Review article

https://doi.org/10.6065/apem.2448218.109
Ann Pediatr Endocrinol Metab 2025;30:59-68

Annals of Pediatric Endocrinology & Metabolism
apem

Myokines and interorgan crosstalk: bridging exercise to health promotion and disease prevention

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Exercise is known to promote physical health and reduce the risk of various diseases. During exercise, skeletal muscle actively contracts to perform movements and secretes hormone-like molecules termed myokines. The beneficial effects of exercise have been assessed with respect to myokine production, and those of irisin on bone, adipose tissue, and the brain have been well documented. Irisin, through its interactions with the integrin αV family, plays a crucial role in bone maintenance, metabolic regulation, and cognitive function. Building on the established understanding of irisin, this discussion will examine the functions and effects of other myokines as key secretory factors in exercise, emphasizing their broader roles in health promotion and the potential for new therapeutic strategies in disease prevention and treatment.

Keywords: Exercise, Muscle, Bone, Adipocyte, Brain, Myokine, Irisin, Integrin

Highlights

- Skeletal muscle and bone act as a secretory organ to interact with other organs.
- Irisin mediates exercise effects on fat, bone and brain via integrin αV family.
- Various myokines have been identified upon different types of exercise.

Introduction

1. Types of exercise

Exercise has positive effects on various organs in the human body. According to the National Institutes of Health, there are four broad categories of exercise: endurance, resistance, balance, and flexibility. Endurance exercise is known to enhance cardiovascular and circulatory system functions; resistance exercise helps to increase muscle size and strength; balance exercise improves the ability to maintain proper posture; and flexibility exercise increases the range of motion in joints, reducing the risk of injury and improving athletic performance [1]. Among these four types of exercise, endurance and resistance exercise have been extensively studied in animal models and in numerous clinical trials. These studies have focused on the cellular effects of exercise in specific organs.

2. Systemic effects of exercise

1) Skeletal muscle

Endurance and resistance exercise induce distinct changes in skeletal muscle, including significantly increasing the ratio of type I to type II muscle fibers [2]. Type I muscle fibers, also known as slow-twitch muscle fibers, have a lower contraction force than type IIB and type IIX fibers but are resistant to fatigue. They primarily utilize lipids as an energy source and produce

Received: 31 August, 2024
Revised: 30 October, 2024
Accepted: 12 November, 2024

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ISSN: 2287-1012(Print)
ISSN: 2287-1292(Online)

Adenosine triphosphate (ATP) through oxidative mitochondrial metabolism. In humans, mitochondria in slow-twitch muscle fibers occupy about 6% of the muscle volume and are characterized by a high-density cristae structure. Additionally, the enzymes involved in the tricarboxylic acid (TCA) cycle in type I slow-twitch fibers are twice as active as fast-twitch fibers, as is the coenzyme oxidation capacity of electron transport [3]. These characteristics of slow-twitch fibers enable the skeletal muscle to produce energy for prolonged periods, supporting endurance exercise [2,3].

Conversely, resistance exercise leads to muscle hypertrophy and an increase in type IIB and type IIX muscle fibers [3]. These fibers, also known as fast-twitch muscle fibers, can generate strong contractions but fatigue quickly. Fast-twitch fibers utilize glucose as their primary energy source and rapidly produce ATP through glycolysis, providing energy for high-intensity, short-duration activities. The activity of phosphofructokinase, the rate-limiting enzyme in glycolysis, is higher in fast-twitch fibers than in slow-twitch fibers. Glycogen, the stored form of glucose, is more abundant in fast-twitch fibers, and the rate of glycogen breakdown is faster in these fibers when skeletal muscle is electrically stimulated to induce contraction. These features of fast-twitch fibers facilitate the performance of resistance exercises [3,4].

