Fighting Fat with Muscle: Bulking Up to Slim Down

Brooke C. Harrison[1] and Leslie A. Leinwand[1,*]
[1]Department of Molecular, Cellular, and Developmental Biology, University of Colorado at Boulder, Boulder, CO 80309, USA
*Correspondence: leslie.leinwand@colorado.edu
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Akt1 is a well-characterized mediator of muscle hypertrophy. In this issue of *Cell Metabolism*, Izumiya et al. (2008) reveal a striking link between Akt1 signaling, fast muscle fiber size, and whole-body metabolism. These results provide new insights into the ability of muscle to combat diet-induced obesity and metabolic dysfunction.

As is becoming increasingly common in many countries, the United States is facing an epidemic of obesity. Given that obesity represents the single most common underlying cause of increased morbidity and mortality due to either metabolic dysfunction or cardiovascular disease, the health care costs associated with this issue are enormous. In fact, the term "metabolic syndrome" has been given to this clustering of risk factors (central obesity, dyslipidemia, and insulin resistance), and this diagnosis can now be applied to roughly a quarter of the US population over the age of 20 and almost half of the population over age 45 (Reilly and Rader, 2003). While current pharmaceutical interventions are moderately effective in treating the clinical symptoms of metabolic syndrome, at this point only rigorous diet and lifestyle modifications (such as endurance exercise) are thought to be capable of significantly preventing harmful increases in fat mass that will ultimately shorten life span. Now, a new report by Izumiya et al. (2008) elegantly demonstrates that fast type IIb muscle fiber hypertrophy in response to Akt1 signaling blocks metabolic dysregulation and weight gain due to a high-fat/high-sugar diet, indicating that increasing fast muscle size via strength training may also be an important intervention for at-risk populations.

Skeletal muscle fibers can be classified by their morphological, contractile, and metabolic characteristics into one of two broad categories: slow (type I) fibers exhibit relatively low contractile velocities and are rich in mitochondria and the enzymes of oxidative energy metabolism, while at the other end of the spectrum (type I ↔ IIa ↔ IId/x ↔ IIb), fast type IIb fibers contract more rapidly and are predisposed toward glycolytic metabolism. In humans, slow muscle fiber percentage and skeletal muscle glucose transport are reduced in obese and diabetic populations, and regular endurance-type exercise can positively impact whole-body metabolism primarily though increased prevalence of, and adaptation to, the slow skeletal muscle fiber populations (Daugaard and Richter, 2001; Hickey et al., 1995). In animal models, altering either the number or function of slow muscle fibers has been shown to directly impact fat mass and the development of obesity due to dietary modification. The phosphatase calcineurin promotes slow muscle fiber gene expression, and transgenic mice expressing a constitutively active form of calcineurin (CnA*) demonstrate increased glucose uptake along with increased expression of the insulin receptor and glucose transporter 4 (GLUT4) (Naya et al., 2000; Ryder et al., 2003). Similarly, skeletal muscle-specific overexpression of constitutively active PPARδ increases slow muscle fiber prevalence and confers resistance to the development of diet-induced obesity (Wang et al., 2004).

While these studies highlight the importance of slow skeletal muscle fibers in modulating whole-body metabolism, the ability of the fast muscle fiber populations to affect blood glucose homeostasis, insulin sensitivity, and the development of obesity is less well understood. Endurance training promotes slow muscle fiber adaptation, while fast muscle fibers are more responsive to resistance training paradigms. In humans, such training has been linked to reduced adiposity and improved insulin sensitivity and is now a recommended mode of exercise for individuals with type 2 diabetes (Albright et al., 2000; Schmitz et al., 2007). In mice, however, little has been done to directly assess the ability of fast muscle size/function to affect diet-induced obesity and associated metabolic dysregulation.

Izumiya et al. (2008) have addressed this question by using Akt1 to stimulate type IIb muscle fiber hypertrophy. The serine/threonine kinase Akt1 (also known as protein kinase B [PKB]) plays a central role in numerous, diverse biological processes and is well known for its ability to promote skeletal muscle fiber hypertrophy via increased protein synthesis. Once activated by phosphatidylinositol 3-kinase (PI3K), Akt1 modulates the activity of several key regulators of protein synthesis, translation, and degradation including the mammalian target of rapamycin (mTOR), 4EBP-1, glycogen synthase kinase (GSK-3β), and the FoxO family of transcription factors (Frost and Lang, 2007) (see Figure 1). Not surprisingly, constitutive activation of Akt1 in skeletal muscle in vivo results in significant muscle fiber hypertrophy and increased glucose uptake in vitro (Hajduch et al., 1998; Lai et al., 2004).

