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Cell's Motor Is a Mountain Climber, Not an Inchworm

Researchers have demonstrated that one of the most important molecular motors for moving cargo within the cell does so with the hand-over-hand motion of a mountain climber, rather than an inchworm-like motion.

Their discovery reveals new information about how the tiny motor, called kinesin, moves membrane components, messenger RNA, signaling molecules and other cargo along highways called microtubules within the cell.

"In a broad sense, a better basic understanding of the mechanisms of such motors will have implications for designing new anti-cancer drugs, as well as understanding the function of existing drugs that target these motors."

— Ronald D. Vale

Since similar motors are responsible for moving chromosomes during cell division, basic understanding of kinesin could inform development of cancer-fighting drugs that target the cancer cells machinery for reproduction, said the researchers.

The scientists published their findings December 18, 2003, in *Science Express*, the online version of the journal *Science*. They were led by Paul Selvin of the University of Illinois at Urbana-Champaign, and Howard Hughes Medical Institute investigator Ronald Vale at the University of California, San Francisco.

While most scientists believed that kinesin moved via a hand-over-hand mechanism, said Vale, some studies have indicated that it traveled in an inchworm-like mode. These two competing theories implied very different mechanisms of how the motility works, said Vale. And if it was an inchworm-like mechanism, our previous understanding of the motor and its structural mechanisms would be incorrect.

To distinguish between the two mechanisms, the scientists used a tracking technique developed by Selvin and the papers first author Ahmet Yildiz,

working in Selvin's laboratory. In this technique, fluorescence imaging one nanometer accuracy (FIONA), a fluorescent dye molecule is attached to the structure to be tracked, and the motion of the dye molecule is followed with great precision using a fluorescence-detecting microscope.

The kinesin molecule consists of two motor units (analogous to feet) that are linked together to a common stalk that attaches to transported cargo. Previous studies had shown that the kinesin molecule moves along the microtubule in steps of eight nanometers, or eight billionths of a meter.

The tracking technique developed by Paul and his colleagues is particularly effective for distinguishing between these two models because of the distinctive differences in how the models would predict the movement of the feet, said Vale. If the inchworm model is correct, then each foot should move only in eight-nanometer steps as the kinesin molecule's center of mass moves. However, if the kinesin molecule is moving in a hand-over-hand motion, then the rear foot should take a step forward of sixteen nanometers during one cycle, and then zero nanometers during the next cycle.

Indeed, Selvin and his colleagues detected approximately 16-nanometer motions of the labeled foot during a cycle. Although they could not measure movements of zero nanometers, they performed a statistical analysis of the timing of the kinesin molecule's steps, which indicated that one of the two feet did not move during a cycle.

So the evidence shows that there is an alternation of displacement from one step to the other, contradicting the inchworm model in which both feet are taking equal eight-nanometer steps, said Vale.

According to Vale, the new findings regarding kinesin — together with earlier findings from Selvin's laboratory about the motor molecule myosin V — offer new insights into the function and evolution of such molecules.

Not all motors are going to move by this mechanism, but what is unique about myosin V and kinesin is that both are utilized in the cell for long distance cargo transport, said Vale. So it makes a great deal of sense to have what is called a processive motor that can reliably and continuously travel long distances in a coordinated manner along a track.

Particularly interesting is that while the processive mechanisms of myosin V and kinesin are not identical, there are certainly many similarities between the two, said Vale. Many of these similarities were probably developed through convergent evolution, in which nature independently evolved a similar strategy for the same task.

While such findings about the mechanism of cargo-carrying kinesins do not have immediate clinical application, said Vale, similar kinesin-like molecules involved in cell division are the targets of new anti-cancer drugs that seek to thwart uncontrolled proliferation of cancer cells.

So, in a broad sense a better basic understanding of the mechanisms of such motors will have implications for designing new anti-cancer drugs, as well as understanding the function of existing drugs that target these motors, he said.

Future studies of the kinesin machinery will aim at using different kinds of fluorescent tags to capture more precise details of how the kinesin molecule changes its shape during the process of motion, said Vale.

Such studies involve attaching fluorescent molecules to different components of the kinesin molecule and measuring how the molecules transfer energy to one another as the molecule moves. Such energy transfer will reveal how the distance between components changes during motion, yielding clues to the mechanism of the molecules movement. These studies will get scientists one step closer to understanding the molecular details of one of the oldest quests in the biological sciences- how living organisms can generate purposeful motion.