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Skeletal muscle as an endocrine organ: PGC-1α, myokines and exercise

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Abstract

An active lifestyle is crucial to maintain health into old age; inversely, sedentariness has been linked to an elevated risk for many chronic diseases. The discovery of myokines, hormones produced by skeletal muscle tissue, suggests the possibility that these might be molecular mediators of the whole body effects of exercise originating from contracting muscle fibers. Even though less is known about the sedentary state, the lack of contraction-induced myokines or the production of a distinct set of hormones in the inactive muscle could likewise contribute to pathological consequences in this context. In this review, we try to summarize the most recent developments in the study of muscle as an endocrine organ and speculate about the potential impact on our understanding of exercise and sedentary physiology, respectively.

Keywords

Skeletal muscle; exercise; myokines; inflammation; PGC-1α

1.1 Skeletal muscle morphology and function

The human body consists of around 600 muscles that contribute to approximately 40%-50% of the total body weight. Similar to cardiac muscle, skeletal muscle is a striated muscle, is attached to the skeleton and thereby facilitates the movement of the body by applying force to bones and joints. Skeletal muscle is composed of myofibers that are formed by the fusion of individual myoblasts during a process called myogenesis. Muscle plasticity, for example the adaptation to exercise, is facilitated by a switch between oxidative, slow-twitch and glycolytic, fast-twitch muscle fibers [1]. The former are characterized by a high mitochondrial number, rich capillary supply, slow twitch frequency and high resistance against fatigue. The ample vascularization and the abundance of heme-containing proteins confer a red color to muscle beds with a high proportion of oxidative fibers. On the other hand, low mitochondrial number, fast twitch contraction kinetics, high peak force and low endurance are the functional hallmarks of glycolytic muscle fibers. Muscle beds consisting of glycolytic fibers appear more whitish in color. In rodents, type I and type IIa fibers are considered oxidative while type IIx and type IIb are more glycolytic. In humans, the spectrum of muscle fiber types is restricted to type I, IIa and IIx as well as hybrid fibers [2].

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Myofibrils are composed of actin and myosin filaments arranged in sequentially repeated units called sarcomeres, the basic functional units of a muscle fiber that enables the muscle to contract. Skeletal muscle cells are the only voluntary type of muscle cells in contrast to cardiac muscle, smooth muscle and myoepithelial cells. Skeletal muscle cells are innervated by motor neurons and action potentials are exclusively initiated by the neurotransmitter acetylcholine in this context. Once a muscle cell is sufficiently depolarized, the sarcoplasmic reticulum releases calcium in a ryanodine receptor-dependent manner. Calcium subsequently binds to the troponin C subunit of the troponin complex. Troponin and tropomyosin are two important regulatory proteins, which are associated with actin to prevent interaction with myosin in the rested state. Calcium-bound troponin C then undergoes a conformational change that leads to an allosteric modulation of tropomyosin, which subsequently allows myosin to bind to actin. ATP-dependent cross bridging between myosin and actin then leads to a shortening of the muscle. Finally, calcium is pumped back into the sarcoplasmic reticulum by sarcoplasmic/endoplasmic reticulum calcium ATPases (SERCA) ultimately resulting in muscle fiber relaxation.

It is important to note that muscle function is not limited to the generation of power, locomotion, posture and breathing. In fact, shivering skeletal muscle is the most important organ for the maintenance of body temperature besides non-shivering thermogenesis by brown adipose tissue. Furthermore, skeletal muscle is one of the largest energy stores with substantial amounts of triglycerides and glycogen, in particular in trained subjects. In addition, anaerobic glycolysis and breakdown of skeletal muscle tissue during starvation releases lactate and amino acids, respectively, some of which subsequently are utilized to fuel hepatic (mainly alanine and lactate) and renal (mainly glutamine) gluconeogenesis. Thus, skeletal muscle has long been known to be capable of secreting factors in order to communicate with non-muscle tissues. However, more recently, such auto-, para- and endocrine mediators produced and released by skeletal muscle have been termed “myokines”, in analogy to the adipokines produced by adipose tissue. These secreted factors potentially have far-reaching effects on non-muscle tissue and thereby could provide a molecular link between muscle function and whole body physiology. This review will mainly focus on the biology of a selection of such myokines.

1.2. Skeletal muscle plasticity

Repeated contractions, for example in training, result in a pleiotropic adaptation of muscle cells with a dramatic remodeling of contractile and metabolic properties. Importantly, the diametrically opposite activation pattern in endurance and resistance training elicit distinct cellular consequences. For example, endurance training results in a switch to oxidative, slow-twitch muscle fibers while resistance exercise increases the proportion as well as the cross-sectional area of glycolytic muscle fibers. Surprisingly, the molecular mediators of these adaptations are only poorly understood [3]. It is clear that slow-type activation results in a more continuous elevation of intracellular calcium with low amplitude whereas these transients are characterized by more intermittent spikes with a high amplitude in glycolytic fibers in resistance training [4]. Nevertheless, it is unclear how the distinct calcium levels are interpreted to result in either a slow- or a fast-type gene program. For example, in both cases, the intracellular increase in calcium activates the catalytic subunit of the phosphatase

