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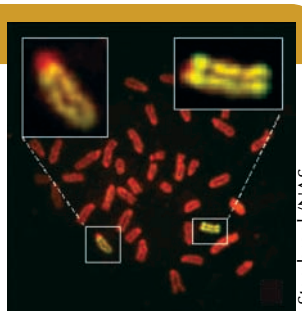
An ES cell caution

Any cell therapy risks introducing mutated and possibly tumorigenic cells. Now results from Peter Stambrook (University of Cincinnati, Cincinnati, OH) and colleagues underline this concern for embryonic stem (ES) cells, which are one possible source for therapeutic cells.

Stambrook constructed a cell line in which he could detect loss or mutation of a heterozygous marker gene. Loss (rather than mutation) of the functional allele was the proximate cause in ~80% of the events with both mouse embryonic fibroblasts (MEFs) and ES cells. But marker-deficient colonies arose 400-times faster in MEFs than in ES cells—good news for ES cell proponents.

But a closer look revealed complications. Whereas all the loss events in MEFs were caused by mitotic recombination, a full 57% of the ES cell events were apparently caused by loss of the entire chromosome, followed by reduplication of the single remaining chromosome. Such events have the potential to uncover multiple mutant alleles on the single remaining chromosome, and thus pose a greater risk than a more spatially limited recombination event.

Does this mean that ES cells are unfit for use? Stambrook thinks not. "This is not an argument against using ES cells for therapeutic uses," he says. "It's just a caution that one should be aware about." Stambrook says it should be possible to screen ES cells for chromosome loss events. Furthermore, the necessary comparisons between cell types have not yet been completed. Loss frequencies for adult stem cells are not yet known, and similar loss events may occur in the MEFs, but be masked by the more frequent mitotic recombination events.


Stambrook/NAS

Large (left, inset) and small (right, inset) centromeres allow for detection of chromosome loss events in ES cells.

Recombination events between nonidentical sequences may be suppressed in ES cells by the mismatch repair machinery, at least according to evidence from homologous recombination experiments. Before looking for a possible cause for increased chromosome loss in ES cells, researchers will need to confirm that there is indeed a difference in rates between ES and somatic cells. ■

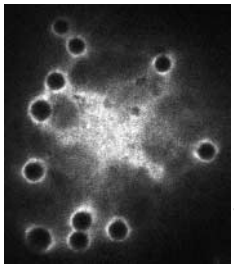
Reference: Cervantes, R.B., et al. 2002. *Proc. Natl. Acad. Sci. USA.* 99: 3586–3590.

Make junction, will travel

Cadherin-based adhesion complexes can trigger actin assembly, according to a proposal from Eva Kovacs, Alpha Yap, and colleagues (University of Queensland, Brisbane, Australia). The actin assembly may, in turn, control how cells recognize and move over one another.

Kovacs and Yap began their study by observing cells moving over a substrate covered with E-cadherin. They noticed that clumps of E-cadherin colocalized with both filamentous actin and components of the actin-nucleating Arp2/3 complex. Similar colocalization was apparent upon addition of E-cadherin beads. Finally, E-cadherin coimmunoprecipitated with Arp2/3 components, even in the presence of the actin-depolymerizing drug cytochalasin D.

The association suggests that cadherin ligation might trigger actin assembly by Arp2/3. "What we'd like to correct," says Yap, "is the notion that cadherin complexes are solely binding to preformed actin filaments." In his view, the adhesion machinery is no longer seen as an inert scaffold, but as a dynamic complex that drives changes in cell shape and movement.


Yap/Elsevier

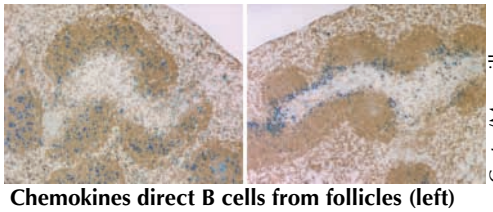
Beads coated with E-cadherin trigger actin assembly.

The connection between E-cadherin and Arp2/3 may or may not be direct. When Yap and his colleagues know more about this interaction, they hope to disrupt it without interfering with cadherin adhesive function, thus testing the importance of the link. They will be looking for defects in processes such as compaction, when cell surfaces extend over one another. ■

Reference: Kovacs, E.M., et al. 2002. *Curr. Biol.* 12:379–382.

A chemokine tug-of-war

B cells troll for antigens in lymphoid organ follicles, but once they have paired up with their antigen, they need help from T cells, which are found in separate T-rich zones. Karin Reif, Jason Cyster (University of California, San Francisco, CA), and colleagues report that activated B cells increase their production of CCR7, a T-zone chemokine receptor, so that they can migrate toward the T-rich zone. Activation of both CCR7 and CXCR5, the receptor for B-zone chemokines, strikes a balance so that the B cells end up at the border of the two zones.


Cyster/Macmillan

Chemokines direct B cells from follicles (left) to the B/T border (right).

Overexpression of the T-zone receptor CCR7 was sufficient to drive nonactivated B cells to the B/T border, whereas overexpression of the B-zone receptor CXCR5 kept activated B cells in the B-rich follicles. But the two chemokine systems are not the only determinants of B cell position. Cells lacking the B-zone receptor CXCR5 still localized to the B/T border after activation. "They're actually being kept out of the center [of the T zone] by something else," says Cyster. He suggests that the B cells may be less responsive than T cells to the T-zone chemokines, or the adhesive properties of the B cells and their later arrival may keep them layered outside of the main mass of T cells. ■

Reference: Reif, K., et al. 2002. *Nature.* 416:94–99.