Meeting report

On the origin of neurons

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A report on the conference 'Neurogenesis 2007', Tokyo, Japan, 15-16 May 2007.

The understanding of embryonic and adult neurogenesis, and their possible medical applications, are highly active fields of research, as became evident at the first international meeting devoted solely to mammalian brain neurogenesis, entitled 'Neurogenesis 2007' and held at the National Museum of Emerging Science and Innovation in Tokyo this May. Exciting new insights into neurogenesis were presented and discussed, encompassing many aspects of neuron generation, such as progenitor cell division, neuronal migration, adult neurogenesis, and stem-cell therapy. The dissection of these processes ranged from detailed cell biological analyses to the unraveling of transcriptional networks. Here we report a few of the highlights of the conference.

Neuronal progenitors

During the development of the mammalian brain, neurons arise from neural stem and progenitor cells, which initially proliferate by symmetric divisions and later switch to both asymmetric and symmetric neurogenic divisions. In the dorsal telencephalon of the embryo, newborn neurons migrate radially to the developing six-layered cerebral cortex. Multiple types of progenitors exist with different cell biological characteristics and modes of division. To control the number, type, and final location of neurons, the transition from proliferative to neurogenic cell divisions requires a complex network of regulation so that neural specification, cell-cycle exit, cell differentiation and neuronal migration can all occur in concert. Subsequently, in the adult brain, a subset of astrocyte-like cells remains as stem cells in the subventricular zone of the lateral ventricle and dentate gyrus of the hippocampus, giving rise to neuronal progenitors that produce neurons throughout life.

Neuronal progenitors in the dorsal telencephalon of rodent embryos fall into two major classes: those that divide at the apical surface (neuroepithelial and radial glial cells, collectively referred to as apical progenitors) and those that divide at the basal side of the ventricular zone and in the subventricular zone and serve as an intermediate progenitor in the lineage from apical progenitors to neurons (called either basal progenitors or intermediate progenitors and here referred to as basal intermediate progenitor cells). Although it has been known that basal intermediate progenitor cells exist from the very onset of neurogenesis throughout all of its stages, a question has been whether they serve as distinct progenitors for specific lineages or layers, or as a general intermediate population to boost neurogenic output for all layers. Using various markers of apical progenitors and basal intermediate progenitor cells, Robert Hevner (University of Washington, Seattle, USA) delineated a transcription factor cascade associated with neurogenesis (Pax6 → Ngn1, Ngn2 → Tbr2 → Tbr1). Hevner presented evidence establishing Tbr2 as a marker for basal intermediate progenitor cells. Using a *Tbr2*-GFP transgenic mouse, he and his colleagues had shown that Tbr2-positive cells adopt bipolar or multipolar morphology and are distinct from neuroepithelial and radial glial cells. *Tbr2*-GFP inheritance also revealed that basal intermediate progenitor cells produce the majority (90%) of neurons in all cortical layers.

Further insight into the precise timetable for Ngn2 and Tbr2 expression during neurogenesis was presented by Takaki Miyata (Nagoya University, Nagoya, Japan). Using elegant time-lapse microscopic analysis of individual cortical progenitors in cortical slice preparations, he has demonstrated that apically born daughter cells initially are negative for

Ngn2 and Tbr2. In the majority of cases only one of the two daughter cells starts expressing Ngn2 and Tbr2, with Ngn2 expression preceding, and later overlapping with, Tbr2 expression. Expression of both markers is initiated while the respective daughter cell still has contact with the apical surface. This observation is in line with the presence of Tbr2-positive cells at the apical surface, as reported by Hevner. These apical-born cells subsequently migrate basally and hence could represent either newborn neurons or basal intermediate progenitor cells.

Basal intermediate progenitor cells as a means of increasing the number of cortical neurons per radial unit were also discussed by one of us (WBH), who concentrated on apical-basal polarity and cleavage plane orientation of apical progenitors. Evidence was presented that Aspm, a microtubule-binding protein associated with the poles of the mitotic spindle and mutations in which cause primary microcephaly, is essential for maintaining a spindle orientation exactly perpendicular to the apical-basal axis, and hence symmetric proliferative divisions of apical progenitors in which their apical constituents are partitioned to both daughters. The reduction in the size of the apical domain, which accompanies the switch from symmetric to asymmetric division, involves the release, into the ventricle, of the midbody, at which certain apical constituents such as the stem cell marker prominin-1/CD133 are concentrated.

From progenitor to neuron

The differentiation of neural progenitor cells into cells committed to a neuronal fate is determined largely by the so-called proneural genes, some of which encode basic helix-loop-helix (bHLH) transcription factors. François Guillemot (National Institute for Medical Research, London, UK) presented work on pursuing the direct targets of these bHLH transcription factors utilizing gene expression microarrays. He reported a direct regulation by Ngn2 of *Rnd2*, a gene encoding a small GTP-binding protein involved in the radial migration of newborn cortical projection neurons.