2) Bone

Bone is the organ that responds to both mechanical stress and hormonal changes during exercise, and numerous studies have been conducted to assess variations in bone upon exercise. For instance, increased bone density in the femur has been demonstrated after chronic regular resistance training in adults, with several biochemical mechanisms elucidated [5-9]. However, the effects of endurance exercise on bone present a more complex picture: some studies have reported positive effects of endurance exercise on bone density [10-13], while others have found no significant changes or even reduced bone density, with an increase in sclerostin, a protein that inhibits bone formation, detected in the plasma following endurance exercise [14]. Therefore, it is crucial to elucidate the effects of different types of exercise on bones, particularly by understanding the biochemical processes involved.

Research on bone cells has primarily focused on osteoblasts and osteoclasts. Osteoblasts are responsible for bone formation, while osteoclasts are involved in bone resorption. When subjected to external physical stimuli, osteoblasts are activated, leading to bone formation. Conversely, during lactation or in cases of calcium deficiency, osteoclasts resorb bone to maintain the body's calcium levels. Bone formation and resorption occur cyclically rather than unidirectionally. In healthy individuals, this cyclical process maintains bone homeostasis by ensuring that old minerals and micro-damaged areas are removed, allowing continuous renewal of bone. However, in conditions where bone resorption exceeds bone formation, as occurs in certain diseases, aging, or menopause, conditions like osteoporosis can develop [15].

The differentiation and activity of osteoblasts and osteoclasts are regulated by external stimuli and internal physiological changes, coordinated by osteocytes. Osteocytes, making up about 90% of bone cells, sense physical stimuli and hormonal changes during exercise to maintain bone homeostasis [15]. Osteocytes are derived from osteoblasts and located in bone canaliculi, where they regulate osteoblasts and osteoclasts to oversee bone remodeling [15,16]. Osteocytes secrete Wingless-related integration site and osteoprotegerin to promote bone formation by activating osteoblasts and inhibiting osteoclasts. Conversely, they secrete sclerostin and receptor activator of nuclear factor κB ligand to promote bone resorption by inhibiting osteoblasts and activating osteoclasts [15]. While the role of osteocytes in maintaining bone homeostasis through specific secretions is well known, research is needed to understand their responses and secretory functions during different types of exercise.

3) Other organs

The positive effects of exercise on health extend beyond the muscles and bones directly involved in physical activity. Exercise can reduce adipose tissue volume and inflammation, mitigate metabolic diseases such as nonalcoholic fatty liver disease, and enhance brain functions like memory. These findings demonstrate that the benefits of exercise are not confined to the muscles and bones but have comprehensive impacts across various body systems. Moreover, the effects on other organs are considered to be the result of complex mechanisms beyond the simple increase in energy expenditure [17].

However, the molecular-level understanding of exercise effects on different organs remains insufficient and requires further research. In particular, to leverage the positive effects of exercise for the development of therapeutic drugs, it is essential to accurately understand the roles and mechanisms of substances secreted during exercise. Therefore, it is essential to conduct biochemical studies on the effects of exercise.

3. Crosstalk between skeletal muscle and other organs upon exercise

As the primary organ recruited during exercise, skeletal muscle not only directly provides the contractile force for exercise, but also mediates the beneficial effects to other organs. For instance, studies have shown that muscle-specific knockout of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), a coactivator protein known to increase mitochondrial biogenesis and oxidative metabolism in skeletal muscle [18-24], leads to disturbance of glucose homeostasis due to hypoinsulinemia and hyperglycemia. The activity of PGC-1α is thought to be limited to skeletal muscle during the transformation to slow-twitch muscle fiber and to promotion of mitogenesis and vascularization. A study by Lin et al. [25] showed that skeletal muscle-specific PGC-1α overexpression leads to the formation of more 'reddish' muscle than the wild-

