can bind to either ankyrin in vitro, what makes the channels preferentially bind to ankyrin G in vivo?

To answer this question, Bréchet et al. homed in on the precise residues in sodium channels that are required for the interaction with ankyrin G. They pinpointed a sequence of residues that looked like a target for phosphorylation by CK2, and sure enough, it was. CK2 phosphorylated the sodium channels and this was required for the channels’ correct positioning along the axon membrane.

In vitro, however, phosphorylation by CK2 prompted the channels to bind both ankyrin G and B. The clue to the sodium channels’ specificity for ankyrin G came when the team looked at the distribution of CK2 in neurons and found that it was also restricted to the AIS and the nodes of Ranvier. The big question now is, what targets CK2? RW

Bréchet, A., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200805169.

The actin flow paradox

Gardel et al. have discovered a perplexing anomaly regarding actin dynamics and cell traction on its extracellular matrix.

In a migrating cell, actin filaments polymerize at the leading edge, and flow back into the body of the cell (retrograde flow). It has been proposed that focal adhesions (FAs)—the cell’s tether points to the extracellular matrix (ECM)—forming at the cell’s leading edge provide handholds for the flowing actin that impede actin’s retrograde movement, and in so doing create the traction needed to push the cell forward. The situation might be likened to a crowd of people being washed downstream and certain individuals gripping rocks (FAs) on the riverbed to work their way back against the flow.

Gardel et al. hypothesized that the speed of actin retrograde flow should be inversely correlated to traction force—the slower the river flows, the easier it is to grip the rocks and work one’s way upstream—and indeed, this is exactly what they discovered. However, this was only true for the actin speeds seen at the front end of the cell (10–30 nm per second). At the frontal tip (where FAs are small), actin retrograde flow was rapid and traction was minimal. A little farther back in the leading edge (where FAs are bigger), traction increased and actin speeds slowed. Back toward the cell body, however, despite actin speeds dropping below 8–10 nm per second, the FAs exerted less traction.

Clare Waterman, who led the study, explains that the switch occurs roughly in the area where the lamellipodia (leading edge) ends, and the cell body begins. There must therefore be something different about the way the FAs and actin combine to generate tension in this region. RW

Gardel, M.L., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200810060.

FHL1 adds some muscle

Cowling et al. report how to build muscle mass with FHL1. The protein partners with and activates the transcription factor, NFATc1. Encouraging this partnership might provide a possible treatment for muscle wasting disorders.

Mutations in FHL1 are present in several myopathies, including reducing-body myopathy (RBM), but until now, both the molecular mechanisms causing the disease, and the regular function of FHL1 in healthy tissue, remained unknown.

To address this, Cowling et al. overexpressed FHL1 in both transgenic mice and cultured myoblasts. The mice developed skeletal muscle hypertrophy, and showed increased strength and endurance. Overexpression in myoblasts also increased cell fusion, resulting in hypertrophic myotubes. These phenotypes are similar to those caused by the calcineurin/NFAT pathway and, indeed, inhibiting calcineurin blocked the effects of FHL1 overexpression in vitro. The authors showed that FHL1 binds to and enhances the transcriptional activity of NFATc1 in vitro and in vivo.

So what goes wrong when FHL1 is mutated? In RBM, mutant FHL1 accumulates in cytoplasmic aggregates called reducing bodies, probably as a result of misfolding. When these mutants were expressed in cultured myoblasts, they also aggregated, and did not induce hypertrophy. Cowling and colleagues found that NFATc1 was sequestered to the aggregates, and was therefore unable to activate its target genes. BS

Cowling, B.S., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200804077.