Cycles of muscle fusion

One round of fusion begets another, according to Meillon et al. (page 909). This positive feedback keeps muscle formation going in the developing fly. Multinucleated muscles are a product of the fusion between one founder cell, which expresses the attractant Duf, and fusion-competent myoblasts (fcms) that produce the Duf ligand. Although as many as 25 myoblasts eventually become one, the founder only fuses with two or three fcms at a time. The new results reveal the basis for this sequence: one round of fusion consumes the founder’s surface-bound Duf, but then triggers the translocation of more Duf from intracellular stores.

Translocation was initiated by adhesion of Duf’s extracellular domain to an fcm ligand. The intracellular domain of the adhered Duf then transmitted an unknown signal that recruited puncta (probably endosomes) containing more Duf to the adhesion site. This Duf was then inserted into the membrane to attract a new fcm to the same spot where the previous fcm fused.

Duf translocation requires another puncta-localized protein called Rols7. In the absence of Rols7, only one round of fusion was possible, as Duf was not replenished. Rols7 must have an additional function during fusion, since a mutant that was missing multiple domains translocated effectively but did not support multiple rounds of fusion.

Links that separate

A linker histone condenses chromosomes so they fit on the mitotic spindle, as shown by Maresca et al. (page 859).

The linker histone H1 seems like an obvious candidate for a condensing activity. But unreplicated sperm chromatids in Xenopus egg extracts look no less condensed when H1 is depleted. The new results suggest that these chromatids do not aptly represent the normal situation. By first replicating the sperm chromatids, the group was able to show that H1 is a condenser.

H1 was enriched on duplicated chromosomes compared with their unreplicated counterparts. It is not clear how H1 is loaded, but it requires passage through interphase, when DNA is replicated. In the absence of H1, other chromosomal proteins, including condensin and cohesin, found their way to chromosomes. But the H1-free chromosomes were longer, failed to align properly on the metaphase plate, and tangled up during anaphase such that segregation failed. Kinetochore function was normal, probably due in part to the presence of CENP-A, a centromere-specific histone variant with some similarity to H1.

The authors propose that, if proteins such as condensin are loaded at specific nucleotide intervals, then the absence of the H1 linker would space them further apart in absolute distance, thus amplifying condensation problems. Chromosomes in cells lacking H1 reached lengths of 60 μm, about twice that of the spindle. Overflowing, unattached arms would be difficult to push to the metaphase plate and then pull to the poles at anaphase.

Tumors feed on collagen

Urino et al. (page 977) find that the ability of tumor support cells to take in and degrade collagen helps tumor growth. Blocking the collagen uptake receptor, they show, keeps murine breast tumors in check.

Collagen, the major component of the extracellular matrix, can be degraded extracellularly by proteases or intracellularly in lysosomes. Mice lacking uPARAP, which mediates the uptake of collagen and thus the intracellular pathway, develop normally. The authors now show that these mice have an advantage over the wild type when it comes to controlling cancer progression.

Stromal cells surrounding breast tumors in the mutant mice did not take in and degrade collagen efficiently. Tumor growth was subsequently restricted in these mice. Proliferation and apoptosis rates of the tumor cells were unchanged, however, so the signals affected by collagen degradation that lead to tumor growth are still unclear.

Blocking the extracellular pathway is also known to limit tumor growth in mice, but this requires the inhibition of many proteases. The intracellular pathway, by contrast, can be blocked by disrupting only uPARAP. This strategy might be useful for the treatment of human cancers and other disorders involving the degradation of connective tissues, such as arthritis, which are all associated with strong intracellular collagen turnover.