type, in which slow-twitch muscle fibers predominate. An additional role of skeletal muscle as a mediator of interorgan crosstalk via secretory factors was suggested by Handschin et al. [26] after investigating the reduction of insulin secretion by pancreatic β cells in skeletal-muscle-specific PGC-1α-knockout mice. The effects of muscle-specific PGC-1α knockout on systemic variations were investigated, and the morphology of pancreatic β cells, especially the size, was significantly reduced in the transgenic mice [19-21]. It was subsequently reported that skeletal-muscle-specific PGC-1α overexpression produced effects in various organs, including increasing thermogenic capacity in subcutaneous fat [27], preventing bone loss, and enhancing cognitive function [28] (Fig. 1). Together, these findings suggest that muscle-specific changes are not confined to the muscle itself but have effects on other organs such as the pancreas. These findings have evoked interest in the interactions between muscle and other organs, particularly focusing on the role of myokines—proteins secreted by skeletal muscle [26]. The crosstalk between skeletal muscle and other organs is thought to be mediated by various molecules, including circulating lipids and peptides and even central nervous system signals. In addition, there is strong evidence that cytokines, including interleukin-6 (IL-6), can act as myokines [29].

4. Secretory factors released during endurance exercise

In response to endurance exercise, muscle tissues release a range of secretory factors known as myokines that mediate diverse physiological effects such as metabolism, inflammation, and tissue repair across the body. Table 1 provides a summary of key myokines induced by endurance exercise, outlining their primary functions, target tissues, and contributions to exercise-induced metabolic and homeostatic adaptations. This compilation emphasizes the critical role of myokines in systemic health and metabolic resilience as part of the body's response to sustained physical activity.

1) Interleukin-6

Both the gene expression and plasma concentration of IL-6, one of the first myokines to be studied extensively, have been shown to increase as a result of endurance exercise. Clinical studies have shown that plasma IL-6 concentrations and skeletal muscle biopsy *IL-6* gene expression were elevated after a marathon compared to pre-race measurements [30]. Increased IL-6 expression is considered a mediator of the effects of endurance exercise. Administration of recombinant human IL-6 can elevate plasma IL-6 to concentrations similar to those measured postexercise and induces an anti-inflammatory response by inhibiting tumor necrosis factor production. Additionally, IL-6 has been confirmed to contribute to increased endogenous glucose production, demonstrating its role in interactions between skeletal muscle and the liver [31-33].

2) FNDC5/Irisin

After researchers first shed light on possible crosstalk between skeletal muscle and other organs, the downstream signaling factor PGC-1α was investigated as a putative mediator (Fig. 1). In response to endurance exercise, the mRNA expression of PGC-1α and of the downstream Fibronectin type III domain containing 5 (FNDC5) increases significantly [27,34-

