miRNAs halt cell cycle

Muscle-specific miRNAs can induce differentiation at least in part by depleting DNA polymerase α mRNA, according to Kim et al. (page 677). Although other factors are also involved in the differentiation process, obliterating the DNA replication machinery is a novel means to bring the cell cycle to a halt in differentiating cells.

Kim et al. started with the miR-1, -133, and -206 miRNAs because they are known to be expressed in muscle and heart. Expression of all three increased when C2C12 myoblast precursors were induced to differentiate into muscle by the withdrawal of serum. In fact, expression of miR-206 was sufficient to induce differentiation even in serum. Conversely, blocking its expression dramatically reduced the fraction of cells that exited the cell cycle and differentiated.

To identify targets of these miRNAs, the researchers looked at microarrays. Several genes were down-regulated in response to the miRNAs and contained target sites complementary to the miRNAs. Some of these targets remain somewhat mysterious as to their differentiation function, but the one that stood out was DNA pol α. The expression of miR-206 alone was sufficient to cleave DNA pol α mRNA and decrease levels of the polymerase protein. Other differentiation factors appear to take over later, but it appears that miR-206 is important for immediate down-regulation of DNA pol α.

A key question is whether other differentiation-promoting miRNAs target the DNA replication machinery, as miRNAs have been found to be involved in differentiation of several other postmitotic cell types. The C2C12 cells used in the current study can also differentiate into adipocytes. The researchers are therefore currently working to see if any of the adipocyte-specific miRNAs also hit DNA replication or cell cycle genes.

Formin localization

Interaction between the NH2- and COOH-terminal regions of formin proteins serves two autoinhibitory functions simultaneously, report Seth et al. on page 701. The first, more familiar function is to block actin nucleation by the COOH-terminal region. More novel is the second function: preventing localization of the protein to the plasma membrane, normally mediated by the NH2-terminal domain.

The Diaphanous-related formins nucleate unbranched actin filaments during cytoskeletal remodeling. In the case of mDia1 formin, this nucleation activity is autoinhibited by interaction between the NH2 and COOH termini of the protein. Seth et al. show that the formin family member FRLα is autoinhibited by the same mechanism.

Blocking autoinhibition via mutation had a second consequence: FRLα moved from the cytoplasm to the plasma membrane. This plasma membrane localization was dependent on the NH2-terminal domain and was enhanced by interaction with the activated form of the RhoGTPase Cdc42.

A similar membrane localization activity was detected in the NH2-terminal region of mDia1. Localization of both proteins had a GTPase-dependent and -independent component, suggesting a still undiscovered membrane-associated formin ligand.

Given the similarities between the two formin proteins, Seth et al. hypothesize that this mutual autoinhibitory pattern involving both activity and localization will be characteristic of the formin family—and may be more broadly found in autoinhibitory proteins in general. Moreover, unique interactions between different formin family members and Rho GTPases likely give each actin nucleator a distinct role in cytoskeletal remodeling, as has been seen with yeast formins.
Muscle activity is driven by spikes of calcium release. Weisleder et al. (page 639) find that aged muscles, when compared with young muscles, have reduced Ca\(^{2+}\) release following stimulation. The dampened response may be caused by a failure to maintain robust membranous compartments that can respond to an input with a single output.

Previous work from the group showed that Ca\(^{2+}\) sparks can be induced in skeletal muscle by osmotic shock and that the sparks resemble those produced during exercise. The group has now found that, compared with young tissue, aged muscle releases fewer of these Ca\(^{2+}\) sparks. The poor response may be a result of the poor state of the sarcoplasmic reticulum (SR) network in aged fibers. This network stores Ca\(^{2+}\) and releases it in response to incoming nerve signals, but in aged fibers the SR was fragmented. Therefore, a significant portion of the stored Ca\(^{2+}\) was unavailable for release during normal action potential-triggered skeletal muscle contraction.

Degradation of the SR may result from a lack of a synaptophysin protein, mitsugumin-29 (MG29), which the group found was expressed at low levels in aged relative to young muscles. Muscle from young mg29-null animals showed a disruption in membrane structure and a weak response to stimulation that was similar to that seen in aged muscle. Weisleder et al. speculate that the putative membrane fusion function of MG29 may help maintain the structure of the SR.