

phonons actually cooperate with the electronic-pairing mechanism<sup>7</sup>, explaining why the films superconduct at higher temperatures than their bulk analogues.

These are exciting results for superconductivity researchers, because they suggest new routes by which high-temperature superconductors can be engineered on the nanoscale. But perhaps more importantly, they are an example of the kind of surprise that might emerge from studies that attempt to harness the power of nanotechnology to explore the

rich but largely uncharted territory of strongly interacting quantum systems. ■

Jan Zaenen is at the *Instituut-Lorentz for Theoretical Physics, Leiden University, 2300 RA Leiden, the Netherlands.*  
e-mail: jan@lorentz.leidenuniv.nl

1. Bednorz, J. G. & Müller, K. A. *Z. Phys. B* **64**, 189–193 (1986).
2. Keimer, B., Kivelson, S. A., Norman, M. R., Uchida, S. & Zaenen, J. Preprint at <http://arxiv.org/abs/1409.4673> (2014).

3. Steward, G. R. *Rev. Mod. Phys.* **83**, 1589–1652 (2011).
4. Wang, Q.-Y. *et al. Chin. Phys. Lett.* **29**, 037402 (2012).
5. Liu, D. *et al. Nature Commun.* **3**, 931; <http://dx.doi.org/10.1038/ncomms1946> (2012).
6. Ge, J.-F. *et al.* Preprint at <http://arxiv.org/abs/1406.3435> (2014).
7. Lee, J. J. *et al. Nature* **515**, 245–248 (2014).
8. Zaenen, J. in *100 Years of Superconductivity* (eds Rogalla, H. & Kes, P. H.) Ch. 2.4, 92–117 (Chapman & Hall, 2011); <http://arxiv.org/abs/arXiv:1012.5461>.
9. Turner, D. W. *Molecular Photoelectron Spectroscopy* (Wiley, 1970).

## NEUROBIOLOGY

# Building a bigger brain

An innovative approach to analysing the functions and gene-expression profiles of neural stem cells in developing human and mouse brains sheds light on the differences – and similarities – between the two species. **SEE LETTER P.264**

FORREST O. GULDEN & NENAD ŠESTAN

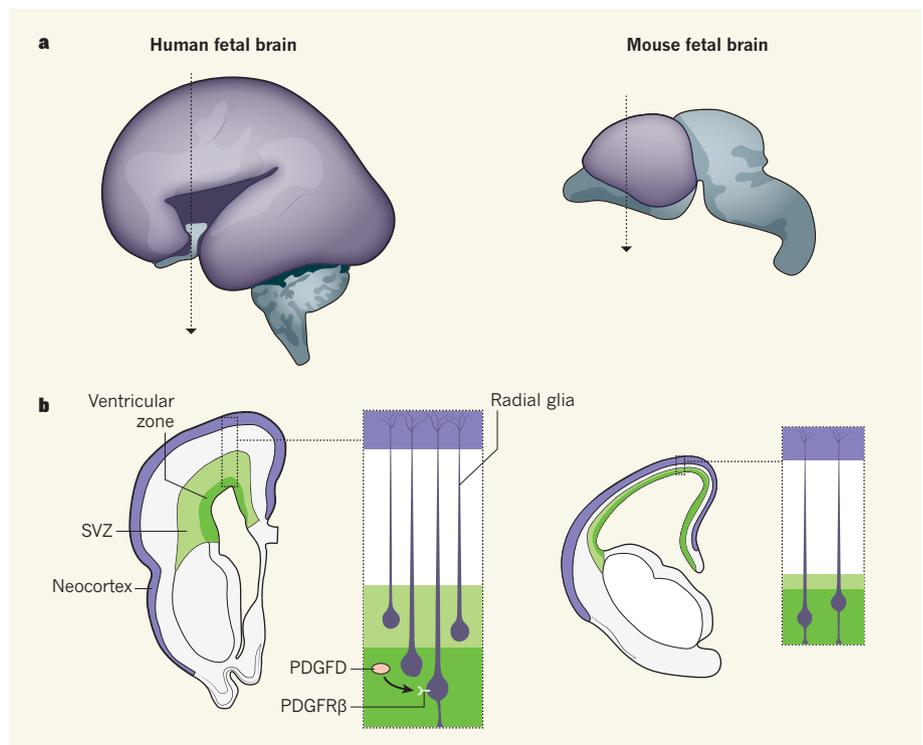
The mammalian cerebral neocortex is a thin mantle of neurons on the surface of the brain's hemispheres that is largely responsible for higher-order mental functions. In different mammalian species, the cortex can vary by more than 10,000-fold in mass<sup>1</sup>, and such variations have been associated with species-specific differences in cognition and behaviour<sup>1–4</sup>. Alterations in the proliferation and differentiation of radial glia – non-neuronal progenitor cells<sup>5–7</sup> that give rise to most of the approximately 16 billion neurons in the human cerebral cortex<sup>1</sup> – are thought to play a crucial part in determining the size of the neocortex. Unfortunately, identifying the genes that regulate development of the radial glia in humans has proved exceedingly difficult. On page 264 of this issue, Lui *et al.*<sup>8</sup> use a sophisticated approach to identify and characterize the role of a secreted protein, PDGFD, in mediating the proliferation of radial glia in humans.

