Centralspindlin — the missing link

Cytokinesis must be coordinated with chromosome segregation to ensure that daughter cells inherit the correct set of chromosomes. The mitotic spindle controls cytokinetic events at the cell membrane and thus has a crucial role in ensuring such coordination. The spindle midzone promotes the contraction of the cleavage furrow, and such contraction proceeds until a microtubule-rich intercellular bridge connects the two daughter cells. The midbody at the centre of the intercellular bridge directs the final membrane abscission reaction. Now, Petronczki and colleagues show that the mitotic spindle is connected to the plasma membrane via centralspindlin, which is a component of the spindle midzone and the midbody.

Centralspindlin is a key regulator of cytokinesis and is composed of two molecules of the kinesin MKLP1 (mitotic kinesin-like protein 1) and two molecules of the RHO GTPase-activating protein (GAP) MgcRacGAP. It recruits and regulates the effector proteins that promote cleavage furrow ingression and membrane abscission. While searching for midzone and midbody proteins that interact with the plasma membrane, the authors observed that centralspindlin contains a C1 domain, which binds to lipids or proteins, in the MgcRacGAP subunit.

Point mutations in the C1 domain or its deletion compromised cytokinesis in HeLa cells. Interestingly, however, this domain was dispensable for the assembly of both the spindle midzone and the midbody and for the assembly and localization of centralspindlin. This indicates that the C1 domain confers to centralspindlin a novel function that is essential for cytokinesis.

To gain insights into this new function, the authors analysed the subcellular distribution of MgcRacGAP C1 domains. By expressing fluorescently tagged fusion proteins of two or four of these domains, they observed

that C1 domains localize to the plasma membrane. Furthermore, C1 domains were found to interact with phosphoinositide lipids *in vitro*, and selective hydrolysis of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P₂) and PtdIns(4)P at the plasma membrane (using a membrane-targeted specific lipid phosphatase) caused the rapid and complete release of C1 domains from the cell envelope. This suggests that the C1 domains of MgcRacGAP associate with the inner leaflet of the plasma membrane by binding to PtdIns(4,5)P₂ and PtdIns(4)P. Solving the crystal structure of the MgcRacGAP C1 domain allowed the authors to model the interaction of this protein domain with the membrane.

To test whether binding to the plasma membrane is the key function of the MgcRacGAP C1 domain during cytokinesis, Petronczki and colleagues replaced the domain with a related C1 domain that could artificially tether MgcRacGAP to the membrane upon chemical treatment. Such treatment induced the translocation of modified MgcRacGAP from the cytosol to the membrane

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and restored successful cytokinesis. This suggests that plasma membrane tethering is essential for centralspindlin to control cytokinesis. This function of centralspindlin is usually carried out by the C1 domain but can be bypassed by artificially targeting MgcRacGAP to the membrane.

Finally, using live-cell imaging, the authors showed that the interaction between the MgcRacGAP C1 domain and the plasma membrane promotes anchoring of the cleavage furrow to the midbody, which is essential to complete cytokinesis.

Thus, this study identifies centralspindlin as the ‘missing link’ that tethers the mitotic spindle to the plasma membrane to secure the completion of cytokinesis in animal cells.

Kim Baumann

ORIGINAL RESEARCH PAPER Lekomtsev, S. *et al.* Centralspindlin links the mitotic spindle to the plasma membrane during cytokinesis. *Nature* **492**, 276–279 (2012)

FURTHER READING Chen, C.-T., Hehnlly H. & Doxsey, S. J. Orchestrating vesicle transport, ESCRTs and kinase surveillance during abscission. *Nature Rev. Mol. Cell Biol.* **13**, 483–488 (2012) | Glotzer, M. The 3Ms of central spindle assembly: microtubules, motors and MAPs. *Nature Rev. Mol. Cell Biol.* **10**, 9–20 (2009)

A human cell at anaphase (left). The spindle midzone is shown in green, the anaphase spindle in red and DNA in blue. The midzone is labelled with an antibody that targets Aurora B kinase. Human cells at different stages of cell division (right). Centralspindlin is shown in red, tubulin in green and DNA in blue. Images courtesy of M. Petronczki, Cancer Research UK, London Research Institute.