

process will have to incorporate the striking correlations observed by Jackson and co-workers^{14,15} for specific residues of the syntaxin transmembrane domain. For the time being, the search for the lining of exocytic fusion pores *in vivo* remains in progress.

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1. Earp, L.J., Delos, S.E., Park, H.E. & White, J.M. *Curr. Top. Microbiol. Immunol.* **285**, 25–66 (2005).
2. Rothman, J.E. *Nat. Med.* **8**, 1059–1062 (2002).

3. Schibli, D.J. & Weissenhorn, W. *Mol. Membr. Biol.* **21**, 361–371 (2004).
4. Xu, Y., Zhang, F., Su, Z., McNew, J.A. & Shin, Y.-K. *Nat. Struct. Mol. Biol.* **12**, 417–422 (2005).
5. Yang, L. & Huang, H.W. *Science* **297**, 1877–1879 (2002).
6. Chernomordik, L.V. & Kozlov, M.M. *Annu. Rev. Biochem.* **72**, 175–207 (2003).
7. Cohen, F.S. & Melikyan, G.B. *J. Membr. Biol.* **199**, 1–14 (2004).
8. Zaitseva, E., Mittal, A., Griffin, D.E. & Chernomordik, L.V. *J. Cell Biol.* **169**, 167–177 (2005).
9. McNew, J.A. et al. *J. Cell Biol.* **150**, 105–117 (2000).
10. Grote, E., Baba, M., Ohsumi, Y. & Novick, P.J. *J. Cell Biol.* **151**, 453–466 (2000).
11. Takahashi, N., Kishimoto, T., Nemoto, T., Kadowaki, T. & Kasai, H. *Science* **297**, 1349–1352 (2002).
12. Suga, K., Yamamori, T. & Akagawa, K. *J. Biochem.* **133**, 325–334 (2003).
13. Armstrong, R.T., Kushnir, A.S. & White, J.M. *J. Cell Biol.* **151**, 425–437 (2000).
14. Han, X., Wang, C.T., Bai, J., Chapman, E.R. & Jackson, M.B. *Science* **304**, 289–292 (2004).
15. Han, X. & Jackson, M.B. *Biophys. J.* **88**, L20–L22 (2005).
16. Hua, Y. & Scheller, R.H. *Proc. Natl. Acad. Sci. USA* **98**, 8065–8070 (2001).
17. Deak, F., Schoch, S., Liu, X., Sudhof, T.C. & Kavalali, E.T. *Nat. Cell Biol.* **6**, 1102–1108 (2004).

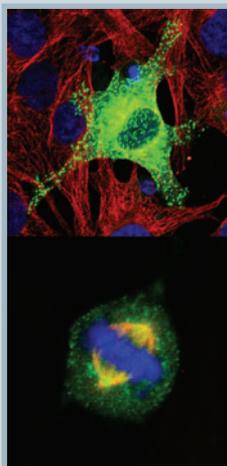
Spindly clathrin

Clathrin is known for its role in coating various transport vesicles inside the cell. Mammalian clathrin is composed of heavy and light chains that form a three-legged protein complex called a triskelion. This complex forms a regular lattice that coats the outsides of vesicles, promoting invagination and pinching off of the membrane and enclosure of proteins to be transported. Clathrin-mediated vesicle formation continues until the cell is ready to divide and enters mitosis.

Mitosis requires the formation of a mitotic spindle, which contains polar and kinetochore microtubules. The latter connect the kinetochore complex on the chromosome with the spindle pole, and these connections are essential for proper segregation of the chromosomes into each half of the dividing cell. Mis-segregation of chromosomes before cell division results in daughter cells not receiving the proper complement of chromosomes and hence genes.

This in turn leads to inappropriate cell growth and development, conditions which can cause cancer and birth defects, respectively. Royle *et al.* (*Nature* **434**, 1152–1157, 2005) now show that clathrin triskelia stabilize the kinetochore microtubule fibers at the spindles and prevent chromosomes from mis-segregating during cell division.

Using GFP-tagged clathrin light chains, the authors show that the distribution of clathrin changes with the cell cycle. In the nondividing cell, clathrin (green dots) is found all over the cell with the Golgi and coated pits (punctate green dots). During cell division when chromosomes (blue) are aligned at the metaphase plate, clathrin is found at the kinetochore fibers (yellow-orange) and mitotic spindles. Interestingly, clathrin is not associated with membranes as the cell divides. Furthermore, none of the proteins involved in clathrin-mediated membrane localization or the assembly of coated pits are found at the spindles or near the kinetochore fibers. These data indicate that clathrin has a second, membrane-independent function at the mitotic spindle.



What is clathrin doing at the spindles? The authors show that depletion of clathrin destabilizes the kinetochore microtubules, leading to mis-segregation of the chromosomes and prolonged mitosis. Clathrin-mediated stabilization of the kinetochore fibers requires formation of the triskelion. The authors propose that the triskelia probably bind to and bridge two to three kinetochore microtubules within each fiber, thereby forming a relatively rigid connection between microtubules. This stabilization ensures the formation of a fiber that is able to attach to and segregate chromosomes within the dividing cell. The lack of a strong attachment between the fibers and the chromosomes triggers the spindle checkpoint, whose persistent activation results in prolonged mitosis.

Clathrin's newly discovered role in chromosome segregation may help explain its role in some cancers such as inflammatory myofibroblastic tumors and renal adenocarcinomas. In these cancers, the heavy chain of clathrin is found as a gene fusion with anaplastic lymphoma kinase or transcription factor TFE3, respectively. Royle *et al.* propose that these fused genes could disrupt processes such as triskelion formation and spindle binding that require the heavy chain of the protein. In effect, the heavy chain would not be able to form the triskelion and thus could not stabilize the kinetochore fibers. Alternatively, the fused clathrin gene product, containing part of a kinase or transcription factor, could still form some kind of a triskelion that could still bind to kinetochore fibers but do so in a way that interferes with proper mitosis. Additional experiments will be required to determine how the fused clathrins are mechanistically involved in these forms of cancer.

The data from Royle *et al.* expand the roles of clathrin in the cell and open the door to additional studies to determine how clathrin switches between its two functions—vesicle formation and kinetochore fiber stabilization—and how these functions are regulated during the cell cycle.

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