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## A New Way of Looking at Molecular Motors

An innovative method of categorizing myosin—one of three molecular “motors” that produce movement within the cells of the body—has dramatically increased the amount of information available about these essential proteins. The studies lay the groundwork for development of treatments for conditions ranging from certain kinds of blindness and kidney disease to neurodegenerative disorders and parasitic diseases such as malaria.

All complex organisms use myosin and its relatives, kinesin and dynein, to move substances around inside cells and to help cells move from one place to the other. Myosins also help parasites enter and infect hosts. Defects in the motors play a role in a variety of human and animal disorders, including retinitis pigmentosa (which causes blindness), polycystic kidney disease, brain development defects, neurodegenerative diseases, muscular dystrophy, skin pigmentation problems, and genetic hearing loss.

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Researchers led by Dominique Soldati, a Howard Hughes Medical Institute (HHMI) international research scholar at the University of Geneva in Switzerland, have developed a new system of classifying myosins. Up to now, researchers have only studied approximately 130 myosins at a time. The new system includes 250 myosins and increases the number of myosin subclasses from 18 to 24, enabling researchers to better understand each myosin's function.

“Myosins that belong to the same class work in similar ways but can have very different functions,” explained Soldati. “We will have to discover the myosins' functions one by one, and the better we understand how they are related, the faster that will occur.”

The new classification system also describes common evolutionary links between subclasses and protein components within myosins themselves. It includes myosins from insects, algae, parasites, and animals that have not been studied before.

The work will appear in the *Proceedings of the National Academy of Sciences*, with advance online publication February 6, 2006. Bernardo Foth, a postdoctoral fellow in Soldati's laboratory, is the first author.

Soldati and Foth became interested in myosins after they discovered that the molecular motors enabled toxoplasmosis and malaria parasites to force their way into human cells.

The researchers say that although their research is theoretical and a long way from clinical applications, the new classification system will help other researchers address important biomedical puzzles more precisely.

“We hope our work will help scientists ask the right questions and perform the right kind of experiments on myosins,” Foth said. “In the long term, that could lead to new drug targets being discovered more quickly.”

Molecular motors run on tracks, like trains, using chemical reactions that involve the chemical compound adenosine triphosphate (ATP) for fuel. Myosin runs on the filaments of actin, a protein found in muscle cells, but kinesins and dyneins use microtubules, which are hollow protein structures inside the cell, as their track.

Movement is created several ways. Biological cargo is transported within cells by single motors that run backward and forward, the way a person moves hand over hand along a rope. Making muscles contract involves a large number of motors that work very fast in neatly arranged teams, quickly letting go of the track once they have completed their “power stroke.”

Most molecular motors have a head, a neck (which powers movement), and a tail. Myosins usually look like two-headed snakes, kinesins like hairpins with a head at each end, and dyneins like three-headed flowers with one stem. Soldati and Foth have confirmed that the motor neck and tail evolved together. That finding helped them define some of their new categories.

Organisms employ all three types of motors at the same time, but in different proportions. For example, yeast uses six kinesins, five myosins, and one dynein while mammals have genes for more than 40 kinesins, 40 myosins and more than a dozen dyneins.

Genetic and acquired defects in the motors cause disease by preventing developing cells from migrating to their necessary destinations before birth or by preventing parts of the body, such as sperm tails or the tiny hairs that keep mucus flowing in the lungs, from moving when they are supposed to. The motors in parasitic organisms contribute to disease by enabling the parasites to break through biological barriers within the human body and actively invade cells.

So far, molecular motors have been found in all organisms but bacteria, red algae, and the parasite *Giardia*. The new myosin classification system should help cell biologists, biochemists, biophysicists, parasitologists, and medical researchers make advances in a wide variety of fields, from veterinary medicine to tropical diseases.

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