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Skeletal Muscle as an Endocrine Organ: The Role of Myokines in Exercise Adaptations

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Exercise stimulates the release of proteins with autocrine, paracrine, or endocrine functions produced in skeletal muscle, termed myokines. Based on the current state of knowledge, the major physiological function of myokines is to protect the functionality and to enhance the exercise capacity of skeletal muscle. Myokines control adaptive processes in skeletal muscle by acting as paracrine regulators of fuel oxidation, hypertrophy, angiogenesis, inflammatory processes, and regulation of the extracellular matrix. Endocrine functions attributed to myokines are involved in body weight regulation, low-grade inflammation, insulin sensitivity, suppression of tumor growth, and improvement of cognitive function. Muscle-derived regulatory RNAs and metabolites, as well as the design of modified myokines, are promising novel directions for treatment of chronic diseases.

The importance of regular physical activity to prevent and treat chronic and degenerative diseases is widely accepted. This does not only include metabolic diseases such as type 2 diabetes and morbid obesity but most if not all widespread and common diseases of the increasingly aging society worldwide. There is growing evidence that regularly performed exercise is a powerful therapy against the progression of cardiovascular diseases, cancer, neurodegenerative diseases, psychiatric disorders, and chronic pulmonary diseases (Pedersen and Saltin 2015). For prevention of these noncommunicable diseases, the World Health Organization (WHO) has developed "global recommendations on physical activity for health" (WHO 2010). These well-acknowledged benefits of exercise go far beyond the molecular adaptations of working skeletal muscle and include enhanced substrate delivery and oxidation capacity and increased mechanical strength and power (Egan and Zierath 2013). For decades, researchers have focused on elucidating the mechanisms by which the energy-demanding mechanical work of skeletal muscle can impact the entire body to promote profound health benefits. In 1961, Goldstein conducted cross-transfusion experiments between resting dogs and dogs in which muscle contraction was induced by electrical stimulation (Goldstein 1961). Based on his data, he postulated the exis-

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tence of humoral components induced by muscular work that enhance glucose utilization in the resting dogs. In 1983, a pyrogenic substance with an estimated molecular weight of 14 kDa was reported in human plasma after 1 h of bicycling, although a specific factor could not be identified (Cannon and Kluger 1983). The detection of increased expression of the cytokine interleukin 6 (IL-6) in human muscle biopsies obtained following exercise (Ostrowski et al. 1998b) and the concomitant release of this muscle-derived IL-6 into the circulation (Steensberg et al. 2000) was then the starting point for a new research field. The concept of myokines was introduced to describe putative cytokines that are produced and released by muscle fibers and exert endocrine effects (Pedersen et al. 2003). Since then, the list of myokines is constantly growing and the classification has become more loosely interpreted to include any secreted protein that is produced in skeletal muscle whether it acts in an autocrine, paracrine, or endocrine manner (Pedersen and Febbraio 2012). The focus of this review is on exercise-regulated myokines and does not touch on the numerous myokines that have been described in differentiating skeletal muscle cell cultures (Henningsen et al. 2010; Chan et al. 2011) in the context of muscle injury (Zeng et al. 2010) or mitochondrial dysfunction (Ost et al. 2016). We will give an overview on the current knowledge of human myokines and discuss the evidence for an autocrine, paracrine, or endocrine role in the health-promoting effects of exercise and the potential therapeutic options.

