MITOSIS

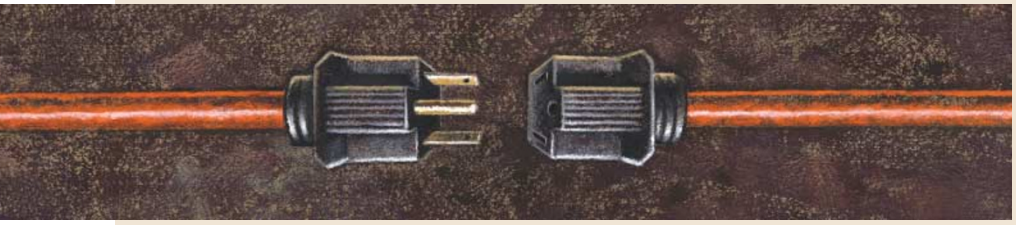
Pulled apart

How spindles assemble has attracted a lot of attention. However, little is known about the mechanism of spindle disassembly, which takes places at the end of mitosis. Now, though, reporting in *Cell*, Yixian Zheng and colleagues have identified the AAA-ATPase Cdc48/p97 and the Ufd1–Npl4 adaptor complex as important regulators of this process.

Given its role in the dissociation of proteins from large cellular structures such as the endoplasmic reticulum, the authors tested whether the Cdc48/p97–Ufd1–Npl4 complex could assist spindle disassembly. They found that, in *Xenopus laevis* egg extracts, a dominant-negative form of *Xenopus* p97 (p97QQ), which was defective in ATP hydrolysis, blocked spindle disassembly and the formation of interphase nuclei and microtubule arrays. And, the Ufd1–Npl4 adaptor complex was also required for spindle disassembly.

Zheng and co-workers found that the microtubule-binding proteins XMAP215 and TPX2, and the spindle-associated Polo-like kinase Plx1, were co-immunoprecipitated with p97–Ufd1–Npl4 from extracts that had been induced to exit mitosis. In addition, compared with p97 wild-type treatment, p97QQ treatment caused increased binding of both XMAP215 and TPX2 to microtubules after mitotic exit. So, p97–Ufd1–Npl4 seems to regulate the binding of certain spindle-assembly factors to microtubules at mitotic exit.

To study the function of p97 *in vivo*, the authors used the yeast homologue, Cdc48, and found that — at the restrictive temperature — the cells of a heat-sensitive mutant strain (*cdc48-3*) arrested in mitosis and the spindles first elongated and then collapsed into medium-length spindles that persisted. A temperature-sensitive mutant of Npl4 also had defects in spindle disassembly, so the authors concluded that Cdc48–Ufd1–Npl4 regulates spindle disassembly in yeast *in vivo*.



Inactivation of the Cdc2 kinase at the end of mitosis also has a role in regulating spindle disassembly. However, Cdc48/p97 is not required for Cdc2 inactivation in either *Xenopus* egg extracts or in yeast.

So, what's the mechanism that Cdc48 uses to mediate spindle disassembly? Zheng and colleagues hypothesized that Cdc48 might regulate spindle disassembly by binding to Cdc5 (the yeast homologue of Plx1) and Ase1 (a microtubule-binding protein) and causing their degradation. This turned out to be correct — Cdc48 interacted with both Cdc5 and Ase1 and is required for their degradation after mitotic exit.

The authors conclude that, at the end of mitosis, both Cdc2 inactivation and the activity of Cdc48/p97–Ufd1–Npl4 are required for spindle disassembly. They further suggest that this complex binds certain spindle-assembly factors and prevents them from promoting spindle assembly.

Arianne Heinrichs

References and links

ORIGINAL RESEARCH PAPER Cao, K. *et al.* The AAA-ATPase Cdc48/p97 regulates spindle disassembly at the end of mitosis. *Cell* **115**, 355–367 (2003)

DEVELOPMENT

Move over!

We know that many of our organs are positioned asymmetrically with respect to the midline. And, in many cases, we know the genes that are involved. But our knowledge of how these 'left–right' (L–R) signals localize organs asymmetrically is somewhat diffuse. A study led by Didier Stainier, though, now provides 'cellular' insight into gut looping in the zebrafish — their findings are reported in *Science*.

Gut looping gives rise to the first leftward bend in the intestine, when a region of a solid rod of endodermal cells, formed during somitogenesis, curves to the left. Because mutations in 'heart and soul' — an atypical protein kinase C (aPKC) that localizes to the epithelial junctional complex — inhibit gut looping, the authors hypothesized that an epithelial tissue is important in gut looping. On examining the gut-looping region, the authors found hardly any aPKCs in the endoderm, but strong expression in the polarized epithelium of the lateral plate mesoderm (LPM). Notably, the left and right sides of the LPM epithelia are asymmetric — the left LPM is dorsal, and the right LPM is ventrolateral, to the endoderm. This asymmetric localization of columnar cells of both sides occurs in the anterior–posterior region of the LPM where gut looping will occur.

On closer inspection of the LPM during development, Stainier's group found that it migrates asymmetrically — before the endoderm is displaced from the midline — and that the right LPM is closely apposed to the endoderm throughout migration. Could the LPM be pushing the intestine to the left by displacing the endoderm? If this were the case, the LPM would still be expected to migrate asymmetrically if the endoderm was absent — which it did. So the force required for gut displacement seems to be solely attributable to the LPM.

Next, the group studied the role of normal L–R positional cues — such as *Nodal* gene expression — in asymmetric LPM migration. Antisense-oligonucleotide treatment against southpaw (*spaw*; a *Nodal* gene) abolished left-specific gene expression and randomized LPM migration and, consequently, gut looping.

So L–R gene expression seems to mediate LPM migration, which then actively moves the endoderm over to the left to induce gut looping. What drives asymmetric LPM morphogenesis is, at present, unclear — active migration and changes in cell shape or proliferative properties are all possibilities that require investigation.

Katrin Bussell

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WEB SITE

Didier Stainier's laboratory: http://www.ucsf.edu/dyrslab/

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