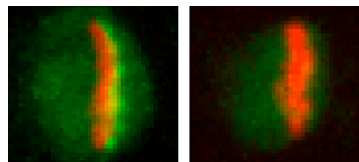


BUB-1 makes kinetochores MAD



Unlike wild-type MAD-1 (green, left), a mutant version unable to bind BUB-1 (right) isn't recruited to the unattached kinetochores of chromosomes (red) on a monopolar spindle.

Moyle et al. describe how the *C. elegans* BUB-1 kinase helps recruit the spindle checkpoint proteins MAD-1 and MAD-2 to unattached kinetochores.

During mitosis, the MAD-1–MAD-2 complex binds to kinetochores

that haven't attached to the spindle and generates a signal that prevents cells from entering anaphase until the correct attachments are formed. Several kinetochore proteins are required to localize MAD-1–MAD-2 to unattached kinetochores in vivo, but whether any of these proteins recruit the checkpoint complex directly is unknown.

Moyle et al. screened a library of kinetochore proteins and

found that *C. elegans* MAD-1 interacted with BUB-1, a kinase required for MAD-1–MAD-2 localization. Mutations in MAD-1's central coiled-coil domain disrupted the protein's interaction with BUB-1 and inhibited the recruitment of MAD-1 and MAD-2 to unattached kinetochores in worms, thereby preventing them from activating the spindle checkpoint and delaying anaphase. MAD-1 interacted with BUB-1's C-terminal kinase domain, and mutations in this domain blocked MAD-1's recruitment to unattached kinetochores. But BUB-1's kinase activity wasn't required for MAD-1's localization, suggesting that BUB-1 recruits MAD-1 to kinetochores directly.

Senior author Arshad Desai now wants to investigate how other kinetochore proteins, such as the microtubule-binding protein Ndc80, contribute to MAD-1–MAD-2 recruitment and ensure that the complex is removed once kinetochores are correctly attached to the mitotic spindle.

Moyle, M.W., et al. 2014. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201311015>.

Lamin-A provides stiff resistance to cell migration

Harada et al. describe how nuclear lamins affect the ability of migrating cells to squeeze through tissues and survive the resulting stress.

Migrating cells must maneuver their large and chromatin-packed nuclei through tiny gaps in the surrounding tissue. A- and B-type lamins assemble in the nuclear periphery and help determine the organelle's mechanical properties, but whether these proteins affect cell migration is unclear. Harada et al. tested the role of lamin-A in several different cell types.

Partially reducing lamin-A levels enhanced the ability of cells to move through extracellular matrix containing small, 3- μ m pores, whereas overexpressing the protein inhibited cell migration. Cells that expressed stoichiometrically high amounts of lamin-B were particularly sensitive to changes in lamin-A levels.

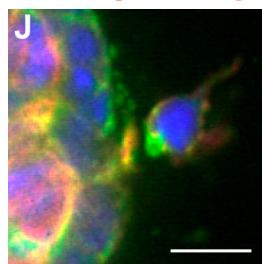
The researchers found that nuclei containing low amounts

of lamin-A were softer, allowing them to squeeze through tiny pores and—due to the spring-like properties of lamin-B—return to their normal shape on the other side. In contrast, high lamin-A levels made nuclei stiff and harder to maneuver, a property that could help keep mesenchymal stem cells, which express large amounts of lamin-A, anchored in their niche.

Nuclei can be too soft for their own good, however. Cells experience stress as they migrate through tissues, occasionally resulting in apoptosis. Cells lacking lamin-A were less resistant to stress and more prone to death, possibly because they expressed lower amounts of the chaperone HSP90. Senior author Dennis Discher now wants to investigate whether the need for HSP90 is merely an indicator of DNA damage that might accumulate as nuclei squeeze through tiny pores in solid tissues.

Harada, T., et al. 2014. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201308029>.

A surprising Twist to cell dissemination



E-cadherin (red) and F-actin (green) are still present at the surface of a disseminating cell expressing Twist1 (blue).

The transcription factor Twist1 can promote the dissemination of epithelial cells without repressing E-cadherin or converting them into mesenchymal cells, Shamir et al. reveal.

Cancer cells are generally thought to metastasize by undergoing an epithelial to mesenchymal transition (EMT), in which transcription factors such as Twist1 down-regulate the intercellular adhesion molecule *E-cadherin*, allowing cells to detach

other and didn't disperse into the surrounding extracellular matrix.

Shamir et al. found that expression of Twist1 was sufficient to induce dissemination of normal cells. Surprisingly, however, rapid cell migration out of the epithelium occurred without transcriptional changes in the expression of *E-cadherin* or other key epithelial markers. Though E-cadherin protein levels were reduced, the adhesion molecule still localized to the plasma membrane, even in single cells migrating away from the mammary epithelium. In fact, knocking out E-cadherin prevented Twist1 from inducing cell dissemination, although the mechanism for this is unclear.

Instead of inducing a transition to mesenchymal fate, Twist1 seems to activate an epithelial motility program involving changes in the expression of genes that regulate the extracellular matrix and cell–matrix adhesion. Many of these genes are also altered in a variety of cancers. Senior author Andrew Ewald now wants to study how this pathway promotes cell dissemination and plans to investigate whether any of Twist1's downstream effectors could be therapeutically targeted to inhibit tumor metastasis.

Shamir, E.R., et al. 2014. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201306088>.

from the tumor and disseminate into the surrounding tissue. However, while studying normal mammary gland development, Shamir et al. discovered that breast epithelial cells don't disseminate in the absence of E-cadherin. Mammary ducts lacking E-cadherin became disorganized and failed to undergo branching morphogenesis in vitro and in vivo, but the epithelial cells remained attached to each