THE HUMAN SKELETAL MUSCLE SECRETOME

The idea of endogenous factors that are released from human skeletal muscle as hormone-like mediators of the preventive and therapeutic effects of exercise has initiated proteomics and transcriptomics profiling approaches to elucidate the composition of the skeletal muscle secretome and to identify novel myokines. Global and targeted proteomic profiling was applied to the secretome of cultured primary human myotubes to provide a comprehensive description of secreted proteins (Hittel et al. 2009; Bouzakri et al. 2011; Le Bihan et al. 2012; Hartwig et al. 2014). About two-thirds of the more than 1000 proteins identified in cultured primary human myotube secretome were predicted or have been annotated as putative secreted proteins, underlining the potency of skeletal muscle to act as an endocrine organ (Weigert et al. 2014). Functional term analysis of these proteins suggests an important paracrine function in skeletal muscle development and regeneration, extracellular matrix (ECM) organization, and angiogenesis. At least a part of the proteins not assigned as potentially secreted forms are carried in microvesicles such as exosomes (Le Bihan et al. 2012).

To investigate exercise-regulated myokines, analyses of transcripts in exercised human skeletal muscle were combined with profiling of secreted proteins in cultured muscle cells (Norheim et al. 2011) or quantification of myokine plasma levels (Catoire et al. 2014b). In vitro exercise by applying electric pulse stimulation to cultured human skeletal muscle cells was used for antibody-based microarray profiling of the supernatant (Raschke et al. 2013a; Scheler et al. 2013). None of these studies came close to providing a complete picture of the exercise-induced release of myokines into muscle interstitial fluid or the circulation. One explanation is that plasma and interstitial fluid represent two of the most challenging secretomes for proteomics profiling, because a few highly abundant protein species are responsible for ~99% of the protein content and these disguise other proteins such as cytokines of comparably very low concentration in the picomolar or femtomolar range (Anderson and Anderson 2002). To circumvent this problem, different approaches have been developed and are currently optimized to enrich the low abundant proteins (Frobel et al. 2015; Gianazza et al. 2016).

The majority of the hitherto assigned exercise-regulated myokines with putative endocrine functions were identified by targeted approaches analyzing transcript and protein level in human skeletal muscle biopsies and plasma following one acute bout of exercise or after training. An overview of exercise-regulated human myokines with exercise-mediated changes

in mRNA and protein abundance in skeletal muscle or plasma is given in Table 1. The proteins secreted by skeletal muscle can often be released from a wide variety of cells, including immune cells, endothelial cells, fibroblasts, osteocytes, hepatocytes, and adipocytes. Therefore, elevated systemic concentrations of these proteins after exercise or in the supernatant of primary human muscle cells only suggest, and do not prove, the existence of an exercise-regulated myokine. The list is dominated by cytokines, growth factors, and regulators or components of the ECM.

Moreover, transgenic expression of transcriptional key regulator peroxisome proliferator-activated receptor coactivator (PGC)1α in skeletal muscle led to the discovery of irisin and meteorin-like as exercise-regulated myokines that stimulate energy expenditure and brown fat–like development in mice (Bostrom et al. 2012; Rao et al. 2014). Meteorin-like as well as myonectin (CTRP15) (Seldin et al. 2012) and musclin (OSTN) (Subbotina et al. 2015) have only been described in rodent studies, and human data on the regulation of intramuscular and systemic levels of these proteins following exercise have not been reported to date.