calcineurin A (CnA) and members of the calcium/calmodulin-dependent protein kinase family (CaMK) leading to a change in the phosphorylation status of different transcription factors and coactivators. These transcription factors include the cyclic-AMP-responsive-element-binding protein (CREB), myocyte-enhancer factor 2C (MEF2C) and MEF2D, and members of the nuclear factor of activated T cells (NFAT) family. In resistance-trained muscle, growth factor signaling, in particular that initiated by the insulin-like growth factor 1 (IGF-1), seems to be an important modifier of the ensuing muscle cell remodeling. In endurance-trained muscle, MEF2C/2D and NFAT regulate the gene expression of slow-type genes. In addition, CREB, MEF2C/2D and NFAT control the transcriptional rate of the peroxisome-proliferator activated receptor γ coactivator 1α (PGC-1α) [5]. This transcriptional coactivator constitutes a regulatory nexus in the adaptation of skeletal muscle to endurance training [6, 7]. Accordingly, in addition to the regulation by calcium signaling, PGC-1α gene expression and posttranslational modifications are affected by every major signaling pathway that is activated in a contracting muscle fiber (Fig. 1). In turn, PGC-1α coordinates the entire program of endurance training adaptation in skeletal muscle. For example, PGC-1α is recruited to more than 7500 distinct sites in the mouse genome and induces and inhibits the transcription of around 984 and 727 genes, respectively, in muscle cells [8]. Such a complex transcriptional response is enabled by a specific interaction with a high number of transcription factor binding partners and furthermore, selective modulation of the PGC-1α activity by additional co-regulators, e.g. competition with the corepressor NCoR1 for binding to the estrogen-related receptor α (ERRα) [9] in the regulation of mitochondrial genes [10]. Thus, when overexpressed in muscle, transgenic mice exhibit a trained phenotype [11] while skeletal-muscle-specific knockout animals for PGC-1α suffer from a reduced endurance capacity as well as other signs of pathological inactivity [12, 13]. In individual exercise bouts, stabilization of existing PGC-1α protein by the p38 mitogen-activated protein kinase (p38 MAPK) [14], phosphorylation by the AMP-dependent kinase (AMPK) [15], other posttranslational modifications and subsequent transcriptional induction ensure a rapid and robust elevation of PGC-1α activity [16, 17]. Upon cessation of muscle contraction, the short half-life of the PGC-1α protein and a reduction in the gene transcription help to revert PGC-1α levels back to baseline expression within hours. Chronic exercise, e.g. in endurance training, promotes a shift towards a higher proportion of slow-type muscle fibers. Due to the fiber-type preference in PGC-1α gene expression, endurance-trained muscle exhibits higher basal transcript levels of PGC-1α while retaining the acute induction in each exercise bout [11, 18]. Due to the potent effect of PGC-1α on muscle function, modulation of the levels and/or activity of this coactivator might provide an interesting therapeutic avenue for metabolic and other diseases that are linked to an inactive muscle [19, 20]. At least experimentally, elevation of PGC-1α and its homolog PGC-1β indeed ameliorated several different muscle wasting pathologies in various mouse models of Duchenne muscular dystrophy [21, 22] and a mitochondrial myopathy [23]. In the context of metabolic diseases, the results are less clear and it seems that *bona fide* physical activity is required to synergize the effect of overexpressed PGC-1α to improve diet-induced insulin resistance [24, 25].

1.3. The broad effect of physical inactivity on health

A sedentary lifestyle is defined by a lack of or irregular physical activity and is one of the leading causes of preventable deaths worldwide [26, 27]. For example, sedentariness can contribute to the development of a number of chronic diseases, such as type 2 diabetes [28], cardiovascular pathologies [29], obesity [30, 31], postmenopausal breast cancer and other tumors [32]. Furthermore, physical inactivity may also play a role in the development of dementia [33], depression [34] and neurodegenerative events [35].

A persistent, sterile, inflammation is one of the most obvious features of physical inactivity [36]. Chronic, systemic inflammation most likely promotes the development of insulin resistance, atherosclerosis, neurodegeneration and tumor growth [36]. Historically, an excess of adipose tissue, as in the context of obesity, has been demonstrated to secrete increased amounts of the pro-inflammatory cytokines tumor necrosis factor-α (TNFα), interleukin 1-β (IL-1β) and IL-6 in both rodents and humans [37, 38], thus, contributing substantially to the chronic systemic inflammation. More recently, other organs, including liver and skeletal muscle, have been discovered as additional sources of pro-inflammatory cytokines in pathological settings [39, 40]. For example, the reduced expression of PGC-1α in skeletal muscle resulting from a sedentary lifestyle or gene ablation results in a low-level local as well as systemic inflammatory response, which then elicits negative impacts on other tissues such as pancreatic β cells [41]. Inversely, PGC-1α reduces the activity of the nuclear factor κB (NFκB), the master regulator of pro-inflammatory gene expression [42]. Thus, by contributing to the production of pro-inflammatory cytokines, inactive muscles in a sedentary individual might negatively affect other organs and ultimately, whole body homeostasis [36].

1.4. Exercise and its beneficial effects on skeletal muscle and whole body metabolism

The beneficial effects of exercise transcend improved skeletal muscle functionality. For example, moderate exercise has been shown to increase life span in rats [43], to improve neuromuscular and neurological performance in mice [44] and to lower hyperglycemia [45, 46], hypercholesterolemia [47] and hypertension [48]. Similarly, systemic responses to exercise have been observed in distal organs like heart, kidney, brain and liver in various animal models [44, 49-51]. Epidemiological studies have likewise linked an active life-style to systemic adaptations and an elongated health-span, thus time of life in good health, in different human cohorts [52]. Intriguingly, many of these effects even occur in elderly individuals that only initiate exercise at advanced age highlighting the high efficacy of exercise as an intervention for the prevention and/or treatment for various ailments. To date, the mechanisms that link physical activity to health remain unknown. Nevertheless, several hypotheses have been proposed to contribute to the beneficial effects of exercise. For example, the sought-after whole body adaptations to exercise could be induced by a general reduction in systemic inflammation since inversely, a persistent, sterile inflammatory state has been linked to the etiology of many chronic diseases [36, 53]. Thus, regular physical activity acutely increases the release of adrenaline, cortisol, growth hormone, prolactin and other factors with immunomodulatory effects [54]. Importantly however, long-term training

is associated with decreased circulating levels of the classical stress hormones. Moreover, exercise reduces the expression of Toll-like receptors at the surface of monocytes that have been implicated as mediators of systemic inflammation [55]. Importantly, very high intensity exercise bouts themselves trigger systemic inflammation, a subsequent immunodepression and thus a higher risk for infections [56]. Muscle function, inflammation and exercise are hence intrinsically linked in a complex manner [36, 40]. Therefore, not surprisingly, many myokines, for example interleukin 6, have also been described as prototypical pro-inflammatory cytokines. Induction of beneficial versus detrimental effects therefore seems highly context-specific and might depend on the amplitude, frequency and other variables in secretion.

2.1. Myokines

It is now firmly established that skeletal muscle tissue produces and secretes cytokines and other proteins, which have been named “myokines” [57]. Myokines subsequently exert auto-, para- and/or endocrine effects (Fig. 2). Thus, skeletal muscle can be classified as an endocrine organ. Since the description of the first members, the list of myokines has constantly been growing demonstrating that skeletal muscle has the capacity to express several myokines, some simultaneously, others in a temporally- or context-controlled manner. For most currently described myokines, contractile activity is the key regulatory element for expression and secretion. In this review we will focus on some of the classical as well as some of the more exotic myokines, describe their regulation in skeletal muscle and their possible systemic effects on distal non-muscle tissues. Furthermore, we will highlight the newest members of the myokine family and their potential application in combating metabolic diseases.

