In This Issue

**Best stiffness for striation**

A small change in substrate stiffness can deter striated muscle differentiation, as shown on page 877 by Engler et al. As stiffness changes of this magnitude are not uncommon in diseased tissues, injections of stem cells may be useless unless the target environment is also treated.

Muscular dystrophy patients suffer from stiffened muscle tissue. Although muscle precursors are abundant in mdx mice, a muscular dystrophy model, they fail to regenerate injured muscle. The new article shows that this failure may be due to their overly stiff environment, which prevents skeletal muscle striation.

Skeletal muscle precursors spread, assumed a spindle shape, and fused into multinucleated cells when grown on surfaces within a wide range of stiffness. However, striation—the alignment of actin and myosin into repeated units—was blocked if the substrates were either too soft (e.g., fibroblasts or weak gels) or too stiff (e.g., glass).

Adhesions were strongest on the stiffest substrate. Differentiation therefore requires enough adhesion to sense the matrix stiffness, but not so much that cytoskeletal changes leading to striation are inhibited. What translates forces felt at adhesion sites into differentiation is unknown, but the membrane-bound scaffold protein N-RAP is one possibility, as it both nucleates actin filaments and regulates transcription.

Striation was most prominent on substrates within just 25% of the stiffness of normal muscle. The authors found that mdx muscle is stiffer than this optimal range, and thus may inhibit differentiation of its own precursors. If cardiac muscles are similarly sensitive, careful application of antifibrotics may be needed before injections of precursor cells can regenerate tissue damaged by heart attacks.

A model of cell death

On page 839, Bentele et al. use a mathematical model to simplify a complex biological problem—programmed cell death. Models are mostly used to study relatively simple and well-understood biological systems. Complex systems, in contrast, have so many unknowns that an overwhelming amount of data is needed to complete a model.

But Bentele et al. show that CD95-induced cell death can be simplified. The authors found that the activity or concentration of many molecules involved in this death pathway (such as caspases and Bcl family proteins) are unaffected by large changes in most parameters (including binding kinetics and reaction speeds). So they broke down their original model into modules—groups of molecules that change in response to changes in the same set of parameters. As a result, only a subset of molecules needs to be examined when certain parameters are changed in simulations.

Using these simulations, the group identified the pathway’s most critical molecules as those that reacted strongly to parameter changes. The concentrations of these critical molecules were measured in lab experiments over time following CD95 activation to estimate some of the remaining unknown parameters and thus refine the model.

Both the refined model and lab experiments predicted that a threshold concentration of CD95 ligand is required for cell death to occur. One candidate that might control the threshold is c-FLIP, whose binding to the CD95-containing complex competes with activation of caspase-8. Death simulations run in the absence of c-FLIP abolished the threshold. Cell death now occurred under low concentrations of the ligand that did not cause death in the presence of c-FLIP. Lab experiments in which c-FLIP expression was inhibited confirmed that c-FLIP is the threshold switch. The authors hope that biologists will use modeling approaches to improve benchwork experiments for finding the important players in complex pathways.