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REVIEW

Myokines in metabolic homeostasis and diabetes

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Abstract

Physical activity exerts multiple beneficial effects and the myokine concept provides a framework for understanding the molecular pathways that integrate contracting muscle in the complex network of organ communication. This network includes multiple distinct and distal organs; however, the autocrine and paracrine effects of myokines within skeletal muscle (in which they are produced) also need specific attention. In humans, the functional allocation of myokines remains limited and recent findings on fibre type-specific myokine signatures point to an additional level of complexity. Myokines are involved in the anti-inflammatory effect of physical activity and, therefore, critically counteract insulin resistance and the metabolic perturbations of obesity and type 2 diabetes. Future work needs to address the role of myokines in concert with other crosstalk molecules, and to define their specific impact for metabolic homeostasis.

Keywords Diabetes · Exercise · Metabolic homeostasis · Myokines · Organ crosstalk · Physical activity · Review

Abbreviations

BAT	Brown adipose tissue
FGF	Fibroblast growth factor
NAFLD	Non-alcoholic fatty liver disease

Introduction

The beneficial effects of physical activity have been known for decades. However, only recently the so-called 'myokine concept' has generated a new understanding of the role that skeletal muscle plays as an active endocrine organ, which is involved in the communication and fine tuning between major metabolic organs [1–3]. The conceptual framework of considering myokines as critical mediators within the organ communication network has been instrumental in developing a new understanding of the molecular basis of physical activity. Given that physical activity undoubtedly represents a key preventive intervention for combating chronic diseases, such as type 2 diabetes and cardiovascular disease [4], extensive research has focused on the identification and functional characterisation of myokines, driven by expectations of finding novel preventative and therapeutic targets [5–7].

Although postulated for a long time, it was only ~20 years ago that the first exercise factor, IL-6, was identified and the term 'myokine' was introduced [8]. Some key facts about myokines are summarised in the Text box. The overarching property of all myokines is secretion or release from skeletal muscle cells. However, many myokines are not released into the circulation but act as autocrine or paracrine factors within

Key properties of myokines

- By definition, a myokine is a peptide or protein that is released from skeletal muscle cells.
- Muscle contraction is a major regulator of myokine expression and release. However, some myokines do not respond to muscle contraction.
- The term 'exercise factor' includes myokines and, also, metabolites. An exercise factor is principally released to the circulation upon muscle contraction.
- Myokines exert multiple autocrine, paracrine and endocrine biological effects.

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skeletal muscle. In addition to myokines, metabolites released by contracting skeletal muscle play an important role as exercise factors [7]. For example, molecules released from skeletal muscle, such as β-aminoisobutyric acid [9] and lactate [10], were shown to convey signalling to the liver, adipose tissue and the brain [11]. This inter-organ metabolic crosstalk [12] is different from myokine-mediated crosstalk due to: (1) the protein-related high capacity of signalling information (covalent modification, protein folding); and (2) the involvement of specific receptors at the target cell. Secretomic studies of muscle cells have shown the presence of hundreds of myokines with mostly unknown functions [13], demonstrating the complexity of organ crosstalk.

This review aims to: (1) highlight the specific role of myokines in the network of organ communication, with specific relevance for humans; (2) consider the different stages of metabolic dysregulation and the role of myokines in these; and (3) address the translation of these findings to potential novel therapeutic strategies.

Exercise-induced myokines and the network of organ communication

The complexity of higher organisms requires a balanced system of cell-to-cell and organ-to-organ communication (organ crosstalk) to adapt and harmonise the physiological functions of different organs. Currently, the best understood element of organ crosstalk is represented by the secreted proteome of muscle, adipose tissue, liver and immune cells [14]. Initially, the adipocyte–myocyte axis was described as a paradigm of negative crosstalk between two tissues [15]. However, based on the myokine concept, a bi-directional crosstalk was proposed, leading to the current view of a network of organ communication. This is illustrated in Fig. 1, which emphasises known myokine targets and depicts key players in this interaction. In the sections below, I focus on the effects of exercise, which leads to metabolic adaptations in a number of distinct organs.