2.2. Myostatin

Myostatin (MSTN) is a member of the transforming growth factor β (TGF-β) superfamily that is expressed in the developing and adult skeletal muscle. The main function of myostatin is to negatively regulate muscle mass [58]. Evolutionarily, actively limiting muscle growth might have helped to prevent the build-up of energy-consuming muscle mass beyond the needs of the current situation. Accordingly, myostatin null mice exhibit a massive muscle hypertrophy that is characterized by an increased fiber cross-sectional area as well as an elevated number of fibers. The hyperplasia in this animal model most likely originates from accelerated primary and secondary myogenesis. Importantly, the myostatin gene is highly conserved among different vertebrate species. For example, myostatin mutations in some domestic breeds of cattle including the Piedmontese, Belgian Blue and Marchigiana result in a so called double-muscling phenotype and hence pronounced muscle hypertrophy [59-61]. Similar double muscling phenotypes have been observed in sheep and the whipped dog breed that leads to increased muscle mass and racing performance in the latter [62]. Finally, a mutation in the myostatin gene has also been associated with muscle hypertrophy in a male child with extraordinary muscularity and several relatives with self-reported unusual strength [63].

In addition to the hypertrophic muscle phenotype, myostatin null mice show reduced total and intramuscular body fat compared to wild-type animals [58, 64]. An increase in muscle mass leads to increased resting energy expenditure (REE), which in turn could account for the reduction in fat mass in myostatin knockout animals [58]. Accordingly, circulating levels of leptin, the “satiety hormone”, are reduced in these mice [64, 65] hence suggesting that despite decreased leptin secretion, myostatin null mice are protected from the counter-regulatory consequence of leptin signaling on energy expenditure. Moreover, myostatin might directly influence the cellular physiology of adipocytes even though the results are conflicting. For example, myostatin inhibits the differentiation of 3T3-L1 preadipocytes and reduces the expression of several adipogenic markers and transcription factors such as the peroxisome proliferator-activated receptor γ (PPARγ), CCAAT-enhancer-binding protein α (C/EBPα), adipocyte protein 2 (aP2) and leptin [66, 67]. In contrast, in a multipotent mesenchymal cell line (C3H10T1/2), myostatin promotes adipogenesis, which would be more in line with the reduced adiposity in myostatin knockout animals [68, 69]. Inversely however, pharmacological administration of myostatin *in vitro* and *in vivo* is not able to increase lipolysis and to reduce fat mass [67] suggesting that the reduction in body fat in myostatin null animals is indeed due to the increased muscle mass and only to a lesser extent to direct effects on adipose tissue.

Even though not called a myokine at the time of its discovery, myostatin is one of the first members of this class of proteins. However, since both aerobic exercise [70-73] and strength training [74-78] in animals and humans significantly reduce expression in skeletal muscle, myostatin is more like an “inverse” myokine compared to most other family members that are elevated by exercise. In addition to transcript levels, serum myostatin also decreases with resistance training in young men [79].

2.3. Decorin

In contrast to myostatin, decorin is a more recently discovered myokine that is elevated in mice and humans after acute and chronic resistance exercise [80]. Overexpression of decorin in transgenic models resulted in a pro-hypertrophic gene program, for example elevated Mighty, MyoD and follistatin gene expression. Decorin seems to act in a paracrine manner by directly binding to and thereby inhibiting the action of myostatin [80]. Therefore, decorin can act as a myokine that antagonizes the effects of another myokine, in this case myostatin, and in addition also neutralize myostatin of non-muscle origin, for example myostatin released from tumor cells in cancer cachexia [81].

2.4. Interleukin-6

Interleukin-6 (IL-6) has originally been classified as a prototypical pro-inflammatory cytokine while later, anti-inflammatory properties have also been described [82]. Besides the production of IL-6 in activated immune cells, the systemic elevation of IL-6 in patients with metabolic diseases has contributed to the link of IL-6 and inflammation. Moreover, overexpression of IL-6 in transgenic mice results in reduced body mass and impaired insulin-stimulated glucose uptake by skeletal muscle [83]. Thus, IL-6 has been proposed as one of the pro-inflammatory factors that promote the development of peripheral insulin

resistance. In stark contrast however, exercise-induced elevation of IL-6 plasma levels lead to increased circulating levels of several potent anti-inflammatory cytokines such as IL-1ra and IL-10, suggesting that IL-6 may also have anti-inflammatory properties [84, 85].

IL-6 is produced by a number of cells *in vivo* including stimulated monocytes/macrophages, fibroblasts and vascular endothelial cells [86]. Skeletal muscle fibers also express and release IL-6 during and after exercise [86-89]. IL-6 production is likewise boosted in connective tissue, the brain and adipose tissue post-exercise [90]. Exercise-induced plasma IL-6 concentrations peak at the end or shortly after cessation of an acute exercise bout and quickly return to pre-exercise levels [91]. IL-6 mRNA levels are generally induced in contracting skeletal muscle [87, 92]: however, exercise further enhances the transcriptional rate of IL-6 if muscle glycogen stores are low [93]. As IL-6 is a classical inflammatory cytokine, it was initially thought that exercise-induced IL-6 is released in response to muscle injury. However, several lines of evidence indicate that substantial amounts of IL-6 are produced independent of muscle injury [85, 87, 94].

When IL-6 was discovered and classified as one of the founding members of the myokine class of proteins, Pedersen et al. suggested IL-6 to possess some of the characteristics of a true “exercise factor”, which exerts is effects both locally within the muscle bed and peripherally on distal organs in an endocrine-like fashion [95]. In skeletal muscle, IL-6 signals through a gp130Rβ/IL-6Rα homodimer leading to the activation of AMPK and/or phosphatidylinositol 3-kinase (PI3K) and, subsequently, to an increase in glucose uptake and fatty acid oxidation [96, 97]. Similarly, enhanced AMPK activity upon IL-6 signaling has also been reported in adipose tissue [98]. Furthermore, IL-6 has been suggested to stimulate hepatic glycogenolysis, gluconeogenesis and glucose release [99]. Furthermore, IL-6 stimulates the secretion of glucagon-like peptide-1 (GLP-1), which results in an enhanced secretion of insulin from intestinal L-cells and pancreatic α-cells [100].

