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From the discovery of myokines to exercise as medicine

Bente Klarlund Pedersen

Centre for Physical Activity Research (CFAS), Copenhagen University Hospital – Rigshospitalet, Denmark

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ABSTRACT

Skeletal muscle is an endocrine organ that produces and secretes hundreds of myokines, allowing for crosstalk between the muscle and other organs. The discovery of myokines has contributed to laying the groundwork for exercise as medicine. Exercise activates multiple signalling pathways of importance for health. However, for the individual and society to benefit from such exercise effects, a true translational perspective on exercise as medicine is needed, ranging from molecular and physiological events to political decisions with direct implications for clinical practice and public health.

KEY POINTS

- Myokines mediate communication between muscle and other organs, including the brain, adipose tissue, bone, liver, gut, pancreas, vascular bed and skin, as well as within the muscle itself.
- The myokine interleukin-6 mediates anti-inflammatory effects with each bout of exercise. Moreover, with training adaptation, abdominal adiposity is reduced, leading to further lowering of pro-inflammatory cytokines.
- Exercise as medicine has proven effective for many diseases, but a true translational perspective on exercise as medicine is needed.

Early in my career, we studied the effect of exercise on the immune system. The main finding was that immune cells such as natural killer (NK) cells and T cells were mobilised to the blood during a bout of ergometer cycling exercise. While searching for a mechanism to explain these exercise-induced immune changes, we came across interleukin (IL)-6 and found that, in relation to an acute bout of aerobic exercise, contracting muscles released IL-6 into the blood whereby systemic levels of IL-6 increased exponentially. This unexpected and serendipitous finding contributed to identify skeletal muscle as an endocrine organ, which together with subsequent findings, e.g., that exercise-induced IL-6 has multiple metabolic and anti-inflammatory effects, further contributed to laying the groundwork for the discipline “exercise as medicine”.

THE MYOKINE CONCEPT

Within the society of human integrative physiology, the search for an exercise factor capable of mediating exercise-induced changes in other organs such as liver and adipose tissue dates back more than 60 years [1]. It became clear that signalling pathways from exercising skeletal muscle to other organs were not solely mediated

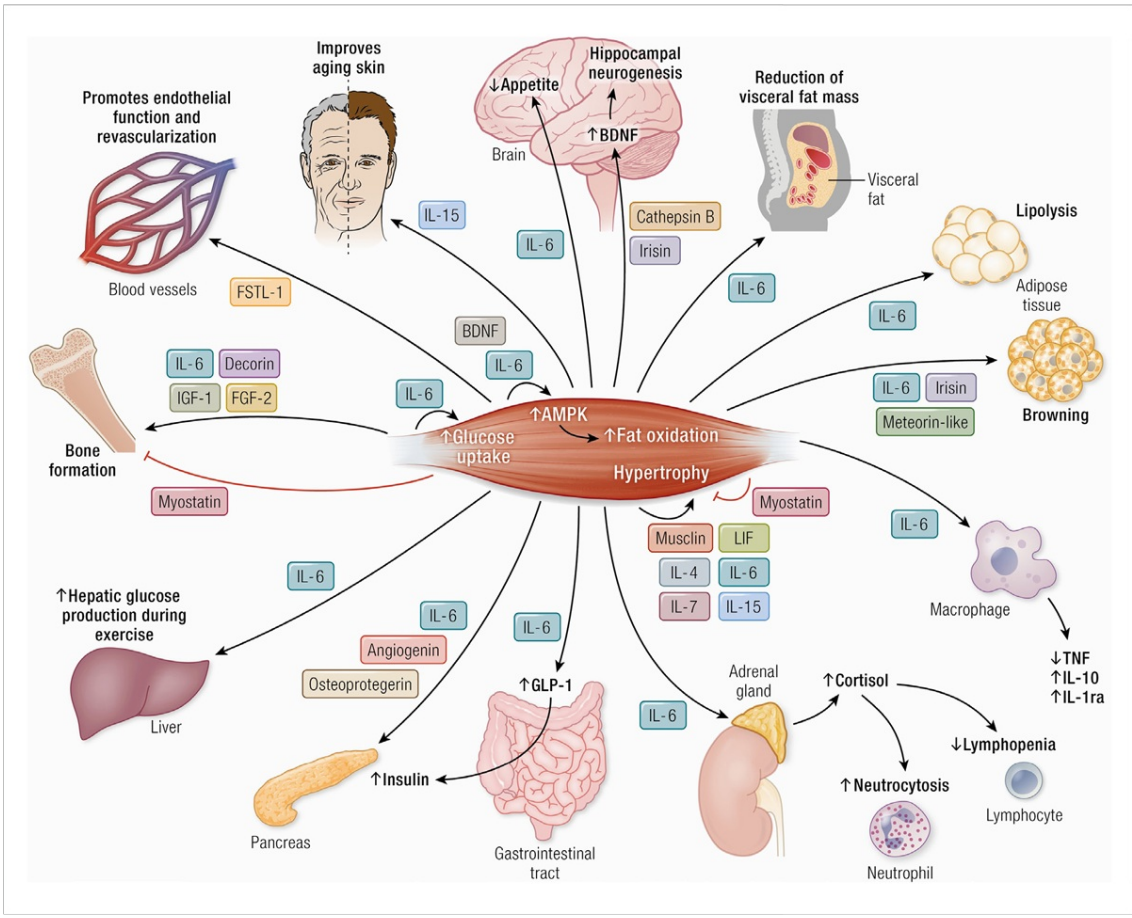
via the nervous system [2]. In 2000, we discovered that contracting skeletal muscle produces and releases IL-6 into the circulation [3]. This finding together with research during the subsequent years demonstrating that IL-6 has multiple metabolic effects in other parts of the body contributed to identify IL-6 as an exercise factor [4].