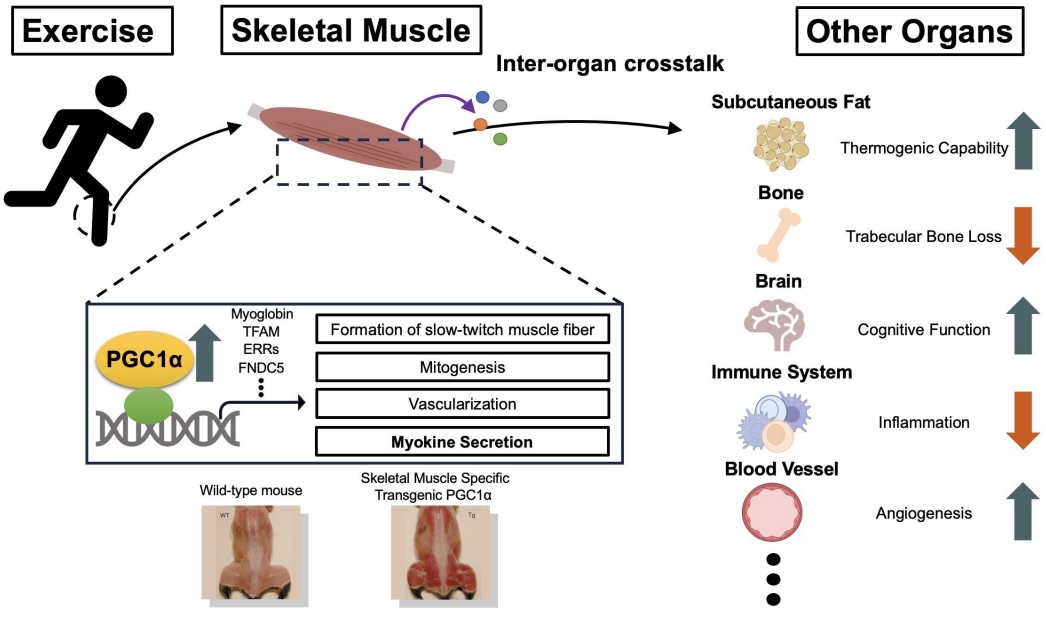

Fig. 1. Scheme of PGC-1α-mediated interorgan crosstalk between skeletal muscle and other organs during exercise. The activity of PGC-1α is not limited to skeletal muscle, but is also evident in other organs including the pancreas and fat. PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; TFAM, mitochondrial transcription factor A; ERRs, estrogen-related receptors; FNDC5, fibronectin type III domain containing 5.

36]. The FNDC5 type I membrane protein is cleaved to form irisin, (named after Iris, the Greek messenger goddess), which is secreted into the extracellular milieu and circulation to be delivered to other organs such as subcutaneous fat, bone, and brain [27,34].

(1) Fat

In subcutaneous adipose tissue, the exercise-induced hormone irisin promotes the expression of thermogenic genes, particularly uncoupling protein 1 (UCP1), a central mediator of mitochondrial heat production. This upregulation of UCP1, along with other thermogenic factors, contributes to an increase in energy expenditure, not only through direct energy consumption during physical activity, but also by enhancing heat generation [27]. Thus, irisin facilitates a key metabolic benefit of exercise through molecular modulation of thermogenesis.

Furthermore, irisin enhances thermogenic capacity in subcutaneous adipose tissue by expanding a specialized subset of adipocyte progenitor cells (APCs) known as beige APCs [37]. These beige APCs, identified by the cell surface marker CD81, play a crucial role in adaptive thermogenesis in response to cold and physical exercise [37]. Notably, CD81 forms a complex with integrins αV/β1 and αV/β5, mediating activation of integrin-focal adhesion kinase (FAK) signaling upon irisin stimulation to drive the proliferation of these progenitor cells [37].

Collectively, irisin enhances basal thermogenesis in subcutaneous adipose tissue by upregulating thermogenic gene expression and promoting the proliferation of thermogenic beige APCs in response to endurance exercise. This process is a critical pathway through which exercise exerts beneficial effects on energy balance and metabolic health as a result of cellular adaptations within adipose tissue.

(2) Bone

The effects of endurance exercise on bone health remain controversial, and the impacts of exercise on bone formation and resorption have not been elucidated fully [5,7-10,12-14]. To determine whether irisin influences bone formation and/or resorption, the impact of FNDC5 knockout in bone

Table 1. Factors secreted during endurance exercise and resistance exercise and their functions and known receptors

