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RESEARCH NEWS

A Novel Signaling Mechanism in Brain Development

A review of: Piao X, Hill RS, Bodell A, Chang B., Basel-Vanagaite L., Straussberg R., Dobyns W. B., Qasrawi B., Winter R., Innes A. M., Voit T., Ross E., Michaud J., Descarie J., Barkovich, A. J., Walsh C. A. 2004 G protein-coupled receptor-dependent development of human frontal cortex. Science 303:2033-2036

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THE CEREBRAL CORTEX is the extensive outer layer of gray matter of the cerebral hemispheres where cortical neurons reside. It is largely responsible for higher brain functions, including sensation, voluntary muscle movement, thought, reasoning, and memory. In larger mammals, the surface of the cerebral cortex becomes folded, creating grooves (sulci) and bumps (gyri). The cortex is divided into discrete areas with distinct functions, such as vision and motor control. However, how these distinct cortical areas attain their identity during development is one of the oldest and most fundamental questions in neuroscience.

Cortical neurons are formed deep in the forebrain, in specialized proliferative regions near the lining of the lateral ventricles, called ventricular zone and subventricular zone. The "protomap" model suggests that neuronal progenitor cells are presaged by a protomap and know to become certain neurons with specific functions, such as visual cells or motor cells, before the arrival of afferent inputs (1). Alternatively, cortical areas may only be specified later by patterns of neuronal interconnections (the "protocortex" model) (2).

Using genetic approaches to study an inherited human brain malformation, bilateral frontoparietal polymicrogyria (BFPP), we recently unveiled a novel signaling mechanism in brain development, and provided data that implicate the "protomap" theory of cortical patterning (3). BFPP, a recessively inherited genetic disorder of human cerebral cortical development, shows severely abnormal architecture in the frontal lobes, with milder involvement of parietal and posterior parts of the cortex (4–6). The normally convoluted gyri are replaced by numerous (poly) and noticeably smaller (micro) gyri. BFPP patients show mental retardation, gait difficulty, language impairment, and seizures, which are consistent with frontal lobe dysfunction (5,6). Cranial magnetic resonance imaging (MRI) reveals a thinner than normal cortex thrown into innumerable small, irregular gyri and sulci, especially in the frontal lobe.

We did linkage analysis and mutational study in 22 BFPP patients from 12 pedigrees and identified 8 independent mutations in a G-protein-coupled receptor (GPCR), called GPR56. In addition, we demonstrated that the mouse *Gpr56* gene is preferentially expressed in the neuronal progenitor cells of the cerebral cortical ventricular and subventricular zones in the mouse developing brain (3). The pattern of *Gpr56* expression and the anatomy of BFPP imply that Gpr56 most likely regulates cortical patterning, and that the regional patterning of the cerebral cortex occurs at early stages of development during production and migration of neurons.

GPCRs comprise one of the largest protein superfamilies, making up about one percent of all genes. This family of transmembrane receptors are responsible for the transduction of a diverse array of extracellular signals, including peptide hormones, growth factors, fatty acid derivatives, odorants, and light. Mammalian GPCRs have been classified into three major groups on the basis of their sequence similarity to rhodopsin (type A), the secretin receptor (type B), and the pheromone receptor (type C) (7,8). GPR56 belongs to a subfamily of type B GPCRs. It was originally identified by two independent groups in 1999 by PCR of human cDNAs with degenerate primers based on conserved regions of secretin-like receptors and by differential display in melanoma cell lines with different metastatic potential, respectively (9,10). GPR56 was thought to be a potential cancer susceptibility gene prior to our recent discovery of its role in brain development, since it is mainly expressed in the poorly and intermediately metastasizing cell lines and markedly downregulated in the most highly metastatic cell lines (10). Whether the role of GPR56 in brain development and its possible role in cancer progression might reflect its common role in regulation of cell proliferation by environmental signals remains an unexplored possibility.

The role of GPCRs in brain development has been previously hinted at by their expression in developing brain (11). The finding that mutations in GPR56 cause cortical malformation is the first direct evidence, and thus raises many interesting questions. For examples, does GPR56 act in radial glia or other cells? Does it affect cell fate, cell migration, or some other process? Does it serve as the receptor for a ligand in the traditional sense, and if so what is the ligand?

During evolution, cerebral convolutions are formed concomitantly with an increase in cortical surface, without a comparable increase in cortical thickness. In fact, the 1000-

fold increase in cortical surface area between human and mouse is accompanied by only an approximate twofold increase in cortical thickness (1). Interestingly, the most severely affected cortical regions in BFPP are strikingly thin and form a larger number of convolutions with a net increase in cortical surface. GPR56 is expressed in both hematopoietic and neural stem cells (12). It is possible that GPR56 is important in keeping stem cell/progenitor cells in a quiescent state to maintain their multi potential. However, further elucidation of the role of GPR56 will require mechanistic analysis in an animal model.

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