Keeping DNA replication below PAR

The polarity proteins PAR-4 and PAR-1 delay cell division in early C. elegans embryos by inhibiting DNA replication. Benkemoun et al. revealed that the nucleus of the posterior blastomere (right) contains fewer sites of active DNA replication than its anterior sister (left). Cells must divide at the right time during development. This is true from the get-go in C. elegans embryos where, at the two-cell stage, the anterior blastomere divides while its smaller, posterior sister is still in S phase. This cell cycle asynchrony is promoted by proteins that regulate embryonic polarity, such as the kinases PAR-4 and PAR-1. In embryos lacking these proteins, the posterior blastomeres speed through S phase so that both cells divide at the same time. But how PAR-4 and Aurora B inhibitors and the microtubule-depolymerizing drug nocodazole can still activate the spindle checkpoint as long as they divide.

Late endosomes uproot focal adhesions

Schiefermeier et al. reveal that late endosomes promote cell migration by transporting a signal transduction scaffold complex that stimulates focal adhesion turnover. p14 and MP1 are two components of an adaptor complex that regulates MAP kinase and mTORC signaling on late endosomes. Schiefermeier et al. noticed that, instead of accumulating in the center of cells like other late endosomes, MP1-positive organelles moved along microtubules toward peripheral focal adhesions attaching the cell to its underlying substrate. In particular, the endosomes targeted the dynamic regions of mature focal adhesions, where adhesion components turn over in order to support cell migration.

The spindle checkpoint’s on-off switch

Matson and Stukenberg describe how the centromeric protein CENP-I cooperates with the Aurora B kinase to control the kinetochore localization of spindle checkpoint proteins. Mad1 and the RZZ complex are critical components of the spindle assembly checkpoint that prevent anaphase onset by binding to kinetochores that aren’t attached to the mitotic spindle correctly. Once spindle microtubules are properly attached, the motor protein dynein strips Mad1 and the RZZ complex away from kinetochores and allows mitosis to proceed. Aurora B helps recruit RZZ and Mad1 to kinetochores in early mitosis, but cells treated with Aurora B inhibitors and the microtubule-depolymerizing drug nocodazole can still activate the spindle checkpoint as long as they express a group of centromeric proteins that includes CENP-I. How CENP-I supports checkpoint activation is unknown, however.

By imaging the replication protein PCN-1, the C. elegans orthologue of PCNA, Benkemoun et al. found that the posterior blastomere in wild-type embryos took longer to complete S phase than the anterior cell because, at every time point, it contained fewer sites of active DNA replication. But in the absence of PAR-4, or its downstream target PAR-1, the posterior blastomere formed just as many replication foci as its anterior sister. Knocking down proteins that initiate DNA replication increased the duration of S phase in the posterior blastomere of PAR-4–deficient embryos, restoring division asynchrony and enhancing embryonic viability.

Senior author Jean-Claude Labbé now wants to investigate how PAR-4 and PAR-1 inhibit replication initiation in the posterior blastomere.

Benkemoun, L., et al. 2014. J. Cell Biol. http://dx.doi.org/10.1083/jcb.201312029.