Telomeres together

An enzyme dissolves a unique pairing connection between telomeres, according to Jasmin Dynek and Susan Smith (New York University, New York, NY).

Overexpression of the enzyme, called tankyrase 1, is known to extend telomere length—it makes TRF1 fall off telomeres so that telomerase can gain access. So presumably too little tankyrase 1 will have the opposite effect, and simply shorten telomeres.

Or not. Dynek and Smith now find that cells lacking tankyrase 1 have a completely unexpected phenotype. They arrest in mitosis when their telomeres, though not covalently linked, nevertheless fail to separate. Tankyrase 1 is a poly(ADP-ribose) polymerase that dissociates TRF1 from telomeres based on the excess negative charge of all those ADP-ribose groups on TRF1. Whether it is TRF1 or another protein that is the relevant target for dissolving telomere pairing is unknown.

Telomere pairing is known to help chromosomes pair during meiosis, and may help damaged telomeres to repair each other by homologous recombination. It appears that the tankyrase mechanism is used especially for regulating telomere pairing, either instead of or in addition to the separase–cohesin system used on chromosome arms. Smith is now interested in how this pairing is regulated during the cell cycle.

Reference: Dynek, J., and S. Smith. 2004. Science. 304:97–100.

Being intolerant of tumors

Sing the immune system to attack cancers is a good idea, but it may only work if Toll-like receptors (TLRs) are activated to break tolerance, say Yiping Yang (Duke University, Durham, NC), Drew Pardoll (Johns Hopkins, Baltimore, MD), and colleagues.

The favored method for delivering cancer immunotherapy has been dendritic cells: they are the central antigen-presenting cells for generating T cell responses; they can be grown in vitro in large quantities; and their use in mice with cancer led to some spectacular results. “That led to a whole wave of excitement,” says Pardoll. “But it hasn’t really panned out.”

Perhaps the biggest problem is tolerance. Most cancer immunotherapy focuses not on tumor-specific antigens, which vary too much because each tumor has different mutations, but on self-antigens that are overexpressed in the tumor. Although some collateral damage of normal self-tissue is alright for many tissues, the real problem is getting the immune response off the ground when it is challenged with a self-antigen.

Now Yang et al. show that viral but not dendritic cell vectors can do the job. Only the viral vectors can suppress tolerance to a cancer self-antigen in a mouse model, thus leading to increased survival. Ligands that activate TLRs also do the trick, and may be more promising in humans, as humans generally mount antibody responses that neutralize viral vectors.

Reference: Yang, Y., et al. 2004. Nat. Immunol. 10.1038/ni1059.

Get out! And don’t come back!

An active mechanism keeps vesicles that are departing the ER from turning round and fusing back to it, say Faustin Kamena and Anne Spang (Max Planck, Tübingen, Germany).

Directionality is a challenge for vesicle traffic. Although vesicles traveling from ER to Golgi and from Golgi to ER have very different job descriptions, recycling of transport proteins ensures that the compositions of the two vesicle types are similar if not identical. The two vesicle types start off with different coats (COPII for ER to Golgi and COPI for Golgi to ER) but shed them soon after departure.

Kamena and Spang figured that vesicles departing from the ER might be prevented from doing a U-turn by the same ER machinery that welcomes fusion of Golgi-derived vesicles. Sure enough, a mutant of the ER protein Tip20p allowed COPII vesicles, recently departed from the ER, to fuse back to the ER.

The researchers were lucky that they tested two different Tip20p mutants. Only one of those mutants (tip20–8, and not tip20–5 or any of the other ER fusion mutants) showed the U-turn phenotype. Now, the team can look for suppressor mutations that rescue tip20–8 but not tip20–5, and isolate proteins that bind only one of the two mutant proteins. Either approach may give clues about what, exactly, is sensed as different about a departing versus an arriving vesicle.

Reference: Kamena, F., and A. Spang. 2004. Science. 304:286–289.