Exercise type	Secretory factors	Functions	Receptor/signaling
Endurance exercise	Interleukin-6	Induces anti-inflammatory response by inhibiting tumor necrosis factor production [30,32] Contributes to increased endogenous glucose production [31]	IL-6R, gp130 [32]/PI3K, AMPK, JAK-STAT3 pathway [91]
	Fibronectin type III domain containing 5 (Shed form: Irisin)	Upregulates thermogenesis and proliferation of thermogenic fat cells [28] Contributes to bone resorption [37] Reduced amyloid-β24 in an Alzheimer disease model and reduced accumulation of α-synuclein fibrils in a Parkinson disease model [40,41]	Integrin αV Family [38]/Integrin-FAK-CREB pathway [37,38]
	Neurin	Promotes transformation of muscle fibers toward slow-twitch fiber phenotype, enhances mitochondrial function, and promotes angiogenesis [55]	RET, GFRα2/RET pathway [57]
	Fibroblast growth factor	Increases fatty acid oxidation and respiratory capacity in mitochondria [34,62]	FGFR, Klotho/ APK pathway [63]
	β-aminoisobutyric acid	Upregulates thermogenic gene expression [66] Contributes to glucose homeostasis by inducing β-oxidation [67,68] Contributes to bone homeostasis by preventing ROS-induced cell death [69]	MrgD/MrgD pathway [92]
	Secreted protein acidic and rich in cysteine	Participates in AMPK-mediated glucose regulation and improves glucose tolerance [93,94]	AMPK pathway [91]
	Musclin, Osteocrin	Stimulate osteogenic differentiation and bone formation [95] Promote mitochondrial biogenesis [96]	NPR/CNP pathway [92]
Resistance exercise	Myostatin	Inhibits fatty acid oxidation and respiratory capacity in mitochondria Inhibits fatty acid oxidation and brown adipocyte formation [84,85] Reduces glucose uptake and insulin sensitivity [86]	ActRIIA, ActRIIB/mTORC1 pathway [84]
	Meteorin-like	Upregulates thermogenic gene expression [88]	IL-4/IL-13 pathway [90]

IL-6R, Interleukin 6 receptor; PI3K, Phosphatidylinositol 3-kinase; AMPK, AMP-activated protein kinase; JAK-STAT3, Janus kinase-signal transducer and activator of transcription 3; Integrin-FAK-CREB, Integrin-focal adhesion kinase-cAMP responsive element binding protein; RET, Ret proto-oncogene; GFRα2/RET, GDNF family receptor alpha 2/Ret proto-oncogene; MrgD/MrgD, Mas-related G protein coupled receptor; NPR/CNP, Natriuretic peptide receptor/C-type natriuretic peptide.

was assessed in the lumbar vertebrae of ovariectomized mice, a model that simulates menopause in humans [38,39]. Surprisingly, FNDC5-knockout mice showed resistance to ovariectomy-induced bone loss [38], suggesting that irisin may contribute to bone resorption in response to endurance exercise.

Interestingly, irisin appears to play distinct roles depending on sex and physiological context [40]. Irisin is essential in the development of the male skeleton, protecting it from calcium deficiency. However, this protective effect does not extend to females, in whom irisin may instead serve a unique role by targeting osteocytes to mobilize calcium stores during lactation, ensuring sufficient calcium availability for offspring.

Irisin's role in bone resorption suggest it as a promising therapeutic target for menopause-related osteopenia and osteoporosis. Plasma irisin concentrations were greater in ovariectomized mice than in a control group [38], and FNDC5 overexpression exacerbated bone loss in ovariectomized mice, particularly in calcium-deficient or hormonally altered states such as menopause [41].

(3) Brain

Irisin is also implicated in cognitive enhancement, as demonstrated in studies using FNDC5-knockout mice and Alzheimer disease (AD) models [42-44]. These studies indicate that irisin decreases amyloid β42 and prevents AD-induced neuronal cell death, contributing to the cognitive benefits of exercise [42-44]. Moreover, irisin has been shown to reduce the accumulation of α-synuclein fibrils in models of Parkinson disease [45], suggesting its potential as a treatment for neurodegenerative diseases including AD and Parkinson disease.

