Myostatin as a Potential Therapeutic Target for Obesity and Insulin Resistance

Kyeong-Hoon Jeong(1), Cheol Soo Choi(1,2)*

Laboratory of Cellular & Molecular Physiology and Metabolism(1), Korea Mouse Metabolic Phenotyping Center(2), Lee Gil Ya Cancer and Diabetes Institute, Gachon University of Medicine and Science, Incheon, Korea

ABSTRACT

Considering that skeletal muscle is a major tissue responsible for whole body glucose and fat disposal, it has long been speculated that increasing muscle mass would be a potential therapeutic strategy to prevent obesity and fat-induced insulin resistance. Myostatin (growth differentiation factor 8, GDF8) is a transforming growth factor β (TGFβ) family member, and is known to act as a negative regulator of skeletal muscle differentiation and growth. Like other TGFβ members, dimeric myostatin mediates Smad signal transduction through its specific cell membrane receptors with serine/threonine kinase activity. Myostatin null (Mstn-/-) mice exhibit a doubling of muscle mass due to muscle hypertrophy and hyperplasia, and are protected against fat-induced obesity and insulin resistance. Other genetic and pharmacologic approaches to inhibit myostatin activity also demonstrate an increase in muscle mass and prevention of obesity and insulin resistance. This review will focus on the effects of myostatin inhibition on obesity and fat-induced insulin resistance, and will discuss the potential underlying mechanisms.

Key words: Myostatin, Muscle growth, Obesity, Insulin resistance

요약

근육(muscle)은 전신 포도당 및 지방소모에서 정량적으로 가장 중요한 장기인 점을 고려할 때, 근육량(muscle mass)을 증가시키는 것은 비만과 인슐린 저항성을 예방하고 치료하는 효과적인 치료전략으로 오랫동안 고려되어왔다. Myostatin (growth differentiation factor 8)은 transforming growth factor β (TGFβ) 그룹에 속하면서, 최근 근육성장 및 변화를 억제하는 기능을 가진 것으로 알려졌다. TGFβ의 작용기전과 유사하게 myostatin은 세포표면에 존재하는 serine/threonine kinase 활성도를 가진 세 포수용체와 결합하여 SMAD신호전달을 활성화시켜 작용하는 것으로 알려지고 있다. Myostatin 적응 마우스는 근육의 과양성 및 비대를 통해 대조군에 비해 2배의 전신근육 증가율을 보였고, 고지방사료에 의한 비만 및 인슐린 저항성 발생을 억제하였다. 또한 최근 다른 유전자조작 및 약물로 myostatin 활성을 억제하였을 때도 근육량의 증가와 함께 비만 및 인슐린 저항성을 억제하는 효과가 보고되어 있다. 따라서 본 종설에서는 최근 myostatin관련 연구 중 비만 및 인슐린 저항성에 대한 myostatin활성 억제효과 및 그 작용 기전을 중심적으로 고찰하였다.

중심단어: myostatin, 근육 증가, 비만, 인슐린 저항성

Received: Sep. 14, 2011; Reviewed: Sep. 29, 2011; Accepted: Sep. 29, 2011
Corresponding author: Cheol Soo Choi, Lee Gil Ya Cancer and Diabetes Institute, Gachon University of Medicine and Science Yeonsu-Gu, Songdo-Dong 7-45, Incheon 406-840, Korea
Tel: 82-32-899-6076, Fax: 82-32-899-6077, E-mail: csschoi@gachon.ac.kr, Mobile: 010-5177-8593
* This work was supported by a grant from the Korea Healthcare technology R&D Project, Ministry for Health, Welfare & Family Affairs: A102060.
Background

Obesity and insulin resistance have been known to play an essential role in the development of metabolic syndrome, which prevalence has been dramatically increased, particularly in aged population, over the past decades among advanced and developing societies. Many major factors have been identified and suggested to contribute to the development of obesity and insulin resistance, and among them is a loss of muscle mass known as sarcopenia. Moreover, muscle mass and insulin resistance or components of metabolic syndrome are shown to be closely and inversely related to each other.

Skeletal muscle is a major organ for energy disposal in both humans and rodents, since it represents 40~50% of total body mass and is mainly responsible for insulin-mediated glucose uptake and basal lipid disposal. Muscle glucose uptake is positively correlated with type I muscle fibers and the amount of muscle mass. A decrease in portion of type I muscle fiber has been observed in obesity and type 2 diabetes, and a decrease in muscle volume is also observed in elderly people who are relatively insulin-resistant compared to young people. Therefore, increase in percentage of type I muscle fiber or muscle mass has been widely expected to improve fat-induced obesity and insulin resistance. However, in contrast to the accumulating evidence that increase in type I muscle fiber improves whole body metabolism, relatively little is known about the metabolic effect of increase in muscle mass on obesity and insulin resistance. Despite the lacking evidence, obese and insulin-resistant type 2 diabetic patients are currently encouraged to increase muscle mass with resistance exercise in addition to aerobic exercise.

As a strategy to increase muscle mass, myostatin has been an attractive research subject. Myostatin, a transforming growth factor β (TGFβ) family member protein, has been shown to function as a negative regulator of skeletal muscle differentiation and growth. Myostatin is primarily produced by skeletal muscle cell and acts on muscle tissues in an autocrine manner (Fig. 1). Myostatin homozygous null (Mstn−/−) mice have double...