Given the manifold physiological, metabolic and immunological effects of exercise, it was obvious to us that more than one exercise factor likely existed. In 2003, we introduced the term “myokines” [5] and proposed that “cytokines and other peptides that are produced, expressed and released by muscle fibres and exert either autocrine, paracrine or endocrine effects should be classified as myokines” [5, 6].

Following the identification of muscle-derived IL-6 as the first myokine, it soon became clear that muscles were able to secrete more than 650 different myokines [7]. The identification of the myokinome has provided a new paradigm and a conceptual basis for understanding by which mechanisms muscles communicate with other organs. It has been proposed that the total sum of all exercise-induced factors released from muscle and other organs into the blood should be named “exerkines” [8, 9]. Exerkines may be released within extracellular vesicles known as exosomes [10], which may contain nucleic acids, peptides, mRNA, miRNA and mtDNA.

The role of myokines has previously been reviewed [6, 11-15]. Myokines are also involved in muscle proliferation, differentiation and regeneration independently of exercise [16, 17, 18]. During exercise, myokines signal within the muscle and mediate muscle-organ crosstalk to the brain, adipose tissue, bone, liver, gut, pancreas, vascular bed and skin [6, 13, 14] (**Figure 1**). In addition, myokines with anti-cancer effects have been recognised [19, 20]. The aim of the present narrative review is to provide an update on our recent advances within the myokine field, focussing on IL-6 and linking this research to clinical medicine.

FIGURE 1 Skeletal muscle is an endocrine organ. The muscle produces and secretes several hundred myokines, which provides a conceptual basis for understanding how muscles communicate with other organs. Cathepsin B and irisin cross the blood-brain barrier and stimulate BDNF production and hippocampal neurogenesis. IL-6 stimulates appetite and lipolysis and decreases visceral fat mass. Irisin, meteorin-like and IL-6 have a role in "browning" of white adipose tissue. IL-15 improves aging skin. Decorin, IL-6, IGF-1 and FGF-2 positively regulate bone formation. Myostatin negatively regulates bone formation. Musclin, LIF, IL-4, IL-6, IL-7 and IL-15 promote muscle hypertrophy. Myostatin inhibits muscle hypertrophy. BDNF and IL-6 are involved in AMPK-mediated fat oxidation. IL-6 enhances insulin-stimulated glucose uptake and stimulates glucose output from the liver, but only during exercise. IL-6 increases insulin secretion by inducing the expression of GLP-1 by the L cells of the intestine. IL-6 has anti-inflammatory effects as it inhibits TNF production and stimulates the production of IL-1ra and IL-10. IL-6 stimulates cortisol production and thereby induces neutrocytosis and lymphopenia. FSTL-1 improves endothelial function and revascularisation of ischaemic blood vessels. Angiogenin, osteoprotegerin and IL-6 possess pancreatic beta-cell protective actions against proinflammatory cytokines. The figure is adapted from [18].