Thus, IL-6 release in response to exercise seems to have pleiotropic effects by increasing glucose uptake and fatty acid oxidation locally in skeletal muscle and enhancing insulin secretion, which further increases glucose uptake into muscle cells. At the same time hepatic glucose output [99] and fatty acid release from adipose tissue [101] are stimulated thereby providing energy substrates for the exercising muscle.

2.5. Interleukin-8

Interleukin-8 (IL-8) is a chemokine that attracts primary neutrophils [102]. In addition, IL-8 associates with the CXC receptor 2 (CXCR2) and thereby promotes angiogenesis [103-105]. IL-8 mRNA levels in skeletal muscle are elevated after exercise [106-108] and IL-8 plasma levels were found to be increased after eccentric muscle contractions [106, 109-112]. Curiously, systemic IL-8 plasma concentrations are unchanged following concentric exercise [106-108, 113], suggesting that the main part of the systemic increase in IL-8 after eccentric exercise, which is associated with a higher degree of fiber damage compared to concentric contractions, may account for a general inflammatory response [95]. Nevertheless, a small and transient net release of IL-8 has been reported across a concentrically exercising limb [107], indicating that muscle-derived IL-8 still acts locally in

an auto- and/or paracrine manner while not substantially contributing to the systemic IL-8 plasma concentration in this context.

Even though the physiological function of IL-8 on skeletal muscle is still unknown, the association with CXCR2 suggests at least a role in promoting exercise-induced neovascularization of muscle tissue. This assumption is further supported by the fact that CXCR2 mRNA and protein levels are induced upon concentric exercise in the vascular endothelial cells in muscle tissue [114].

2.6. Interleukin-15

Interleukin-15 (IL-15) is a pro-inflammatory cytokine with structural similarities to IL-2 and regulates T and natural killer cell activation and proliferation [115, 116]. IL-15 binds and signals through the IL15Rαβγ complex, which is upstream of the Janus kinases 1 and 3 (JAK1, 3) and signal transducer and activator of transcription-3 and 5 (STAT3, 5) [117, 118]. Expression of IL-15 mRNA has been detected in several human tissues including heart, lung, liver and kidney, but most abundantly in placenta and skeletal muscle. Similarly, peripheral blood mononuclear, epithelial and fibroblast cells seem to express significant levels of IL-15 [116].

Originally, IL-15 has been described as an anabolic factor in skeletal muscle. For example, even one bout of resistance training accordingly elevated IL-15 mRNA expression in human skeletal muscle [119]. Furthermore, IL-15 stimulates the production of contractile proteins [120] and overexpression of IL-15 *in vitro* results in muscle cell hypertrophy [121]. Moreover, IL-15 treatment of tumor-bearing rats antagonizes cancer cachexia [122] demonstrating the therapeutic potential in muscle wasting diseases. More detailed analyses of these *in vivo* studies however provided a different picture [123]: for example, administration of IL-15 did not affect muscle mass in the healthy control animals [122]. Transgenic overexpression of IL-15 [121] and muscle-specific ablation of the IL-15 receptor α [124] strongly implicated IL-15 in promoting an oxidative, high-endurance muscle phenotype. Accordingly, IL-15 promotes skeletal muscle glucose uptake and fatty acid oxidation [125, 126]. Moreover, twelve weeks of endurance training resulted in an elevation of IL-15 protein in skeletal muscle of human volunteers, even though mRNA expression and IL-15 plasma levels remained unchanged [127]. Thus, future experiments will have to elucidate whether the assignment of IL-15 as an anabolic factor has been spurious and based on *in vitro*-specific effects or if a dual role for IL-15 in both resistance as well as endurance training adaptation could be possible in a context-specific manner. Interestingly, diametrically opposite to the postulated anabolic effects on skeletal muscle, IL-15 inversely shrinks adipose tissue mass. In humans, a negative correlation between IL-15 plasma levels and trunk fat mass has been demonstrated and likewise, IL-15 overexpression in mouse skeletal muscle decreases visceral fat mass [128]. Besides the strong IL-15-dependent remodeling of skeletal muscle, this reduction in fat mass might also be associated with the effects of IL-15 on liver metabolism. For example, chronic administration of IL-15 decreases hepatic lipogenesis [129] and, at the same time, boosts hepatic fatty acid oxidation [126]. Together, these two effects potentially reduce the export of very low density

lipoproteins (VLDL). Accordingly, IL-15 treatment of animals diminishes circulating VLDL levels in comparison to non-treated control animals [130].

Finally, IL-15 administration decreases brown adipose tissue (BAT) mass in rats. At the same time however, the transcript levels of the uncoupling proteins 1 and 3 (UCP1, 3), lipid-related transcription factors and other proteins involved in membrane and mitochondrial transport and fatty acid oxidation are induced [131] and thereby, BAT thermogenesis and fatty acid oxidation are boosted.

2.7. Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, is strongly expressed in the brain [132] and to a lesser extent in skeletal muscle [133]. In the CNS, BDNF regulates neuronal development and modulates synaptic plasticity, playing a role in the regulation of survival, growth and maintenance of neurons [134, 135]. Furthermore, hypothalamic BDNF has been identified as a key factor in the control of body mass and energy homeostasis [136]. BDNF also influences learning and memory [137] and brain samples of patients with Alzheimer's disease exhibit reduced expression of BDNF [138]. Similarly, BDNF serum levels of patients with depression, obesity and type 2 diabetes are decreased [139, 140]. Inversely, exercise increases circulating BDNF levels in humans [141] and recent studies suggest that the brain contributes 70-80% of the circulating BDNF in this context [142]. BDNF mRNA and protein levels are also increased in skeletal muscle in response to exercise and contribute to enhanced fat oxidation by activating AMPK [133]. However, muscle-derived BDNF seems not to be released into the circulation in significant amounts indicating that BDNF primarily acts in an auto- and/or paracrine manner. Accordingly, besides the effects on metabolic properties, the main consequences of modulation of muscle BDNF extend to myogenesis, satellite cell activation and skeletal muscle regeneration [143, 144]. Other members of the neurotrophin factor family, in particular neurotrophin-3 (NT-3) and NT-4/5, have also been found in skeletal muscle tissue [145, 146]. However, even though a potential role of NT-3 and NT-4/5 in the repair of peripheral nerve injury has been suggested [145], the regulation and function of NT-3 and NT-4/5 in muscle remains unclear.