Ryoichiro Kageyama (Kyoto University, Kyoto, Japan) showed that Hes bHLH repressor genes regulated by Notch signaling maintain proliferation of progenitor cells, and function not only in orchestrating the neurogenic program but also in the patterning of the developing central nervous system, which is partitioned into many compartments (differentiating regions) by boundaries (signaling centers). By real-time imaging analysis at the single-cell level, it was shown that, in the compartmental cells, *Hes1* expression oscillates, allowing expression of the proneural gene *Mash1*, and in the boundary cells Mash1 is sustained at low levels and Hes1 is consistently kept high, preventing neurogenesis. This difference in expression pattern between *Mash1* and *Hes1* regulates the compartment versus boundary-cell characteristics.

Neuronal migration and specification

Once formed, neurons migrate to their final positions. The migration of cortical neurons is orchestrated in a birth date-dependent manner, where newborn neurons migrate radially and successively pass the earlier-born neurons to stop at the uppermost layer, beneath the marginal zone, which contains reelin-secreting Cajal-Retzius cells. One key question is whether neurons already acquire laminar fate information in the ventricular zone or whether they need to reach the marginal zone to acquire their laminar fate identity. Kazunori Nakajima (Keio University, Tokyo, Japan) provided evidence for a birth date-dependent preferential segregation mechanism of migrating neurons that is independent of the marginal zone and reelin signaling. Using reaggregation co-culture of dissociated embryonic day 16 (E16) ventricular zone cells (proliferating progenitors) and intermediate zone cells (newborn migrating neurons), he and his colleagues found that the intermediate zone cells preferentially clustered in the center of the aggregates. Nakajima also reported that this was not a property of cell location (intermediate zone), but a property of shared birth date (E14). Interestingly, this birth-date-dependent segregation was also observed in the reelin-signaling-deficient *yotari* cells. These findings suggest that cortical neurons acquire a birth-date-dependent segregation mechanism before their somas reach the marginal zone.

Further insight into the roles of Cajal-Retzius cells and reelin signaling was presented by Elizabeth Grove (University of Chicago, USA), who has genetically ablated, by *Wnt3a*-Cre-specific activation of diphtheria toxin, the major source of cortical Cajal-Retzius cells, the cortical hem. Cajal-Retzius cells were virtually absent from these hemless mice, but contrary to what might be expected from the reelin-signaling-deficient *reeler* cortex phenotype, where layers are inverted and disorganized, cortical lamination was normal.

Adult neurogenesis and its medical implications

The transcription factor Pax6 is known to be expressed in apical progenitors and neural stem cells during embryonic and adult neurogenesis. Noriko Osumi (Tohoku University, Sendai, Japan) presented research on the role of Pax6 in embryonic and adult rat neurogenesis in a study of the function of one of its downstream genes, *FABP7*, which they identified by microarray analysis. FABP7 is a fatty-acid-binding protein that maintains proliferation of embryonic neuroepithelial cells in the cortex and is similarly implicated in adult neuronal stem cells (distinguished as cells positive for glial fibrillary acidic protein) in the dentate gyrus. Osumi also reported behavioral experiments showing that *Pax6* heterozygous mutant rats could provide a model for studying human mental diseases such as schizophrenia.

Adult neurogenesis in the hippocampus is influenced by neuronal activity, as demonstrated by Tatsuhiro Hisatsune

(University of Tokyo, Japan). He reported that in the dentate gyrus, transiently amplifying neural progenitor cells receive direct GABAergic input, in response to which they depolarize and become neurogenic. Underlying this enhanced hippocampal neurogenesis by the activation of progenitor cells is a typical hippocampal network activity, the theta oscillations.

Medical applications resulting from research on neurogenesis were highlighted by Hideyuki Okano (Keio University), who discussed possible therapeutic approaches to brain and spinal cord injury. The reactive astrocytes accumulating in the injured area, which have long been thought to be harmful by causing glial scar formation, have now been found to also exert beneficial roles in the damaged central nervous system. Administration of a new semaphorin 3A-inhibitor (SM-216289) was shown by Okano to result in enhanced regeneration of injured axons.

What is the relevance of adult neurogenesis for humans? Kirsty Spalding (Karolinska Institute, Stockholm, Sweden) presented the innovative approach of exploiting the peak of atmospheric ^{14}C resulting from nuclear weapons testing to radiocarbon-date neurons in human post-mortem brains. She showed that there is no significant long-term stable integration of new neurons in the adult human neocortex. However, in line with observations in rodents, preliminary results indicate that neurogenesis does occur in the adult human hippocampus.

The meeting revealed neurogenesis as a very dynamic, fast-growing field of research that certainly needed, and will need in the future, its own conference. As Ron McKay (NIH, Bethesda, USA), a pioneer in the stem-cell field, noted in his keynote lecture, translating basic research on embryonic and adult neurogenesis into medical applications is likely to yield new therapeutic approaches for neurological disorders and injuries. We look forward to Neurogenesis 2009.

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