EXERCISE-REGULATED HUMAN MYOKINES

Experimental evidence for an exercise-induced production in and secretion from human muscle is provided for several cytokines, including IL-6, IL-8, IL-10, IL-15, CC-chemokine ligand (CCL)2, IL-1 receptor antagonist, calprotectin S100A9, and vascular endothelial growth factor (VEGF) with increased interstitial fluid concentrations in skeletal muscle following exercise or a net release from skeletal muscle measured as arterial–venous differences (see Table 1 for details). At least increased mRNA and protein abundance in human skeletal muscle following acute exercise or training is described for angiopoietin-like 4 (ANGPTL4), brain-derived neurotrophic factor (BDNF), connective tissue growth factor (CTGF), cysteine-rich angiogenic protein 61 (CYR61), fractalkine, and nicotinamide phosphoribosyl transferase (NAMPT). An increase of cytokines in the muscular interstitial fluid can be seen after 30 min of one-legged knee extensor exercise or rowing and may occur independent of a transcriptional response (Rosendal et al. 2005; Rue et al. 2014). However, elevated transcript or protein levels are not always paralleled by increased systemic concentrations, as reported for CTGF, CYR61, IL-8, IL-15, LIF, and VEGF (Ostrowski et al. 1998a; Nieman et al. 2003; Broholm et al. 2011; Catoire et al. 2014b; Landers-Ramos et al. 2014). In general, systemic cytokine responses are more pronounced after exercise with a higher degree of muscle damage such as downhill running, eccentric exercise, and resistance training (Paulsen et al. 2012). Moreover, a robust elevation of the transcript abundance of several cytokines and chemokines in skeletal muscle is regularly described after exercise bouts with long duration or high intensity (Nieman et al. 2001; Suzuki et al. 2006; Neubauer et al. 2014) but less pronounced or absent after more moderate intense physical activity (Catoire et al. 2014b; Hansen et al. 2015b). Notably, the increased expression and release of IL-6 and to some extent of other cytokines occurs independent of muscle damage. The increase in IL-6 is not linked to the release in tumor necrosis factor α (TNF-α) (Steensberg et al. 2002; Keller et al. 2006) or other markers of tissue injury (Croisier et al. 1999; Starkie et al. 2001) but is regulated by carbohydrate availability and proposed to serve as a sensor of the metabolic status of the muscle (Keller et al. 2001; Steensberg et al. 2001; MacDonald et al. 2003). Low muscle glycogen content preexercise results in higher IL-6 and IL-8 transcript levels postexercise (Chan et al. 2004). Furthermore, carbohydrate ingestion before exercise attenuates the increase in these transcripts (Nieman et al. 2003). In addition, a recent study in rodents shows that the release of the bone-derived hormone osteocalcin induces part of the exercise-induced increase in IL-6 and enhanced substrate oxidation capacity (Mera et al. 2016), which shows the ability of bone to sense mechanical forces and to act as regulator of myokines in response to exercise.

Not all of the exercised-regulated cytokines are localized to myofibers; satellite cells, fibro-

Table 1. Regulation of myokines following exercise in humans

Myokine	Release: cultured muscle cells[a]	Response to exercise (E) or training (T) in humans[b]							
		Muscle mRNA		Muscle protein		Plasma/serum		Muscle release	
ANGTPL4	Staiger et al. 2009	E:↑	Catoire et al. 2014a	E:↑	Catoire et al. 2014a	E:↑	Kersten et al. 2009		
Apelin	Besse-Patin et al. 2014	T:↑	Besse-Patin et al. 2014			T:↑	Kadoglou et al. 2012		
BDNF	Le Bihan et al. 2012	E:↑	Matthews et al. 2009	E:↑	Matthews et al. 2009	E:↑	Ferris et al. 2007; Saucedo Marquez et al. 2015		
CCL2	Raschke et al. 2013a; Scheler et al. 2013	E:↑	Tantiwong et al. 2010; Catoire et al. 2014b	E:↑	Hubal et al. 2008; Della Gatta et al. 2014	E:↑	Peake et al. 2005; Andersson et al. 2010	Int	Rue et al. 2014
CHI3L1	Le Bihan et al. 2012; Hartwig et al. 2014	E:↑	Gorgens et al. 2016			E:↑	Gorgens et al. 2016		
CTGF	Le Bihan et al. 2012; Hartwig et al. 2014	E:↑	Heinemeier et al. 2013; Catoire et al. 2014b	E:↑	Kivela et al. 2007				
CTSB	Norheim et al. 2011; Hartwig et al. 2014	T:↑	Norheim et al. 2011			T:↑	Moon et al. 2016		
CYR61		E:↑	Catoire et al. 2014b; Hansen et al. 2015b	E:↑	Kivela et al. 2007				
Decorin	Kanzleiter et al. 2014	E:↑	Heinemeier et al. 2013			E:↑	Kanzleiter et al. 2014		
Fractalkine		E:↑	Catoire et al. 2014b; Della Gatta et al. 2014	E:↑	Stromberg et al. 2016	E:↑	Catoire et al. 2014b		
FSTL1	Gorgens et al. 2013	T:↑	Norheim et al. 2011			E:↑	Gorgens et al. 2013		
IGF1	Le Bihan et al. 2012	E:↑	Bamman et al. 2001; Hameed et al. 2003			E:↑	Bang et al. 1990; Cappon et al. 1994	A-V	Brahm et al. 1997
								Int	Berg et al. 2007
IL-6	Bartoccioni et al. 1994	E:↑	Ostrowski et al. 1998b	E:↑	Hiscock et al. 2004	E:↑	Ostrowski et al. 1998a	A-V	Steensberg et al. 2000
								Int	Rosendal et al. 2005
IL-7	Haugen et al. 2010	T:↑	Haugen et al. 2010			E:↑	Andersson et al. 2010		
IL-8	Raschke et al. 2013a; Scheler et al. 2013	E:↑	Chan et al. 2004; Louis et al. 2007; Covington et al. 2016	E:↑	Della Gatta et al. 2014	E:↑	Nieman et al. 2001; Andersson et al. 2010	Int	Rue et al. 2014