Muscle–adipose crosstalk With the discovery of brown adipose tissue (BAT) in adult humans and the beneficial effects of this specific depot on metabolic homeostasis, an extensive number of studies addressed the question of whether exercise and certain myokines may promote BAT activity and the so-called browning of white fat [16]. In 2012, irisin was reported to be released from skeletal muscle after physical activity and to induce a white-to-brown transition in both rodents and humans, potentially mediating the beneficial effects of physical activity [17]. However, irisin remains one of the most controversial myokines, with its function still being ill-defined, especially in humans [18, 19]. In rodents, the transplantation of subcutaneous adipose tissue from trained to sedentary mice improved metabolic control, supporting the notion of exercise-induced adipose tissue adaptation [20]. As pointed out by Wright and co-workers [21], this is a complex process potentially involving a rise in catecholamines, activation of lipolysis, activation of AMP-activated protein kinase (AMPK), induction of mitochondrial biogenesis and browning. Interestingly, myokines such as IL-6 and the recently discovered meteorin-like protein, appear to be involved in this process [21]. In humans, the browning of white fat in response to exercise has remained controversial [22], thus requiring future studies on the functional impact of myokines on human adipose cells. Since only 5% of the myokinome is currently linked to a specific function, bioinformatic approaches will be needed to integrate the muscle–adipose crosstalk in the multi-organ communication network.

Muscle–liver crosstalk Systematic reviews of the effect of exercise training on non-alcoholic fatty liver disease (NAFLD) suggest that exercise, independent of weight loss, ameliorates hepatic steatosis [23]. The role of myokines in this process has remained under-explored. Experimental data suggest that IL-6 upregulates hepatic peroxisome proliferator-activated receptor α (PPARα) and fatty acid oxidation. Most likely, the release of hepatokines in response to physical activity plays a key role in preventing the development of NAFLD. IGF-I and fibroblast growth factor (FGF)-21 are hepatokines that are upregulated in response to exercise in humans [24, 25] and the crosstalk between these molecules and muscle and adipose tissue improves metabolic performance and prevents the development of NAFLD. In a recent study, Drevon and co-workers [26] showed that long-term exercise improves insulin sensitivity by changing the circulating level of the hepatokine fetuin-A and NEFA, potentially involving a reduction in toll-like receptor 4 signalling.

Muscle–bone crosstalk The tight functional association between muscle and bone is well known but, only recently, the 'bone–muscle unit' was described as a paradigm of multidirectional crosstalk between different tissues, involving not only muscle and bone but also adipose tissue, cartilage and tendon [27]. In this scenario, secreted myokines play an important role, most likely in a paracrine fashion [28], with IL-6 being confirmed to play a role in bone formation in human studies. Many other myokines affect bone metabolism either positively (e.g. IGF-I, FGF-2, IL-15) or negatively (e.g. TGF-β) [29].

Muscle–beta cell crosstalk Several reports point to the existence of a muscle–pancreas axis, with myokines playing an important role in this crosstalk [30, 31]. This concept has been substantially reinforced by a recent study wherein a fibre type-specific myokine signature was demonstrated and the beta cell protective effect of angiogenin and osteoprotegerin (type II muscle-specific myokines) was reported [32]. Thus, it was shown that these tricep-specific myokines reduce apoptosis

