A cytokine that packs a punch

Muscle cells undergo an unusual developmental program in which several partially differentiated cells called myoblasts fuse to form a multinucleated myotube. This nascent myotube undergoes further maturation and growth, which requires the addition of nuclei by fusion of more mononucleated myoblasts with myotubes. Valerie Horsley, Grace Pavlath, and colleagues (Emory University, Atlanta, Georgia) have found that nascent myotubes promote fusion, and thus their own growth, by secreting a cytokine normally associated with immune cells.

The cross-system cytokine is IL-4, which is required in immune cells for macrophage fusion. Not one to throw away a good thing, nature evidently coopted the system for muscle cells. As in immune cells, IL-4 expression in nascent myotubes is driven by a member of the NFAT transcription factor family.

Myotubes lacking either IL-4 or the NFAT factor were smaller and had fewer nuclei than wild-type cells. Recovery from muscle injury was also diminished by the lack of IL-4 or the IL4 receptor.

Myoblasts are the targets of IL-4 action, which may promote fusion by inducing myoblast expression of adhesion molecules such as integrins (as in macrophages) or VCAM. Alternatively, IL-4 may act as a chemokine, as it does for osteoblasts, to stimulate migration of myoblasts toward myotubes. Whatever the mechanism, stem cell therapies for disorders such as muscular dystrophies may be improved by expression of IL-4 to increase the fusion capacity of the muscle stem cells.

Reference: Horsley, V., et al. 2003. Cell. 113:483–494.

Cyclin B knows its place

In mammalian cells the work of the cell cycle is divided between two workhorses: Cdk2/cyclin E for S phase and Cdk1/cyclin B for mitosis. Now, Jonathan Moore, Jane Kirk, and Tim Hunt (Cancer Research UK London Research Institute, London, UK) show that this apparent specificity is achieved by limiting access to substrates. By denying entrance to the nucleus, cells prevent Cdk1–cyclin B from jumpstarting S phase at inopportune times.

In frog egg extracts, S phase is induced in nuclei by Cdk2–cyclin E, but not by Cdk1–cyclin B. This difference has often been construed as specificity in cyclin substrate preferences, but the new results show that cyclin/Cdk pairs are in fact surprisingly promiscuous enzymes. Hunt’s group simply replaced the nuclear localization signal for Cdk1 and found that this altered Cdk1–cyclin B promoted both DNA replication and mitosis.

“It’s a biochemist,” says Hunt. “I tend to think in terms of specificity between substrate and enzyme. So it was a shock to find the different [CDKs] might not discriminate their substrates.” Vertebrate cells apparently avoid the danger that cyclin B might initiate S phase via its cytoplasmic localization and low levels during G1. In yeast, a single cyclin can, under some circumstances, promote both S phase and mitosis. Yeast may not have as severe a need to restrict cyclin activities because the G2 to M transition is less clear than in higher eukaryotes. “Maybe it’s okay to start mitosis early in yeast because chromosomes are still able to replicate as they are set on the metaphase plate,” Hunt suggests.

Reference: Moore, J., et al. 2003. Science. 300:987–990.

Apoptosis leaves its mark on chromatin

DNA gets condensed and chopped up during apoptosis. Despite these extensive changes, only one histone modification event—phosphorylation of histone H2B—has been specifically associated with apoptosis. Now, Wang Cheung, David Allis (University of Virginia, Charlottesville, VA), and colleagues provide evidence that this single change may be sufficient to induce the DNA changes during apoptosis.

Using a phosphospecific antibody, the authors identified the residue that is modified during apoptosis as a serine in the NH2-terminal tail of H2B. The antibody reacted with chromatin in dying cultured human cells and in clusters of cells undergoing apoptosis during tail resorption in developing frogs, indicating that the modification is well conserved.

The authors also show that the kinase responsible for H2B’s death is Mst1, which is cleaved at the onset of apoptosis by caspase-3. Mst1 phosphorylates H2B in vitro, and the cleaved form moves to the nucleus just before H2B phosphorylation in vivo. Expression of a truncated Mst1 induced H2B phosphorylation and DNA condensation and even led to cell death in the absence of proapoptotic insults. Although it is not clear how phosphorylation and condensation are linked, the authors found that phosphorylated H2B tends to aggregate in denaturing conditions and thus may be intrinsically sticky. Alternatively, phosphate-modified H2B may recruit some as-yet-unidentified protein that condenses DNA.

Reference: Cheung, W., et al. 2003. Cell. 113:507–517.

Phosphorylated H2B is found in condensed chromatin in dying cells.