In This Issue

One cyclin for adult neurogenesis

In recent years, scientists have found evidence that new neurons arise in the brains of adult mammals, but little is known about the underlying mechanisms. Now, on page 209, Kowalczyk et al. find that in neurogenic regions of the adult brain only one cyclin D protein, cyclin D2, is required for neural precursors to enter the cell cycle. To determine which cyclins were required for adult neurogenesis, the team analyzed mice lacking either the cyclin D1 or D2 gene. Neuronal proliferation in the hippocampus, which is the region required for memory formation, was completely inhibited in cyclin D2 mutants, but was unaffected in cyclin D1 mutants. Astrocytes continued to proliferate in mice lacking D2, albeit to a limited extent, suggesting that the gene is absolutely required for neurogenesis but not for glial cell proliferation.

By contrast, dividing neural precursors isolated from mouse pups contain all three cyclin D proteins, 1, 2, and 3. Thus, there is a mechanistic distinction between adult and developmental neurogenesis. The researchers hope to use cyclin D2’s newly defined role in adult neurogenesis to test how neural proliferation relates to the formation or extinction of memories in adult animals.

Vesicle biogenesis potentiation

The AP-3 adaptor protein exists in two forms, A and B. Loss of the ubiquitously expressed AP-3A complex leads to widespread problems in lysosome functions. Now, on page 293, Nakatsu et al. show that loss of neuronal-specific AP-3B function causes defects in hippocampal function in mice, increases the magnitude of long-term potentiation, and makes the animals susceptible to seizures.

The team generated mice lacking the 3B-specific subunit μ.3B. The animals had no gross morphological brain defects, but were prone to spontaneous and triggered seizures. At hippocampal synapses the number and size of synaptic vesicles was reduced, although baseline release of the neurotransmitters GABA and glutamate were normal. However upon neural stimulation, the mutants released less GABA, the inhibitory neurotransmitter, than did wild-type animals. Nakatsu et al. found that synaptic vesicles had reduced integration of the GABA-specific transporter VGAT but normal levels of the glutamate transporter VGLUT.

The team hypothesizes that AP-3B is critical for the biogenesis of a subset of synaptic vesicles in hippocampal neurons and that VGAT may be a specific cargo for AP-3B. Also, because there is more glutamate than GABA available in the system, a reduction in glutamate vesicle biogenesis may be compensated for by efficient vesicle recycling at the plasma membrane. JCB

One protein, two pools

The cytoplasmic protein β-catenin is essential for both intercellular adhesion and intracellular Wnt signaling. Invertebrates have multiple genes to cover the multiple functions, but on page 339 Gottardi and Gumbiner propose that vertebrate cells make do with one gene by maintaining different pools of protein for the different roles. Different folding may distinguish the adhesion and proliferative signaling functions.

Cofractionation experiments showed that β-catenin that interacts with cadherin is in a heterodimer with α-catenin, but Wnt signaling induces a monomeric form of β-catenin that interacts with a transcription factor complex. After enriching for cadherins, β-catenin can be detected using antibodies to either NH$_2$-terminal or COOH-terminal regions; but in the cadherin-free fraction only the NH$_2$-terminal antibody binds. The team hypothesizes that the β-catenin protein is folded back on itself in its monomeric form and, as such, is available for transcription complex binding but not for adhesion duties.

Gottardi speculates that a post-translational modification is responsible for the conformational change but does not yet know what that modification is. Furthermore, she thinks this sort of molecular segregation may be a common mechanism cells use to allow one protein to do multiple jobs, without the more common function soaking up all the protein required for a temporally regulated one. JCB
**Tugging and pulling in asymmetric cell divisions**

In asymmetric divisions, the cell alters the normal process that centers the spindle in the mother cell, but how it regulates the timing of spindle movement is unclear. Now, on page 245, Labbé et al. describe a tethering system that resists premature movement of the mitotic spindle during asymmetric cell divisions in *C. elegans* embryogenesis.

It was known that when researchers cut spindle microtubules with a laser, both centrosomes moved toward their respective cell poles, but the posterior one moved more quickly. To find out what establishes these uneven pulling forces and when the asymmetry first arises, Labbé and his colleagues used a laser to sever microtubules at different times throughout the first cell cycle. If they destroyed the anterior centrosome in prophase, the posterior centrosome moved posteriorly. But after destruction of the posterior centrosome the anterior one stayed centered, suggesting that there is a force pulling toward the tail of the embryo and something resisting it—but not actively pulling—on the anterior end.

When the team ablated microtubules near the anterior centrosome but on the cortical side, they found that the whole spindle moved toward the posterior pole. They hypothesize that the cut releases a tether that anchors the anterior centrosome to the anterior cortex and resists the posterior pulling forces. By metaphase, the tether releases and the spindle moves to the posterior of the embryo in preparation for the asymmetric division.

Because microtubules are known to be more stable at the anterior cortex compared with the posterior, the researchers speculate that such asymmetry might contribute to the tether. They are exploring this hypothesis by monitoring changes in microtubule dynamics at the cell cortex throughout the cell cycle. *JCB*

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**Slipping through the middle**

In the 1960s scientists saw evidence in electron micrographs that leukocytes migrate through the middle of endothelial cells in vivo. But when others couldn’t replicate the findings in vitro and instead saw the immune cells slip between the endothelial cells, the field largely abandoned the idea of transcellular movement. Finally, on page 377, Carman and Springer show in vitro evidence that leukocytes can pass through the middle of cells as they leave the blood vessels and move into the tissue.

The team found that once a leukocyte attaches to the surface of an endothelial cell, microvilli protrude from the vascular cell surface, partially surrounding the immune cell. Adhesion proteins in the microvilli appear to realign the integrin molecules in the leukocytes, providing them with directional information. Meanwhile, a pore in the membrane of the endothelial cell forms and the leukocyte squeezes through.

So why did Carman and Springer see transmigration where others have not? Unlike previous studies, which relied on junctional vascular markers, the Harvard team also used antibodies against ICAM-1, an adhesion protein that lines the whole intravascular surface of the endothelial cells. With high resolution imaging, they could distinguish endothelial surface from junctional events even if the surface events occurred near a junction. Lower resolution images just couldn’t distinguish exactly where the changes were happening. Other groups now hint that they see similar results.

Carman speculates that transcellular migration and passage between cells are probably used in different tissues and under different inflammatory conditions. But just what molecules regulate how an immune cell chooses its route remains unclear.

Meanwhile, on page 223, Weis et al. provide insight into how tumor cells move from the blood into surrounding tissue. Tumor cells in the blood secrete VEGF, an angiogenesis factor that compromises the integrity of the endothelial barrier. When the team injected tumor cells into mice deficient for either Src or Yes signaling kinases, few cancer cells passed through the endothelial barrier, relative to wild-type controls. VEGF appears to work through the kinases to disrupt VE-cadherin-β-catenin complexes, which maintain junctions between endothelial cells. *JCB*