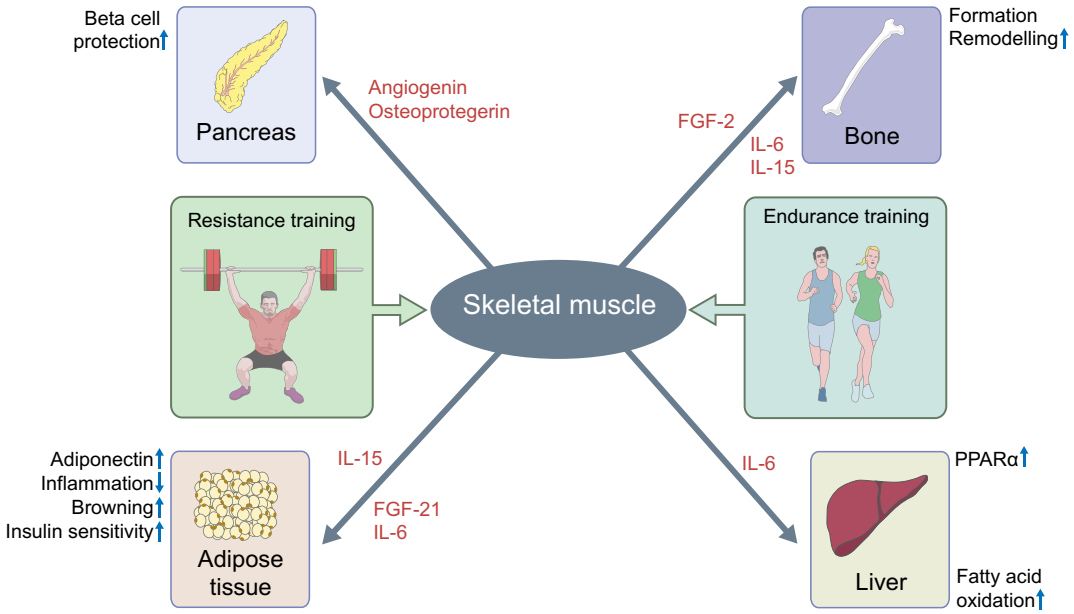

Fig. 1 The network of organ communication and the specific role of myokines. Both resistance and endurance training stimulate the release of a host of myokines from skeletal muscle; many of the myokines acting within the muscle as exercise factors are shown. Adipose tissue is a major target for the biological effects of myokines, including increased expression of adiponectin and white-to-brown transition of the tissue. Exercise-stimulated myokines also act on the liver although the release of hepatokines during exercise, such as fetuin-A and IGF-I, may be more important for improving metabolic performance. Muscle–bone crosstalk involves a number of different myokines that both positively and negatively modulate bone metabolism. The muscle–pancreas axis involves fibre type-specific myokines exerting beta cell protection. PPARα, peroxisome proliferator-activated receptor α. This figure is available as a downloadable slide

of beta cells. Specifically, both myokines prevent beta cell apoptosis induced by proinflammatory cytokines or by conditioned medium from insulin-resistant myotubes [32]. These observations are of general interest for the exercise and myokine field, and future studies need to address the impact of fibre type-specific myokines on organ crosstalk.

Metabolic dysregulation and the role of myokines

Persistent energy excess and an increased demand for lipid storage leads to adipocyte hypertrophy, cellular stress and low-grade chronic inflammation. As a result, obesity is characterised by an altered adipose tissue secretome that has a large impact on organ crosstalk, leading to insulin resistance and type 2 diabetes [14]. Physical inactivity is associated with a network of chronic diseases, including neurodegeneration, type 2 diabetes, cardiovascular disease, and different forms of cancer that involve enlargement of the visceral fat depot and induction of multiple systemic inflammatory pathways [33]. Moreover, physical inactivity, per se, is a major driver of metabolic disorders; the changes it induces in the muscle secretome and myokine profile most likely contribute to metabolic dysfunction, as evidenced by bed-rest studies, in which transcription of more than 4000 genes was found to be altered [34]. Given the existence of fibre type-specific myokine signatures, it can be anticipated that lack of exercise may compromise the regulatory crosstalk of the myokinome; however, this issue remains mostly unexplored.

Physical activity is known to exert an anti-inflammatory effect that, in addition to a reduction in body weight and visceral fat mass, may be due to an increased level in immune-modulatory agents, exerting a direct effect on the immune system [35]. Further, the paradigm myokine IL-6 is thought to induce an anti-inflammatory cascade by triggering the release of anti-inflammatory cytokines, such as IL-10, IL-1 receptor antagonist and soluble TNF receptor [3], jointly reducing systemic inflammation. At the local level, the novel myokine chitinase-3-like protein 1 (CHI3L1) was recently reported to exert an auto-protective function by inhibiting TNF-α-induced activation of NF-κB, inflammation and insulin resistance in myotubes [36]. These autocrine and paracrine functions of myokines and their regulation by exercise are presently underappreciated and future studies may identify myokines with potential therapeutic implications (see 'Novel myokines as potential targets for diabetes therapy' section, below).

An additional level of complexity surrounding the myokine field results from the different protocols used in studies of exercise training vs acute exercise (in laboratory settings), and the different findings obtained from human and rodent studies [6]. Moreover, some myokine studies have used a combination of endurance and strength training, with many different protocols of intensity and duration being used in these studies [6]. Furthermore, the number of myokines with

proven functions in humans is very limited [6]; at present, robust data only exist for IL-6, IL-8, IL-13, IL-15, FGF-21, angiopoietin-like 4 (ANGPTL4), among a few others. Thus, the vast majority of myokines await functional assessment in humans. Consequently, more work is needed to integrate the myokine and inflammation network and to fully understand the role of myokines in metabolic dysregulation in humans.

