A tumorigenic culprit in ES cells

In the debate over whether ES cells or somatic stem cells have better prospects for stem cell therapies, ES cell proponents admit that their pluripotent cells carry an increased risk: ES cells can form teratomas. But now Kazutoshi Takahashi, Kaoru Mitsui, and Shinya Yamanaka (Nara Institute of Science and Technology, Nara, Japan) have found that a newly discovered Ras gene may be at the heart of this problem.

ERas, previously thought to be a pseudogene, was found by the group as being expressed specifically in ES cells. The other genes in this expression class are also expressed in early embryonic tissues such as the inner cell mass and epiblast, but no expression of ERas is evident in the embryo. The lack of phenotype of ERas knockout mice adds to the mystery.

Yamanaka suggests that ERas may be connected to the LIF/Stat3 pathway, which is dispensable for normal mouse development but necessary in ES cells and for the extended survival of mouse blastocysts (a process called diapause). Only in the ES cells and during diapause must pluripotency be extended past a few days, and this extension may be helped by LIF or ERas expression. The situation is clouded further in humans and monkeys, however, as both have apparently functional ERas genes but lack diapause.

Whatever the function of ERas, “ERas null cells should be much safer for clinical applications,” says Yamanaka. ERas has residues characteristic of activated Ras proteins, and is found largely in the activated, GTP-bound form. Its addition transforms cells, whereas its deletion from ES cells sharply reduces their tumor-forming ability. Growth is also reduced in ERas knockout cells, but Yamanaka says that rich culture conditions largely correct for this and thus slow growth should not hold back the use of altered ES cells. Direct human applications will not, however, come from Yamanaka’s group in the foreseeable future, as there are extensive bureaucratic hurdles involved in experimentation on human ES cells in Japan.

Reference: Takahashi, K., et al. 2003. Nature. 423:541–545.

WASPs with memory

Memory may not be confined to brain cells. Eduardo Torres and Michael Rosen (University of Texas Southwestern Medical Center, Dallas, TX) have found that the actin polymerization activator WASP has at least the potential to be a memory device. Such a capacity could switch cells into an altered state in which they respond more acutely to a stimulus the second time around.

Rosen was intrigued initially by the location of a tyrosine in WASP that others had found was phosphorylated. In structural models, Tyr 291 is buried in the fold that forms in the autoinhibited form of WASP. Sure enough, Tyr 291 could only be phosphorylated (thus further activating WASP activity) when the structure was opened up via addition of the activating Cdc42.

Both Tyr 291 phosphorylation and Cdc42 activation can be driven by Src family kinases. But Cdc42 activation and opening of WASP take some time, so only a persistent Src signal will still be around to phosphorylate Tyr 291 by the time it is exposed. WASP could then act as a memory device if Src maintains the Tyr 291 phosphorylation until after Cdc42 is turned off (as might happen if a GTPase activating protein drops by and shuts off Cdc42). Torres and Rosen showed that this form of WASP clasps and protects the phosphorylation on Tyr 291 so it is resistant to removal by phosphatases. In contrast to the initial, unphosphorylated form of WASP that took such a sustained signal to activate, the phosphorylated WASP is now in a primed form. A future signal need only tickle the Cdc42 system to achieve full activation.

For now, the site of action of these mechanisms are unknown. “What we’ve found is exclusively biochemical,” says Rosen. “We don’t know where this will occur in vivo.” But, he says, “having this as the biochemical concept will drive the kind of work needed to put the findings in context. Rosen is looking for places where later responses might be affected by earlier experience. The best candidate is in neurite outgrowth, where N-WASP phosphorylation has been seen to persist long after the kinase stimulus has vanished. Perhaps such phenomena allow neurites to keep extending even through areas that have temporary drops in outgrowth factors.

Reference: Torres, E., and M.K. Rosen. 2003. Mol. Cell. 11:1215–1227.