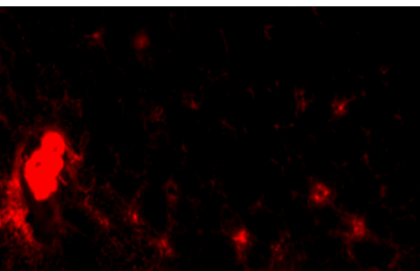
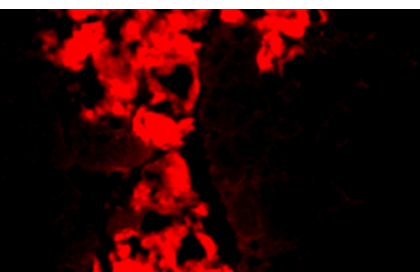


Cytochrome b5 (green) normally localizes in the ER, but without its targeting sequence is redirected to the outer segment (right).



Unstable muscle membranes in the *mdx* mouse (top), indicated by infiltration of a dye, are stabilized by sarcospan (bottom).

No direction? Join the crowd

Sometimes you can get to your destination just by following the crowd. Baker et al. report that photoreceptor proteins lacking targeting sequences end up in the right place thanks to their more abundant, and more goal-oriented, fellow travelers.

Rod and cone cells are divided into four compartments: a synaptic terminal, a nuclear region, an inner segment for protein and lipid synthesis, and an outer segment that contains a highly folded membrane packed with proteins such as light-sensitive rhodopsin. Rhodopsin and some other outer-segment proteins contain targeting signals directing them there, but most outer-segment proteins do not.

To understand how these signal-lacking proteins reach their destination, the authors examined the trafficking of two proteins: R9AP, which is almost exclusively found in the outer segment, and the structurally similar syntaxin 3, localized to the inner segment. Switching the transmembrane domains of the two had no effect on their final destinations, and neither did whittling away at R9AP's cytoplasmic domain. Removing the cytoplasmic domain of syntaxin-3, on the other hand, led the protein to accumulate in the outer segment, whereas adding this domain to R9AP led the protein to accumulate in the inner segment. Syntaxin's cytoplasmic domain thus specifically targets proteins to the inner segment, and without it proteins head to the outer segment by default. The case for the outer segment as the default destination was clinched by removing signal sequences from multiple proteins, all of which then ended up in the outer segment.

R9AP and other signal-lacking proteins might be randomly packaged into vesicles bound for all destinations, but since rhodopsin-bearing vesicles headed for the outer segment are so abundant, "directionless" proteins will wind up where they belong just by going with the crowd.

Baker, S.A., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200806009.

Sarcospan, a little protein for a big problem

The overlooked and undervalued protein, sarcospan, just got its moment in the spotlight. Peter et al. now show that adding it to muscle cells might ameliorate the most severe form of muscular dystrophy.

In Duchenne muscular dystrophy (DMD), the mutated dystrophin protein fails to anchor correctly to its membrane glycoprotein complex. Without this anchoring, muscle cells experience severe contraction-induced damage. Sarcospan is part of the anchoring complex, but because mice without sarcospan don't seem any worse for its absence, it hasn't received much attention. Sarcospan's structure, however, suggests it might help stabilize the membrane complex, so the authors decided to test the effects of increasing sarcospan expression in a DMD mouse model.

The increase did not improve the dystrophin–glycoprotein interaction, but instead, the team was surprised to find sarcospan coaxed a dystrophin relative called utrophin to spread out on the muscle membrane. Utrophin is normally restricted to the neuromuscular junction, where it serves a function similar to that of dystrophin.

The extra sarcospan prompted higher levels of utrophin in the cell, but not by increasing its expression. Sarcospan instead stabilized extrajunctional utrophin complexes, which normally form early in development and then disappear after the first few weeks of life.

Mouse muscle cells were protected by sarcospan, but the true importance of this discovery will lie in its potential for human therapeutics, specifically gene therapy. In that regard, sarcospan's small gene size is significant—at 600 bp, it is easily packaged into the safest viral vectors, unlike either dystrophin or utrophin, which are about 700 times larger and require more immunogenic vectors.

Peter, A.K., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200808027.

BBB building

Construction of the brain's border fence is supervised by Wnt/ β -catenin signaling, report Liebner et al.

Like many a nation, the brain requires tight border security to maintain levels of nutrients and keep out toxic substances. The blood–brain barrier (BBB) is a virtually impermeable network of