(4) Mechanism of action for irisin

The molecular mechanism by which irisin binds to target receptors and transduces signals in target organs is not known. Members of the integrin αV family were identified as irisin receptors in a study using the murine osteocyte like cell line osteocyte cell line after applying quantitative proteomics utilizing mass spectrometry [38]. Osteocytes act as command-control cells to maintain bone homeostasis [15]. To determine the specificity of these receptors for irisin, the irisin-integrin binding assay was performed and confirmed that the integrin αV family directly interacts with irisin. Additionally, irisin-integrin binding motifs were identified through hydrogen-/deuterium-exchange mass spectrometry and mapped at an atomic level using cryogenic electron microscopy (cryo-EM) [46]. Furthermore, the molecular mechanism of irisin-mediated effects of endurance exercise in fat, bone, and brain has been studied through signaling response and function tests upon integrin αV family-irisin interactions [47]. Previous studies of integrin signaling have established phosphorylation of FAK integrin as the major signal transduction event of integrin activation [48-50], and various irisin functional assays have confirmed this activity. The gene expression of sclerostin, which is essential for bone resorption and known to be induced by irisin, has been investigated in irisin-treated osteocytes co-incubated with inhibitors of integrin-ligand binding, such as RGDS peptide [51,52] and echistatin [53], and integrin αV-ligand binding inhibitors such as cyclo-RGDyK peptide [54,55]. The results indicated the activity of integrin αV family members as irisin receptors to mediate the effects of endurance exercise through FAK signaling pathways. Furthermore, cell and in vivo studies have shown that CD81 is essential for irisin-integrin αV signaling and its role in beige fat [37].

3) Neurturin

Since irisin was identified, people have tried to identify other exercise-induced hormones [56]. One such compound is neurturin, a myokine secreted by skeletal muscle in response to endurance exercise and has been reported to impact motor neurons [57]. In 1996, a novel neurotrophic factor that contributes to cell survival was discovered during the culture of sympathetic neurons, and this factor was named neurturin [58,59]. In the skeletal muscle of genetically modified mice with muscle-specific overexpression of the *PGC-1α* gene, which mimics endurance-trained mice, neurturin is secreted [60]. Similarly, the gene expression of neurturin was upregulated in skeletal muscle from mice that underwent chronic endurance exercise training [57]. Increased secretion of muscle-derived neurturin contributes to the crosstalk between skeletal muscle and motor neurons [57]. Neurturin promotes motor neuron remodeling to induce a slow motor neuron phenotype [57], which leads to the transformation of muscle fiber types toward slow-twitch fibers by improving mitochondrial function, promoting angiogenesis, and reprogramming glucose and lipid metabolism for muscle cells to perform fatty acid oxidation [57]. Therefore, the induction of skeletal-muscle-derived neurturin during endurance exercise improves motor coordination and exercise performance.

4) Fibroblast growth factor 21

Fibroblast growth factor 21 (FGF21) is primarily recognized as a hepatokine, originating from the liver, but its expression and function are also well-documented in adipose tissue [61] and the pancreas [61,62]. Overexpression of FGF21 in the liver or pharmacological administration of recombinant FGF21 protein has produced various effects, including increased insulin sensitivity and reduced blood glucose and plasma triglyceride concentrations in mice fed high-fat diets. In addition, FGF21 receptors are the conjugated form between FGF receptor 1c and an essential cofactor Klotho including α-Klotho and β-Klotho [63]. Physiologically, plasma FGF21 concentration increases in response to stressors such as exercise or cold. In skeletal muscle, FGF21 is expressed as a myokine, upregulated in plasma by endurance exercise [35,64,65], and has been shown to influence energy metabolism [66]. Muscle-derived FGF21 acts on white adipose tissue to increase fatty acid oxidation and respiratory capacity [61].

5) β-Aminoisobutyric acid

Intermediate metabolites of signaling proteins can also serve as mediators of exercise effects by being secreted from muscle. The metabolite β-aminoisobutyric acid (BAIBA) is secreted in mice that overexpress the muscle-specific PGC-1α gene as a model of endurance training [67]. The BAIBA metabolite increases the expression of thermogenic genes in subcutaneous white adipose tissue [68]. In addition to its effects on white adipose tissue, BAIBA contributes to glucose homeostasis by inducing β-oxidation in the liver [69,70]. Moreover, BAIBA secreted from skeletal muscle during exercise acts on osteocyte mitochondria, preventing cell death caused by reactive oxygen species and contributing to bone homeostasis [71]. The BABA metabolite may be secreted and act as a hormone to impart the effects of exercise on other organs. Further studies of the roles of other exercise-induced metabolite hormones, such as N-lactoyl-phenylalanine [72] and succinate [73], offer a deeper understanding of exercise.

