In This Issue

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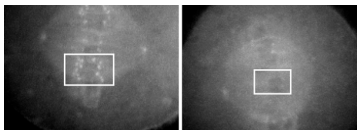
A team of rivals at the kinetochore



PPI is lost from kinetochores when its binding site on KNL1 is mutated (right).

Protein phosphatase I (PPI) is specifically recruited to kinetochores to counteract the Aurora B kinase, report Liu et al. The opposing enzymes combine to ensure chromosomes segregate correctly in mitosis.

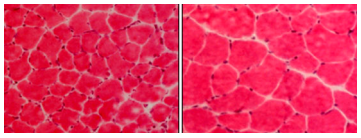
In metaphase, the kinetochores of sister chromatids must connect to microtubules emanating from opposite spindle poles. Incorrect attachments are eliminated by Aurora B, which phosphorylates kinetochore proteins to reduce their microtubule-binding capacity. Correct attachments generate tension and pull the kinetochore proteins out of Aurora B's reach, but phosphate groups added by the kinase must be removed to stabilize the kinetochore–microtubule interaction. PPI is a good candidate for this job, but its role at kinetochores has been difficult to study as it has multiple functions in the cell.

Liu et al. found that the kinetochore protein KNL1 binds and recruits PPI. Preventing PPI targeting to kinetochores by mutating KNL1 resulted in increased phosphorylation of Aurora B substrates and unstable microtubule attachments, even at kinetochores aligned correctly on the mitotic spindle. PPI is therefore needed to reverse Aurora B activity and stabilize microtubules at kinetochores, but PPI's recruitment is itself regulated by Aurora B, the researchers found. Phosphorylation of KNL1 blocked its association with PP1, indicating that Aurora B excludes PP1 from kinetochores until correct attachments and tension pull KNL1 away from the kinase.

Small amounts of PPI could then dephosphorylate KNL1 and promote the recruitment of further PPI molecules, says author Michael Lampson. This might make the transition between stable and unstable microtubule binding sharper, a proposition Lampson and co-author Iain Cheeseman now want to investigate using phospho-site mutants of KNL1.

Liu, D., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201001006.

Disuse TWEAKs muscle loss



Muscle fibers grow smaller after denervation (left), but are protected when TWEAK activity is inhibited by a neutralizing antibody (right).

Mittal et al. identify a cytokine signaling pathway that induces the breakdown of disused skeletal muscle. Blocking this pathway could prevent immobilized patients from losing their muscle tissue.

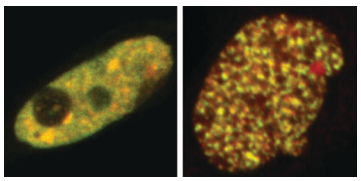
Skeletal muscle wastes away when its activity is reduced by—for example—the loss of stimulatory motor neurons. Although the mechanism by which muscle fibers break down is understood fairly well, how the process is triggered remains unknown. The TNF-related cytokine TWEAK can induce muscle loss, but whether it does so in disused muscle is unclear.

Mittal et al. compared how mice expressing different amounts of TWEAK responded when the nerve innervating their hind legs was severed. Mice producing excess TWEAK lost their muscle more quickly than wild-type animals, whereas mice lacking this cytokine were largely protected from muscle breakdown. TWEAK levels also correlated with the amount of fibrosis, another common symptom of muscle disuse. Inhibiting TWEAK with a neutralizing antibody was sufficient to block muscle loss following denervation, suggesting that the pathway could be a viable therapeutic target. TWEAK signaling activated the transcription factor NF-κB to up-regulate the ubiquitin ligase MuRF-1, which targets components of the muscle thick filament for destruction.

Rather than stimulating TWEAK production, denervation increases expression of the cytokine's receptor, Fn14. The next question, says lead author Ashok Kumar, is how this receptor is up-regulated when muscle use is curtailed.

Mittal, A., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200909117.

Arf and Miz1 cause cells to lose their grip



Myc (red) and Miz1 (green) are recruited by Arf (right panel) into heterochromatin complexes that repress cell adhesion genes and initiate apoptosis.

Two proteins that act independently to arrest the cell cycle can combine to inhibit cell adhesion and drive apoptosis instead, say Herkert et al.

The transcription factor Miz1 arrests damaged cells by inducing the production of cyclin-dependent kinase (Cdk) inhibitors. The tumor suppressor Arf, meanwhile, can either arrest cells or kill them following oncogenic stress, although what determines each of these two outcomes remains unknown. Miz1 and Arf have several interacting proteins in common, but Herkert et al. found that the two proteins also bind each other directly.

Surprisingly, rather than synergizing to block the cell cycle more efficiently, Arf prevented Miz1 from activating Cdk inhibitors. Instead, when combined, Arf and Miz1 assembled into a DNA-binding complex that silenced genes by inducing changes in their histone methylation states. As well as repressing the Cdk inhibitor genes, this complex also switched off many genes associated with cell–cell and cell–matrix adhesions, causing cells expressing Arf and Miz1 to lose their attachments and undergo apoptosis. This pathway could help tissues eliminate cells that have picked up potentially oncogenic mutations, the authors suggest.

Assembly of the repressive complex relied on the interaction of both Arf and Miz1 with the transcription factor Myc, suggesting that Myc levels may be crucial in switching Arf's function from arrest to cell death. In addition, association with Arf and Myc triggered Miz1's modification by the ubiquitin-like molecule SUMO. Lead author Martin Eilers now plans to investigate how this modification helps the complex repress its target genes.

Herkert, B., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200908103.