

# 'Marathon mice' elucidate little-known muscle type

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Researchers report in the January issue of the journal *Cell Metabolism*, published by Cell Press, the discovery of a genetic "switch" that drives the formation of a poorly understood type of muscle. Moreover, they found, animals whose muscles were full of the so-called IIX fibers were able to run farther and at higher work loads than normal mice could.

The findings could ultimately lead to novel drugs designed to change the composition of muscle, the researchers said. Such treatments might have the potential to boost physical strength and endurance in patients with a variety of muscle wasting conditions.

The research team, led by Bruce Spiegelman of Harvard Medical School, found that increasing activity of the gene known as PGC-1 $\alpha$  in the skeletal muscles of mice caused them to become crowded with IIX muscle fibers, which are normally much less prevalent.

"One reason why less is known about IIX fibers is that no one muscle group is packed with them," Spiegelman said. "For the first time, we have a mouse model very enriched in IIX fibers. These mice show a greatly increased capacity to sustain physical activity."

Skeletal muscle converts chemical energy into motion and force, ranging from rapid and sudden bursts of intense activity to continuous low-intensity work, the researchers said. At one functional extreme, muscles such as the soleus--a broad, flat muscle found in the calf of the leg--perform slow but steady activities such as maintaining posture. At

the other extreme, muscles such as the quadriceps typically perform intense and rapid activities.

To fulfill these varied roles, muscles vary in their proportion of "slow-twitch" muscle fibers (types I and IIA), ideal for slow and constant roles, and "fast-twitch" fibers (type IIB), better suited to rapid and sudden activity of shorter duration. The fiber types are defined by which "myosin heavy chains" (MHCs) they contain and by their metabolic capacity, a feature largely determined by the number of energy-producing mitochondria they house. Myosins are motor proteins that consist of both "heavy" and "light" amino acid chains.

While most muscles in mammals contain a mixture of slow- and fast-twitch fiber types, some muscle beds are enriched for one type or the other, Spiegelman said. However, adult skeletal muscles also contain fibers with an abundance of a fourth MHC, type IIX, about which much less is known.

IIX fibers seem to have the oxidative metabolism of slow-twitch fibers mixed with the biophysical properties of fast-twitch fibers. Oxidative metabolism is by far the most efficient way of generating energy, Spiegelman said.

In the current study, the researchers produced mice with higher than normal levels of the transcriptional coactivator PGC-1 $\alpha$  in their skeletal muscles. Transcriptional coactivators work with other cellular factors and machinery to control the activity of other genes. While earlier studies had found that the related coactivator PGC-1 $\alpha$  plays a role in determining muscle type, the role of PGC-1 $\alpha$  wasn't known.

"The muscle from the PGC-1 $\alpha$  transgenic mice was strikingly redder in appearance than wild-type controls," indicative of their increased mitochondrial content, the researchers now report. Upon further

examination, the researchers were surprised to find that the fibers showed a reduction in I, IIA, and IIB MHCs and as much as a 5-fold increase in IIX MHC.

Nearly 100% of muscle fibers in the transgenic animals contained abundant MHC IIX mRNA and protein, they found, as compared to only 15%–20% in normal animals. PGC-1 $\alpha$  also changed the muscles' metabolic characteristics by driving the activity of genes that spark proliferation of mitochondria.

The PGC-1 $\alpha$  animals with more IIX muscle fibers showed a greater capacity for aerobic exercise, they found. Transgenic mice were able to run, on average, for 32.5 min to exhaustion, compared to 26 min for their normal littermates, Spiegelman's group reported.

"These data have potential importance for the therapy of a number of muscular and neuromuscular diseases in humans," Spiegelman's group concluded.

"Many conditions accompanied by loss of physical mobility, including paraplegia, prolonged bed rest, and muscular dystrophies, involve a loss of oxidative fibers and their replacement with glycolytic fibers. This, in turn, results in a further loss of resistance to fatigue, exacerbating the patient's condition in a downward spiral. The identification of PGC-1 $\alpha$  as a potential mediator of the development of oxidative type IIX fibers suggests new ways to modulate muscle fiber type in health and disease."

Citation: Arany et al.: "The Transcriptional Coactivator PGC-1 $\beta$  Drives the Formation of Oxidative Type IIX Fibers in Skeletal Muscle."

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