Seeing muscle evolution

As vertebrate and invertebrate ancestors split, vertebrates acquired a novel mechanism for controlling skeletal muscle contraction, report Di Biase and Franzini-Armstrong on page 695.

Vertebrates use two different systems for controlling muscle contraction, with DHPR calcium channels acting as voltage sensors in both. In skeletal muscle, tetrads of DHPR proteins associate directly with ryanodine receptors (RyRs). In response to electrical stimulation, DHPRs directly signal RyRs, causing release of internal stores of calcium and muscle contraction. By contrast, DHPR and RyR in cardiac muscle are located near one another in adjoining membranes but do not interact directly. For DHPR to activate RyR, the channel must allow a flood of extracellular calcium into the cell. All invertebrate muscles use this latter system.

Using structural analysis of muscle samples from four species that characterize the vertebrate–invertebrate evolutionary junction, the authors found a correlation between lying on the vertebrate side of the evolutionary tree and having an organized DHPR–RyR structure.

Although the functional difference between the systems is metabolically important, it can be reversed with some simple genetics. Previous work showed that substitution of either DHPR or RyR skeletal proteins with the cardiac isoform causes a shift toward the cardiac structure and function in tissue culture cells. JCB

Clipping coreceptors

The heparan sulfate proteoglycan (HSPG) coreceptor is not like another. On page 729, Ding et al. show how two HSPGs, both capable of acting as growth factor coreceptors, have distinct functions on cancer cells. Glypican-1 acts as a long-term growth factor coreceptor, whereas syndecan-1 is shed and helps spread metastasis-promoting proteinase.

Upon stimulation with fibroblast growth factor-2 (FGF2), the initial responses of pancreatic cancer cells could be facilitated either by glypican-1 or syndecan-1. Yet the cells rapidly became dependent on glypican-1. The researchers found that the extracellular domain of syndecan-1 was proteolytically clipped off the membrane in response to FGF2. No evidence of glypican-1 cleavage was found. Noncleavable syndecan-1 blocked syndecan-1 shedding and kept cells responsive to FGF2, even in the absence of glypican-1.

Stimulation by FGF2 induced activation of matrix metalloproteinase-7 (MMP7), which was responsible for the shedding of the extracellular domain of syndecan-1. Because MMP7 is normally docked on cell surfaces by binding to HSPGs, its activation by FGF2 induced its own release, in association with shed syndecan-1 ectodomains.

The team thinks that growth factor–induced release of MMP7–syndecan-1 complexes from tumor cells enhances the ability of MMPs to diffuse out of tumors and degrade surrounding extracellular matrix, an early step in metastasis. MMP7 is known to facilitate metastasis, and recent evidence indicates that forcing tumor cells to shed syndecan-1 constitutively also makes them more aggressive in vivo. JCB

Nonubiquitous autophagy

Cells use autophagy for bulk degradation, in what is often thought of as a nonspecific process. That perception, however, might not be accurate, according to data from Bjørkøy et al. (page 603). Some autophagy substrates are polyubiquitinated and appear to be targeted for destruction.

Protein aggregates, such as those found in Huntington’s disease, contain polyubiquitinated proteins, as well as the polyubiquitin-binding protein p62.

The team found that p62 accumulation into protein aggregates depended on its polyubiquitin binding domain and on a polymerization domain, PB1, which allows large chains of p62 to form. p62 also colocalized with LC3, a protein that binds to the autophagosomal membrane. Moreover, inhibition of autophagy blocked p62 degradation.

In cells expressing a mutant huntingtin protein, aggregates containing p62 and LC3 were even more common than in the HeLa cells initially studied. Reducing the amount of p62 expressed caused a higher proportion of the cells in the population to undergo apoptosis.

The data suggest that p62 helps identify substrates for autophagy via its polyubiquitin binding domain. Using its PB1 domain p62 forms a shell around the aggregate and somehow facilitates an interaction with LC3, which is likely an early step in targeting to autophagosomes. The work provides a molecular link between recognition of polyubiquitinated protein aggregates and garbage disposal by autophagy, and suggests that cells may use protein aggregation as a protective response. JCB

Organized channels allow vertebrates to make muscles more efficient.