Radial glia serve both as progenitors and as migratory guides for the daughter cells they give rise to, and so provide for the production and placement of appropriate cell numbers and types in the developing neocortex<sup>5–7,9</sup>. Changes to division of radial glia, the length of their cell cycle or the rate at which they proliferate may therefore have profound effects on the size, composition and functional repertoire of the neocortex<sup>2–7</sup>. These cells can be efficiently studied experimentally in mice and many other model organisms, but ethical and practical barriers hinder similar tests in humans. As such, genetic studies have identified many genes that both control proliferation in mice and regulate the size of the human neocortex<sup>2,10,11</sup>, but the identities of genes involved in

the development of radial glia only in humans or in non-standard laboratory animals have remained elusive.

A complete list of the genes expressed within a sample or cell type, together with information about the abundance of transcripts

produced from each of these genes, is called a transcriptome. When a transcriptome is generated from a complex biological tissue such as the neocortex, it is an amalgamation of the transcriptomes of the millions or billions of cells that make up that tissue. However, cells of the same type and developmental stage tend to have more-similar transcriptomes than those of different cell types and, furthermore, cells of a given type are generally not distributed evenly throughout a tissue. Thus, it stands to reason that the expression levels of all of the genes expressed by a given cell type will rise and fall in unison as the abundance of that cell type varies in different regions of the tissue under analysis. This provides the basis for identifying the transcriptome of a single



**Figure 1 | Transcriptional control in radial glia.** **a**, Side-on views of human and mouse brains at equivalent developmental stages (not to scale). The developing cerebral neocortex is indicated in purple. **b**, A cross-section of one brain hemisphere from each species, taken from the dotted lines shown in **a**. The magnified sections show the distribution of cells in the brain called radial glia. Lui *et al.*<sup>8</sup> report that the protein PDGFD, acting through the receptor protein PDGFR $\beta$ , signals to the radial glia of humans but not to those of mice. PDGFD signalling correlates with increases both in proliferation of radial glia and in the distribution of cells resembling radial glia throughout the ventricular zone and subventricular zone (SVZ).

cell type, even when starting with a mixed population of cells<sup>12,13</sup>.

Following this reasoning, the authors generated transcriptomes from 87 cross-sections of tissue taken from a single human fetal neocortex. From these data, they identified 55 groups of genes, called modules, in which gene expression rose and fell together, reflecting differences in the cellular composition of each cross-section. Six of these modules contained genes that are already known to be expressed by radial glia in mice, suggesting that these modules each represented a portion of the transcriptome of human radial glia. Importantly, these six modules contained several genes that the researchers found to be expressed in human, but not murine, radial glia. Lui and colleagues chose to focus on just one of these genes, *PDGFD*.

This gene encodes a secreted growth factor that has not previously been implicated in neocortical development<sup>14</sup>. The authors report that inhibiting PDGFD protein signalling in slices taken from the human neocortex reduced the proliferation of radial glia. Conversely, introducing abnormally high levels of either PDGFD or a permanently activated form of its receptor protein, PDGFR $\beta$ , into the developing mouse neocortex resulted in an increase in the proportion of radial glia undergoing cell division. Combined, these results suggest that, in normal conditions, PDGFD–PDGFR $\beta$  signalling drives the proliferation of radial glia in humans, but not in mice (Fig. 1).

Nearly all murine radial glia reside in an area of the developing brain called the ventricular zone. In some species, however, additional progenitor populations take up residence adjacent to the ventricular zone, in another proliferative region called the subventricular zone (SVZ)<sup>3–7</sup>. These cell types, including outer radial glia, have been implicated in the expansion of the neocortex of humans and other species<sup>3,4,7</sup>. Lui and co-workers found that, in mice expressing the activated form of PDGFR $\beta$ , cells resembling radial glia were distributed not only throughout the ventricular zone, but also throughout the SVZ. PDGFD-induced signalling may thus help to explain the establishment and proliferation of SVZ progenitors and, therefore, the expansion of the neocortex that has occurred in some mammals.

What particular type of progenitor cell Lui *et al.* observed in the SVZ remains unclear. Although these cells expressed a molecular marker for radial glia, they were not clearly identified as any one specific progenitor-cell population. Whether the effects of PDGFD–PDGFR $\beta$  signalling extend to all types of neural progenitor is also yet to be investigated. Furthermore, because the authors compared radial glia only between human and mouse, we do not know whether the role of PDGFD is unique to humans or common to the development of radial glia in other species with an expanded neocortex. Finally, possible

associations between mutations in genes encoding members of the PDGF pathway and human neurodevelopmental abnormalities, in particular microcephaly (an abnormally small head circumference)<sup>2,10,11</sup>, should now be pursued.

