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CELL CYCLE

Getting to the centre

The location of the cleavage site during animal cell division is dictated by the position of the mitotic spindle. Kiyomitsu and Cheeseman now find that positioning the spindle to the centre of dividing cells, so that they divide symmetrically, depends on both cortex-localized dynein and asymmetric plasma membrane elongation.

Astral microtubules, which radiate from centrosomes towards the nearby cell cortex at the spindle poles, interact with the motor protein dynein at the cell cortex. This is known to contribute to spindle positioning during metaphase as cortical dynein–dynactin complexes exert pulling forces on microtubules. It had previously been shown that during metaphase dynein is recruited to the cortex via its binding partner NuMA (nuclear and mitotic apparatus protein), which interacts with a membrane-bound complex containing the protein LGN (also known as GPSM2). Here, the authors identify an anaphase-specific pathway to recruit NuMA and dynein to the cortex that depends on the band 4.1 proteins 4.1G and 4.1R. Depletion of either LGN, 4.1 proteins or both suggested that the LGN-dependent pathway targets NuMA and dynein to the cortex in metaphase and keeps it there throughout anaphase. By contrast, the 4.1 protein-dependent pathway acts in parallel to recruit a second pool of NuMA and dynein during anaphase.

Depletion of both LGN and 4.1 proteins in HeLa cells, which normally divide symmetrically, did not affect spindle structure during anaphase even though cortical localization of dynein was impaired, but resulted in asymmetric cell division (the production of two daughter cells of unequal size). Importantly, these defects were rescued by expression of a membrane-tethered version of 4.1G that recruits NuMA and dynein to the cortex, which suggests that cortical dynein is important for symmetric cell division.

Kiyomitsu and Cheeseman went on to analyse the dynamics of placing the spindle at the centre of the cell, both during early anaphase (before cells start elongating) and late anaphase (when cells elongate). Some cells entered early anaphase with a misoriented spindle, but this was corrected through a process largely dependent on dynein. Interestingly, however, 25% of control (normal) cells still had off-centred spindles at the end of early anaphase but could correct the spindle position during late anaphase. The authors observed an unexpected mechanism by which spindle positioning is corrected at this stage: cells elongated asymmetrically during late anaphase so that only the plasma membrane closest to the chromosome–spindle structure elongated, thus repositioning the spindle to the centre of dividing cells. Importantly, this repositioning was dependent on cortical dynein anchoring it to the stationary cell cortex.

The exact molecular mechanisms underlying asymmetric membrane elongation remain to be elucidated, although the authors found that membrane blebbing is involved. They also observed that the cortical localization of anilin and myosin was lower in places where chromosomes were close to the cortex, and that such altered localization was dependent on chromosome-derived RAN•GTP signals. Hence, they suggest that this reduction in cortical actomyosin regulators could potentially contribute to membrane remodelling events, including blebbing.

This work shows that dynein-dependent cortical pulling forces and membrane elongation during anaphase both contribute to the positioning of the mitotic spindle to achieve symmetric cell division. It will be interesting to study how these two processes are regulated in symmetrically and asymmetrically dividing cells in a developmental context.

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ORIGINAL RESEARCH PAPER Kiyomitsu T. & Cheeseman, I. M. Cortical dynein and asymmetric membrane elongation coordinately position the spindle in anaphase. *Cell* **154**, 391–402 (2013)