SOUTHWESTERN NEWS

EMBARGOED FOR THURSDAY, AUG. 20 AT 5 p.m. EDT

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UT SOUTHWESTERN RESEARCHERS FIND GENETIC SWITCH THAT EXPLAINS EFFECT OF EXERCISE ON MUSCLES

DALLAS — Aug. 20, 1998 — The creation of a drug that would mimic some of the health-promoting benefits of regular exercise could be possible because UT Southwestern Medical Center at Dallas researchers have found a genetic switch that tells muscles how to behave.

UT Southwestern scientists have found the molecular pathway that tells muscle fiber to be either the fast strength muscle seen in weight lifters or the slow endurance muscle developed by aerobic enthusiasts. Using cultured muscle cells, investigators, led by Dr. R. Sanders Williams, chief of cardiology and director of the Frank M. Ryburn Jr. Cardiac Center, delineated a biochemical-signaling mechanism that converts one muscle-fiber type to another. The findings were reported today in the journal of *Genes and Development*.

This discovery could make it possible to restore endurance muscle tissue in people who have lost it due to congestive heart failure. People with diabetes might also benefit from a drug that would enhance slow endurance-promoting muscle, which is more sensitive to insulin.

"We believe this pathway provides a molecular explanation for the important effects of aerobic exercise in increasing physical endurance and reducing risk for cardiovascular disease," Williams said. "When people go jogging, molecular events happen in the muscles they are exercising that both enhance their capability to exercise further and improve their health.

"We have shown both in cultured cells and in animals that there is a signaling pathway we can modify to stimulate or reverse what exercise does naturally. We believe it is possible to design a drug which would have this effect."

The study provides evidence that three proteins called calcineurin, NFAT (Nuclear Factor of Activated T cells) and MEF2 (Myocyte Enhancer Factor 2) participate in a pathway that activates a specific subset of genes. These regulatory factors act in concert to control the

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abundance of proteins found in slow, oxidative skeletal-muscle fibers characteristic of highly fit endurance athletes. When a muscle is tonically active, during jogging for example, the concentration of calcium ions is increased within the muscle cell. When the calcium level stays high for a sustained period of time it turns on calcineurin, which modifies NFAT so that it moves from the cytoplasm to the cell nucleus. Once NFAT reaches the nucleus, it partners with MEF2 and other proteins to turn on the genes specific for slow, oxidative muscle fibers.

The scientists will investigate further to clarify how this calcium-regulated, calcineurin-dependent pathway affects other muscle types and how it interacts with other cellular activities. This will help them learn if this molecular pathway for converting fast muscle cells to slow muscle cells works the same in humans and if it can be used for a pharmaceutical solution for those unable to exercise.

Other researchers involved in the study were internal medicine postdoctoral fellows, Dr. Eva Chin and Dr. Weiguang Zhu; Dr. Eric Olson, chairman of molecular biology and oncology, director of the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer, and holder of the Nancy B. and Jake L. Hamon Distinguished Chair in Basic Cancer Research; Dr. James Richardson, associate professor of pathology; Dr. Rhonda Bassel-Duby, associate professor of internal medicine; cell and molecular biology graduate student Hai Wu; and internal medicine researcher scientists Caroline Humphries and John Shelton. Williams also holds the James T. Willerson, M.D., Distinguished Chair in Cardiovascular Diseases

Grants from the Dallas Sweetheart Ball and the National Institutes of Health supported their research.

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