MedicalXpress

Key factor in brain development revealed, offers insight into disorder

March 26 2008

In the earliest days of brain development, the brain's first cells – neuroepithelial stem cells -- divide continuously, producing a population of cells that eventually evolves into the various cells of the fully formed brain. Now, scientists have identified a gene that, in mice, is critical for these stem cells to divide correctly. Without it, they fail to divide, and die.

The finding offers insight into the first steps of brain development, and may shed light, the scientists say, on a rare pediatric disorder known as lissencephaly, or "smooth brain" disease.

The senior author of the study was Anthony Wynshaw-Boris, MD, PhD, the recently recruited chief of the Division of Genetics in the Department of Pediatrics, and the Institute for Human Genetics at the University of California, San Francisco. He carried out the research while a professor at the University of California, San Diego. Several co-authors of the study moved with Wynshaw-Boris to the UCSF lab.

Scientists have known that loss of one of the two copies of the human form of the gene, known as LIS1, prevents immature nerve cells from migrating from deep in the brain up to the surface of the emerging cerebral cortex. These immature cells, produced from so-called radial glial progenitor cells – which in turn evolve from neuroepithelial stem cells – stall at mid point in their migration, creating a thick layer of tissue.

As a result, the cerebral cortex, lacking an influx of properly connected nerve cells, develops a smooth surface, devoid of convoluted nerve tissue. The resulting disease, lissencephaly, varies in severity, but often leads to retardation, seizures and early childhood death.

Scientists have had evidence that, in addition to their role in migration in immature nerve cells, the human and mouse forms of the gene may play a role in cell division and proliferation processes in radial glial progenitor cells. However, scientists have not known what that role would be. Nor have they known what role, if any, the gene plays earlier on in brain development -- in neuroepithelial stem cells, themselves.

In their study, reported in the Feb. 8 issue of *Cell*, the scientists investigated embryonic mice genetically engineered to completely lack Lis1 in their cells at various stages of embryonic development. In a surprising finding, they discovered that Lis1 is essential for cell division in neuroepithelial stem cells. It also is important, though not essential, for cell division in the radial glial progenitor cells.

Lis 1, they showed, plays a critical role in ensuring that neuroepithelial stem cells divide symmetrically, so that both daughter cells receive the full set of duplicated chromosomes and the molecular components that support cell functions. It does so by helping regulate the orientation of the cells' mitotic spindles -- the microtubules that draw the two sets of chromosomes into position on either side of the dividing mother cell and that demarcate, at their center, the cleavage point of cell division.

Specifically, Lis 1 makes sure that the mitotic spindle is oriented perpendicular to the top and base components of the neuroepithelial stem cells, so that each daughter cell not only receives the appropriate genetic material but also contains molecular components at the top and bottom, or the basal and apical, portion of the cell membrane, respectively.

“In neuroepithelial stem cells, the apical and basal plasma membranes are only a tiny fraction of the total cell membrane, so the orientation of division must be precisely controlled either to make sure that both sides of each of the daughter cells are attached at both the apical and basal surfaces as they rapidly divide or to distribute apical and basal components equally to the daughter cells,” says Wynshaw-Boris.

The scientists hypothesize that Lis1 carries out the role by directing the movement of a molecular motor known as dynein to the surface of both sides of the cell membrane. There, dynein takes a fixed position and, like a molecular hook, pulls the microtubules that emanate from the middle of the cell toward it.

“Just like a pulley, dynein draws the microtubules through it and that, in turn, rotates the spindle,” suggests Wynshaw-Boris.

Loss of Lis1, results in reduced and weakened microtubules and an inability of the mitotic spindle to rotate the microtubules properly in the apical-basal axis.

Of note, while loss of Lis1 is catastrophic in neuroepithelial stem cells, it is not so in radial glial progenitor cells. The reason is not entirely clear, says Wynshaw-Boris, but the scientists hypothesize that neuroepithelial stem cells require a greater tightness of control of the plane of cell division. In support of this notion, while neuroepithelial stem cells appear to always divide symmetrically, radial glial progenitor cells often divide asymmetrically to produce one daughter cell (radial glial progenitor cell) and one newborn nerve cell.

“The study sheds some light on the differences in the regulation of symmetric and asymmetric divisions in neuroepithelial stem cells and radial glial progenitor cells,” says Wynshaw-Boris.

More broadly, he says, the findings suggest that neural migration birth defects, such as lissencephaly, may be caused by defects in other processes, as well, including proliferation, division and, in this case stem cell division. “It gives insight,” he says, “into these rare diseases and what’s important for normal brain development.”

Source: University of California - San Francisco