DEBATES ARE CURRENTLY RAGING in the United States over health-care reform. Certain political circles are advocating the implementation of a tax on sugary products to reign in ballooning costs associated with treating the one in three individuals in the United States now classified as obese. Now, this is certainly not the appropriate forum to rant over taxes. But, given the ever emerging liability of obesity and related comorbidities to not only quality of life, but financial solvency of individuals and industries, a discussion apropos the latest scientific findings surrounding this epidemic is deserved.

The recent paper by Paturi and Blough et al. (9) “Impaired overload-induced hypertrophy in obese Zucker rat slow-twitch skeletal muscle” has suggested a link between obesity and impaired muscle growth attributed to impaired insulin signaling. Desensitization of the insulin receptor (IR) is a hallmark trait of obesity and is a key factor in the development of the now commonly referred to metabolic syndrome—an aggregation of signs that contribute to the onset of coronary artery disease, stroke, and diabetes. Chronic stimulation of the IR, brought about through elevated circulating levels of insulin, amino acids, and/or inflammatory mediators, all signs associated with the metabolic syndrome, promotes for the ultimate demise of IR function.

In addition to its role in promoting the uptake and storage of glucose, the IR plays an indispensible role in the promotion of skeletal muscle hypertrophy. The IR, a member of the receptor tyrosine kinase family, promotes for activation of the insulin receptor substrate-1 (IRS-1) through binding growth agonists such as insulin and insulin-like growth factor-1. Most of the messaging transduced through IR/IRS-1 binding is mediated through phosphatidylinositol-3 kinase (PI3K) and downstream to Akt, collectively referred to as the IR/PI3K/Akt signaling axis. Upon activation, Akt phosphorylates and inactivates hamartin (TSC2), a suppressor of the mammalian target of rapamycin complex-1 (mTORC1)—an assembly of proteins including mTOR, raptor, and G protein β-subunit-like (GβL or LST8), which together drive skeletal muscle hypertrophy. As a result of TSC2 inhibition, mTORC1 activates key downstream molecules, among which includes p70s6k, a ribosomal associated protein that assists in facilitating protein translation initiation.

Interestingly, this cell signaling pathway purportedly can regulate itself, in that activation of p70s6k promotes phosphorylation of the IRS-1 on select Ser/Thr residues, which flags the protein for degradation (10). This negative feedback loop is mediated through mTOR, as administration of rapamycin, a known mTOR inhibitor, rescues IRS-1 from phosphorylation and degradation (11). As such, chronic stimulation of the IR/PI3K/Akt signaling axis through chronic elevations in growth agonists results in the ultimate demise of the signaling pathway, leading to not only deficiencies in insulin-stimulated glucose transport, but perhaps impaired skeletal muscle growth. However, the link between IR/PI3K/Akt dysfunction and skeletal muscle hypertrophy as it relates to obesity and related comorbidities is largely unknown.

The paper by Paturi and Blough et al. (9) provides evidence that molecular disruption resulting from obesity and insulin resistance indeed blunts skeletal muscle hypertrophy. Unlike wild-type animals in which TSC2 phosphorylation was unchanged with overload, TSC2 phosphorylation was increased nearly threefold with overload in obese Zucker rats. Although corollary in nature, the response in TSC2 mirrored the response in AMPK phosphorylation upon overload in both wild-type and obese Zucker rats. AMPK, a chief metabolic sensor within muscle and known inhibitor of mTOR activity (1), may be playing a strong role in dampening overload-induced hypertrophy associated with insulin resistance and obesity (Fig. 1). AMPK phosphorylation can inhibit mTORC1 function through activation of TSC2 through phosphorylation on alternative Thr/Ser residues (i.e., Thr1227, Ser1345) (4, 7) and through phosphorylation of the mTOR-binding partner raptor (3). Furthermore, AMPK activates FoxO-dependent gene transcription and can potentially regulate FoxO activity through phosphorylation on Akt-independent Ser/Thr sites (2). Activation of

Fig. 1. A hypothetical model depicting the negative impact of obesity/insulin resistance on anabolic signaling associated with overload-induced skeletal muscle hypertrophy. During muscle overload, obesity/insulin resistance promotes for an increased phosphorylation of AMPK, which can negatively impact mTORC1 function through 1) phosphorylation of TSC1/2 on select Ser/Thr residues, which hydrolyzes GTP to GDP on Rheb and inhibits its association with mTOR, and 2) phosphorylation and inhibition of the mTOR-binding partner, raptor. As a result, signaling downstream to anabolic molecules, such as p70s6k is attenuated. IR, insulin receptor; fragmented IR denotes insulin resistance; θ, activation of a molecule; θ, inactivation of a molecule; dashed arrow denotes a poorly defined pathway.

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FoxO1 can negatively regulate mTORC1 function through enhancing expression of genes attributed to the ubiquitin-proteasome system resulting in breakdown of raptor (12). As seen in the paper, a blunted response in raptor protein expression was exhibited in overloaded muscle of obese, Zucker rats. All together, it is possible that the AMPK may be playing a role in suppressing overload-induced muscle hypertrophy with obesity and associated insulin resistance through inhibiting mTORC1 function imposed via a FoxO-associated mechanism.

Although muscle hypertrophy is clearly influenced by growth factor signaling down through the IR/PI3K/Akt axis, muscle hypertrophy can result from IR/PI3K/Akt-independent mechanisms, as well. For instance, mechanical strain of muscle activates alternative pathways involving phosphatidic acid (a major constituent of cell membranes) (5), and mVps34 (a class III PI3K) (8), both of which bypass the IR/PI3K/Akt axis to converge directly upon mTORC1 to induce hypertrophy. Granted, activation of these alternative pathways may be reliant on the presence of a functional insulin receptor and thus may be impacted by insulin resistance conferred through chronic obesity. Nevertheless, alterations in the cellular milieu resulting from obesity may negatively impact upon noninsulin dependent/mechano-sensitive specific signaling pathways vital for inducing muscle hypertrophy associated with overload.

Although not a focus of the paper, it is interesting to note that soleus muscle mass had a strong tendency to be reduced in nonoverloaded obese Zucker rats. This reduced muscle mass occurred in the presence of elevated p70s6k phosphorylation. This elevation in p70s6k phosphorylation was coupled with a trend for an increase in mTOR phosphorylation. While mTORC1 appears vital for the promotion of overload-induced hypertrophy, this complex may not play a critical role in the maintenance of muscle mass, as administration of rapamycin, a known mTOR inhibitor, does not reduce muscle size under non-overloaded conditions (6). Thus enhanced mTORC1 signaling during nonoverloaded conditions may play a priming influence for the development of insulin resistance and eventual downregulation of IR/PI3K/Akt signaling, leading to deficiencies in insulin-stimulated glucose transport and promotion of metabolic-associated pathologies. Precisely how these perturbations in insulin-associated signaling are linked to blunting of normal skeletal muscle growth as a result of obesity requires further exploration.

As those afflicted with metabolic syndrome undoubtedly will rise in the coming future, it will be important to piece together the molecular interdigitation between metabolism and anabolic signaling to derive optimal interventions to thwart potential muscle wasting resulting from challenges to cellular energy handling. With childhood obesity rates tripling in the past 20 years, particular attention should be heeded to the potential impact of the metabolic syndrome on normal muscle growth and development within this population. Furthermore, as sexual dimorphisms exist as it relates to metabolism, adiposity, and endocrinology, studies examining the impact of obesity and related comorbidities on skeletal muscle anabolism between men and women are in dire need.

REFERENCES