2.8. Ciliary neurotrophic factor

Like BDNF, ciliary neurotrophic factor (CNTF) is also a member of the neurotrophin family with important functions in the regulation of neural survival, development, function and plasticity [132]. Surprisingly, CNTF is also involved in the regulation of osteoblasts. For example, female CNTF-deficient mice exhibit increased bone mass and osteoblast activity compared to control animals. Moreover, CNTF decreases the mineralization and production of the osteoblast differentiation factor osterix in osteoblasts *in vitro* [147].

Recently, CNTF has been identified as a myokine that negatively regulates osteoblast gene expression together with the soluble CNTF receptor [148]. Therefore, muscle-derived CNTF could be a molecular link that underlies reduced bone formation in inactive individuals and therefore might contribute to osteoporosis boosted by a sedentary life-style. Inversely

however, CNTF production in inactive or resting muscle fibers may prevent heterotopic ossification of the muscle or regulate periosteal expansion during bone growth.

2.9. Vascular endothelial growth factor and secreted phosphoprotein 1

Vascular endothelial growth factor (VEGF) is a mitogen with specificity for vascular endothelial cells [149] and is a crucial regulator of embryonic vascular development (vasculogenesis) as well as blood vessel formation (angiogenesis). In fact, VEGF is most likely the most important pro-angiogenic growth factor in most tissues including skeletal muscle [150]. VEGF mRNA and protein levels are upregulated in skeletal muscle following an acute bout of exercise [151-153]. Furthermore, interstitial VEGF levels likewise increase markedly after exercise [152, 154] suggesting that VEGF is indeed secreted from contracting skeletal muscle fibers. This is further supported by a study showing that electrostimulation of cultured muscle cells leads to the secretion of VEGF into the culture medium [150]. Thus, skeletal muscle controls its own capillary supply be secreting VEGF into the extracellular space where VEGF acts on the vascular endothelial cells to increase blood vessel formation, and thus ultimately improve oxygen and energy substrate transport to the exercising muscle. In many different cell types, VEGF activity is determined by the hypoxia inducible factor 1α (HIF-1α), one of the main regulators of VEGF gene transcription, in addition to a strong regulation at the post-transcriptional level [155]. In contracting skeletal muscle tissue, an alternative, HIF-1α-independent regulation of VEGF transcription has been discovered centered on PGC-1α, in functional interaction with ERRα [156] and the activator protein-1 (AP-1) [8]. Interestingly, VEGF-induction by PGC-1α is further coordinated with a PGC-1α-dependent elevation of the secreted phosphoprotein 1 (SPP1). SPP1, a new myokine, that helps to orchestrate physiological angiogenesis by stimulating macrophages and in turn, activating endothelial cells, pericytes and smooth muscle cells [157].

2.10. Fibroblast growth factor 21

Fibroblast growth factor 21 (FGF21) belongs to the FGF super family with major functions in modulating cell proliferation, growth and differentiation as well as metabolism [158, 159]. FGF21 is predominantly expressed and secreted by the liver [160] but also by adipose tissue, pancreas and skeletal muscle [161]. The liver mainly secretes FGF21 in response to fasting [162] while BAT secrets FGF21 upon noradrenergic stimulation [163]. In the liver, FGF21 induces the expression of PGC-1α that in turn increases fatty acid oxidation, TCA cycle flux and gluconeogenesis [164].

In adipose tissue, FGF21 stimulates glucose uptake and transgenic overexpression of FGF21 protects mice from diet-induced obesity. Furthermore, FGF21 administration to diabetic rodents lowers blood glucose and triglyceride levels demonstrating its potential therapeutic application [165].

A recent study suggests that FGF21 is an insulin-regulated myokine that is expressed in skeletal muscle in response to insulin stimulation [166]. Moreover, cold-induced FGF-21 in muscle could contribute to an activation of thermogenesis [167]. FGF21 expression in skeletal muscle is also increased in a mouse model for a mitochondrial myopathy and the

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ensuing FGF21 elevation in the circulation promotes a starvation-like response in this disease context [168]. These results suggest that FGF21 might be more of a stress-induced than a “classical” exercise-induced myokine.

2.11. Irisin, meterorin-like and β-aminoisobutyric acid

Since PGC-1α is a crucial regulator of skeletal muscle plasticity after exercise [16] and accordingly, PGC-1α levels often correlate with those of myokines [169], PGC-1α gain- and loss-of-function models have been used to identify novel myokines. For example, screening of muscle cells that overexpress PGC-1α in three recent studies led to the identification of three new PGC-1α-dependent myokines, irisin [170], BAIBA [171] and meteorin-like [172]. Intriguingly, all three myokines seem to be involved in promoting beige fat thermogenesis.

2.11.1. Irisin

Irisin is cleaved off from FNDC5, a membrane-bound protein in skeletal muscle that is induced by exercise and muscle shivering [167]. Irisin exerts its action on white adipose tissue cells to stimulate UCP-1 expression and other brown fat-like genes thereby inducing browning and thermogenesis of white adipose tissue. Collectively, these effects lead to an increase in energy expenditure and result in an improvement of adiposity and glucose homeostasis [170]. Besides skeletal muscle, FNDC5 is also expressed in the brain [173, 174]. By elevating systemic irisin levels, endurance exercise induces FNDC5 expression in the hippocampus in a PGC-1α-dependent manner, which then leads to increased hippocampal BDNF expression and ultimately neurogenesis in this brain region. Accordingly, peripheral delivery of FNDC5 via adenoviral vectors is sufficient to induce BDNF expression in the brain [175]. Therefore, FNDC5/irisin might be the molecular mediator of exercise-induced neurogenesis in a direct skeletal muscle-brain cross-talk.