Novel myokines as potential targets for diabetes therapy

The myokine concept has triggered extensive research efforts to identify novel myokines that might represent potential therapeutic targets to combat obesity and associated metabolic disorders.

Irisin gained considerable interest because it was claimed to increase thermogenesis and energy expenditure as a result of inducing the browning of white fat [17]. It is possible that irisin is present in the human circulation at very low concentrations, although the effect of exercise on irisin levels remains controversial. Spiegelman and colleagues reported a slight increase (20%) after 12 weeks of exercise [37]. However, a meta-analysis of randomised controlled studies showed a decrease in irisin levels after chronic exercise [38]. Given the lack of evidence for browning of white fat in humans in response to exercise [18], the function of irisin remains to be established.

FGF-21 is a protein preferentially expressed in the liver but is also described as being a myokine [39]. However, studies on the effect of exercise on FGF-21 have remained controversial [4]. The ability of FGF-21 to normalise glucose and lipid metabolism and to prevent the development of obesity and diabetes was first reported in 2005 [40]. Since then, the metabolic functions of FGF-21 have been studied in detail and it is now evident that this protein represents a paradigm for orchestrating the multi-organ crosstalk between fat, liver, brain and the vasculature [41]. FGF-21 stimulates glucose uptake in muscle and fat, the synthesis and release of adiponectin, and the white-to-brown shift of adipocytes leading to an increased energy expenditure. These beneficial properties raised substantial expectations that FGF-21 might represent a new target for diabetes therapy. However, native FGF-21 has a half-life ($t_{1/2}$) of about 1 h and modifications of the molecule have been developed so that it may be administered as a drug [42]. Today, a new class of FGF-21 molecules is available, comprising analogues with an improved $t_{1/2}$ [42]. A substantial number of these molecules is under development for the therapy of non-alcoholic steatohepatitis (NASH) and type 2 diabetes, and both Phase 1 and Phase 2 studies are currently ongoing.

Chemokine (C-X3-C motif) ligand 1 (CX3CL1; also referred to as fractalkine) is known to play a role in leucocyte adhesion. It has also been identified as a myokine with potential function in muscle injury and repair [43]. Interestingly, fractalkine was found to act as a novel player in regulating insulin secretion and beta cell function, and a recent study demonstrated that chronic administration of a long-acting fractalkine analogue caused persistent improvement of glucose tolerance, increased glucose-stimulated insulin secretion and reduced apoptosis of beta cells in different rodent models of obesity [44]. Due to an additional effect on hepatic insulin sensitivity, fractalkine may be of great interest for future development as a new agent for type 2 diabetes therapy.

Conclusions

Higher organisms need complex regulatory systems that contribute to adaptation and fine tuning of metabolic activities. The organ crosstalk network is an important component of this process and serves to communicate immediate and long-term information for functional adjustments in different tissues. Multiple signals are involved in this phenomenon and myokines are part of this information transmission pathway, certainly playing an important overall role in positive metabolic control. The myokine concept discussed in this paper has provided a new understanding of the role that skeletal muscle plays as an active endocrine organ. However, the precise understanding of myokine biology is currently hampered by the huge number of myokines mostly identified in cell cultures or animals. In humans, functional allocation of myokines has been very limited so far. Future directions should address the fibre type-specific myokine signatures and the autocrine and paracrine actions of myokines. This may provide new insight into muscle physiology and diseases such as cachexia and sarcopenia, both of which are under-explored areas in myokine research.

Muscle contraction and, thus, physical activity is a major regulator of myokine secretion, but physical activity and exercise training are part of a healthy lifestyle and the precise dissection of myokine action from other signalling events is very difficult. Myokines most likely act in an integrated way with metabolites, exosomes and other crosstalk signals. It may also be important to study individual myokine signatures to further explore the therapeutic value of certain myokines. As shown for irisin, a great deal of caution is required when extrapolating data obtained in rodent studies to humans. However, FGF-21 is a good example of an organokine that may turn out to be of great therapeutic value.

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