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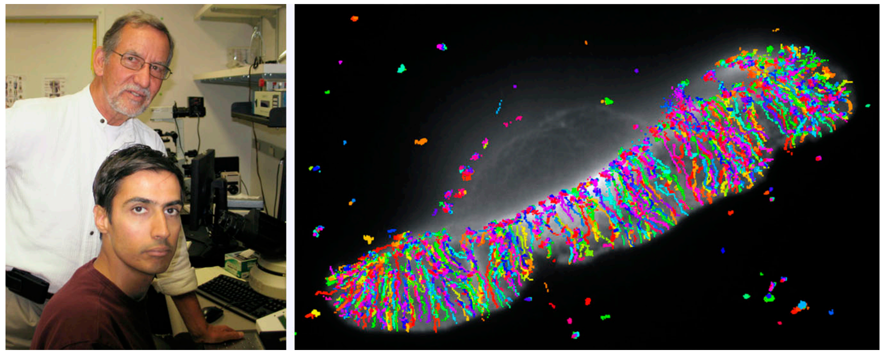
Myosins pull together—separately

Study suggests that asynchronous molecular motors can integrate their actions.

Focal Point



Sivaraj Sivaramakrishnan (foreground) and James Spudich put myosin VI motors through their paces. Their conclusion is that the molecules can team up to move cargo. The colored tracks on the diagram are the paths of laden myosin motors along the actin cytoskeleton.

Don't tell your high school football coach, but it is possible to have teamwork even if nobody's in charge. Inside a cell, for example, myosin VI motors work in concert to haul cargoes along the actin cytoskeleton, Sivaramakrishnan and Spudich reveal (1).

Instead of providing muscle power, myosin VI is one of the unconventional myosins whose job is intracellular transportation. Researchers have long suspected that myosin VI ferries endocytic vesicles away from the cell membrane along actin tracks (2). But the molecule's maneuvers inside cells are tricky to follow. In a study published in May (3), researchers first used detergent to bare the actin cytoskeleton, and then followed the movement of fluorescently tagged myosin dimers along the fibers. The results demonstrated for the first time that myosin VI travels from the plasma membrane toward the cell interior.

However, researchers still haven't gotten a grip on how these molecules move cargo. Myosin VI monomers are underachievers—they perform one power stroke while bound to actin and then fall off. A vesicle might get further using multiple myosins to remain attached to the actin track for longer. But myosin VI seems an unlikely team player. If one molecule in the team tried to jump forward along the actin and take the vesicle with it, the other myosins still attached to actin would hold the cargo back. These observations have prompted some scientists to argue that myosin VI is immobile in cells (4). Sivaraj Sivaramakrishnan and James Spudich used experiments and simulations to determine that multiple myosins can band together to produce forward movement.

> **"Our work shows that multiple myosin VI motors can coordinate to bring about long-range transport."**

The researchers first observed myosin VI dimers creeping along an actin network isolated from lamellipodia of fish keratocytes, a type of epidermal cell. The myosins lugged fluorescent nanospheres that simulated vesicles and made them easier to follow. Beads powered by one dimer could eke out about one micron before releasing. Beads hefted by 10 dimers crawled about 10 times as far, the entire span of the actin mesh.

To probe how myosin teamwork might keep cargo rolling, the researchers crafted a model that emulates transportation along a digitized version of the actin mesh from skin cells. The simulation showed that a pair of dimers could shift a payload long distances. Although a myosin monomer stagnates, what about a group of them? The model predicted that four monomers could progress about the same distance as two dimers, as long as each monomer was sufficiently flexible, allowing it to store and release energy like a spring. Whether myosins are connected or not, the model suggests, they can collaborate to move a load in the same direction. Experiments with dimer- or monomer-coated beads confirmed these predictions. Both arrangements toted the beads at about the same speed.

That leaves the question of whether large numbers of myosins put the brakes on vesicle movement. Nobody knows how many myosins cooperate to haul a cargo, but estimates suggest between 10 and 100. To find out whether so many motors are a drag, the team attached 100 dimers or 200 monomers to each bead. These myosin centipedes could still crawl, but they were slow, indicating that having excessive numbers of motors impedes transportation but doesn't halt it.

The work suggests that far from being immobile, myosin VI can pull off some impressive moves—as long as it gets help. "Our work shows that multiple myosin VI motors can coordinate to bring about long-range transport," says Sivaramakrishnan. Collaboration might also work for other unconventional myosins such as myosin V, which ships its cargo in the opposite direction as myosin VI, from the cell interior toward the plasma membrane.

Researchers still have much to learn about how myosins work together on real cargo in cells, including how many molecules collaborate, how they are arranged on the vesicle, and which proteins match a vesicle to its transporters. Also mysterious is how the load on an individual myosin transporter affects its behavior. The researchers plan to use a technique called single molecule optical trapping to answer this question.

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