5. Secretory factors induced by resistance exercise

In addition to endurance exercise, resistance exercise also prompts the secretion of distinct myokines from muscle tissue. 1 presents an overview of key myokines stimulated by resistance exercise, describing their primary roles and target tissues to underscore their impact on the body's adaptive response to strength training.

1) Myostatin

Myostatin, identified in the early 2000s as a myokine directly involved in the regulation of muscle size by direct interaction with activin type II receptors [74-79], has been a primary target for research regarding muscle hypertrophy induced by resistance exercise [80] and therapeutic agents for muscle-wasting diseases [81-83]. Research has highlighted that the expression and secretion of myostatin decrease during resistance exercise, leading to increased muscle size. However, a proportional increase in muscle strength has not been reported, and the strength per unit muscle area was found to be less than in wild-type mouse models [81-84]. Various interpretations have been proposed for this phenotype. From an energy metabolism perspective, it is thought that the reduction in mitochondrial respiration in muscle lowers the beta-oxidation of fatty acids, which is a major energy supply factor [85]. The role of myostatin as a myokine has also been studied with respect to its interactions with adipose tissue and the liver. Myostatin inhibits beta-oxidation of fatty acids and brown adipose tissue formation [86,87]. In the liver, myostatin is associated with reduced glucose uptake and insulin sensitivity, potentially increasing insulin resistance [88].

2) Meteorin-like

Research on the PGC-1α4 isoform led to the discovery of a distinct myokine known as meteorin-like (Metrnl) [89]. Muscle-cell-specific overexpression of PGC-1α4 in mice resulted in increased skeletal muscle mass and strength, as well as elevated expression of thermogenic genes, including UCP1, in both subcutaneous and visceral adipose tissues. Similarly, gene microarray and mass spectrometry analyses identified Metrnl in primary myotubes overexpressing PGC-1α4. It was also confirmed that Metrnl secretion increases in the skeletal muscle of exercise-trained mice [90]. Secreted Metrnl promotes activation of adipose tissue macrophages through IL-4 and IL-13 secreted from eosinophils [90]. The IL-4/IL-13

