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Protein Regulates Growth of the Cerebral Cortex

A protein that escalates the rate of growth of the cerebral cortex in young mice may help scientists explain how changes in a relatively small number of genes that regulate neural development may have contributed to increases in the size of the brains of higher mammals.

In an article published in the July 19, 2002, issue of the journal *Science*, HHMI physician postdoctoral fellow Anjen Chenn and Christopher A. Walsh at Beth Israel Deaconess Medical Center and Harvard Medical School reported that the cerebral cortex of transgenic mice bearing an altered form of the protein β -catenin expanded horizontally in area but not in thickness. These changes produced characteristic crests and grooves, called gyri and sulci, which anatomically distinguish human brains from those of lower animals. The cerebral cortex is the region of the brain responsible for higher intellectual functioning.

It has long been known that during evolution, the size of the cerebral cortex expanded disproportionately relative to the rest of the brain, said Chenn. But not very much was known about the developmental mechanism underlying that expansion. One theory is that the number of progenitor cells increased during evolution, and these cells gave rise to neurons that made up a greater number of repeating functional units called cortical columns. According to this theory, said Chenn, the greater number of progenitor cells might result from immature cells that continue to divide to produce even more progenitor cells, before ultimately committing to develop into neurons.

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Chenn and Walsh theorized that β -catenin might be responsible for regulating the proliferation of progenitor cells because it is known to control cell growth and it has been implicated in the growth of specific brain tumors. An additional piece of evidence emerged from Chenn and Walsh's experiments which showed that β -catenin is present at junctions between progenitor cells, in the embryonic epithelium, where a protein that regulates cell division would be expected to be located.

We found that beta-catenin was expressed in the right cells at the right time and the right place, said Chenn. So, that led us to ask the question of whether it was actually regulating cell division and differentiation.

To understand β -catenin's role in regulating neural growth, the scientists generated transgenic mice with an altered β -catenin gene that produced a protein that was resistant to the normal degradation that regulates levels of the protein. We saw that the brains of these mice were greatly increased in size so that, compared to normal mice, their brains at a particular age were about two- to three-fold increased in volume, said Chenn. And the striking thing about these brains was that when we made sections through them, we observed that the increase in brain size was not due to an increase in thickness of the cerebral cortex but an increase in its surface area of the cortex. The cortex had expanded so much in surface area that it began to fold in on itself and generate the grooves and bumps that are reminiscent of the sulci and gyri in higher animals.

Chenn and Walsh next investigated why the mice developed larger brains. They knew that there were at least three possible explanations: the increase could have been due to faster cell division; it could have been caused by a reduction in normal programmed cell death -- called apoptosis -- that occurs during brain development; or because an increase in the number of progenitor cells continued to multiply before maturing.

Their detailed studies of the brain cells of the transgenic mice confirmed that the increase in brain size was caused by the over-production of progenitor cells. This study is important because it gives us a better understanding of how beta-catenin works by regulating the decision of cells to either keep dividing or stop dividing, said Walsh. And secondly, the study shows how, with a simple metabolic switch, nature might be able to shift to a larger cerebral cortical size, but still maintain relatively normal architecture.

Chenn emphasized, however, that it remains uncertain whether the increased cortical size would result in enhanced intelligence. Without doing true functional studies, we cannot really conclude that these mice function at a higher neurological level, he said. However, we did look at the expression of a variety of markers of cell differentiation. From these studies, we can say that the pattern of distribution of the expression of these markers is preserved in the transgenic animals. So, their brain tissue is not disordered like a tumor, and, in fact, maintains a relatively ordered pattern of differentiation.

Although the pattern of cellular differentiation appeared normal, these animals are not healthy, Chenn said. They don't live past birth, and we're not sure why. So, this is only the first step in understanding how brain size can be increased. We are certain that the increase in brain size over evolution is going to be more complicated than just changes in one gene. The major scientific significance reported in the article, said Chenn, is the discovery that the embryonic epithelium plays a role in cell differentiation.

According to Walsh, their findings pose some interesting questions for further study. We would like to determine whether beta-catenin actually does regulate the size of the cerebral cortex, by analyzing the protein in different species with different sized cortexes. Also, we could explore whether there are mutations in beta-catenin associated with human diseases in which the cerebral cortex is either too big or too small respectively megalencephaly known as and microcephaly.