AMPK = 5'-AMP-activated protein kinase; BDNF = brain-derived neurotrophic factor; FGF = fibroblast growth factor; FSTL = follistatin-related protein; GLP = glucagon-like peptide; IGF = insulin-like growth factor; IL = interleukin; IL-1ra = IL-1 receptor antagonist; LIF = leukaemia inhibitory factor; TGF = transforming growth factor; TNF = tumour necrosis factor.

INTERLEUKIN-6 – ENERGY SENSOR AND ENERGY ALLOCATOR

Muscle contractions as such stimulate the production of muscle-derived IL-6. However, low muscular glycogen further stimulates the production and release of IL-6 into the circulation, which classifies muscle-derived IL-6 as an energy sensor [21]. Inspired by Professor Daniel Lieberman, the well-known evolutionary biologist, and his PhD student Tim Kistner, we proposed that IL-6 has a role in short-term energy allocation, especially during sustained, strenuous endurance physical activity [22]. In humans, the half-life of IL-6 appears to be context dependent. The myokine IL-6 production during aerobic exercise is dependent on metabolic stress within the

muscle. Furthermore, IL-6 mobilises stored energy from adipose and skeletal muscle, primarily by promoting lipolysis. Lastly, myokine IL-6 promotes differential uptake of liberated energy in myocytes by increasing muscular insulin sensitivity and transiently downregulating inflammation [22].

INTERLEUKIN-6 CAN WORK AS AN ANTI-INFLAMMATORY CYTOKINE

Lack of exercise is associated with low-grade chronic inflammation, not least when a physically inactive lifestyle is associated with obesity. Chronic inflammation is associated with most chronic diseases, and more than 50% of all deaths worldwide are attributed to chronic inflammatory diseases, including cancer, cardiovascular disease, dementia, stroke and diabetes [23].

Aerobic exercise induces anti-inflammatory effects with each bout of exercise and via long-term training adaptation [24].

The exercise-induced acute increase in IL&;6 promotes the production of the two anti-inflammatory cytokines IL&;1 receptor antagonist and IL&;10 [25]. Moreover, in healthy humans, we showed that a bout of exercise or an IL-6 infusion prior to endotoxin infusion totally blunted the increase in circulating levels of tumour necrosis factor (TNF)&;α that was observed during a resting situation [26]. Thus, an acute bout of exercise induces anti&;inflammatory effects that may in part be mediated by IL&;6, not excluding the contribution of other anti-inflammatory factors such as epinephrine and cortisol [27].

Exercise also induces anti-inflammatory effects via an exercise-mediated reduction in abdominal fat [28]. When visceral fat is accumulated, it represents an important place of origin of chronic systemic inflammation, as it was shown to be more inflamed than subcutaneous fat, constituting an important source of inflammatory markers [29]. Lack of exercise provokes accumulation of visceral fat and thereby enhances inflammation and hence a network of chronic diseases, whereby a vicious circle of chronic inflammation is established [13]. Recent evidence substantiates that exercise training decreases the amount of visceral and cardiac fat mass [30-32] via a mechanism that involves an exercise-induced increase in IL-6 [30]. A human study from our group [33] found that IL-6 delays the rate of gastric emptying, which is the most significant regulator of postprandial glucose. As hyperglycaemia causes inflammation, lowering postprandial glucose levels further contributes to lowering chronic inflammation.

MUSCLE-IMMUNE-CANCER CROSSTALK

Epidemiological studies suggest that physical activity in leisure time reduces the risk of at least 13 cancer types [19, 20, 34, 35]. People who are physically active after a diagnosis of prostate cancer, colorectal cancer and breast cancer have a higher survival rate than physically inactive people suffering from the same cancer types [36].

Pernille Hojman and her team explored the effects of wheel-running on tumour growth in preclinical models [20]. They first established a B16F10 melanoma model and randomised tumour-bearing mice to voluntary wheel running or control. Running mice demonstrated a marked reduction in tumour volume and incidence across six tumour models. The inhibitory effects of exercise on tumour growth were mediated via a direct regulation of NK cells, where these cells were mobilised to the circulation and redistributed to the tumour tissue by a mechanism involving both epinephrine and IL-6. Blocking IL-6 signalling during exercise abolished the exercise-induced inhibition of tumour growth. These findings in mice indicate that IL-6 may have a role in mediating anti-cancer effects [19, 37-40]. Indeed, a recent pilot study in humans suggests that supervised high-intensity interval exercise training prior to surgery may have the potential to increase tumour NK-cell infiltration in men with localised prostate cancer [41].

