Scientists find power switch for muscles

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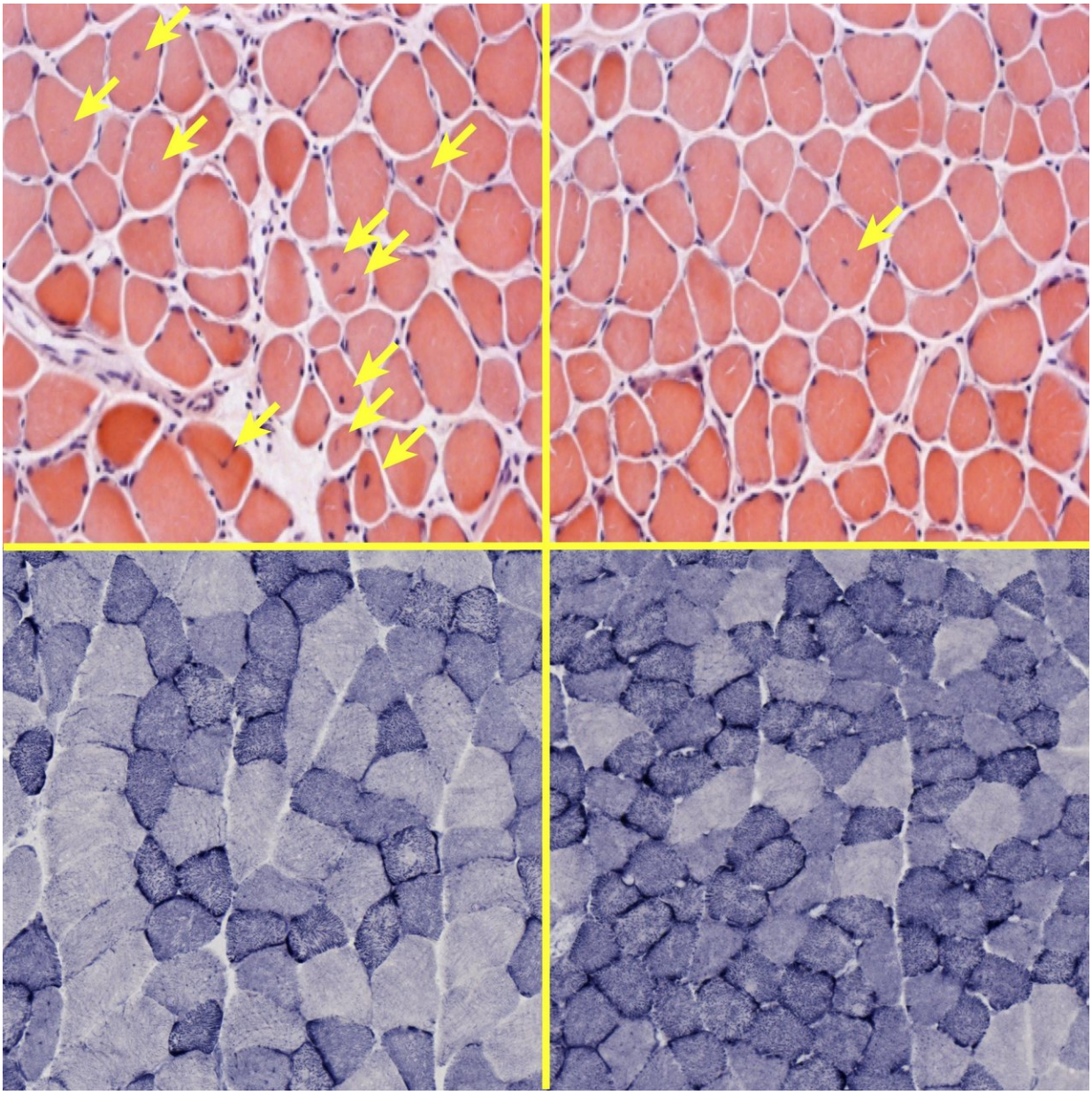

Top left: PGC1 deficiency leads to severe muscle damage, evidenced by

numerous centralized nuclei (highlighted with arrows), which is likely due to impaired mitochondrial energy metabolism (bottom left: blue staining shows impaired mitochondrial activity). Such muscle damage and mitochondrial impairment is largely rescued by ERRγ overexpression (top and bottom right). Credit: Salk Institute

If you've ever wondered how strenuous exercise translates into better endurance, researchers at the Salk Institute may have your answer. In a study published in the journal *Cell Reports* on March 6, 2018, scientists in Ronald Evans' lab have shown that the protein ERRγ (ERR gamma) helps deliver many of the benefits associated with endurance exercise.

"ERRγ helps make endurance exercise possible," says Ronald Evans, who is professor and director of the Gene Expression Laboratory and co-senior author on the paper. "It gears up the energy-creating cellular power plants known as mitochondria, creating more blood vessels to bring in oxygen, take away toxins and help repair damage associated with muscle use. This makes ERRγ a really interesting potential therapeutic target for conditions with weakened muscles."

The story starts with the PGC1α and PGC1β proteins, which stimulate 20 other proteins associated with skeletal muscle energy and endurance exercise, including one from the Evans lab called ERRγ. In turn, ERRγ, a hormone receptor, acts to turn on genes. The Evans lab researchers wanted to precisely understand ERRγ's role in skeletal muscle energy production and how that impacts physical endurance.

To unravel this relationship, the Salk team studied mice without PGC1α/β. In some, they increased ERRγ selectively in skeletal muscle cells. This approach allowed them to measure how ERRγ and PGC1 act independently, as well as how they function in combination.

Losing PGC1 had a negative impact on muscle energy and endurance. However, boosting ERRγ restored function. The team found ERRγ is essential to energy production, activating genes that create more mitochondria. In other words, they found the power switch for skeletal muscles.

The lab also showed that increased ERRγ in PGC1-deficient mice boosted their exercise performance. By measuring voluntary wheel running, they found that increasing ERRγ produced a five-fold increase in time spent exercising compared to mice with no PGC1 and normal ERRγ levels.

"Now that we have detected this direct target (ERRγ) for exercise-induced changes," says Weiwei Fan, a Salk research associate and the paper's first author, "we could potentially activate ERRγ and create the same changes that are being induced by exercise training."

In addition to increasing the number of mitochondria in skeletal muscle cells, ERRγ also increased muscular blood flow.

"You have to get more blood supply in to get more energy and take away toxic metabolites," says Michael Downes, a Salk senior scientist and co-senior author on the paper. "ERRγ boosts vascularization as well as mitochondria."

But perhaps the most important finding is that ERRγ could be a significant therapeutic target in helping to repair damaged muscles.

"Mitochondria play such a central role in cells throughout the body, but particularly in muscle cells, which tend to require more energy," says Evans. "We now know that, by increasing mitochondria energy output, ERRγ can actually rescue damaged muscle. If we can identify small molecules that specifically target ERRγ, we hope to help people with

muscular dystrophy and other skeletal muscle conditions."

Provided by Salk Institute