

# Super athletic mice are fit because their muscles burn more sugar

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This is Daniel P. Kelly, M.D., scientific director at Sanford-Burnham's Lake Nona campus in Orlando, Fla. and senior author of the study Credit: Sanford-Burnham Medical Research Institute

Muscle performance and fitness are partly determined by how well your muscle cells use sugar as a fuel source. In turn, exercising improves the muscle's ability to take up sugars from the bloodstream and burn them for energy. On the flip side, conditions that reduce physical activity -- such as obesity or chronic disease -- reduce the muscle's capacity to burn sugar. A new study by researchers at Sanford-Burnham Medical

Research Institute (Sanford-Burnham) unravels a mechanism that reprograms metabolic genes in muscles in a way that increases their capacity to use sugar. When activated in mice, this metabolic reprogramming dramatically improves exercise performance.

These findings, published Dec. 1 in [Genes & Development](#), reveal new targets that could be explored to increase the ability of muscles to burn sugars -- an avenue that could ultimately lead to new prevention or treatment methods for [obesity](#), metabolic syndrome, and diabetes.

"Essentially, these transgenic mice are capable of storing and burning sugars at rates usually only seen in the trained athlete. This allows for supranormal athletic performance," said Daniel P. Kelly, M.D., scientific director at Sanford-Burnham's Lake Nona campus in Orlando, Fla. and senior author of the study.

Dr. Kelly's mice are special because they're engineered to produce the protein PPAR $\beta/\delta$  in their muscle tissue. PPAR $\beta/\delta$  is a nuclear receptor, a type of protein that binds DNA to turn genes on or off in response to outside signals -- in this case, genes specific to muscle metabolism. Previous studies have shown that mice with high PPAR $\beta/\delta$  levels in their muscles have increased exercise capacity. In this study, the researchers discovered why that is -- the muscles of PPAR $\beta/\delta$  mice are better than normal mice at taking up sugar from the [bloodstream](#), storing it, and burning it for energy.

Dr. Kelly and his team also found that PPAR $\beta/\delta$  mice are super fit. Compared to normal mice, they ran longer and faster yet generated lower amounts of lactic acid, considered the chief mediator of exercise-induced muscle pain.

How does PPAR $\beta/\delta$  pull it off? It turns out that exercise stimulates cells to assemble a complex of three proteins: 1) PPAR $\beta/\delta$ ; 2) a protein that

maintains cellular energy balance (adenosine monophosphate-activated protein kinase or AMPK); and 3) a protein that helps activate muscle-specific genes (MEF2A). Together, these proteins switch on the gene that produces lactate dehydrogenase, an enzyme that directs sugar-derived metabolites into mitochondria, where complete burning of the fuel is possible -- effectively converting sugar to energy. It's likely that this novel mechanism helps activate other genes involved in muscle fitness as well.

"Given the association of obesity and insulin resistance with diets enriched in simple sugars, we find these results promising as a step towards new therapeutics," Dr. Kelly said. "Previously, members of the PPAR protein family have proven to be difficult drug targets due to the wide variety of effects they have in a cell. However, the findings in this study suggest that strategies for activating only a subset of events downstream of PPAR $\beta/\delta$  are possible. This could lead to favorable metabolic effects on muscle and other tissues."

Provided by Sanford-Burnham Medical Research Institute

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