Continued

Table 1. *Continued*

Myokine	Release: cultured muscle cells[a]	Response to exercise (E) or training (T) in humans[b]							
		Muscle mRNA		Muscle protein		Plasma/serum		Muscle release	
IL-10	Scheler et al. 2013; Hartwig et al. 2014	E:↑	Nieman et al. 2003			E:↑	Smith et al. 2000	Int	Rue et al. 2014
IL-15	Raschke et al. 2013a	E:↑	Nielsen et al. 2007	T:↑	Rinnov et al. 2014	E:↑	Riechman et al. 2004; Tamura et al. 2011	Int	Pierce et al. 2015
IL-1RN		E:↑	Nieman et al. 2003			E:↑	Ostrowski et al. 1998a; Peake et al. 2005	Int	Rue et al. 2014
Irisin		T:↑	Bostrom et al. 2012			T:↑	Jedrychowski et al. 2015		
LIF	Broholm et al. 2011	E:↑	Broholm et al. 2008; Covington et al. 2016						
Myostatin	Hittel et al. 2009	E,T:↓	Louis et al. 2007; Heinemeier et al. 2013; Hjorth et al. 2016	T:↓	Hittel et al. 2010	T:↓	Walker et al. 2004; Hittel et al. 2010		
NAMPT	Le Bihan et al. 2012	T:↑	Alfieri et al. 2015	T:↑	Costford et al. 2010; Brandauer et al. 2013	E:↑	Ghanbari-Niaki et al. 2010		
S100A9		E:↑	Mortensen et al. 2008			E:↑	Fagerhol et al. 2005; Mooren et al. 2006	A-V	Mortensen et al. 2008
SPARC	Norheim et al. 2011	T:↑	Hjorth et al. 2015			E:↑	Aoi et al. 2013		
VEGF	Raschke et al. 2013a; Scheler et al. 2013	E:↑	Gavin et al. 2004	E:↑	Hoier et al. 2013	E:↑	Wahl et al. 2011	Int	Hoier et al. 2013

E:↑(↓), increased (decreased) following acute exercise; T:↑(↓), increased (decreased) following training; A-V, net release into plasma from the exercising muscle; Int, increased concentration in the interstitial fluid of the exercising muscle during or following acute exercise; mRNA, messenger RNA.

[a]Release from unstimulated human skeletal muscle cells in vitro.

[b]Shown are only the studies in which regulation of the respective myokine following exercise or training was detected. When numerous studies exist, only one of the first significant contributions is included.

