Stem cells to synapses: regulation of self-renewal and differentiation in the nervous system

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Discovering how stem cells are maintained in a multipotent state and how their progeny differentiate into distinct cellular fates is a key step in the therapeutic use of stem cells to repair tissues after damage or disease. We are investigating the genetic networks that regulate neural stem cells in *Drosophila*.

Stem cells can divide symmetrically to expand the stem cell pool, or asymmetrically to self-renew and generate a daughter cell destined for differentiation. The balance between symmetric and asymmetric division is critical for the generation and repair of tissues, as unregulated stem cell division results in tumourous overgrowth. Symmetrically dividing stem cells exist in the optic lobe of the brain, where they convert to asymmetrically dividing neuroblasts. By comparing the transcriptional profiles of symmetrically and asymmetrically dividing stem cells, we identified Notch as a key regulator of the switch from symmetric to asymmetric division. During asymmetric division cell fate determinants, such as the homeodomain transcription factor Prospero, are partitioned from the neural stem cell to its daughter. By identifying Prospero's targets throughout the genome we showed that Prospero represses genes for self-renewal and activates differentiation genes. In *prospero* mutants, differentiating daughters revert to a stem cell-like fate: they express markers of self-renewal, continue to proliferate, fail to differentiate and generate tumours.

The systemic regulation of stem cells ensures they meet the needs of the organism during growth, and in response to injury. A key point of regulation is the decision between quiescence and proliferation.

During development, Drosophila neural stem cells transit through a period of quiescence separating distinct embryonic and post-embryonic phases of proliferation. Neuroblasts exit quiescence in response to a nutrition-dependent signal from the fat body. We identified a population of glial cells that produce Insulin/IGF-like peptides in response to nutrition, and show that the Insulin/IGF Receptor pathway is necessary for neuroblasts to exit quiescence.

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Professor Andrea H Brand is the Herchel Smith Professor of Molecular Biology at the Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge. Professor Brand's lab studies the genetic networks that regulate the transition from a multipotent neural stem cell to a specialised neuronal or glial cell type. With sufficient knowledge of these networks, it should be possible to manipulate stem cells to proliferate, to remain quiescent, or to differentiate into specialised, predefined, cell types. Professor Brand was awarded the Royal Society Rosalind Franklin Award in 2006, the William Bate Hardy Prize in 2004, the Hooke Medal of the British Society of Cell Biology in 2002 and Special Award of Excellence at the Wellcome Biomedical Imaging Awards, 2001. She was elected a Fellow of the Royal Society in 2010, a Fellow of the Academy of Medical Sciences in 2003, and a member of the European Molecular Biology Organization in 2000.

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Transitions in division mode of neural stem cells during cortical development

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In the developing mammalian brain, elongated neuroepithelial cells function as neural stem cells. These cells initially undergo symmetric divisions to proliferate, and subsequently initiate asymmetric divisions that continuously generate a self-renewing daughter (radial glia or apical progenitors) and a differentiating daughter cell (neurons and intermediate progenitors). This transition from a proliferative to a neurogenic mode plays a critical role in determining brain size. In the neurogenic mode, the self-renewing daughters of radial glial divisions inherit the complete epithelial structure including both apical and basal processes, therefore maintaining the pseudo-stratified brain organization. Our recent live imaging studies, however, have revealed that, on occasion, these radial glia also undergo oblique cleavages that separate the dividing radial glia into the apical and basal part. The basal daughters, which inherit only the basal process, generate a different type of self-renewing progenitor cells; they migrate out from the ventricular zone (VZ), undergoing asymmetric neurogenic divisions. These progenitors are very similar to the outer subventricular zone (OSVZ) progenitors, a major type of progenitors in gyrencephalic animals, revealing the presence of OSVZ progenitors in rodents. Thus, the self-renewing progenitors in the developing mammalian cortex undergo two transitions in the division mode, first from symmetric to asymmetric divisions of radial glia, and then subsequently from radial glia to OSVZ progenitors. We have proposed that this second transition is initiated by oblique cleavages that split the apical and basal part of the dividing radial glia. Mutant mice defective in cleavage plane orientations generate a number of the OSVZ progenitors as seen in the LGN-mutant strain, and using these mice as a model makes it possible to analyze properties and genetic defects of the OSVZ progenitors, which may affect human cortical development.

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SHORT BIOGRAPHICAL SKETCH

Fumio Matsuzaki received his doctorate at the University of Tokyo in 1984, and carried out postdoctoral research, first at the Tokyo Metropolitan Institute of Medical Science, then in the laboratory of Gerald Edelman at the Rockefeller University. He was a section chief in the National Institute of Neuroscience in Japan from 1989 to 1998. In 1998, he was appointed professor in the Institute for Development, Aging and Cancer at Tohoku University and remained there until taking his current position as group director at the RIKEN CDB in 2002.
He has been interested in genetic programs and plastic mechanisms underlying neural development. He began genetic research of neurogenesis using *Drosophila*, and discovered asymmetric segregation of Prospero during neural stem cell divisions. Since then, his lab studies how neural stem cells divide asymmetrically. His lab is currently using both *Drosophila* and mouse as model systems to understand how brain development is controlled by neural stem cell function.