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. reveal that 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 blastomere speeds through S phase so that both cells divide at the same time. But how PAR-4 and PAR-1 inhibit replication initiation in the posterior blastomere?

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 adapter 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. Matson and Stukenberg found that CENP-I stabilized RZZ and Mad1’s interaction with kinetochores, limiting their dissociation and preventing dynein from stripping them away prematurely. Thus, when Aurora B activity is lowered by inhibitors, CENP-I helps retain enough RZZ and Mad1 at unattached kinetochores to activate the spindle checkpoint.

On the other hand, Aurora B promoted RZZ and Mad1’s association with kinetochores. The kinase’s activity was enhanced by so-called PreK-fibers, microtubule bundles nucleated by the kinetochores themselves. In prometaphase cells lacking the stabilizing influence of CENP-I, checkpoint proteins only accumulated at kinetochores with PreK-fibers and high levels of Aurora B activity. Under normal circumstances, however, Aurora B and CENP-I combine to regulate checkpoint signaling at individual kinetochores according to their microtubule attachment status.

Matson, D.R., and P.T. Stukenberg. 2014. J. Cell Biol. http://dx.doi.org/10.1083/jcb.201307137.