In This Issue

**Defaulty neurons**

Given a choice, embryonic stem (ES) cells prefer to join the neural lineage, according to findings on page 79. The results from Smukler et al. imply that other cell types arise only when the neural lineage is actively blocked.

Uncovering the default pathway for ES cells is tricky. The cells must be shielded from any signals that influence their development. Yet media devoid of instructive signals are not very supportive of cell survival. Smukler and colleagues indeed found that 75% of cells derived from mouse ES cells plated on serum-free media died within a day.

But by wading through this massive cell death, the group found that most of the cells that survived on media lacking all instructive cues rapidly acquired neural stem cell (NSC) characteristics. Even before their first mitosis, the ES cells expressed markers indicative of a cell type intermediate between ES cells and NSCs. The group calls these cells primitive NSCs, because they can still adopt some nonneural fates if given the right growth conditions. Primitive NSCs then produce definitive NSCs, which are committed to this state and can be passaged indefinitely.

Survival factors, including cAMP, did not change lineage choice, but did allow more of the ES cells to survive and thus become primitive NSCs. Blocking apoptotic pathways also improved NSC production. Once they became primitive NSCs, the cells produced their own survival factors—FGFs, which also increased proliferation.

Smukler imagines that the evolutionary emergence of the nervous system conferred an increased fitness. A strong selective pressure might therefore exist to ensure that neural tissue develops at all costs. The default nature of the neural stem cell fate helps guarantee that neural tissue production perseveres even if instructive cues are faulty or absent.

Although neural master regulatory genes have not yet been identified, the findings suggest that they would be repressed during early development, when other tissues are emerging. Only by relieving this inhibition would the nervous system develop. These functions might be performed in vivo by BMPs, which block neural fates, and by node-secreted factors, which antagonize BMPs and organize neural tissue formation. JCB

**Big bones in p53 mutants**

On page 115, a famous tumor suppressor is uncovered as a suppressor of bone development. Wang et al. show that p53 curbs bone growth by inhibiting osteoblast differentiation and proliferation.

Mice deficient in p53 have a high incidence of tumor formation and often die prematurely from lymphomas. Few developmental abnormalities had been found, however. The authors suspected a bone defect might exist, since they had shown that c-Abl, a kinase that interacts with p53, is required for osteoblast differentiation. By looking beyond bone morphology, they indeed found abnormalities in the p53 mutant skeletons. The deficiencies were able to rescue the differentiation defect of mice lacking c-Abl.

Mice lacking only p53 had increased bone mass. The effects were due to accelerated differentiation of bone-forming osteoblasts. Mutants also had more osteoblasts, suggesting that p53 slows both differentiation and proliferation of these precursors.

The effects are due to increased expression of an osteoblast-specific transcription factor called osterix. p53 has the ability to repress osterix transcription directly, although in this case it did not need to bind to the osterix promoter. It is possible that p53 might sequester the p300 core transcription factor, with which it has been shown to associate, and thereby repress transcription.

The bone defects are partially corrected by a negative feedback pathway that increases the number of bone-destroying osteoclasts. The increased osterix in the p53 mutant osteoblasts induced increased M-CSF expression; this M-CSF then induced osteoclast differentiation.

Early embryos have high levels of p53, which might help to block premature bone mineralization. The mineralization occurs later, after p53 levels have dropped, but osteoblasts up-regulate p53 again later during differentiation. Its return might put on the brakes before bone formation gets out of hand. JCB
Xorbiting the spindle

The Xorbit microtubule-binding protein, say Hannak and Heald (page 19), keeps the spindle from getting away from its passenger DNA.

Xorbit is a spindle-localized microtubule plus-end binding protein whose loss causes defects in spindle formation and chromosome alignment. To understand its specific function, the authors used video microscopy to compare spindle assembly in real time in frog egg extracts with and without Xorbit.

The videos revealed a stabilizing effect of Xorbit on microtubules at the DNA. In extracts lacking centrosomes (in which the DNA is responsible for spindle assembly), spindle microtubule polymerization required Xorbit; no spindles formed in its absence. Microtubules organized by centrosomes, however, were not affected by Xorbit. Perhaps Xorbit is only activated by something on or near the chromatin, such as RanGTP.

Xorbit also keeps a check on the necessary instability that occurs during anaphase, when microtubules depolymerize. When the authors depleted Xorbit at anaphase, the entire spindle rapidly disassembled, leaving behind the unsegregated chromosomes. The spindle-stabilizing mechanism is not yet clear. Xorbit might directly protect plus ends or possibly counteract a depolymerizing activity.

Xorbit may also physically link the kinetochore to the spindle, given the chromosome misalignment defects seen in its absence. The link might be through CLIP-170, which the authors found interacts with Xorbit. They also noted an interaction between Xorbit and CENP-E, suggesting Xorbit might connect chromosomes to the motors that drive their movements.

Selective calcium blockade

Bcl-2 blocks deadly, persistent Ca^{2+} increases but allows signaling Ca^{2+} oscillations to proceed, according to Zhong et al. (page 127). As a result, this anti-apoptotic protein can save T cells from death without interfering with other Ca^{2+}-regulated cell functions.

Calcium has a hand in many physiological processes, including the proliferation of activated T cells. So the authors were a bit perplexed when they previously discovered that Bcl-2 inhibited IP_{3/R}-regulated Ca^{2+} oscillations that favor cell survival. These oscillations are blocked by Bcl-2. RNAi-mediated loss of IP_{3/R} also did not prevent Ca^{2+} oscillations. Perhaps, in T cells, oscillations are IP_{3/R}-independent or require only very few of these receptors.

Bcl-2 expression in T cells is temporarily down-regulated in the thymic cortex, where positive and negative selection occur. Its loss thus allows strong TCR reactions—as caused by self-antigens—to kill the T cell. In the periphery, however, the presence of Bcl-2 might protect mature T cells that encounter a strong antigen.