Biologist modifies theory of cells' engines

December 11 2008

Biologists have known for decades that cells use tiny molecular motors to move chromosomes, mitochondria, and many other organelles within the cell, but no one has been able to understand what "steers" these engines to their destinations. Now, researchers at the University of Rochester have shed new light on how cells accomplish this feat, and the results may eventually lead to new approaches to fighting pathogens and neurological diseases.

Michael Welte, associate professor of biology, shows in a paper published in today's issue of Cell that the mechanisms that control the molecular motors are quite different from what biologists have previously believed. Before these findings, scientists assumed that the number of motors attached to an organelle determined how far and fast the organelle could travel, but Welte and colleagues have discovered that it is not the number of motors, but yet-to-be-discovered molecules that are likely the master regulators.

"The fact that motor number has nothing to do with regulating transport is extremely surprising, and somewhat unsettling to people working in vitro," says Welte. "It says we're really missing something when we study these motors only in the test tube instead of in a living cell."

Intracellular transport is crucial to a cell's health, says Welte. For instance, during cell division, one copy of each of the cell's chromosomes migrates to one side of the cell while the other copy moves to the other side. If this movement is disturbed, it could cause an imbalance of chromosomes in the daughter cells, which might die or become cancerous. Similarly, neurons, some of which are as much as three feet in length, manufacture proteins and organelles at one end and then must move that precious cargo all the way to the far end where they'll be used. This is an enormous task, says Welte, and defects in this transport are thought to cause a number of neurological diseases.

Given the difficulty of investigating these tiny motors acting within the cell, biologists have performed basic experiments on them outside of the cell in a carefully controlled environment. This led them to believe that the speed and distance an organelle could be transported depended on how many motors were pulling it, says Welte. Thus, the scientists reasoned, perhaps the cell simply attaches the right number of motors to an organelle to send it the right distance. Although this "multi-motor" hypothesis is very simple and elegant, says Welte, whether it actually holds true within living cells had never been tested.

Welte's graduate student, Susan Tran, decided to perform that test. She created fruit-fly eggs lacking a type of molecular motor called kinesin and found that certain organelles stopped moving—strong evidence that kinesin is responsible for their transport. Tran then made another type of mutant eggs, this time ones that produced only about half the number of kinesin motors of a regular egg. In both types of eggs, organelles were transported with the same speed and the same distance.

Welte needed to know if this equality was because the normal egg was simply utilizing only half the available kinesin motors, or if some master regulator was controlling the organelle's progress, regardless of the number of motors moving it. To do this, Welte turned to Steven Gross, associate professor of developmental and cell biology at the University of California. Gross' group uses an apparatus called "optical tweezers" that employs laser light to measure the tiny forces the motors generate. The team found that organelles in regular cells are pulled with twice the force of Tran's mutant, low-kinesin cells.

"That clinched it for us," says Welte. "Yes, there are multiple motors moving organelles around, but exactly how many doesn't matter. There is something else in the cell that's controlling all the motors. That opens up a big area for research—find what's driving these motors and maybe we can control them all by controlling one thing."

Welte and his team are now looking at where in the cell this signal comes from and how it influence the motors. Although Welte's team studied fruit fly eggs, the motors moving the organelles are present in all animals and employed for many tasks, including transport in human neurons.

Welte also points out that viruses, including HIV, make use of the same kind of motors to move about the cell, first to get from the site of penetration to the nucleus, where they multiply, and then to get progeny viruses back to the cell surface. If Welte and others can figure out how cells normally control these motors, it may be possible to prevent HIV from taking control of the motors and thus to keep it, and other intracellular pathogens, at the edge of the cell where they can do little harm.

Source: University of Rochester