Perhaps most intriguing is the relatively limited number of genes whose expression seems to differ between human and murine developing radial glia. The authors developed a method to identify genes expressed in human radial glia and, as they had hoped, subsequently found a molecular pathway not shared by humans and mice. But the majority of the gene-expression data collected in this study emphasizes the remarkable commonalities between two transcriptional programs that diverged roughly 75 million years ago<sup>15</sup>. ■

**Forrest O. Gulden and Nenad Šestan are in the Departments of Neurobiology and Psychiatry, Kavli Institute for Neuroscience and Program in Cellular Neuroscience, Neurodegeneration and Repair, Yale School of Medicine, New Haven, Connecticut 06510, USA.**

## NEUROSCIENCE

# Towards unified vesicle endocytosis

**An ultrafast, temperature-dependent mode of endocytosis, a process that is required for neurons to repeatedly fire, challenges current thinking and brings an old model back into the spotlight. SEE ARTICLE P.228**

VLADAN LUČIĆ

Information is propagated between neurons at specialized junctions called synapses. Electrical signals generated at the presynaptic neuron cause neurotransmitter molecules to be released from synaptic vesicles into the synapse, and the neurotransmitter then binds to a receptor on the postsynaptic neuron, passing the signal on. To prevent depletion of synaptic vesicles during neuronal stimulation, vesicles are recycled through a process called endocytosis. Different types of synaptic-vesicle endocytosis have been described, but the mechanisms, and even the existence of one of the types, are still contested<sup>1</sup>. In this issue, Watanabe *et al.*<sup>2</sup> (page 228) describe an ultrafast mode of endocytosis that operates at physiological temperatures. In doing so, they might provide a way to reconcile the diverging evidence on synaptic-vesicle endocytosis.

There are thought to be three main modes of synaptic-vesicle endocytosis, differing with respect to speed, capacity and the molecular

*e-mails: forrest.gulden@yale.edu; nenad.sestan@yale.edu*

1. Herculano-Houzel, S., Manger, P. R. & Kaas, J. H. *Front. Neuroanat.* **8**, 77 (2014).
2. Hill, R. S. & Walsh, C. A. *Nature* **437**, 64–67 (2005).
3. Dehay, C. & Kennedy, H. *Nature Rev. Neurosci.* **8**, 438–450 (2007).
4. Lui, J. H., Hansen, D. V. & Kriegstein, A. R. *Cell* **146**, 18–36 (2011).
5. Noctor, S. C., Flint, A. C., Weissman, T. A., Dammerman, R. S. & Kriegstein, A. R. *Nature* **409**, 714–720 (2001).
6. Breunig, J. J., Haydar, T. F. & Rakic, P. *Neuron* **70**, 614–625 (2011).
7. Taverna, E., Götz, M. & Huttner, W. B. *Annu. Rev. Cell Dev. Biol.* **30**, 465–502 (2014).
8. Lui, J. H. *et al. Nature* **515**, 264–268 (2014).
9. Evsyukova, I., Plestant, C. & Anton, E. S. *Annu. Rev. Cell Dev. Biol.* **29**, 299–353 (2013).
10. Thornton, G. K. & Woods, C. G. *Trends Genet.* **25**, 501–510 (2009).
11. Dixon-Salazar, T. J. & Gleeson, J. G. *Ann. NY Acad. Sci.* **1214**, 156–167 (2010).
12. Oldham, M. C. *et al. Nature Neurosci.* **11**, 1271–1282 (2008).
13. Kang, H. J. *et al. Nature* **478**, 483–489 (2011).
14. Bergsten, E. *et al. Nature Cell Biol.* **3**, 512–516 (2001).
15. Mouse Genome Sequencing Consortium *et al. Nature* **420**, 520–562 (2002).

machinery that regulates them<sup>1</sup> (Fig. 1a). So far, the best explained, and apparently predominant, mode is the clathrin-dependent pathway, in which synaptic vesicles merge with the cell's plasma membrane, and vesicles are regenerated directly from membrane-derived buds coated in clathrin protein. In the 'kiss-and-run' pathway, synaptic vesicles release a neurotransmitter through a transiently opened membrane pore and then quickly detach from the membrane without ever fully combining with it. Finally, in bulk endocytosis, which has the highest capacity of the three modes, large sections of the plasma membrane become internalized, forming endosomes from which synaptic vesicles can then bud.

Watanabe and colleagues combined sophisticated genetic techniques that stimulate neurons with high-pressure freezing to arrest endocytic processes at well-defined time points. They then determined the sequence of endocytic events by studying the process using electron microscopy, and showed that, at physiological temperatures (34–37°C),