How to start a motor

The longest journey may begin with a single step, but, in the case of myosin motor proteins moving along actin filaments, the start of the walking stride has been nearly impossible to observe. Now Burgess et al., reporting on page 983, reveal the prepower stroke conformation of myosin on actin, clearing a major hurdle to understanding myosin activity.

Previous work on myosin has focused primarily on myosin II, which has the unfortunate habit of dissociating from actin in the presence of ATP, making its prepower stroke conformation all but impossible to observe. As motor domains are highly conserved among different myosins, Burgess et al. looked at myosin V, a highly processive motor that drives mRNA, vesicle, and membrane trafficking. By combining electron microscope images of myosin V with crystallographic data from myosin II heads, the authors developed high resolution models of myosin conformations on and off actin and in the presence and absence of ATP.

The results provide a detailed model of myosin movement. When ATP is added to myosin V molecules not on actin, there is a gross change such that the myosin bends by ~90° at the junction of the motor domain and lever arm. When attached to actin, the leading head has a similar bent structure, but its attachment to the trailing head results in distortion either at the junction of the motor domain and lever arm or throughout the lever arm. When the trailing head detaches, the leading head straightens, and the release of this distortion, combined with the reversal of the bending induced by ATP, drives movement along the actin filament.

The work gives strong support to a longstanding hypothesis that ATP-driven shape changes within myosin heads generate motive force, but shows that cycles of distortion are also important.

Using acid to find direction

For a cell with signaling receptors distributed uniformly on its plasma membrane, deciding which direction to move in response to a stimulus is a serious problem. Earlier work traced this polarity decision to the amplification of phosphoinositide signaling at the cell’s leading edge. But on page 1087, Denker and Barber follow the signal back one step further, to the highly conserved ion exchange protein NHE1. The exchanger appears to be necessary not only for defining the front and rear of the cell, but also for coordinating events at the two ends.

The authors previously found that NHE1 is not only a sodium proton exchanger, but also a plasma membrane anchor for the cytoskeleton. Both functions are needed for PI-3 kinase activation and localization of ion exchange at the leading edge of lamellipodia.

In fibroblasts expressing a mutant form of NHE1 that is defective in ion translocation but retains the ability to anchor the cytoskeleton and localize to lamellipodia, focal adhesions appear to form, but they are not properly remodeled or disassembled. The result is fan-shaped lamellipodia and elongated cell tails, and an inhibition of migration. Cells expressing a form of NHE1 that is a functional ion transporter but defective in cytoskeletal anchoring and localization develop multiple pseudopodia extending in all directions, also slowing migration.

Others have shown that migratory receptors stimulate ion transport by NHE1, which should increase cytoplasmic pH at the leading edge and possibly activate actin-regulating proteins such as ADF/cofilin and gelsolin. As yet, changes in pH have not been seen in migrating cells, perhaps because the available techniques for measuring pH lack the necessary resolution. And other questions remain. It is not clear, for example, what determines the initial localization of NHE1 to the leading edge, or what signal NHE1 generates at the front of a cell to regulate events at the rear.