In addition to these endocrine effects, irisin also positively regulates muscle metabolism. Myocytes treated with irisin *in vitro* express higher levels of PGC-1α, nuclear respiratory factor 1 (NRF-1), mitochondrial transcription factor A (TFAM), glucose transporter 4 (GLUT4), UCP3, and irisin implying a positive autoregulatory loop between PGC-1α and FNDC5 [176]. Thereby, energy expenditure and oxidative metabolism in muscle cells is elevated by irisin. Importantly, while data in mice are robust, the regulation and function of irisin in humans is currently under debate. Future studies will have to show why irisin is only induced in some, but not all exercise cohorts. As with other factors, irisin regulation could depend on the specific training protocol (e.g. intensity, endurance vs. resistance, acute vs. chronic, time of blood sampling after exercise), age, gender, ethnicity, fitness and other variables. Second, the presence of circulating irisin in humans will have to be further investigated since the human FNDC5 gene lacks a functional start codon and detection of the protein has been questioned due to supposed suboptimal antibody specificity [177]. Notably however, 2-4% of eukaryotic genes contain an atypical start codon and nevertheless can be transcribed [178, 179]. Moreover, circulating human irisin has been described in several studies using different antibodies and assays such as highly sensitive mass spectroscopy [167].

2.11.2. Meteorin-like

Meteorin-like (Metrnl) is a hormone that has been identified as a myokine which is induced in skeletal muscle upon exercise and in white adipose tissue upon cold exposure [172]. Interestingly, in contrast to FNDC5/irisin, Metrnl primarily is dependent on the PGC-1α isoform 4 (PGC-1α4). PGC-1α4 is a splice variant of PGC-1α with a very distinct gene regulation pattern [74]. In contrast to the other known PGC-1α variants that primarily promote an oxidative, high endurance muscle phenotype, PGC-1α4 is induced by resistant training and enhances muscle hypertrophy and strength [74]. Nevertheless, even though the regulation of irisin and Metrnl is specific, Metrnl also increases whole body energy expenditure and improves glucose tolerance in obese/diabetic mice by indirectly activating the browning gene program in white adipose tissue via stimulation of an eosinophil-macrophage signaling cascade to ultimately activate a pro-thermogenic program [172].

2.11.3. BAIBA

BAIBA (β-aminoisobutyric acid) is an atypical myokine inasmuch BAIBA is not a cytokine-like molecule or even a protein. Nevertheless, BAIBA behaves clearly in a myokine-specific manner by being secreted from PGC-1α-expressing myocytes and subsequently activating the thermogenic program and beigeing of white adipose tissue [180]. In a similar endocrine fashion, BAIBA increases β-oxidation in hepatocytes both *in vitro* and *in vivo* by activating the transcription factor PPARα. In mice and in humans *in vivo*, circulating BAIBA levels increase with exercise and are inversely correlated with cardiometabolic risk factors in humans. Thus, exercise-induced circulating BAIBA has been suggested to protect from metabolic diseases [171].

Strikingly, all of these three newly identified PGC-1α-dependent myokines exert a strong endocrine effect on white adipose tissue by promoting a browning/thermogenic response and thereby increasing energy expenditure. The subsequent improvement of adiposity and whole body metabolism is of obvious interest for the treatment of obesity and obesity-associated diseases like type 2 diabetes. Moreover, increased adrenergic signaling during exercise can at least mechanistically be linked to a browning effect [181]. Nevertheless however, browning of white adipose tissue and, as a consequence, elevation of energy expenditure in the context of exercise raises interesting conceptual questions. With a degree of efficiency of around 15-25%, exercising muscle already produces significant heat that has to be dissipated by vasodilation and sweating in order to sustain prolonged contractions. It thus seems counterintuitive for skeletal muscle to directly initiate a myokine-dependent program that results in even further heat production in beige adipose tissue and as a consequence, usage of energy substrates that should optimally be available for muscle, and not adipose tissue, both for contractions as well as post-exercise refueling of energy stores. In the original manuscript, the authors speculated that such a program could be an evolutionary consequence of shivering thermogenesis that became increasingly important in higher organisms [170]. Indeed, recent work identified irisin and FGF-21 as cold-induced endocrine activators of thermogenesis in humans [167]. In fact, irisin secretion closely correlated with shivering intensity further supporting the hypothesis of a specification of skeletal muscle to sustain and coordinate both shivering in muscle as well as non-shivering thermogenesis in beige and brown adipocytes [182].

2.12. Anti-tumorigenic myokines: SPARC and OSM

An active life-style is not only associated with a decreased risk for the development of metabolic diseases such as cardiovascular pathologies and type 2 diabetes, different studies also imply a possible link between physical activity and certain types of cancer [27, 183]. For example, the World Cancer Research Fund proposed that exercise reduces the risk for developing breast and colon cancer by 25-30% [184]. There is a growing list of potential mechanisms how exercise may exhibit anti-tumorigenic effects, even though the molecular pathways are still largely unknown. Recently, two myokines have been identified, secreted protein acidic and rich in cysteine (SPARC) [185] and oncostatin-M (OSM) [186], which suppress tumor formation in the colon and inhibit mammary cancer cell growth, respectively. Both myokines inhibit proliferation and induce apoptosis of cancer cells. While such effects are of obvious therapeutic importance, the physiological roles of these two myokines remain unclear. Future studies might elucidate whether SPARC and OSM likewise regulate cell proliferation and apoptosis after being produced and secreted in contracting muscle fibers or if these two myokines have completely different effects in non-tumor cells.

3.1 Training, myokines and “exercise factors”

As described in the individual sections above, a clear regulatory and functional role linked to exercise has been found for some myokines. For example, IL-6 expression closely correlates with muscle contraction [91]. In turn, e.g. by promoting hepatic gluconeogenesis [99] and lipolysis in adipose tissue [98], IL-6 subsequently contributes to an adequate supply of energy substrates for the contracting muscle by affecting distal organs. Accordingly, IL-6 has been declared to constitute a *bona fide* “exercise factor” [95]. For other myokines, such a direct link to exercise is lacking; in some cases, the physiological relevance of the consequences of myokine action in the context of exercise remains enigmatic (e.g. the increase in brown fat-associated thermogenesis). Accordingly, the definition of “exercise factors” as a subgroup of myokines has been proposed based on the following criteria [187]: “exercise factors” are regulated by exercise and subsequently released into the circulation in order to exert distal effects. Non-exercise factor myokines are not necessarily controlled by muscle contraction and might not have a systemic function. Importantly, myokines do not have to be exclusively produced by skeletal muscle – indeed, the vast majority of the currently described myokines are also found in other tissues [187]. Finally, “exercise factors” can furthermore be stratified as acute or chronic based on their secretion pattern since skeletal muscle will elicit dramatically different phenotypic consequences in distal tissues following an acute bout or long-term training [188]. Based on these criteria and the presence of a complete chain of evidence, Catoire and Kersten proposed IL-6, SPARC, Angptl4, CX3CL1 and CCL2 as myokines with the highest potential to constitute “exercise factors” in humans [187]. Obviously, more work is needed to refine and expand this list in the future.

