LIPIDS

Orientating with PtdIns(3,4,5)P_3

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Just as mountaineers must orientate themselves before starting an ascent, so must cells orientate their spindles before division. But whereas mountaineers have compasses, it is not clear how cells orientate themselves. For instance, cell–cell contacts, cell-polarity cues and integrin signalling can all come into play. Now, Toyoshima *et al.* show that phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P_3) can act as a compass needle to orientate the spindle by coordinating dynein–dynactin motor complexes.

Given that integrin signalling — which was recently shown by Toyoshima and colleagues to affect spindle orientation in HeLa cells — regulates phosphatidylinositol 3-kinase (PI3K) and affects PtdIns(3,4,5)P_3 production, the authors examined whether either or both are involved in spindle orientation. Staining experiments revealed that PtdIns(3,4,5)P_3 accumulates in the cortical midsection (where the spindle subsequently forms) during metaphase in HeLa cells. In addition, downregulation of β1 integrin, which results in the inhibition of PI3K activity, reduces the accumulation of PtdIns(3,4,5)P_3 along the midsection. Treatment of HeLa cells with PI3K inhibitors results in spindle misorientation, whereas the spindles of untreated cells orientate in parallel with the substratum.

The authors found that the dynein–dynactin motor complex, which is involved in spindle positioning in budding yeast, also localizes to the cortical midsection in HeLa cells during metaphase, hinting at a mechanism for the action of PtdIns(3,4,5)P_3. Indeed, PI3K inhibitor treatment results in a more dispersed localization of dynactin in the cortex, and this dispersal causes spindle rotation along the Z-axis and subsequent spindle misorientation. Furthermore, downregulation of the phosphatase PTEN, which results in an overabundance of PtdIns(3,4,5)P_3, also causes dispersion of dynactin and spindle misorientation.

Thus, PtdIns(3,4,5)P_3 can act as a compass needle, aligning the direction of dynein–dynactin pulling forces and thereby orientating the spindle during metaphase in HeLa cells (but not in all cell types, the authors note). PI3K and PTEN appear to be crucial for maintaining the appropriate PtdIns(3,4,5)P_3 accumulation, and the authors suggest that positive and negative feedback mechanisms may be involved. These findings also indicate a new direction for researchers, as further experiments are needed to identify the molecules that link PtdIns(3,4,5)P_3 to the dynein–dynactin complex.

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ORIGINAL RESEARCH PAPER Toyoshima, F. *et al.* PtdIns(3,4,5)P_3 regulates spindle orientation in adherent cells. *Dev. Cell* **13**, 796–811 (2007)
FURTHER READING Gachet, Y. & Tournier, S. Lost your orientation? Find your way with PtdIns(3,4,5)P_3. *Dev. Cell* **13**, 753–754 (2007)

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