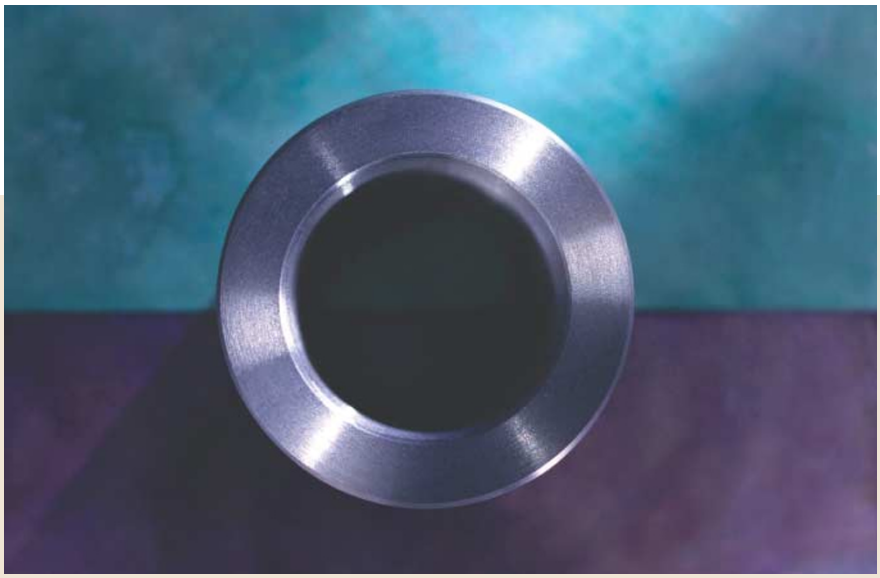

EXOCYTOSIS

Every fusion pore has a protein lining

Xue Han, Meyer Jackson and colleagues, reporting in *Science*, show that the fusion pore that forms in Ca^{2+}-regulated exocytosis has a protein lining. Until now, the molecular composition of this important intermediate was unknown and the possibility that it was composed of lipids could not be ruled out.

The authors reasoned that if the fusion pore is composed of protein, neurotransmitter flux through this pore should be affected by mutations that alter the size of amino-acid side chains lining the pore. They focused their study on syntaxin for several reasons: for example, it is essential for exocytosis and it is the only essential plasma-membrane protein that contains a transmembrane segment.

By mutating residues in this segment, in turn, to tryptophan and taking measurements of neurotransmitter flux through the fusion pore, Han *et al.* could elucidate whether each mutation obstructed the fusion pore. They identified three mutations — I269W, G276W and I283W — that significantly reduced flux through the fusion pore: these residues all lie along one face of the syntaxin transmembrane α-helix.

To further examine this effect, the authors created a series of mutants such that, at each of the positions mentioned above, the amino-acid side chain gradually increased in size. As expected, increasing the side-chain size at these positions produced a graded reduction in neurotransmitter flux through the pore. Mutating non-pore-lining residues in this way had no effect on flux.

Han *et al.* therefore propose that the plasma-membrane-spanning part of the fusion pore is a barrel that, from their model, is composed of 5–8 copies of the syntaxin transmembrane segment (although they acknowledge that further proteins and/or lipids might also constitute the pore). Furthermore, they suggest that this syntaxin-lined pore is linked to a complementary protein (synaptobrevin)-lined pore in the vesicle membrane by SNARE complexes.

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References and links

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FURTHER READING Chen, Y. A. & Scheller, R. H. SNARE-mediated membrane fusion. *Nature Rev. Mol. Cell Biol.* **2**, 98–106 (2001)
WEB SITE
Meyer Jackson's laboratory:
http://www.physiology.wisc.edu/jackson.html

CELL CYCLE

Sisters come unstuck

To prevent inaccurate chromosome segregation from occurring during mitosis, duplicated sister chromatids are held together by so-called cohesin proteins until the cell is ready to divide into daughter cells. Two mechanisms regulate chromatid segregation — first, cohesins dissociate from the chromosomal arms during prophase, and then the remaining cohesins at the centromere are cleaved at the onset of anaphase. Now, Jasmin Dynek and Susan Smith report that there is a third mechanism — telomere-specific cohesion — with an essential role in chromatid separation.

When the authors inhibited tankyrase-1 expression in cultured mammalian cells, the cells arrested and a threefold increase in the G2–M cell population was detected by fluorescence-activated-cell-sorting analysis. The arrested cells, which contained abnormal mitotic chromosomes of three distinct phenotypes, were rescued by re-expression of tankyrase-1. This indicated that tankyrase-1 is important for cell-cycle progression. Close examination of the abnormal chromosomes revealed separated centromeres, which indicated that cells were arrested in anaphase. But what causes this cell-cycle arrest?

The progression from metaphase to anaphase is regulated by the anaphase-promoting complex, which functions normally in the tankyrase-1-deficient cells. As tankyrase-1 regulates telomere length, the authors wondered whether abnormal telomeres were responsible for the cell-cycle arrest. Telomeres were capped normally and there was no evidence of DNA damage or telomeric-fusion products in the tankyrase-1-deficient cells. So, cell-cycle arrest was not the result of defective telomeres.

Next, the authors analysed the telomeres using fluorescence *in situ* hybridization. The telomeric regions in cells that lacked tankyrase-1 expression appeared as two singlets, whereas in control cells telomeric regions generally appeared as doublets. Double staining of chromosomal arms and telomeres in the same cell showed that the chromosome arms were separated in tankyrase-1-deficient cells (they appeared as doublets), whereas telomeres appeared as singlets. So, although chromosomes replicated normally in these cells, only the arms — but not the telomeres — separated.

Presumably, replicated telomeres are held together by telomere-specific cohesion complexes, which are somehow released by tankyrase-1. Whether these cohesion complexes contain cohesin remains to be established. This new regulatory mechanism for sister-chromatid separation could represent a checkpoint, which ensures that intact chromosomes are passed on to daughter cells.

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References and links

ORIGINAL RESEARCH PAPER Dynek, J. N. & Smith, S. Resolution of sister telomere association is required for progression through mitosis. *Science* **304**, 97–100 (2004)