MUSCLE-ADIPOSE CROSSTALK

Exercise-induced IL-6 has major effects on fat metabolism [36, 42]. Cell culture studies and studies in rodents show that IL-6 may enhance lipolysis and fat oxidation via a mechanism that involves AMP-activated protein kinase activation [4]. Moreover, in vivo studies show that infusion of recombinant human IL-6 enhances lipolysis and fat oxidation in healthy humans [43, 44].

To further explore the role of IL-6, abdominally obese humans were randomised to tocilizumab (IL-6 receptor antibody) or placebo during a 12-week intervention with either aerobic exercise training or no exercise [30, 45]. As expected, exercise training produced a reduction in visceral adipose tissue mass. However, this effect was abolished by IL-6 receptor blockade [30]. Moreover, IL-6 receptor blockade abolished the exercise-induced loss of cardiac fat [32]. In another placebo-controlled, non-randomised participant-blinded crossover study [46], we used tocilizumab to further investigate the role of endogenous IL-6 in regulating systemic energy metabolism at rest and during exercise and recovery in lean and obese men using tracer dilution methodology. We found that blocking endogenous IL-6 signalling with tocilizumab impairs fat mobilisation, which may contribute to expansion of adipose tissue mass and thus affect the health of individuals undergoing anti-IL-6 therapy.

EXERCISE AS MEDICINE

Today, noncommunicable diseases (NCDs), such as diabetes, cardiovascular diseases, cancer, chronic respiratory diseases and mental disorders, are responsible for more than 68% of deaths worldwide and 75% of deaths in low- and middle-income countries [47]. Two millennia ago, Hippocrates observed that “walking is man's best medicine”. Already then, the benefits of physical activity to health were recognised. Since then, the benefits of physical activity in lowering the risk of death from any cause and improving longevity have been well documented, and today exercise is prescribed as medicine for many chronic diseases [48].

The finding that exercise-induced myokines may mediate communication from muscle to distant organs contributes to providing a conceptual basis for prescribing exercise training as medicine for NCDs such as type 2 diabetes, cardiovascular disease, pulmonary diseases and cancer.

Here, I will mention just one example of an “Exercise-as-medicine” project. To test the effects of an intensive lifestyle intervention, we conducted a randomised study in 98 adult participants with type 2 diabetes who had been diagnosed for less than ten years. Participants were randomly assigned to the lifestyle group (n = 64) or to the standard care group (n = 34). All participants received standard care with individual counselling and standardised, blinded, target-driven medical therapy. Additionally, the lifestyle intervention included 5-6 weekly partly supervised aerobic training sessions (duration 30-60 minutes) of which 2-3 sessions were combined with resistance training. Participants were followed for 12 months. Reduction in glucose-lowering medications occurred in 73.5% of the participants in the lifestyle group and in 26.4% in the standard care group. After 12 months, 56% of the patients in the lifestyle group were without glucose-lowering medication [49]. Evidence exists that exercise has the potential to improve beta cell function and that this is associated with a decrease in low-grade inflammation [50, 51].

MAKING MORE PEOPLE MOVE

The physiology and molecular biology of exercise suggests that exercise activates multiple signalling pathways of major health importance. However, a need exists to close the gap between knowledge and practice and to translate basic research both into clinical practice and into political statements. In other terms: How do we make more people move?

