From wimp to jock: How a cell motor gets pushy

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This artist's conception -- which will be the cover art for the April 16 issue of the journal *Cell* -- shows three molecular motors that help move cells and things inside them. The details of how such motors work are outlined in a new study by University of Utah biophysicist Michael Vershinin and colleagues in California and New York. Each motor, a protein named dynein, looks like a pair of doughnuts with legs. The first two motors have two other proteins attached to them: LIS1, which looks like a pair of olives, and NudE, which looks like a rope or leash holding the LIS1 "olives" to the dynein molecule. Because the first two motors have the two other proteins attached, they are strong enough to move along a microtubule, essentially a "road" within the cell (extending from center bottom to center right in the illustration). But the third motor lacks the other two proteins, and thus is unable to stay on the "road" or move bigger objects. Credit: For Cell by David Meikle, University of Utah.

A University of Utah researcher helped discover how a "wimpy" protein motor works with two other proteins to gain the strength necessary to move nerve cells and components inside them. The findings shed light on brain development and provide clues to a rare brain disorder that often kills babies within months of birth.

"It's like the 'Transformers' films: You start with this puny little car and it becomes a big robot capable of moving big things," says biophysicist Michael Vershinin, a coauthor of a new study to be published Friday, April 16 in the journal *Cell*.

Vershinin, an assistant professor of physics, and his colleagues in New York and California uncovered details of how two proteins - named LIS1 and NudE (for nuclear displacement protein E).- bind to and strengthen another protein named dynein, which serves as a motor to move components around inside cells and, at times, to move the cells themselves. A cell contains hundreds to thousands of these microscopic motors.

"We found these two proteins, NudE and LIS1, make a special arrangement with dynein," Vershinin says. "All three can bind together, and NudE and LIS1 conspire to get dynein to move heavy objects like the nucleus more efficiently in the cell. Dynein is kind of wimpy. If you pull on it hard enough, it tends to give up pretty easily. With NudE and LIS1 in place, it doesn't."

Mutant LIS1 has been linked previously to the classic form of lissencephaly, a devastating brain malformation due to defective migration of nerve cells within the developing brain. The disorder occurs in about one in 100,000 live births.

Lissencephaly means smooth brain and is characterized by a lack of development of brain folds and convolutions. There are about 20 forms,

including at least three caused by defective genes. Viral infections and inadequate blood flow are other causes. Mutant LIS1 is present in more than half of lissencephaly cases, Vershinin says.

Infants born with the disorder suffer severe mental retardation, seizures and early death, as well as a small head, failure to thrive and malformed fingers and toes. Newborns with lissencephaly generally live only months. Few survive into their teens.

The new study analyzed dynein, NudE and LIS1 in laboratory glassware, not in animals, so "much work remains to link our findings to the full complexity of what happens in cells," Vershinin says. "This is several layers away from any clinical advance."

Nevertheless, "I hope someday it [the new findings] will mean we can design a therapy or drug that will help," he adds. "If we understand what can possibly go wrong [with the cell motors during cell migration], then we can design a therapy."

Vershinin conducted the study with biochemist Richard McKenney, a graduate student in cell biology at Columbia University in New York; theoretical biophysicist Ambarish Kunwar, a postdoctoral researcher at the University of California, Davis; Richard Vallee, a professor of pathology and cell biology at Columbia; and biophysicist Steven Gross, a professor of developmental and cell biology at University of California, Irvine. Vershinin worked with Gross at Irvine before joining Utah's faculty.

Understanding How Dynein Motors Work

"If you can understand the details of how motors are controlled, you can hope to understand how things get distributed and moved in cells," Vershinin says.

"By analogy, if you have a house, come in, find the lights are out and you're looking for the light switch and circuit breaker, you want to know how everything is arranged. What we had originally [in understanding cell motors] were a bunch of parts. We didn't know exactly how they were laid out and exactly what they did in the cell."

The new study "clarifies that to a certain extent," he says.

Researchers already knew the dynein motor, a protein molecule, "basically looks like two donuts with legs," Vershinin says. "They can move step by step along a 'road' [inside cells] called a microtubule."

In general, dynein motors move various cell parts along the microtubule "roadways" and toward the nucleus. Another kind of motor, known as kinesin, moves things away from the nucleus and toward the cell periphery.

Vershinin says when one cell signals another chemically, dynein pulls the incoming chemical signal from the cell membrane into the cell. When cells divide, dynein motors help them divide neatly and evenly. Dynein and kinesin help distribute energy-producing mitochondria where needed within cells.

Without molecular motors inside, "a cell is like a city without cars and trucks: dead," says Vershinin. "Moreover, it's not always about moving small things around. Sometimes a cell needs to move large things like its nucleus, and sometimes a cell itself needs to move, and such processes often need motors. If motors do not work properly that is often either the cause or a key consequence of a disease."

Previous research suggests that Alzheimer's disease, other dementias and Parkinson's disease all involve disruption of the kinesin motor, and, to a lesser extent, disruption of the dynein's ability to stay on the microtubule

"road," Vershinin says.

Getting Horsepower for Big Jobs

There are different kinds of dynein motors. The new study involved cytoplasmic dynein, the motors within cells. Other kinds are found in cilia and in the flagella bacteria use to swim. Vallee's laboratory discovered cytoplasmic dynein more than a decade ago.

Vallee's team previously showed that dynein, LIS1 and NudE "worked together in very young neurons, and were key to these neurons moving into their proper positions in the developing brain" - like caterpillars using internal muscles to crawl," Vershinin says. "But the question remained: how do these proteins work together?

In the new study, "we have clarified how these proteins interact and found a few previously unknown but crucial details," Vershinin says.

Researchers previously knew that LIS1 and NudE bind to the dynein motor, but "until our study it was not clear how this binding worked," and how the three proteins interacted, he says.

"Arguably, the most important finding is that the dynein motor alone does not withstand load very well. It gives up pretty fast. So that's bad if you are trying to move large objects inside of cells and if you eventually try to move the entire cell," says Vershinin. But dynein plus the other two proteins "hang on under load much longer."

He says the study is significant because it shows "that dynein's mode of force production and motor activity can be regulated in very sophisticated ways."

Another key finding is that "LIS1 binds to dynein only at a specific time

when its binding is crucial for moving large cargoes," and it helps dynein stay on the microtubule "road," he says.

Vershinin says the researchers believe NudE holds LIS1 in place so it is available to bind to dynein when needed, and so it doesn't diffuse away when not needed.

"It's like a little leash," Vershinin says of the NudE protein.

Provided by University of Utah