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Myokines and adipokines: Involvement in the crosstalk between skeletal muscle and adipose tissue

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ABSTRACT

Skeletal muscle and adipose tissue are the two largest organs in the body. Skeletal muscle is an effector organ, and adipose tissue is an organ that stores energy; in addition, they are endocrine organs that secrete cytokines, namely myokines and adipokines, respectively. Myokines consist of myostatin, interleukin (IL)-8, IL-15, irisin, fibroblast growth factor 21, and myonectin; adipokines include leptin, adiponectin, resistin, chemerin, and visfatin. Furthermore, certain cytokines, such as IL-6 and tumor necrosis factor-α, are released by both skeletal muscle and adipose tissue and exhibit a bioactive effect; thus, they are called adipo-myokines. Recently, novel myokines or adipokines were identified through the secretomic technique, which has expanded our knowledge on the previously unknown functions of skeletal muscle and adipose tissue and provide a new avenue of investigation for obesity treatment or animal production. This review focuses on the roles of and crosstalk between myokines and adipokines in skeletal muscle and adipose tissue that modulate the molecular events in the metabolic homeostasis of the whole body.

Contents

Abbreviations: ACC, acetyl-CoA carboxylase; Akt, protein kinase B; AMPK, AMP-activated protein kinase; ERK, extracellular-signal regulated kinase; FABP, fatty acid binding protein; FAT/CD36, fatty acid translocase; FATP, fatty acid transport protein; FGF21, fibroblast growth factor -21; FNDC5, fibronectin type III domain-containing 5; GLUT, glucose transporter type; IGF, insulin like growth factor JAK Janus-activated kinase; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor-kappa B; PGC-1α, peroxisome proliferator-activated receptor γ co-activator 1α; SIRT1, silent information regulator 1; STAT, signal transducer and activator of transcription; SVF, stromal vascular fraction; UCP2, uncoupling protein 2; WAT, white adipose tissue.

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1. Introduction

The prevalence of obesity has reached pandemic proportions, becoming a major public health problem in numerous developed countries where being overweight and obese results in more deaths than malnutrition. In 2014, ~39% of adults worldwide aged ≥18 years were overweight, and 13% were obese [1]. One of the major advances in obesity research over the past decades is the discovery that adipose tissue, especially white adipose tissue (WAT), acts as an endocrine organ and modulates metabolism by signaling other organs [2].

An extensive body of *in vivo* and *in vitro* research has explored the capacity of skeletal muscle and adipose cells to produce cytokines [3–6]. The concept of adipocytes as major secretory cells that release "adipokines" has more recently received greater attention owing to the development of a parallel concept in skeletal muscles. Identification of muscle as a "myokine"-producing organ has laid the foundation for a new field of research. Unfortunately, very few studies have considered the interrelation between skeletal muscle and adipose tissue, although a direct relationship between skeletal muscle mass or activity and adipose tissue mass has been indicated in some studies [4,5,7,8]. Multiple determinants play a key role in this complex process. In this review, we address the effects of only myokines and adipokines on skeletal muscle and/or adipose tissue. Furthermore, particular emphasis is placed on protein and energy metabolism in myocytes and/or adipocytes.

2. Skeletal muscle and adipose tissue

2.1. Skeletal muscle

Skeletal muscle, the largest organ in the human body, is a major metabolic tissue that is responsible for approximately 85% of the insulin-stimulated glucose uptake via glucose transporter type 4 (GLUT4)-mediated transport and for lipid metabolism [9,10]. More than a decade ago, contracting human skeletal muscle was elucidated to release significant amounts of interleukin (IL)-6 into the circulation during prolonged single-limb exercise [11,12]. The identification of muscle as a myokine-producing organ consequently provided a conceptual basis to explain how muscles communicate with other organs, even *in vitro*. During proliferation, myocytes tend to secrete myokines that suppress neurogenesis and adipogenesis; during differentiation, myocytes release myokines that specifically promote myotube formation, vascularization, and neurogenesis [5]. It has been suggested that the cultured muscle cells secrete different types and amounts of myokines at different developmental stages to communicate with various types of cells.

2.2. Adipose tissue

Adipose tissue functions not only as an energy reserve organ but also as a major endocrine organ, secreting adipokines involved in maintaining homeostasis. Adipose tissue includes two fractions: mature adipocytes and stromal vascular fraction (SVF). The SVF includes preadipocytes and shares numerous phenotypic features with pro-inflammatory macrophages, including the capacity to secrete factors such as IL-6, tumor necrosis factor (TNF)-α, and monocyte chemotactic protein-1 (MCP-1). Adipocytes in adipose tissue secrete a wide range of factors, considered adipokines, similar to myokines released from skeletal muscle. However, there has been uncertainty over whether this concept should also be applied to other forms of adipocytes, such as brown and brite tissue. Specifically, the different forms of adipocytes could interconvert. Although brown adipocytes definitely secrete specific proteins [13], the extent of the secretory protein profile of brown adipocytes, as well as brite adipocytes, is currently unclear. The wide spectrum of molecules secreted by adipose cells indicates that this tissue is very important for the regulation of energy homeostasis.

2.3. Muscle-adipose axis

There are multiple adipose tissue sites (locations) or depots within an organism, and skeletal muscles also share the key characteristics required to secrete cytokines that have endocrine or paracrine functions [14]. Because adipose tissue is adjacent to the muscle, it can induce different signaling pathways. Therefore, location plays a key role in the physiological interactions between adipose tissue and closed muscle, depending on whether it is subcutaneous, intermuscular, or intramuscular fat. Skeletal muscle is also located in different areas and has various muscle fiber types including type I and type II (a, b, x) [15]. Crosstalk between myogenic cells and adipocytes might play a significant role in the rate and extent of myogenesis, adipogenesis, protein turnover, and lipogenesis/lipolysis [16–18]. Furthermore, crosstalk between myocytes and adipocytes has been supported by co-culture models using both cell types [4,19]. Myokines and adipokines secreted from corresponding tissues have an important effect in maintaining a balanced ratio of skeletal muscle to fat and thus, may play a key role in the modulation of body composition and even in the production of muscle in animals (Fig. 1).