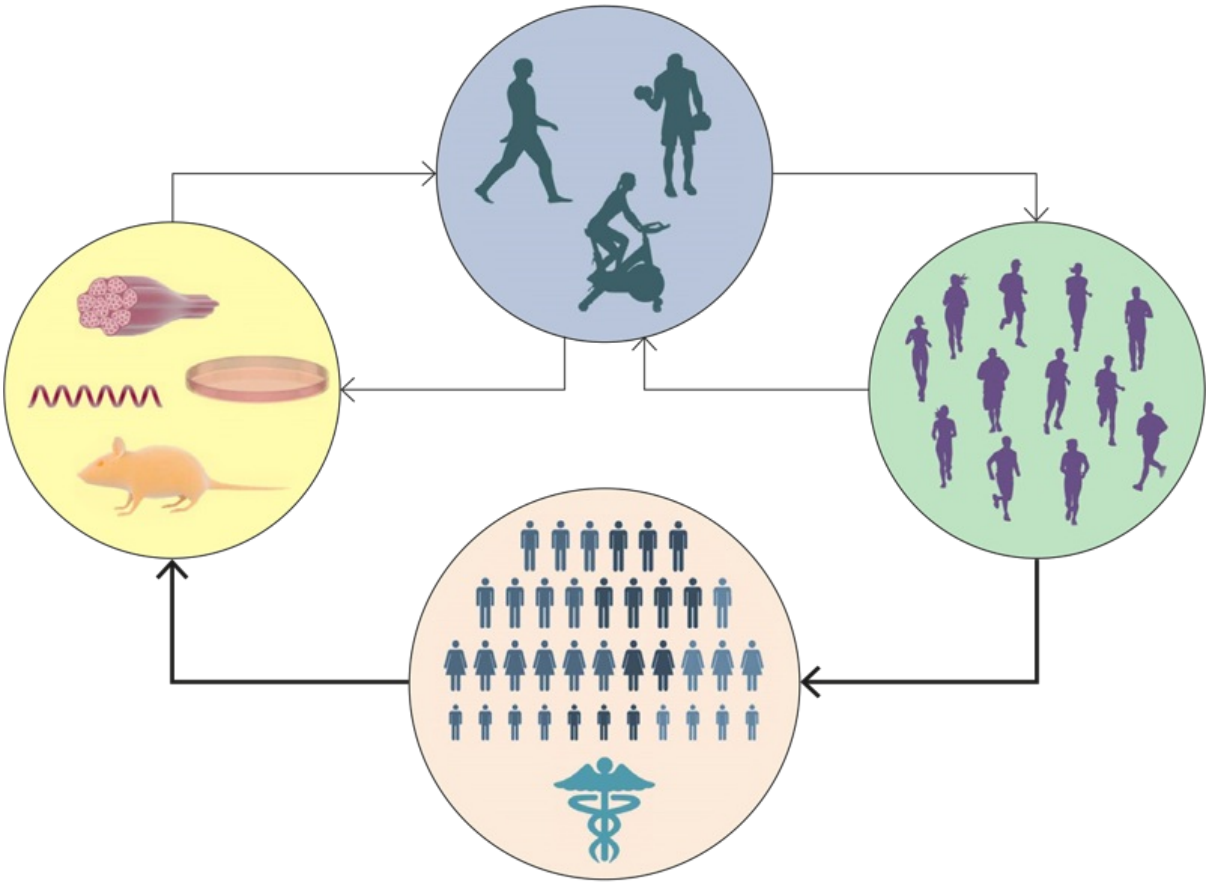
History clearly demonstrates that structural changes in a society have more impact on health than any group interventions or sophisticated discovery strategies [52]. Therefore, structural changes that make a healthy lifestyle more accessible to these communities will reduce health disparities [53].

Such physical activity interventions should include promoting walking and cycling as means of transportation. In addition, urban planners, schools and workplace designers should prioritise physical activity in their plans [54, 55]. We move more when the environment is interesting, aesthetic, green or with shops and restaurants nearby [54, 55]. We do not move simply because we are told to do so. We move to get forward!! We move when the context compels us to do so.

CONCLUSION

A translational research perspective on skeletal muscle as an endocrine organ and its relevance for exercise as medicine includes a bi-directional continuum from molecular events to sub-cellular, cellular, tissue and organ function, at the organism level using preclinical models, in human small-group studies and in human populations with direct implications for clinical practice and public health (**Figure 2**).

FIGURE 2 The model illustrates the translational structure of the Centre for Physical Activity Research. Effects of exercise on skeletal muscle can be studied: in vitro (e.g., human muscle cells in culture); in preclinical in vivo models; by applying classic human integrative physiological models; and in municipality and/or hospital-based settings to implement, anchor, and change praxis. The figure is modified from [36].



Correspondence *Bente Klarlund Pedersen*. E-mail: bente.klarlund.pedersen@regionh.dk

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