention and the development of strategies to repair damage to the nervous system due to genetic defects, tumors, or injuries to the brain or spinal cord.”

The cerebral cortex, the outermost layer of neurons commonly referred to as gray matter, is the largest and most complex component of the brain. Although initially all stem cells in charge of building it are created equal, they quickly commit irrevocably to forming specific cortical regions. How the stem cells' destiny is determined, however, has remained an open question.

During embryonic brain development, the stem cells that will give rise to the cerebral cortex pass through a series of tightly regulated stages. Early during neurogenesis, stem cell-like progenitor cells known as neuroepithelial cells undergo cell division to expand their own pool. Later, they differentiate into more mature progenitor cells called radial glia, which produce a constant stream of both progenitors and neurons, the latter migrating outward to establish the gray matter of specialized cortical regions. The defining characteristic of the progenitor cells that will go on to form the cerebral cortex is their expression of a transcription factor called Emx1.

After discovering that a specific member of the fibroblast growth factor family of morphogens controls the timing of the critical transition period bridging the early expansion phase of neuroepithelial cells and the later neurogenic phase of radial glia, O'Leary hypothesized that the regional identity of progenitors in the Emx1 lineage may involve one or more transcription factors that define unique subpopulations of progenitors via differences in their expression levels. A promising candidate was the LIM transcription factor Lhx2, which is expressed in all progenitors of the Emx1 lineage but at different levels in a graded regional pattern. By creating a new genetically engineered mouse line, his team deleted Lhx2 from neuroepithelial cells at different times during embryonic development and demonstrated that Lhx2 regulated their destiny.

These findings may help expand understanding of the genetic underpinnings of many neurodegenerative disorders, as well as eventually provide the means to direct stem cells to repair specific parts of the brain ravaged by disease or injury.

For more information, please visit
salk.edu/faculty/o'leary.html



Left to right:

Front row: Yoo-Shick Lim, Andreas Zembrzycki, Dennis O'Leary, Rosalind Carney, Haydee Gutierrez

Back row: Adam Stocker, Zoila Babotriera, Scott May, Carlos Perez-Garcia, Berta Higgins, Setsuko Sahara, Suzanna Chan, Todd McLaughlin, Shen-Ju Chou