In This Issue

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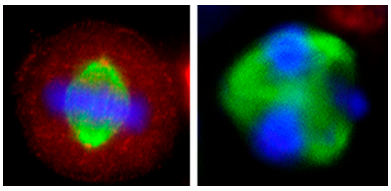
Spindle assembly at a BRISC pace



Compared with a control cell (left), microtubules (green) form a multipolar spindle in a cell (right) lacking the BRISC component ABRO1 (red). DNA is labeled blue.

Yan et al. describe how a deubiquitinating enzyme complex regulates the mitotic spindle assembly factor NuMA.

BRCC36 is a deubiquitinating enzyme that preferentially cleaves lysine 63–linked polyubiquitin chains. As part of the Rap80 complex, BRCC36 regulates the repair of DNA double-strand breaks, but the enzyme can also assemble into a distinct complex, known as BRISC.

Yan et al. found that knocking down BRCC36, or a subunit unique to the BRISC complex called ABRO1, caused mitotic cells to assemble multipolar spindles that frequently aligned and segregated chromosomes incorrectly. These defects could not be rescued by a catalytically inactive version of BRCC36. In wild-type mitotic cells, BRISC accumulated at the spindle poles, bound to the minus ends of stable, kinetochore-attached microtubules. Early in mitosis, BRISC also localized near the kinetochores themselves, where it promoted the chromosome-dependent nucleation of spindle microtubules.

Yan et al. discovered that BRISC binds and deubiquitinates the spindle assembly factor NuMA, which captures and focuses microtubules at spindle poles. In the absence of BRISC, ubiquitinated NuMA showed an increased association with both importin-β and dynein, which regulate the protein's function.

BRISC therefore promotes bipolar spindle assembly by deubiquitinating NuMA. Senior author Genze Shao says that BRISC may have other mitotic substrates as well. Because some BRISC-deficient cells progress through mitosis, despite their disorganized spindles, he is particularly interested in whether the deubiquitinase can regulate the spindle assembly checkpoint.

Yan, K., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201503039

Ribosomes have a NAC for nascent chain processing

Nyathi and Pool describe how a chaperone complex helps ensure nascent polypeptides are correctly processed as they emerge from ribosomes.

Newly synthesized proteins must be quickly modified, folded, and targeted to their correct destination within the cell. Many of the factors responsible for these processing steps bind to the same "universal adaptor site" (UAS) on ribosomes, allowing them to target nascent polypeptides as soon as they emerge. How the binding of these factors is coordinated so that each polypeptide gets processed correctly remains unclear.

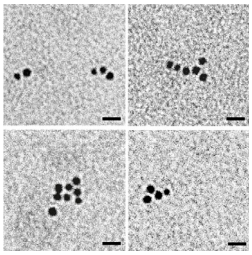
Nyathi and Pool found that Map1, a budding yeast enzyme that cleaves the N-terminal methionine off of most cytosolic proteins, also binds to the UAS, adjacent to the α subunit of a ribosome-associated chaperone complex called NAC. Overexpressing Map1 displaced the signal recognition particle (SRP), which guides nascent secretory and membrane proteins to the ER, suggesting that Map1 and SRP compete for a binding site within the UAS.

Overexpressing SRP, however, failed to displace Map1 from ribosomes unless the researchers removed NAC—particularly its β subunit—from the cells. Under these circumstances, cytosolic proteins retained their N-terminal methionines and formed insoluble aggregates, indicating that NAC regulates the competition between Map1 and SRP by suppressing the latter complex's association with the UAS.

Yet NAC's α subunit can assist the SRP in translocating secretory proteins to the ER. At low temperatures, or when SRP levels are diminished, nascent secretory polypeptides go unrecognized, causing them to aggregate and inhibit cell growth. These defects were exacerbated by the loss of NAC's α subunit, and alleviated by its overexpression. The authors think that conformational changes in the ribosome and/or NAC in response to the presence or absence of a nascent secretory polypeptide might determine whether SRP binding is promoted or suppressed.

Nyathi, Y., and M.R. Pool. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201410086

Cadherin clusters solidify adhesions



Cis interactions allow wild-type Ecad molecules (labeled with gold nanoparticles) to form small clusters in the plasma membrane.

Strale et al. reveal that interactions between neighboring E-cadherin (Ecad) molecules help to strengthen their connection to the actin cytoskeleton and stabilize cell–cell contacts.

Ecad is the major component of adherens junctions, holding cells together by forming "trans" interactions with Ecad molecules in the plasma membrane of adjacent cells. Crystal structures of Ecad indicate that the protein can also form "cis" interactions with Ecad molecules in the same cell membrane, but whether these interactions help organize Ecad in vivo, and how this might affect the function of adherens junctions, remains unclear.

Using gold-labeled nanobodies and electron microscopy to detect single Ecad molecules within the plasma membrane, Strale et al. found that wild-type Ecad was organized into small clusters of 2–10 molecules. These clusters were dispersed by a point mutation that abolishes Ecad's cis-interaction site. Surprisingly, however, cis-mutant Ecad was still able to support the assembly of adherens junctions between epithelial cells, although Ecad's stability within these junctions was decreased when it was unable to form oligomeric clusters.

Disrupting Ecad's cis interactions also reduced the association of adherens junctions with the actin cytoskeleton, perhaps because clusters of Ecad molecules are less likely to let go of actin filaments. Adherens junctions were therefore weaker in the absence of Ecad clustering, reducing cells' ability to maintain their attachments and coordinate their movements as they attempted to undergo collective cell migration. Author René-Marc Mège thinks that modulating Ecad's cis interactions could therefore regulate the cohesion and behavior of epithelial tissues.

Strale, P.-O., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201410111