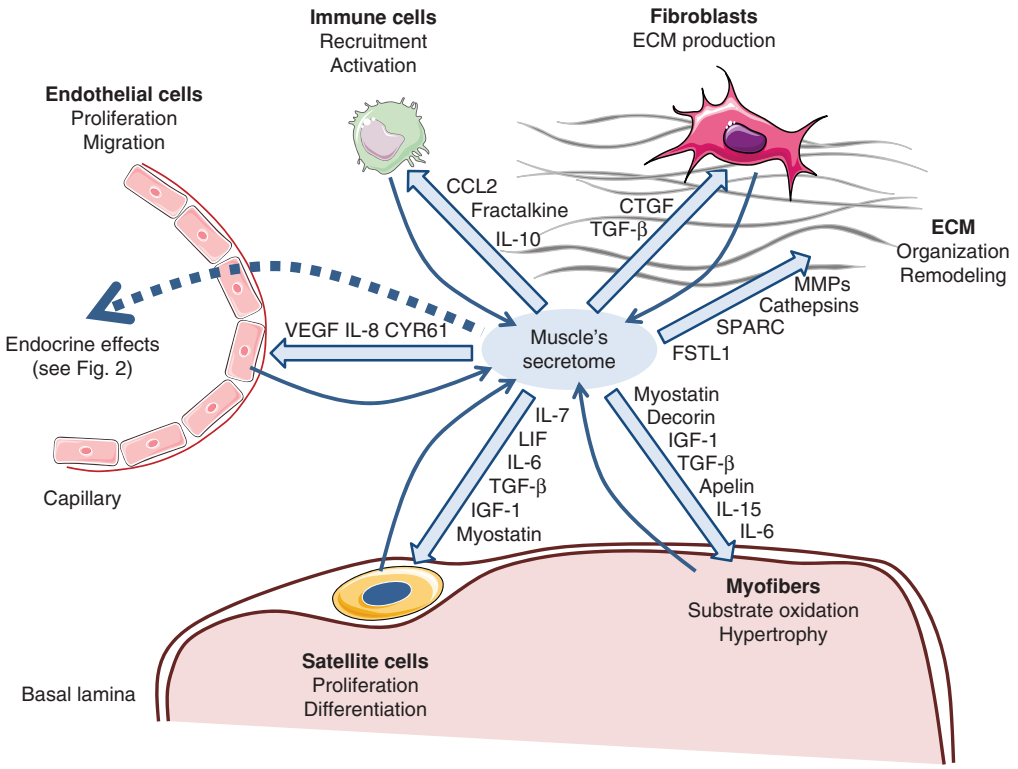

Figure 1. Autocrine and paracrine effects of exercise-regulated human myokines. Myofibers, satellite cells, fibroblasts, immune cells, and endothelial cells contribute to the secretome of muscle, which also includes proteins of the extracellular matrix (ECM). Shown are the autocrine and paracrine functions of exercise- or training-regulated human myokines on the different cell types and structures within muscle tissue. The effect of myokines can be both stimulatory or inhibitory. CCL2, CC-chemokine ligand 2; CTGF, connective tissue growth factor; TGF-β, transforming growth factor β; IL, interleukin; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor; SPARC, secreted protein rich in cysteine; FSTL1, follistatin-like 1; LIF, leukemia inhibitory factor; IGF-1, insulin-like growth factor 1. (Figure created using illustrations provided by Servier Medical Art.)

blasts, endothelial cells, and macrophages residing in muscle tissue can contribute to muscular abundance and release of proteins (Fig. 1). IL-6 is primarily localized in myofibers (Hiscock et al. 2004), but also detected in satellite cells (McKay et al. 2009) and fibroblasts (Malm et al. 2004). CCL2 is detected in macrophages and satellite cells (Hubal et al. 2008; Della Gatta et al. 2014), LIF in endothelial cells (Malm et al. 2004), IL-8 in macrophages and blood vessels (Della Gatta et al. 2014), and fractalkine in the endothelium (Stromberg et al. 2016). VEGF is localized to myofibers, endothelial cells, and pericytes (Hoier et al. 2013). It is common practice to use the term "myokine" irrespective of the validation of myofibers as origin of the released protein.

