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Editorial

Myokines and Signal Crosstalk between Skeletal Muscle and Adipose Tissue

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Abbreviations

ActRIIB: Activin Receptor Type IIB; ActRIIA: Activin Receptor Type IIA; WAT: White Adipose Tissue; BAT: Brown Adipose Tissue.

Skeletal muscle is the largest organ in the body and plays critical roles in smooth body movement, homeostasis, maintenance of body temperature, energy expenditure and insulin sensitivity. Skeletal muscle also serves as an "endocrine organ" because it secretes a variety of hormones and cytokines, which are referred to as myokines. In this editorial, I would like to mention about two types of myokines: myostatin and related TGF-β family members, and the newly discovered myokine known as irisin. In 1997, myostatin was discovered as a skeletal muscle-derived member of the TGF-β family, which potently inhibits muscle growth [1]. Myostatin knockout mice showed skeletal muscle hypertrophy and hyperplasia. Regulation of skeletal muscle mass is of scientific interest and clinically attractive because effective therapy to prevent muscle atrophy are needed for genetic diseases that cause muscular atrophy, sarcopenia and cachexia. Intriguingly, the absence of myostatin not only increases muscle mass but also reduces body fat accumulation. Myostatin gene ablation suppresses the genetically obese phenotype and diet-induced obesity [2]. There are multiple ways to block myostatin activity. Stabilized myostatin propeptide is a unique myostatin inhibitor, and transgenic myostatin propertied expression prevents diet-induced obesity and insulin resistance [3]. Follistatin is a potent myostatin and activin inhibitor and increases muscle mass [4]. Follistatin-derived myostatin inhibitor has been developed and transgenic expression of this inhibitor in skeletal muscle not only increases muscle mass but also decreases adipose tissue mass, and prevents diet-induced obesity and hepatic steatosis [5]. Interestingly, daily subcutaneous injection of follistatin 288, which is a potent follistatin isoform, into mice results in an increase in skeletal muscle mass with an associated decrease in fat mass. Therefore, systemic administration of follistatin would be effective for reducing fat accumulation as well as muscle wasting [6]. Mechanistically, in addition to the effects on myogenic stem/precursor cells, inhibition of myostatin activity in adulthood causes muscle hypertrophy by enhancing protein synthesis independent of the regulation of satellite cells [7,8]. Myostatin pathway induces repression of several miRNA including miRNA-486, which results in an increase in PTEN level and inhibition of the Akt/mTOR pathway. Therefore, myostatin inhibition leads to activation of the Akt/mTOR anabolic pathway [9]. This is one of the mechanisms of regulation of skeletal muscle size by myostatin inhibition. Recent investigations have revealed that activins are also involved in muscle atrophy and adipogenesis, and activin inhibition by antagonists is effective in inducing muscle hypertrophy [4,10,11]. Activins are structurally related to myostatin, and they are produced in various tissues including gonads and the nervous system. Activin isoforms including activin A, B and AB are expressed in adipose tissues, and they play important roles in the physiological and pathological development of adipose tissue, adipose tissue fibrosis, energy homeostasis and insulin sensitivity [10,11].

Both myostatin and activins signal through two types of transmembrane serine kinase, called activin type II receptors (ActRIIB and ActRIIA) and activin receptor-like kinases 4, 5 and 7 (ALK4, 5 and 7) [12]. Intracellularly, activated receptors phosphorylate Smad2/3, and then Smad2/3 forms a complex with Smad4. The Smad complex translocates into the nucleus to regulate gene expression. ActRIIB and ActRIIA are shared by myostatin, activin and several growth differentiations factors/bone morphogenetic proteins such as GDF11. Pharmacological inhibition of the myostatin/activin pathway by the soluble extracellular domain of ActRIIB or neutralizing antibody results in substantial increase of skeletal muscle mass. Intriguingly, pharmacological ActRIIB inhibition also suppresses diet-induced obesity and accompanying metabolic deregulation [13,14]. This is caused by an increase of energy expenditure. Effects on adipose tissue by myostatin/ActRIIB inhibition are likely to be secondary to skeletal muscle hypertrophy [5,15]. However, a unique effect on adipose tissue is also proposed as described below. Surprisingly, ActRIIB inhibition activates brown fat-like thermogenic program in white adipose tissue (WAT) and enhances mitochondrial function and uncoupling respiration in brown adipose tissue (BAT), resulting in enhanced cold tolerance and increased energy expenditure [13,14]. Browning in WAT is also reported in myostatin knockout mice [16]. Therefore, two mechanisms have been proposed for the increase in energy expenditure by myostatin/ActRIIB pathway inhibition: an increase in skeletal muscle mass, and the browning of WAT and activation of BAT. WAT is a tissue for energy storage, and BAT is an important tissue for dissipating energy via fat and glucose oxidation and heat generation to maintain body temperature. Enhanced browning of WAT is a unique result of blocking the ActRIIB pathway using soluble ActRIIB or neutralizing antibodies [13,14]. However, one report showed that soluble ActRIIB was not effective in reducing fat mass in already obese mice [17]. Therefore, ActRIIB inhibition could be a promising therapeutic strategy for obesity at the preclinical stage.

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Recently, an effective monoclonal antibody against activin type II receptors, ActRIIB and ActRIIA, called BYM338, has been developed to treat muscle atrophy [18]. Whether the antibody is effective in reducing fat mass remains to be determined.

Irisin, a cleavage product of a type I membrane protein FNDC5, is secreted from skeletal muscle [19]. Irisin promotes the formation of brown adipocyte-like cells in WAT, especially in subcutaneous fat depots, and protects against insulin resistance and obesity, even in mice at an obese state [19]. Interestingly, browning of WAT by irisin and myostatin/activin blocking using soluble ActRIIB or follistatin are similar. A study of the association between levels of irisin and follistatin has been performed in humans [20]. In a cohort of healthy young men with normal BMI, irisin levels correlated with follistatin levels but not with myostatin or activin A levels [20]. The same tendency was observed in morbidly obese individuals. Furthermore, serum levels of both irisin and follistatin increase by exercise. Because there is an association between circulating levels of irisin and follistatin, and both myokines have similar functions, it is possible that there is interplay between the signaling pathways of the two myokines [21].

In summary, the actions of myokines and their inhibition, along with the crosstalk between skeletal muscle and adipose tissue, were reviewed in this editorial. Because multiple ligands could be blocked by soluble ActRIIB, type II antibody or follistatin, precise mechanistic analyses are essential before clinical application. The role and function of irisin must be more precisely determined before testing its therapeutic effect. However, analyses of the signal crosstalk between skeletal muscle and adipose tissue via myokines will definitely pave the way for the fight against obesity and diabetes.

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