Research Roundup

Muscle cells take heart

Skeletal muscle harbors cells that can form heart cells. The population, identified by Steve Winitsky, Neal Epstein, and colleagues (National Heart, Lung, and Blood Institute, Bethesda, MD), should benefit both clinical and basic research.

While isolating cells from mouse skeletal muscle, the authors noticed that a few floating cells in their culture were beating. These cells (which they named Spoc cells) eventually adhered and developed into normal looking and functioning cardiac myocytes. Spocs are the first heart precursors shown to beat and develop in vitro without long-term culture. They may finally provide a convenient set of cultured beating cardiac cells from the various transgenic mice used by cardiac researchers.

Spocs also know their place in vivo. The group injected the freshly isolated cells into the bloodstream of a mouse with a recent heart attack injury. Within days, the precursor cells were visible in the injured region of the heart (fusion was ruled out). By 3 months, the cells had striations associated with mature cardiomyocytes.

Why skeletal muscle holds these cells, and why these cells do not normally repair heart injuries, remains unknown. Heart muscle that is too abundant or too thick can be deadly. “So maybe,” Epstein says, “we need the active suppression of stem cells in the heart.” But that does not explain why nature keeps them around elsewhere. “It’s definitely a mystery,” says Epstein.

Reference: Winitsky, S.O., et al. 2005. PLoS Biol. doi:10.1371/journal.pbio.0030087.

Folding in a crowd

Proteins fold better in a crowd, as predicted by a biophysical model from Margaret Cheung, Dmitri Klimov, and D. Thirumalai (University of Maryland, College Park, MD).

Interactions between a protein and large nearby molecules produce repulsive forces at distances that can be as large as the protein itself. The group modeled the energetic effects of these interactions on folding of a WW domain and found that it folds faster and has a more stable folded state in a crowded environment. The more spread out the protein, the more likely it is to experience unfavorable interactions with macromolecules. Compaction, in contrast, promotes its isolation.

Folding rates reach a maximum when 10% of the solution volume is taken up by other large molecules, but even at high densities the folding rates were still well above that in dilute solution. Approximately 40% of a bacterial cell is occupied by macromolecules. Thirumalai suggests that crowding effects may relieve some of the evolutionary pressure to produce rapidly folding sequences. “An optimal design may not be necessary,” he says. “Maybe in fact moderately well-designed amino acid sequences are good enough.”

The influence of crowding was also mimicked by folding proteins in a confined spherical space. These calculations were simpler than those done using crowding agents. Confinement may thus prove useful for future studies, including determining whether so-called natively unfolded proteins are actually at least partially structured in vivo.

Reference: Cheung, M.S., et al. 2005. Proc. Natl. Acad. Sci. USA. 102:4753–4758.

APC proteolysis not overdone

Smart antigen-presenting cells (APCs) use proteolysis with restraint, according to Lélia Delamarre, Ira Mellman, Sergio Trombetta, and colleagues (Yale University, New Haven, CT). Although perhaps contrary to prevailing assumptions, this less-is-more approach may prevent excessive or premature peptide processing.

“We’ve been led to believe that, since so many different antigens have to be made, APCs need a large, diverse set of [protease] activities,” says Mellman. But dendritic cells (DCs) and B cells are no more endowed with lysosomal proteases than is the average fibroblast, based on the new results. Of the APCs tested, only macrophages were particularly protease packed.

DCs carry antigens from peripheral tissues to lymph nodes, where T cells await antigen exposure. As this trek can take days, restricted proteolysis may ensure that antigens are not chopped beyond recognition before their arrival. Indeed, the group saw that antigens survived much longer in DCs than in macrophages. And most of the antigens retained at lymph nodes resided in DCs.

Antigens that were more resistant to degradation were also more likely to be presented by APCs. “A less effective environment for protease digestion may be more favorable to the production of peptides that are suitable for presentation,” says Mellman. Antigen formulations that are more resistant to lysosomal degradation may thus prove more effective as vaccines.

Reference: Delamarre, L., et al. 2005. Science. 307:1630–1634.