IL-6—A MULTITALENTED MYOKINE

IL-6 is the best-studied myokine and can serve as a prime example for the potential of exercise-regulated myokines with well-described auto-, para-, and endocrine effects. Acting in an autocrine/paracrine manner in skeletal muscle, IL-6-dependent STAT3 signaling was detected in human satellite cells after muscle-lengthening contraction (Toth et al. 2011). IL-6 is important for hypertrophic muscle growth and myogenesis in mice (Serrano et al. 2008). Myotube for-

mation is reduced in IL-6-deficient primary mouse skeletal muscle cells (Hoene et al. 2013). Endocrine effects assigned to the exercise-induced release of IL-6 fit into the concept of health-promoting myokines. IL-6 increases insulin-stimulated glucose disposal and glucose oxidation (Carey et al. 2006) and stimulates lipolysis and fat oxidation (van Hall et al. 2003; Petersen et al. 2005). On the molecular level, these effects are mediated via IL-6-dependent activation of AMP-activated protein kinase (AMPK) (Ruderman et al. 2006), regulation of insulin receptor substrate-1 (Weigert et al. 2006), and PI3-kinase (Al Khalili et al. 2006). Rodent studies provide evidence that IL-6 enhances expansion of pancreatic α cells (Ellingsgaard et al. 2008) and improves insulin secretion and hyperglycemia via stimulation of glucagen-like peptide 1 (GLP1) secretion from the L cells in the intestine and pancreatic α cells (Ellingsgaard et al. 2011). IL-6 promotes the alternative activation of macrophages, which is involved in the protection from obesity-induced tissue inflammation and insulin resistance (Mauer et al. 2014). Recently, exercise was reported to reduce tumor size and growth in mice via IL-6-dependent natural killer cell mobilization (Pedersen et al. 2016). To conclude, the exercise-induced release of IL-6 may partly account for important beneficial effects of exercise, including improved glycemic control, loss of fat mass, suppression of tumor growth, and maintenance of muscle mass.

MYOSTATIN—RENEWED INTEREST IN AN "OLD" MYOKINE

The first identified myokine, even though not termed a myokine at the time of its discovery, was myostatin (McPherron et al. 1997). Myostatin is the myokine with probably the most pronounced effects on muscle mass and body fat composition. Myostatin is expressed and secreted by skeletal muscle and acts as a negative regulator of skeletal muscle growth (McPherron et al. 1997). Mutations in the human *MSTN* gene leading to reduced production of mature myostatin protein increase muscle mass with a concomitant loss of adipose tissue (Schuelke et al. 2004). Myostatin received new attention as a potential target to treat the metabolic syndrome because myostatin transcript levels are higher in skeletal muscle of type 2 diabetes patients (Palsgaard et al. 2009) and myostatin plasma levels are elevated in obese women (Hittel et al. 2009). Regular exercise reduces myostatin transcript levels in skeletal muscle of obese subjects and people with impaired glycemic control, but decreased mRNA abundance was also found after one acute bout of exercise in healthy people (Table 1). Myostatin deficiency or inhibition of myostatin signaling improves insulin resistance in old and obese mice (Zhao et al. 2005; Wilkes et al. 2009; Camporez et al. 2016). The underlying mechanisms are not completely clear, because direct effects of myostatin on insulin signaling in skeletal muscle cells or adipocytes could not be detected (Hjorth et al. 2016).

ROLE OF MYOKINES IN EXERCISE ADAPTATIONS

Myokines are involved in many of exercise-induced adaptations. In the following sections, the potential contribution of myokines to an enhanced exercise capacity and the benefits for whole-body metabolism and prevention of chronic diseases is presented. To date, functional data are mainly based on mouse and in vitro studies.

