Sometimes size does matter

During myofibroblast differentiation in vitro, “supermature” focal adhesions (FAs) arise due to increased physical stress, report Goffin et al. (page 259). Additionally, increased tension induces accumulation of α-smooth muscle actin (α-SMA) in stress fibers that are anchored at these FAs.

In vivo, the extracellular matrix rearranges and increases in rigidity in response to wounding. This change, along with the release of growth factors, induces fibroblasts to take on a contractile phenotype, including expression of α-SMA. The question remains, however, as to what triggers incorporation of α-SMA into stress fibers in these cells.

When differentiated myofibroblasts were cultured on flexible substrates, FAs remained relatively small. However when the cells were grown on rigid substrates, supermature FAs formed. Once formed, supermature FAs were able to withstand substantially larger physical forces and generated higher intracellular tension than did FAs of a more typical size. This higher tension in turn triggered α-SMA recruitment to stress fibers, which did not occur in cells with smaller FAs.

The team is working to identify the cellular component that senses the increased tension in stress fibers and recruits α-SMA. In the meantime, they are convinced that tension and size are intimately linked in the formation of supermature FAs and α-SMA stress fibers. JCB

NO induces myoblast fusion

Nitric oxide (NO) functions at numerous points in muscle development and function. On page 233, Pisconti et al. add one more item to that list: NO stimulates myoblast fusion via cGMP signaling and follistatin. Increasing NO in vivo stimulates muscle fiber formation, which suggests a potential therapeutic approach for muscular dystrophy.

Addition of an NO-releasing compound to cultures of embryonic myoblasts or satellite cells, which function as stem cells in adult muscles, stimulated cell fusion. Conversely, addition of an inhibitor of nitric oxide synthase blocked fusion.

When the team added NO to cells but blocked production of cGMP, a known mediator of NO signaling, fusion was inhibited in a cGMP-reversible manner. Significantly, prolonged exposure of the myoblasts to a nonhydrolysable analogue of cGMP induced the formation of abnormally large muscle fibers in culture. A similar effect was not observed with extended exposure to an NO donor.

RT-PCR analysis of NO-treated myoblasts showed that follistatin, a protein known to trigger myoblast fusion, was up-regulated relative to untreated cells. Another fusion-promoting protein, insulin growth factor-1 (IGF-1) was not increased.

The results suggest that NO donors may be valuable as therapies for muscular dystrophy. Preliminary testing in animal models supports that idea. JCB

Mobile genes

On page 177, Brown et al. follow the nuclear positioning of the globin genes during erythroid differentiation and find that they are often close to each other during active transcription. However, such associations do not appear to be a requirement for transcriptional regulation, but rather a consequence of it.

The α- and β-globin genes are highly transcribed for a brief time during the maturation of red blood cells, with each gene producing about the same amount of mRNA. But the chromosomal contexts for the genes are very different. The human α-globin genes lie in a gene-dense subtelomeric region that is constitutively in an open chromatin conformation. The β-globin genes are in an AT-rich region that is open only during erythroid development.

At the point of maximal transcription, the α-globin genes were frequently decondensed and distinct from their chromosomal territories. By contrast, the β-globin genes remained close to their native chromosome arms, as did the mouse α-globin genes, which lie in a less gene-rich region than their human counterparts.

Moreover, the human α-globin alleles associated near one another in approximately half of the transcribing cells examined, as did α- and β-globin alleles. β-globin alleles, in contrast, were almost never in close proximity to each other. Finally, the α-globin alleles were more likely to be in contact with large aggregates of splicing factors called speckles.

Thus, despite the functional similarities of human and mouse α- and β-globin genes, the loci show differing patterns of nuclear localization and interaction. Brown et al. conclude that gene positioning in the nucleus depends on multiple factors, including gene density and chromosomal location. They hypothesize that rapidly transcribed genes—or at least those that are potentially mobile—can be pulled near one another as large aggregates of transcription and processing factors accumulate in their vicinity. Already, they have seen similar associations between other coexpressed genes. JCB