Scientists discover genetic switch that increases muscle blood supply

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University of Texas Health Science Center at Houston (UTHealth) researchers Vihang Narkar, Ph.D., and Sabina Lorca are among the authors of a preclinical study that has implications for the treatment of the most severe form of peripheral artery disease. Credit: The University of Texas Health Science Center at Houston (UTHealth)

Many people suffer from a devastating condition known as critical limb ischemia (CLI) that can lead to muscle wasting and even amputation. The disease is linked to the blockage of blood flow to the skeletal muscle and current treatment options include rehabilitative exercise and surgical bypass of blood vessels. New preclinical research suggests there may be a way to restore blood supply in skeletal muscle without traditional intervention.

Scientists at The University of Texas Health Science Center at Houston (UTHealth) and the Salk Institute for Biological Studies announced in the March 2 print issue of the journal Cell Metabolism that they have identified a genetic switch that can increase the number of blood vessels in the skeletal muscle of non-exercising mice.

Skeletal muscle is composed of two types of fibers: slow twitch fibers that inherently have a dense supply of blood vessels and fast twitch fibers that have fewer blood vessels. The researchers used a gene switch known as estrogen-related receptor gamma (ERR gamma) that when activated in fast twitch fibers of mice by genetic engineering, converts these fibers into slow twitch fibers.

"This consequently resulted in a striking increase in muscle blood supply as measured by imaging and angiography," said Vihang Narkar, Ph.D., lead investigator and assistant professor of molecular medicine at the UTHealth Medical School. "These genetically-transformed muscles also acquire other characteristics of slow muscles, such as improved metabolic capacity and fatigue resistance that can be additionally beneficial in resolving muscle vascular disease."

Narkar, whose UTHealth laboratory is in the Center for Diabetes and Obesity Research at the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, said, "The identification of the estrogen-related receptor gamma vascular switch will open potential therapeutic avenues for treating CLI and other cardiovascular diseases linked to defective blood supply."

Colin Barker, M.D., assistant professor of cardiology at the UTHealth Medical School, said new research is needed to help people with peripheral artery disease, particularly those with the most severe form - critical limb ischemia. "Poor circulation in the legs can lead to muscle wasting, infections, severe pain and amputation," he said. "Dr. Narkar's

work potentially has many useful applications. It is very much in the translational medicine arena."

"Understanding the gene network that specifies high vascular supply to muscle gives us a new and very powerful tool to promote improved muscle performance and the promise of fitness, especially for those who cannot work out," says Ronald M. Evans, Ph.D., senior author, Howard Hughes Medical Institute Investigator and professor in the Salk's Institute's Gene Expression Laboratory. "This is good news for people with heart disease, frailty, peripheral vascular disease and more generally those who have a variety of medical problems where exercise could be helpful but is not possible to achieve."

In 2010, an estimated 2.8 to 3.5 million U.S. citizens suffered from critical limb ischemia, according to a report by THE SAGE GROUP, an independent research and consulting company specializing in peripheral artery disease. CLI risk factors include diabetes, obesity and smoking.

"Exercise is an important part of any intervention strategy to prevent or treat diabetes mellitus and obesity," said Perry Bickel, M.D., associate professor of medicine at the UTHealth Medical School and director of the UTHealth Center for Diabetes and Obesity Research. "Results by Drs. Narkar and Evans support the notion that in the future we may be able to design drugs that produce the benefits of exercise in order to counteract the damage that diabetes and obesity cause to the body, such as blockages of blood vessels."

Narkar and Evans collaborated on a highly-publicized study published in the journal *Cell* in 2008 in which they used two investigational exercise mimetic drugs – GW1516 and AICAR – to increase the endurance of non-exercising mice. These drugs target different genetic switches, namely PPAR delta and AMPK.

More information: "Exercise and PGC1-alpha-Independent Synchronization of Type I Muscle Metabolism and Vasculature by ERR gamma," *Cell Metabolism*.

Provided by University of Texas Health Science Center at Houston