The formation of new neurons (neurogenesis) results from the complex interplay of many variables: cell proliferation, migration, cell fate choice, and survival. Recent papers identify factors involved in each of these aspects of neurogenesis and indicate how these variables may be integrated during development and adulthood. This recent work includes the report of a kinase that controls cell division in neural progenitors and a study suggesting that autoimmune T cells are positive regulators of neurogenesis. Other intriguing findings link planar cell polarity to neural tube development in zebrafish and the migration of neuroblasts in adult mice.

**A Doublecortin-like Kinase on the Road to Mitosis**

Li-Huei Tsai and colleagues (Shu et al., 2006) report that a doublecortin-like kinase (DCLK) regulates the mitotic spindle in dividing neural progenitors of the developing cerebellum. DCLK was isolated by Shu et al. (2006) as a microtubule-associated protein that is enriched in the cerebellum of mice at postnatal day 8. Except for the presence of a CaM kinase II-like kinase domain, DCLK is very similar to doublecortin, a protein involved in the migration of neurons in the neocortex. Neural precursor cells overexpressing DCLK are arrested at prometaphase and have mitotic spindles that are monopolar. Knockdown of DCLK by RNAi also disrupts mitotic spindle formation and leads to cell-cycle arrest at prometaphase. In both cases of DCLK perturbation, progenitors are biased towards a neural fate. Determining how the regulation of mitotic progression biases cell fate in favor of neuronal differentiation will be an important question to address in future studies and may be related to the orientation of the mitotic spindle, which has also been shown to bias cell fate choice. Interestingly, previous work has shown that there are multiple splice variants of DCLK that are developmentally regulated and have different activities. Future studies should lead to the discovery of substrates for DCLK and should determine whether DCLK isoforms act similarly in adult neurogenesis as they do during development.


**Planar Cell Polarity Is Lost and Found in the Neural Tube**

The neural tube is the embryonic precursor to the brain and spinal cord. Alexander Schier and colleagues (Ciruna et al., 2006) now report that planar cell polarity signaling is required in the neuroepithelium for neural tube formation. In wild-type zebrafish, following cell division in the neuroepithelium the daughter cell that had maintained contact with the basement membrane regains polarity and returns to its original position, whereas the daughter at the medial position regains polarity and integrates into the neuroepithelium on the opposite side of the midline. In the absence of Vangl2 (Van Gogh-like 2), a transmembrane protein that modulates the noncanonical Wnt signaling pathway governing planar cell polarity, the medial daughter cell can no longer integrate in the neuroepithelium on the opposite side of the midline. As a consequence, cells accumulate between the adjacent apical surfaces of the neuroepithelium, thereby disrupting neural tube formation. Interestingly, blocking cell division improves neural tube formation in Vangl2-deficient zebrafish but does not rescue other defects associated with loss of planar cell polarity. It is thought that regions of neurogenesis in the adult, such as the ventricular zones of the brain, may retain some primordial characteristics of the developing neuroepithelium. Although intercalation of daughter cells across the midline is a phenomenon limited to neurulation, this study raises the question of whether noncanonical Wnt signaling and planar cell polarity might also couple mitosis and cell fate decisions during adult neurogenesis.


**Genetic Variety Is the Spice of Life**

Neurogenesis in the adult hippocampus varies dramatically from one mouse strain to another. Fred Gage and colleagues (Kempermann et al., 2006) have used this observation as a starting point to find genes whose expression covaries with quantifiable measurements of neurogenesis. Kempermann et al. (2006) examined cell proliferation, cell survival, and the number of new neurons in the adult hippocampus of 52 inbred strains of mice. Interestingly, from these initial analyses, the authors find that differences in neuronal survival, rather than cell proliferation, explain the majority of the variability in the number of new neurons generated between strains. This may be an important consideration when trying to establish factors to promote neurogenesis experimentally or therapeutically. The authors then correlated their quantitative analysis of neurogenesis with microarray expression data from the Gene Network database (http://www.genenetwork.org) and generated a list of 190 genes whose expression might explain the variability in neurogenesis observed between strains. This list includes many factors that could plausibly be involved in neurogenesis, including some that are already associated with stem cell self-renewal, such as musashi and...
prominin. This study emphasizes that neurogenesis is governed by a network of factors. Understanding this network at the genetic level may help to identify the factors that affect neurogenesis in humans, which likely vary with age, illness, and between individuals.


**Neuroblasts Go with the Flow**

Arturo Alvarez-Buylla and coworkers (Sawamoto et al., 2006) have shown that the movement of cerebrospinal fluid is essential for the migration of nascent neurons in the adult brain of mice. Neuroblasts migrate through a complex network of pathways in the subventricular zone, where they are born, to the rostral migratory stream that leads them to the olfactory bulb, where they form functional connections. Cerebrospinal fluid in the ventricles has a directional flow due to the beating of cilia on ependymal cells, which are aligned by planar cell polarity. When Sawamoto et al. (2006) studied mice bearing a genetic mutation that affected the formation of these cilia, the chains of migrating neuroblasts in the subventricular zone became disoriented and most neuroblasts failed to reach the olfactory bulb. Because the normal direction of movement for these migrating cells mirrors the movement of the cerebrospinal fluid, Sawamoto et al. (2006) tested whether the directional flow creates a gradient of the chemorepulsive factor, Slit. Slit has previously been shown to repel migrating olfactory neurons and is secreted by the choroid plexus (also where cerebrospinal fluid is generated in the caudal part of the ventricle). In support of their model, they found that when Slit 2 tagged with alkaline phosphatase is injected into the ventricles of the mouse brain, a gradient forms in wild-type mice but not in mice lacking ciliary movement. Moreover, if the choroid plexus is transplanted from a donor mouse to an anterior location, rostral neuronal migration is disrupted. This remarkable discovery raises many new questions. For instance, what other gradients besides Slit proteins are created by the beating of ependymal cilia, and could these gradients also serve functions other than guiding migrating neuroblasts?


**Autoimmunity Gives Neurogenesis a Lift**

Given the link between autoimmunity and diseases such as multiple sclerosis, it is no wonder that T cells in the brain that recognize self-antigens have a bad reputation. However, new work by Schwartz, Kipnis, and colleagues argues (Ziv et al., 2006) for a more complex view of these much maligned cells. Their work suggests that, rather than always being detrimental, self-recognizing T cells can also support neurogenesis in adult mice if well-controlled. Previous work from the Schwartz lab has shown that the recruitment of autoimmune T cells to sites of neuronal injury promotes neural cell survival by altering the behavior of local microglia. This new report suggests that similar immune-based mechanisms may also operate during normal adult neurogenesis. In support of their argument, Ziv et al. (2006) demonstrate that neurogenesis is impaired in the hippocampus of immune-deficient mice. Moreover, unlike wild-type mice, neurogenesis in immune-deficient mice is not stimulated by enriching the mouse’s environment. Remarkably, neurogenesis is restored by the introduction of autoimmune T cells that recognize a self-antigen (in this case myelin basic protein) but is not restored by T cells that recognize a non-self-antigen. The presence of autoimmune T cells also improves the performance of mice in the Morris water maze, a spatial memory task that has been linked to neuronal activity in the hippocampus. One of the far-reaching implications of the study is that it suggests mechanisms by which age-related changes in the immune system could be linked to cognitive decline in humans. Future work may also establish the precise mechanisms by which T cells regulate microglia to foster an environment that supports neuronal survival.


Robert P. Kruger