Regulation of Metabolic Pathways

The beneficial effect of exercise on glycemic control and lipid homeostasis was one of the initial driving forces in searching for muscle-derived factors as "exercise-mimetics" for the treatment of metabolic disorders such as type 2 diabetes. Besides the exercise-induced acute increase in IL-6 and the reduction in myostatin, other exercise-regulated myokines play a potential role in the regulation of metabolism following exercise.

The exercise-induced increase in ANGPTL4 plasma levels has been involved in the regulation of plasma triglycerides by decreasing lipoprotein lipase (LPL) activity (Dijk et al. 2016) and promoting adipose tissue lipolysis (Gray et al.

2012). Beyond that, ANGPTL4 was recently described in mice as mediator of hyperplasia of pancreatic α cells (Ben Zvi et al. 2015). Apelin is a ligand of the G-protein-coupled receptor APJ. In rodents, apelin increases glucose uptake and mitochondrial oxidative capacity in skeletal muscle (Dray et al. 2008; Attane et al. 2012). However, the contribution of skeletal muscle-derived apelin to plasma levels is questionable (Yamamoto et al. 2011). IL-15 signaling might be involved in regulation of muscle fiber composition, contractility, and body fat composition. Mouse models lacking the IL-15α receptor in skeletal muscle suggest an intramuscular role for IL-15 in defining the shift to fast glycolytic fibers, with the loss of IL-15α receptor signaling increasing oxidative exercise capacity and resistance to fatigue (Pistilli et al. 2011). Conversely, transgenic mice with skeletal muscle overexpression of IL-15 also have a high endurance capacity (Quinn et al. 2013). Moreover, mice with oversecretion of IL-15 from skeletal muscle showed increased lean body mass and decreased body fat content (Quinn et al. 2009). NAMPT is the rate-limiting enzyme in the NAD salvage pathway responsible for converting NAM to NAD. Increased NAMPT protein levels in skeletal muscle following training are related to enhanced mitochondrial density in athletes (Costford et al. 2010; Brandauer et al. 2013). However, the increase in intracellular NAMPT is probably not associated with a regulation of extracellular eNAMPT, also known as Visfatin (Revollo et al. 2007). Irisin is cleaved from the fibronectin type III domain-containing protein 5 (FNDC5) and induces browning of white fat and thermogenesis in mice (Bostrom et al. 2012). After its discovery in mice, the existence of irisin in humans was questioned (Raschke et al. 2013b), and questions were raised regarding the validity of the commercial ELISA kits used for quantification of human irisin (Albrecht et al. 2015). Recently, irisin was identified in human plasma by mass spectrometry (Jedrychowski et al. 2015).

To conclude, several myokines have been implicated in the reduction of subcutaneous and visceral fat and enhanced substrate oxidation capacity, two main effectors of whole-body insulin sensitivity. Further exercise adaptations presented in the next sections, such as the increase in muscle mass, the increase in muscle capillarization, and the reduction in systemic inflammation also contribute to the improvement in substrate oxidation and glycemic control.

The Anti-Inflammatory Effect of Exercise

From the first report regarding the production and release of inflammatory cytokines by contracting skeletal muscle, the notion that exercise induces muscle damage and inflammation has been discussed. An important paracrine function of these cytokines in the muscle is to attract immune cells to control inflammatory processes and to support muscle regeneration following exercise. CCL2, also known as monocyte chemotactic protein (MCP)1, and fractalkine, also known as chemokine (C-X3-C motif) ligand (CX3CL)1, regulate migration and infiltration of monocytes and macrophages. These factors are involved in the recruitment of macrophages and other immune cells in muscle and are important for tissue repair following injuries (Pillon et al. 2012). IL-10 and the IL-1 receptor antagonist are part of the anti-inflammatory response counteracting the function of other cytokines on multiple levels (Maynard and Weaver 2008). Moreover, muscle-specific overexpression of IL-10 prevents diet-induced inflammation and insulin resistance (Hong et al. 2009).

