Protein directs brain folding during development

As the mammalian brain evolved, the size of the cerebral cortex greatly increased, requiring an intricate folding process to allow all of the brain mass to fit. As a result, mammalian species with greater cognitive abilities have more intricately folded cortices. In humans, the developing brain remains smooth until partway through gestation, when the brain begins to fold as its mass increases. The mechanisms behind this expansion in the brain remain poorly understood, however.

The cerebral cortex of the brain expands in two directions: tangentially, or along the surface, and radially, or away from the center. A new study, led by Magdalena Götz (Ludwig-Maximilian University Munich, Germany), shows that a single protein, called *Trnp1*, regulates growth in both of these dimensions in the brain. She and her collaborators at Helmholtz Center Munich (Germany) looked at how the presence of this protein changed in the mouse cortex during embryonic development (*Cell* 153, 535–549; 2013). They found that *Trnp1* is

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highly expressed early on, specifically in newborn neurons, followed by a swift drop in levels of the protein.

Next, they tested the function of the protein in live mice by genetically manipulating their levels of *Trnp1*. When levels of *Trnp1* were increased, the brain expanded tangentially, resulting from three times as many new cells being created. In contrast, when *Trnp1* levels were reduced, other types of brain cells increased their numbers, causing the developing cortex to expand radially. This demonstrates that *Trnp1* plays changing roles in different stages

of brain development, all of which contribute to expansion of the number of brain cells.

The massive influx of new cells as the brain develops causes the cortex to undergo a complex series of folds, or gyrification, in order to increase the surface area and make room for increasing brain matter. The researchers live-imaged the cortex of a mouse to observe directly what happens when levels of *Trnp1* are increased. The murine brain, which usually has a smooth cortex, expanded and folded extensively as a result of increasing expression of this one protein.

The researchers next confirmed the relevance to humans by looking at levels of *TRNP1* mRNA expression in sections of cortex from human specimens at similar developmental stages. Differences in *TRNP1* expression were associated with differences in the extent of folding. The scientists suggest that species differences in brain expansion and cortical mass may therefore be due to differences in levels of this single protein.

Kara Rosania

BIOENGINEERED KIDNEYS AT WORK IN RATS

Kidney failure affects nearly 1 million people in the US. Without treatment, it results in the retention of excess water and waste products in the body. Renal failure can be reversed by transplanting kidneys from matched donors, but the supply of donated kidneys is insufficient to meet demand, and ~20% of transplants undergo organ rejection within 5 years. Bioengineered artificial kidneys, created from patients' own cells, that act as permanent transplants could provide an alternative treatment for patients with renal failure. To be viable, the bioengineered organs must recapitulate both the architecture and the functions of the kidney, including perfusion, filtration, secretion, absorption and drainage of urine.

Scientists led by Harald C. Ott (Massachusetts General Hospital, Boston) now report for the first time the successful creation, transplantation and function of artificial kidneys in rats. The bioengineered kidneys could filter blood and produce urine, although they did not work as well as conventional transplants. With further development, however, this approach could help the many patients with renal failure who await organ transplants. "Based on this initial proof of principle, we hope that bioengineered kidneys will someday be able to fully replace kidney function just as donor kidneys do," Ott told *NIH Research Matters*. His team is now refining the technique and working to create human-sized organs.

The researchers used a three-part procedure to create the bioengineered kidneys before transplanting them into rats (*Nat. Med.* doi:10.1093/nm3154; published online 14 April 2013). First, they used detergents to delicately strip the cells from donor organs, leaving behind a protein scaffold that wouldn't be rejected by a recipient's immune system. The decellularization procedure preserves the structure of the organ, maintaining intact the vascular, cortical and medullary architecture; the collecting system; and the ureters in the scaffold.

Next, the kidney scaffolds were repopulated with living epithelial and endothelial cells, and the repopulated scaffolds were then incubated in a whole-organ bioreactor for several days. The artificial kidneys produced rudimentary urine *in vitro*. Finally, Ott's team transplanted the bioengineered kidneys into recipient rats, where the organs produced urine and successfully filtered and reabsorbed certain molecules. The scientists did not observe any bleeding or thrombosis associated with the transplants.

The next steps in developing this technology for human application are to scale up the procedures to human-sized scaffolds and to isolate, differentiate and expand the required cell types. Ott's group hopes that refining the cell types and culture conditions will improve the function of the bioengineered kidneys.

Monica Harrington