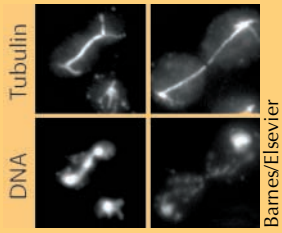
Research Roundup

Flicking the chromosome–attachment switch

Iain Cheeseman, Georjana Barnes (University of California, Berkeley, CA), and colleagues have peered into a 28-protein mix and found the individual residues responsible for attaching and detaching chromosomes and microtubules. The phosphorylation of these residues by Ipl1p (an Aurora kinase) apparently allows budding yeast cells to convert monopolar chromosome spindle attachments to bipolar attachments.

The group used the mass spectrometry (MS) expertise of Scott Anderson and John Yates (Scripps Research Institute, La Jolla, CA) to identify 28 yeast kinetochore proteins (including 5 previously unidentified proteins) in 4 subcomplexes. The same analysis identified 18 phosphorylation sites, 10 of which appear to be Ipl1p targets.

Mutation of individual sites for Ipl1p phosphorylation did not yield any phenotype. But mutation of four sites in the microtubule-binding Dam1p was lethal, and mutant combinations focused on Dam1p led to either constitutive attachment of kinetochores to microtubules (when sites were converted to alanines) or weakened attachment (when sites were converted to phosphorylation-mimicking aspartate residues).



Chromosomes lag (left) or are stuck at one pole (right) depending on the phosphorylation status of the Dam1p subcomplex.

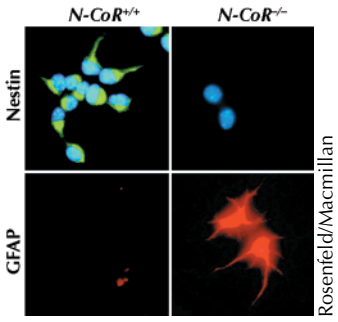
The identification of specific sites for kinetochore–attachment regulation is a victory for the MS approach. "It's one thing to find kinase targets," says coauthor David Drubin, "but it's another to find the important target." ■

Reference: Cheeseman, I.M., et al. 2002. *Cell.* 111:163–172.

Repressing differentiation

The discovery of MyoD was stunning: it suggested that a few critical activators might determine the differentiated states of tissues such as, in this case, muscle. Now Ola Hermanson, Kristen Jepsen, and Michael Rosenfeld (University of California, San Diego, CA) have found that the undifferentiated state also has critical determinants. This time, however, the determinant is called N-CoR, and it is a corepressor.

Hermanson and colleagues found that mice lacking N-CoR had a decrease in the size of certain brain regions, and cells cultured from the mice had lost the ability to self-renew. Instead, the cells differentiated, in the absence of the normal differentiating signals, into something resembling astroglia. The cells were not responsive to signals favoring neuronal differentiation.



Cells lacking N-CoR form astroglia (bottom) but not neurons (top).

CNTF induces differentiation of normal neural precursors into astroglia. The authors found that this involved Akt-mediated phosphorylation of N-CoR. Phosphorylated N-CoR translocated out of the nucleus, and thus could no longer act as a corepressor for several transcription factors.

N-CoR is active in tissues other than the brain. But, says Rosenfeld, "it would be totally naïve to consider that the absence of N-CoR is all it takes to differentiate." He does believe, however, that the N-CoR results demonstrate a larger principle. "You need a dedicated apparatus to maintain a proliferative or dedifferentiated state, often involving repressors," he says. "I think there is a huge cohort of repressors mediating this, probably as many as there are activators for differentiation." ■

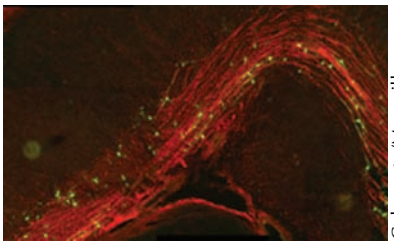
Reference: Hermanson, O., et al. 2002. *Nature.* 10.1038/nature01156.

Switch to survival

A single factor can promote both proliferation and differentiation of oligodendrocytes, according to Holly Colognato, Charles ffrench-Constant (University of Cambridge, Cambridge, UK), and colleagues. The added ingredient that makes the difference, and switches the signaling pathway downstream of the growth factor, is the extracellular protein laminin.

The laminin is found on axons in the central nervous system—the target of the oligodendrocytes. Before arriving at this target, the oligodendrocytes proliferate under the influence of several factors including neuregulin, whose actions are pro-proliferation and anti-differentiation.

As the cells mature, a proapoptotic protein called BAD accumulates. This may result in the death of excess oligodendrocytes that are far away from their target. But the Cambridge group found that cells close enough to an axon could counteract the accumulation of BAD. The ligation of oligodendrocyte integrin α6 with axon-supplied laminin causes a switch in signaling downstream of neuregulin. The PI3K proliferation signal is replaced with a MAP kinase differentiation signal that also phosphorylates and thus inactivates BAD.



Oligodendrocytes (green) get modified by their target axons (red).

Colognato does not yet know whether integrin interferes at the level of the plasma membrane or further down the signaling cascade. But she is intrigued to see whether developmental regulation of the pathways might explain a mystery of repair: that newly arriving oligodendrocytes often fail to myelinate adult axons in diseases such as multiple sclerosis. ■

Reference: Colognato, H., et al. 2002. *Nat. Cell Biol.* 10.1038/ncb865.