New study finds a genetic basis for muscle endurance in animal study

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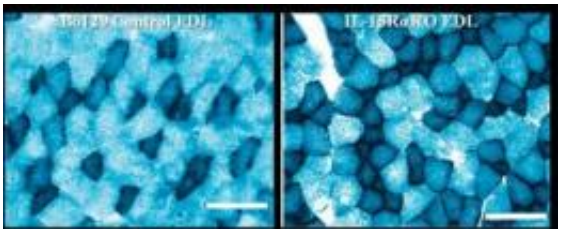

Muscles from mice lacking IL-15R-alpha and control mice were processed for presence of a mitochondrial marker. The mice lacking IL-15R-alpha show a greater number of darkly stained muscle fibers (right), indicating an increase in their mitochondrial content caused by reprogramming due to the lack of IL-15R-alpha. Credit: Emidio E. Pistilli, PhD, & Tejvir S. Khurana, MD, PhD, Perelman School of Medicine, University of Pennsylvania. Image is based on a Figure from Pistilli et al. 2011. *Journal of Clinical Investigation*.

Researchers at the Perelman School of Medicine at the University of Pennsylvania have identified a gene for endurance, or more precisely, a negative regulator of it. Not having the gene relates to greater endurance in the knockout mice that were studied. The investigators also showed that the gene is linked to Olympic-level athletes in endurance sports such as swimming compared to athletes in sprint sports such as the 100-meter dash. The study appears online this week in the *Journal of Clinical Investigation*. The work has implications for improving muscle performance in disease states including metabolic disorders, obesity, and aging.

"We have shown that mice lacking the gene run six times longer than control mice and that the fatigable muscles of the mouse -- the fast muscle in the front of the leg -- have been reprogrammed and are now fatigue-resistant," explains senior author Tejvir S. Khurana, MD, PhD, professor of Physiology and member of the Pennsylvania Muscle Institute. "This has wide ramifications for various aspects of muscle biology ranging from athletics to treating muscle and metabolic diseases."

The gene codes for a protein called Interleukin-15 receptor-alpha (IL-15R-alpha), which acts alone or in conjunction with the IL-15 protein. IL-15R-alpha is important in the immune response, but it also has other functions. IL-15 and IL-15R-alpha have been implicated in muscle physiology, but the exact role in muscle function has not been defined.

"We found a previously unrecognized role for IL-15R-alpha in defining muscle function, and manipulation of this gene has the potential to improve muscle performance in disease states including metabolic disorders, obesity, and aging." says lead author Emidio E. Pistilli, PhD, who was a postdoctoral researcher at Penn and is now an assistant professor in the Division of Exercise Physiology at the West Virginia School of Medicine.

Slow Vs. Fast

Slow muscles are used for endurance and fast muscles are used for speed. The champion fast muscles are the muscles moving the eye, but they are also fatigue-resistant, the only muscles like this.

In the IL-15R-alpha knockout mouse used in this study, fast muscles behave like slow muscles. These mice ran 6.3 times greater distances and had greater ambulatory activity than controls. Their fast muscles

displayed fatigue-resistance and slower contractions compared to fast muscles in control mice.

They also showed that the loss of IL-15R-alpha induces a shift in how energy is burned in fast muscles, substantially increasing fatigue resistance and exercise capacity.

The molecular signature of the muscles in the knockout mice included a greater number of active transcription factors, which indicates more muscle fibers with more mitochondria, and the machinery to better process calcium since this chemical drives muscle contraction. Mitochondria are the energy storehouses of the cell.

Morphologically, the fast muscles had a greater number of muscle fibers, smaller fiber areas, and a greater number of nuclei per fiber. The alterations of physiological properties and increased resistance to fatigue in the fast muscles are consistent with a shift towards a slower, more oxidative muscle type in the knockout mice.

The study also found significant associations between the gene and elite endurance athletes and hence supports the possibility that these athletes had a genetic predisposition or advantage.

From these two lines of evidence, the researchers concluded that IL-15R-alpha plays a role in defining the function of fast skeletal muscles.

Importantly, the study demonstrates that muscles can be reprogrammed to perform much better at endurance sports and hence IL-15R-alpha manipulation is of great importance from an athletic doping standpoint as currently it is neither tested for nor do methods exist to detect its misuse by athletes. The investigators are working toward this.

This research identifies a "druggable target" that allows possible

reprogramming of muscle function by increasing genes, proteins and pathways typically expressed in slow or fatigue-resistant muscle, similar to adaptations seen after endurance exercise. It is widely accepted that these types of adaptations would be beneficial or protect against obesity, diabetes and aging and may help ameliorate pathology in myopathies such as muscular dystrophy. Hence, say the researchers, the identification of this pathway should facilitate better understanding of these diseases and aid in the development of rational therapies drugs for these disorders.

From a translational research point of view the team will test the role IL-15R-alpha plays in obesity, diabetes, aging, and muscle diseases, as well as develop methods to harness the therapeutic potential of it for patients.

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