4.1. Conclusion

The discovery of myokines has opened a vast new and exciting field in the study of muscle, and, in particular, exercise physiology. Even now, members of the myokine group of signaling molecules cover a whole range of auto-, para- and endocrine effects. Importantly, different *in vitro* and *in vivo* approaches identify novel potential myokines at a breath-taking pace. For example, recent secretome analyses of cultured human muscle cells, with or without electrical stimulation, revealed over 50 novel candidate proteins [189-191]. Obviously, a myokine function of these proteins remains to be tested in murine and human *in vivo* models. Likewise however, a complete chain-of-evidence of the skeletal muscle cell origin of many myokines described *in vivo* is still missing. Therefore, future studies aimed at the identification and characterization of novel myokines will optimally combine *in vitro* and *in vivo* experiments. Next, the current studies aimed at the identification of exercise-induced myokines might be combined with a “myokine-ome” analysis of the inactive, sedentary muscle. So far, only myostatin or CNTF might fit that description – however, it would be surprising if myostatin and CNTF were the only “sedentary” myokines. Finally, non-protein myokines such as BAIBA might gain further relevance in the future to explain systemic plasticity initiated by skeletal muscle. Intriguingly, muscle-mediated conversion of kynurenine to kynurenic acid, a metabolite unable to cross the blood brain barrier, could underlie the beneficial effect of physical activity on stress-induced depression and thereby provide another example for a metabolite link between muscle and brain [192]. In any case however, myokines not only provide a molecular explanation for the extensive cross-talk between muscle and other tissues in our body, but also reveal novel therapeutic avenues for the treatment of a myriad of chronic diseases that are associated with a sedentary life-style. Thus, the study of myokines will remain an extremely interesting research topic for our understanding of basic as well as translational aspects of skeletal muscle physiology in the years to come.

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Abbreviations

AMPK	AMP-dependent kinase
AP-1	Activator protein 1
aP2	Adipocyte protein 2
BAIBA	β-Aminoisobutyric acid
BAT	Brown adipose tissue
BDNF	Brain-derived neurotrophic factor
CaMK	Calcium/calmodulin-dependent protein kinase

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C/EBPα	CCAAT-enhancer-binding protein α
CnA	Calcineurin A
CNTF	Ciliary neurotrophic factor
CREB	Cyclic-AMP-responsive-element-binding protein
CXCR2	CXC receptor 2
ERRα	Estrogen-related receptor α
FGF21	Fibroblast growth factor 21
GLP-1	Glucagon-like peptide-1
GLUT4	Glucose transporter 4
HIF-1α	Hypoxia inducible factor 1α
IGF-1	Insulin-like growth factor 1
IL	Interleukin
JAK	Janus kinase
MEF	Myocyte-enhancer factor
Metrnl	Meteorin-like
MSTN	Myostatin
NFAT	Nuclear factor of activated T cells
NFκB	Nuclear factor κB
NRF-1	Nuclear respiratory factor 1
OSM	Oncostatin-M
p38 MAPK	p38 mitogen-activated protein kinase
PGC-1α	Peroxisome-proliferator activated receptor γ coactivator 1α
PI3K	Phosphatidylinositol 3-kinase
PPAR	Peroxisome-proliferator activated receptor
REE	Resting energy expenditure
SERCA	sarcoplasmic/endoplasmic reticulum calcium ATPase
SPARC	Secreted protein acidic rich in cysteine
SPP1	Secreted phosphoprotein 1
STAT	Signal transducer and activator of transcription
TFAM	Mitochondrial transcription factor A
TGF-β	Transforming growth factor β
TNFα	Tumor necrosis factor α

UCP	Uncoupling protein
VEGF	Vascular endothelial growth factor
VLDL	Very low density lipoproteins

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Highlights

- Besides its traditional functions, skeletal muscle has recently been discovered to be an endocrine organ
- Myokines are signaling molecules with auto-, para- and/or endocrine functions that are secreted from skeletal muscle cells
- Myokines affect most organs and thereby provide a molecular explanation for the cross-talk between skeletal muscle and other tissues

