Scientists Determine 3-D Structure of Myosin: a Muscle Protein Critical to Life

La Jolla, CA. July 2, 1993 -- In the culmination of a 10-year collaborative effort, researchers have determined the three-dimensional structure of myosin, a muscle protein essential for breathing, movement and blood flow in humans and animals. Using x-ray crystallography, a technique in which x-rays probe the structure of crystals of pure protein, the scientists determined the structure of a critical portion of myosin down to the precise arrangement of its individual atoms. Their results are described in two articles in the July 2, 1993, issue of Science.

"Human motion, indeed the breath of life, depends on the contraction of skeletal muscle," says Dr. Richard Lymn, Director of the Muscle Biology Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, which supported much of this research. These results, he says, "further our understanding of the inner workings of the molecular motors responsible for muscle power."
Myosin is a "molecular motor," harnessing chemical energy to generate motion the way an engine uses gasoline to make a car move. A second protein, actin, makes up the "roadways" or "tracks" along which the molecular motors travel. Found in all animals as well as plants and fungi, myosin and actin power diverse types of movement ranging from the transport of substances within individual cells, to cell division and contractions of the heart and body muscle.

Myosin makes it possible for single cells to move within the body, aiding processes such as blood clotting, wound healing and response to infection. The energy required for this is produced when myosin burns a chemical fuel, adenosine triphosphate (ATP), which is produced from the food we eat.

"The primary importance of the findings reported here lies in our understanding of how the molecules in muscle use energy to produce force and motion," says Dr. Lymn. "Since motion is essential to human activity and energy balance is important for health, these studies are basic to understanding both normal body function and musculoskeletal fitness."

The three-dimensional structure of the portion of myosin that generates motion is described in an article by Dr. Ivan Rayment and his colleagues at the University of Wisconsin, Madison, and the Robert Wood Johnson Medical School, Piscataway, New Jersey. This work is a significant advance because myosin has more complex functions and is larger than most proteins that have been studied by crystallographic techniques. "It took almost six years to work out a way to get good crystals; it took another three years to solve the crystal structure," says Rayment. In fact, researchers have been trying to crystallize myosin since the 1960s.
In a second article in the same issue, this detailed picture of myosin and a similar picture of actin were combined with information obtained by examining muscle filaments at very high magnification in an electron microscope. "X-ray methods give us extremely detailed pictures of the individual muscle components but provide no information about the way in which the components fit together to form a muscle filament. This type of information is provided by electron microscopy. Taken together, these efforts are a big step forward in allowing scientists to understand how muscles, including the heart, function at the molecular level," according to Dr. Ronald Milligan, explaining the synergistic relationship of the two methods used in the work.

Milligan's group at The Scripps Research Institute in La Jolla, Calif., together with Dr. Kenneth Holmes and colleagues at the Max Planck Institute in Heidelberg, Germany, collaborated with the researchers at University of Wisconsin on this study.

The result is a view of one stage in the interaction of the molecular motor and its track. The work "sets forward a structural model of how chemical energy gets changed into movement," says Rayment. "Many details are still missing from the model but having the crystal structure of myosin is exciting because it allows us to test our model in future studies. This will help us understand all processes that use myosin-based motors."

The results of these two papers fill a gap in understanding the workings of molecular motors and muscle contraction. Skeletal muscle, the most studied site of myosin action, has a highly ordered structure made up of multiple repeats of the basic unit, the sarcomere. The contractile machinery of the sarcomere consists of alternating rows of thin filaments containing actin and thick filaments containing myosin. During contraction, the portion of the myosin that sticks out from the thick filaments -- the part
studied in the papers discussed here -- grabs onto a neighboring thin filament and pulls, causing the sarcomere to shorten. The motion of individual actin and myosin proteins generates forces that add up to produce whole body motion and strength.

Muscle function is essential for eating, breathing, moving and pumping blood through the body. Laboratory studies on invertebrates have shown that serious defects in the contractile proteins are lethal, and this is presumably true for humans as well. Some rare diseases, such as familial hypertrophic cardiomyopathy (FHCМ) -- a heart condition that is the leading cause of sudden death in apparently healthy, young athletes -- are caused by defects in myosin.

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