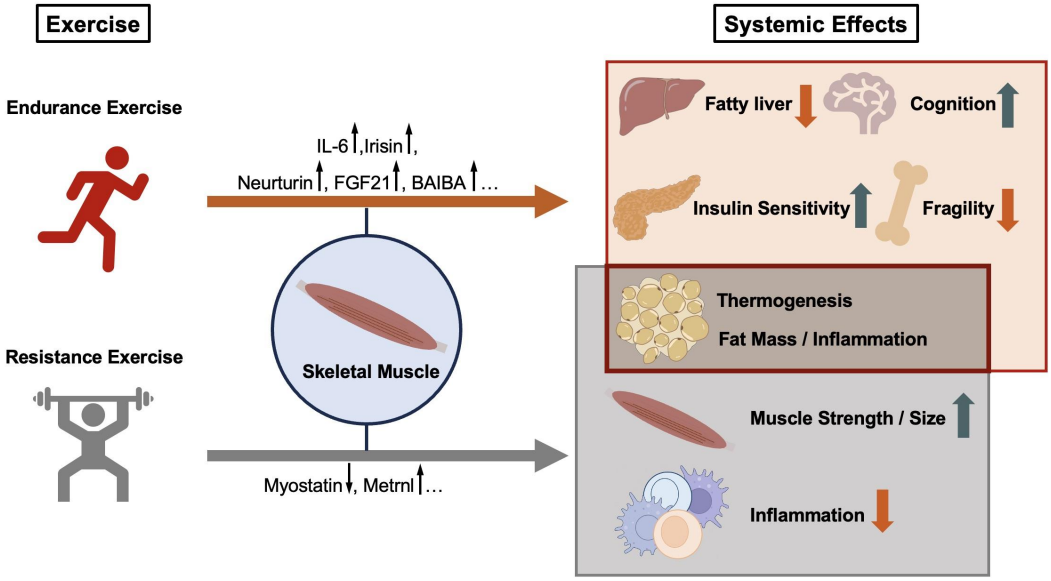

Fig. 2. Secretion of skeletal-muscle-derived protein and metabolite hormones during different types of exercise induces systemic effects on many organs. IL-6, interleukin-6; FGF21, Fibroblast growth factor 21; BAIBA, β-aminoisobutyric acid; Metrnl, meteorin-like.

signaling pathway induces the expression of thermogenic genes in subcutaneous and visceral white adipose tissue, inducing browning and contributing to enhanced energy expenditure

Conclusion

Skeletal muscle, as the organ most directly impacted by physical exercise, undergoes specific structural and biochemical changes depending on the type and intensity of activity. Different exercise modalities influence muscle fiber composition distinctly, creating a mosaic of possible adaptations that extend to various body systems through the secretion of myokines and metabolic hormones [2-4]. These muscle-derived factors such as protein hormones like irisin [27] and neurturin [57] and metabolic compounds including BAIBA [67], N-lactoyl-phenylalanine [72], and succinate [73] are mediators that extend the effects of exercise beyond muscle tissue itself, promoting metabolic, musculoskeletal, and neurological health benefits (Fig. 2). However, while the biochemical understanding of exercise-induced benefits is evolving, many molecular mechanisms remain unclear, and targeted therapeutic strategies based on obtained insights are under development.

The potential of exercise as a therapeutic intervention has been demonstrated across various health conditions, with strong evidence supporting its role in preventing metabolic disorders (e.g., obesity, diabetes, nonalcoholic fatty liver disease), musculoskeletal diseases (e.g., sarcopenia, muscular dystrophy, osteoporosis), and neurodegenerative conditions (e.g., AD, Parkinson disease). Additionally, exercise has shown promise in reducing the risk of certain cancers, such as colorectal and breast cancer, and may even delay progression in some cases. To harness these benefits fully, there is an urgent need to understand the molecular processes involved in exercise tolerance and plasticity, particularly through myokine research. Notably, further studies into myokine expression and secretion across muscle fiber types could reveal crucial biochemical pathways driving exercise adaptations. For instance, examining the roles of FNDC5 and irisin secretion in specific muscle fiber types may provide valuable insights into the effects of distinct muscle characteristics on whole-body health outcomes.

Biochemical studies of exercise should include a comprehensive range of analyses—from genetic to protein-level changes and their post-translational modifications—considering the unique responses of each fiber type to physical stimuli. This knowledge will be instrumental in advancing therapeutic strategies that replicate the effects of exercise, particularly for populations where direct exercise interventions are challenging due to age or physical limitations. With an aging society facing an increasing incidence of exercise-modifiable diseases, the development of therapeutic agents that can mimic the effects of physical exercise is critical. Such agents could not only facilitate effective management of age-associated metabolic, musculoskeletal, and neurological disorders, but also contribute to cancer prevention strategies. Ultimately, research that deepens our understanding of muscle fiber-specific myokine expression and secretion will pave the way for next-generation therapeutics that target the unique biochemical effects of each muscle fiber type, providing tailored interventions that mimic the multifaceted benefits of exercise.

Notes

Conflicts of interest: Hyeonwoo Kim holds a patent related to irisin (WO2019157495A3). Except for that, no potential conflict of interest relevant to this article was reported.

Funding: This study was supported by a grant from the National Research Foundation of Korea (NRF; RS-2023-00213512).

Author contribution: Conceptualization: HK; Data curation: HK, JH, SS; Funding acquisition: HK; Project administration: HK; Visualization: HK, JH, SS; Writing - original draft: HK, JH, SS; Writing - review & editing: HK, JH, SS

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