Here, Izumiya et al. show that targeted expression of constitutively active Akt1 (myrAkt1*) to fast type IIb muscle fibers results in significant muscle fiber hypertrophy, increased muscle mass, increased strength, and reduced running capacity. To investigate the ability of this hypertrophy to impact diet-induced obesity and metabolic dysfunction, Izumiya et al. exposed both control and transgenic mice to a high-fat/high-sucrose (HF/HS) diet. In this context, activation of Akt1 triggered a striking reduction of body mass due to decreased visceral fat mass and white adipocyte atrophy. These effects of enhanced Akt1 signaling on diet-induced obesity were directly related to muscle hypertrophy—blocking hypertrophy with

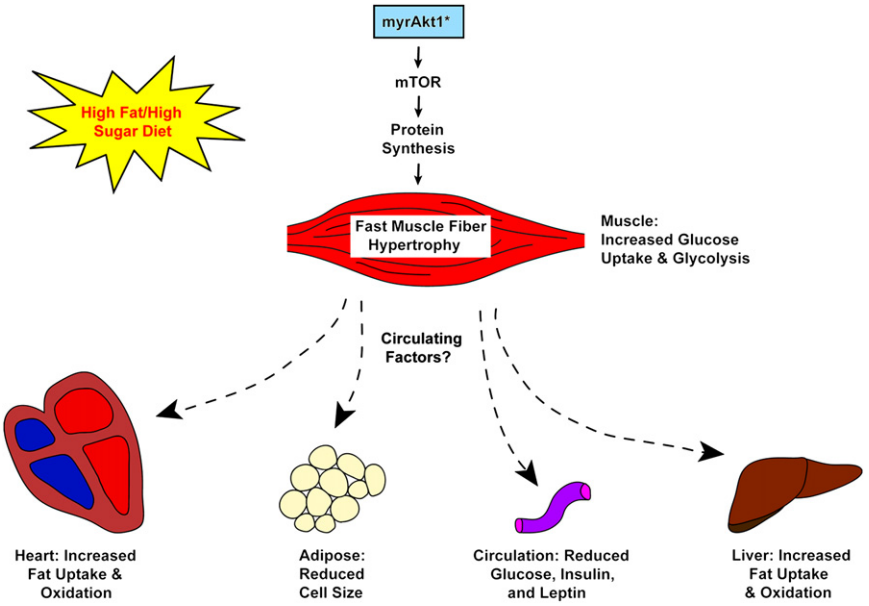

Figure 1. Akt1-Mediated Skeletal Muscle Growth Alters Whole-Body Metabolism and Prevents Diet-Induced Obesity and Metabolic Dysfunction

Induction of the Akt1 signaling pathway in fast skeletal muscle results in type IIb fiber hypertrophy and increased muscle mass via activation of the mammalian target of rapamycin (mTOR) and subsequent downstream regulatory molecules. When subjected to a high-fat/high-sucrose diet, *Akt1* transgenic mice exhibit reduced fat mass, increased muscle glucose uptake, and reductions in plasma glucose, insulin, and leptin levels. In non-transgene-expressing tissues such as the liver and heart, fat uptake and oxidation are enhanced.

rapamycin completely abolished the effects of transgene induction on body and fat mass.

As mentioned above, hallmarks of the metabolic syndrome include elevated levels of blood glucose, insulin, and leptin. This compromised metabolic state was induced by the HF/HS diet in control animals, but not in the *Akt1* transgenic mice. While glucose uptake was 2-fold higher in transgenic gastrocnemius as compared to control gastrocnemius, glucose uptake tended to be lower in non-transgenic tissues such as heart, white adipose tissue, liver, and slow skeletal muscle (soleus). Analysis of skeletal muscle gene expression with and without *Akt1* transgene induction revealed significant increases in transcripts for the key glycolytic genes hexokinase, phosphofructokinase, and lactate dehydrogenase A combined with significant decreases in transcripts for the oxidative genes PGC-1α, PPARα, and PPARδ.

Interestingly, *Akt1* transgenic mice demonstrated enhanced oxygen consumption coupled with reduced physical activity levels and a lowered respiratory exchange ratio, indicating a greater reliance on fatty acid oxidation for metabolic energy requirements. As predicted, exposure to the HF/HS diet had widespread effects on liver gene expression, with >1200 genes significantly altered by diet. Remarkably, Akt1-mediated fast skeletal muscle hypertrophy reversed 67% (861 of 1281 genes) of these diet-induced changes in liver gene expression. Notably, *Akt1* transgene induction increased levels of genes involved in both gluconeogenesis and fatty acid metabolism in the liver and resulted in enhanced fatty acid oxidation in isolated liver samples.

These findings raise several intriguing questions for future research. Given that this study focused on type IIb fiber hypertrophy in selected skeletal muscles, would the same effects be observed for other fast fiber types (IIa or IId/x) or other muscles? What is the smallest degree of hypertrophy that would confer these protective effects? As the authors comment, how does Akt1-induced muscle hypertrophy alter the expression of specific circulating factors (i.e., myokines) that may have systemic effects on substrate uptake and utilization? Given that males typically show greater hypertrophy in response to resistance exercise and lose more weight in response to exercise than females do, are there gender-specific differences in the ability of skeletal muscle size and/or function to modulate whole-body metabolism?

In summary, the work of Izumiya et al. (2008) reveals the intricate interplay between diet, energy balance, and the function/morphology of diverse tissue systems such as skeletal muscle and liver. These findings indicate that interventions designed to increase skeletal muscle mass in at-risk human populations may prove to be critical weapons in the fight against obesity and obesity-related comorbidities including diabetes, heart disease, stroke, hypertension, and cancer.

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