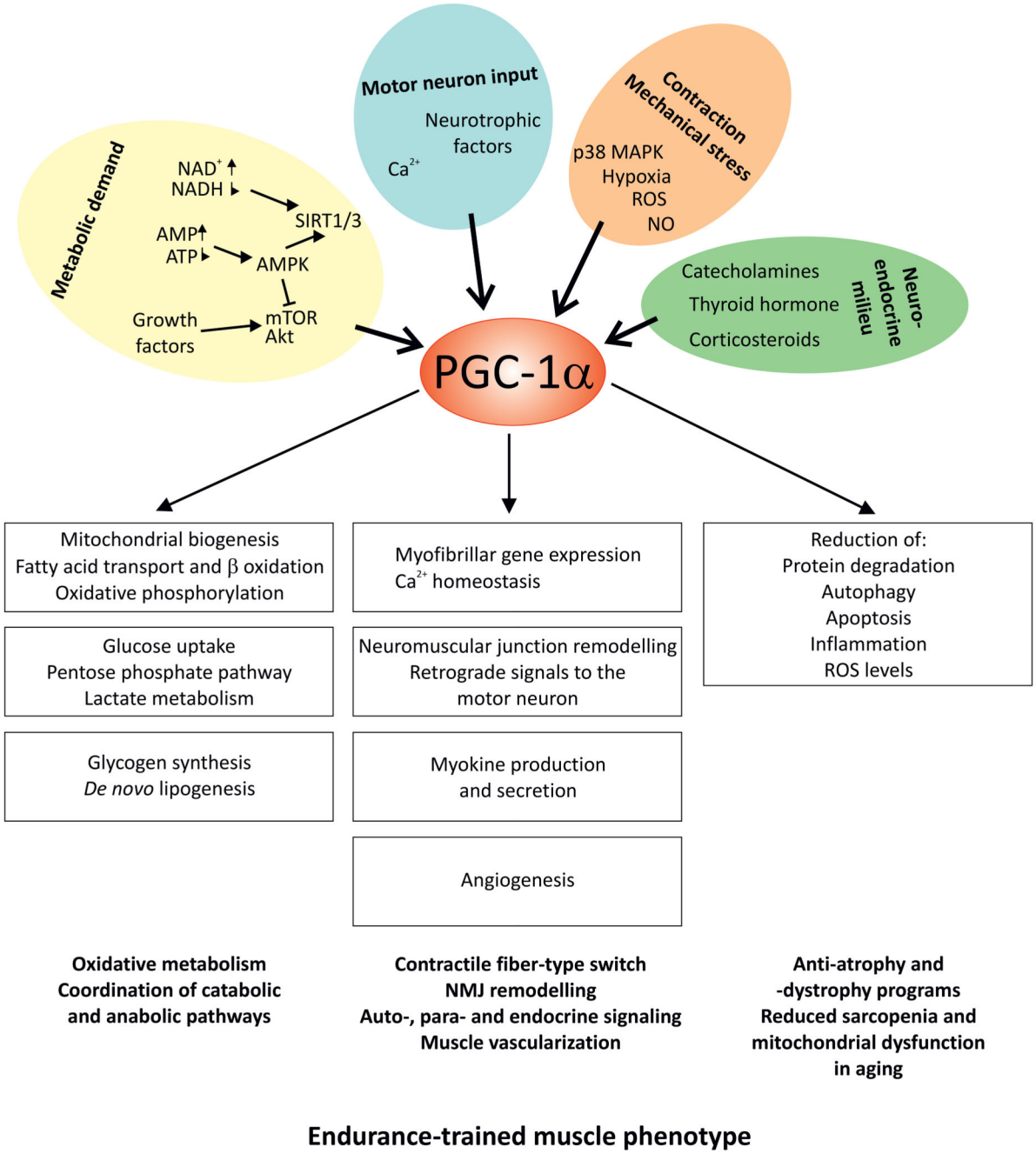

Fig. 1. Central role of PGC-1α in the regulation of skeletal muscle cell plasticity

Every major signaling pathway that is activated in a contracting muscle fiber during and after endurance training converges on PGC-1α by modulating PGC-1α gene expression and/or post-translational modifications of the PGC-1α protein. As a consequence, PGC-1α in turn coordinates the transcriptional network that controls the biological program of exercise-induced muscle remodeling.

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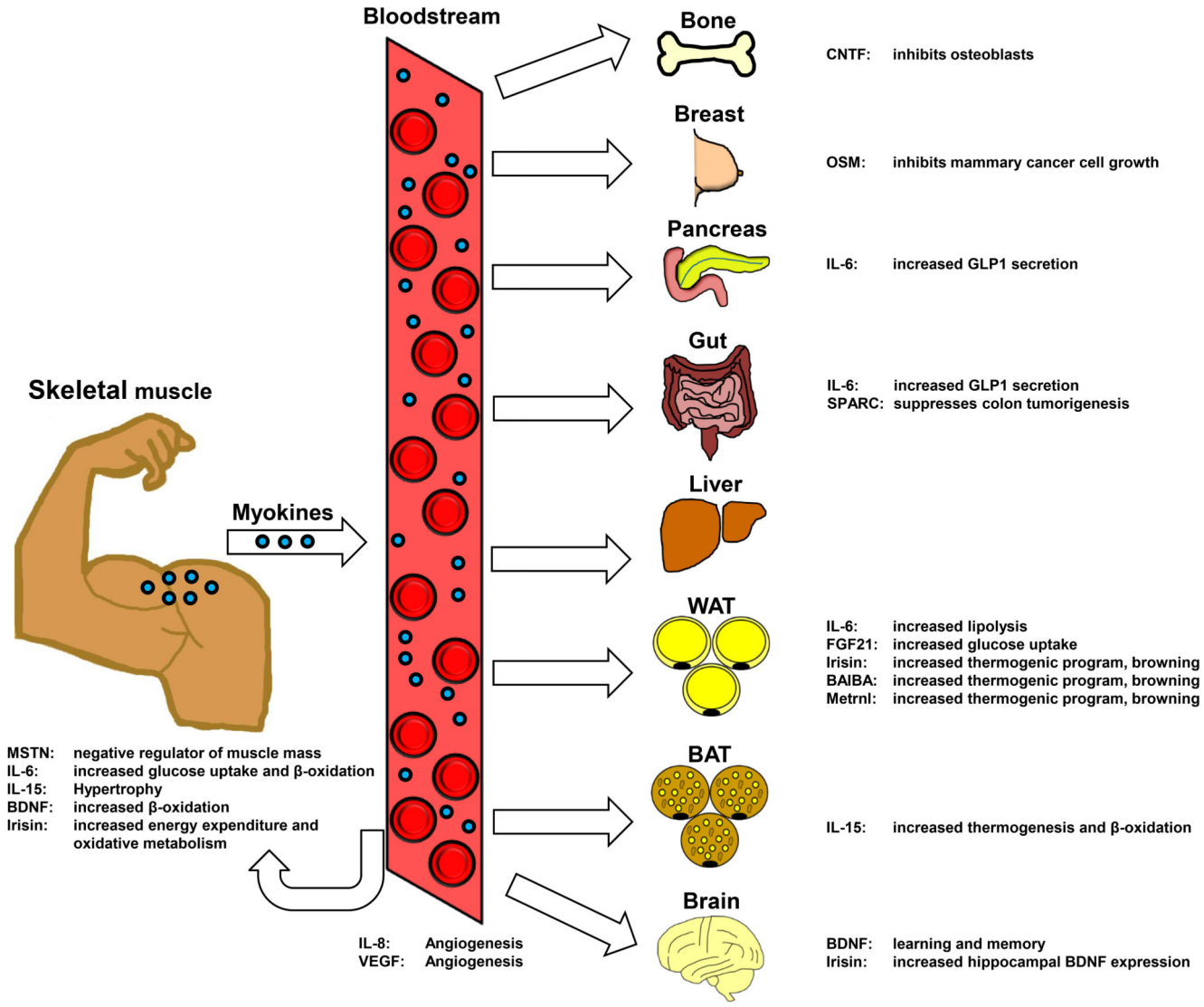

Fig. 2. Auto-, para- and endocrine effects of myokines

Selected examples of the physiological consequences of the production and release of myokines on skeletal muscle and other organs are depicted.