Scientists discover how molecular motors go into 'energy save mode'

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Structural rendering of kinesin's two heads, called motor domains, cross-linked by a bound tail domain (green). Credit: Carnegie Mellon University

The transport system inside living cells is a well-oiled machine with tiny protein motors hauling chromosomes, neurotransmitters and other vital cargo around the cell. These molecular motors are responsible for a variety of critical transport jobs, but they are not always on the go. They can put themselves into "energy save mode" to conserve cellular fuel and, as a consequence, control what gets moved around the cell, and when.

A new study from Carnegie Mellon University and the Beatson Institute for Cancer Research published in the Aug. 12 issue of *Science* describes

how the motors fold in on themselves, or save energy, when their transport services aren't required. According to the researchers, the solution to this molecular puzzle provides new insight into how molecular motor proteins are regulated, and may open new avenues for the treatment of various neurodegenerative diseases, such as Alzheimer's and Huntington's.

"Molecular motor proteins play a major role in all eukaryotic cells, but they are particularly critical to nerve cells," said David Hackney, professor of biological sciences in the Mellon College of Science, and one of the paper's authors. "Nerve cells have this special problem where proteins, such as receptors for neurotransmitters, get synthesized in the cell body and have to be shipped all the way down the axon. Problems in this transport system may play a role in a number of neurological conditions."

Hackney focuses his research on kinesin-1, the principle motor protein that moves cargo from the nerve cell body down the axon. A typical kinesin molecule has two tails on one end that attach to the cargo and two globular heads on the other end that crank along fibers inside the cell called microtubules, pulling the cargo forward. The movement of the heads, or motor domains, is fueled by the breakdown of ATP, a molecule that stores the energy that drives cellular work. When cargo isn't attached, kinesin folds in upon itself to prevent ATP from being squandered. Although scientists knew that one tail binds to the two heads to keep it in a folded "autoinhibited" state, the molecular mechanism remains unclear. Several possibilities have been proposed, but these latest findings suggest only one solution.

Hackney worked with Hung Yi Kristal Kaan and Frank Kozielski at the Beatson Institute for Cancer Research in Glasgow, Scotland, who crystallized a key portion of the kinesin molecule — a tail that was bound to the heads. The crystal structure confirmed that the complex

contained two head domains and only one tail domain. Hackney then carried out biochemical manipulations to determine precisely how the tail interacts with the heads, which turned out to be what the authors refer to as a "double lockdown."

"It was actually a big surprise," Hackney said, "because it ruled out all of the obvious things that had been proposed for how the tail domain autoinhibits the motor domain. It does not cause a conformational change, and it does not block the surfaces that interact with ATP or the microtubular track."

Kinesin's heads are typically joined together at one spot, called the hinge. In the new structure, the heads swing in toward each other and are bridged by the tail domain, effectively cross-linking the heads at the site of tail binding. This double lockdown — at the hinge and at the bridge — prevents the heads from separating. Because the heads need to be separate from each other to break down ATP, the double lockdown effectively stops the molecule from generating fuel to power the motor.

The researchers suggest that other kinesins may be regulated by the same autoinhibitory mechanism. Humans have dozens of different kinesin motors that transport a variety of cargo, including proteins associated with Alzheimer's, Huntington's and Parkinson's diseases. Kinesins are also involved in separating chromosomes during cell division, making the motors a target for cancer therapies that seek to stop the motors from transporting chromosomes, which would prevent cancer cells from multiplying.

Provided by Carnegie Mellon University

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