The anti-inflammatory potential of exercise is reflected by the decrease in systemic concentrations of several inflammatory cytokines following training interventions, which is particularly observed in chronic diseases that are associated with a low grade systemic inflammatory state such as obesity and insulin resistance, cardiovascular diseases, atherosclerosis, and neurodegenerative disorders (Gleeson et al. 2011; Lancaster and Febbraio 2014). The reduction in systemic levels of proinflammatory cytokines is mediated by multiple mechanism including a reduction in visceral fat mass, increased production and release of anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist presumably via IL-6 (Steensberg

et al. 2003), down-regulation of toll-like receptor signaling (Stewart et al. 2005; Oliveira and Gleeson 2010), a shift in the monocyte populations in blood to a less proinflammatory phenotype (Timmerman et al. 2008), and activation of immune suppressive T cells (Yeh et al. 2006). Other myokines such as IL-7 or CHI3L1 may contribute as well to the anti-inflammatory effects (Schluns et al. 2000; Gorgens et al. 2014), but the specific contribution of single myokines to the anti-inflammatory effect of exercise is difficult to unravel because of their multiple sources and their tightly interacting network.

The exercise-induced release of inflammatory cytokines can be seen as a hormetic mechanism, that is, a beneficial response to a stress-inducing condition involved in the improvement of exercise capacity, substrate oxidation, and the anti-inflammatory effect of regular performed exercise. In this regard, interfering with the exercise-induced inflammation by nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the acute increase in skeletal muscle protein synthesis (Trappe et al. 2002) and the activation of satellite cells (Mikkelsen et al. 2009); but studies investigating the effect of chronic consumption of NSAIDs during training on the gain in muscle mass or strength showed no interference or even a beneficial effect in older adults (Trappe et al. 2011; Jankowski et al. 2013). In rodent studies, NSAID treatment has in general negative effects on muscle regeneration, muscle hypertrophy, but also on mitochondrial adaptations (Machida and Takemasa 2010; Urso 2013). These data support a role of the exercise-induced inflammatory response beyond immune modulatory functions. The importance of cellular stress signals in the health-promoting effects of exercise is further emphasized by the adverse effects of antioxidant treatments during training, which reduce the improvement of muscle mitochondrial function and insulin sensitivity, implicating the generation of reactive oxygen species as mediators of exercise adaptations (Ristow et al. 2009; Strobel et al. 2011). Whether an altered myokine response is involved in the undesired effects of NSAIDs and antioxidant treatment during exercise remains to be proven.

Regulation of Myogenesis and Muscle Hypertrophy

Increases in muscle mass and muscle hypertrophy are important adaptations to regular training, in particular to resistance exercise. The insulin-like growth factor 1 (IGF-1) locally increases in exercising muscle and is proposed to mediate some of the effects of training on muscle mass by promoting hypertrophy (Velloso 2008). Other exercise-regulated myokines increase the proliferation of primary human skeletal muscle cells, including decorin (Li et al. 2007), LIF (Broholm et al. 2011), and CHI3L1 (Gorgens et al. 2016) or, as already mentioned for IL-6 and is also shown for IL-7, are involved in myogenesis (Haugen et al. 2010). The reduced abundance of the muscle growth inhibitor, myostatin, in trained skeletal muscle and altered regulation of myostatin activity can also contribute to muscle hypertrophy. Decorin enhances skeletal muscle regeneration in mice by inhibiting myostatin and increasing promyogenic factors (Kanzleiter et al. 2014).

Adaptation of the Vascular System

Exercise training induces pronounced systemic cardiovascular adaptations, such as increased cardiac output and enhanced blood volume. Muscle-derived factors have been implicated in mediating the local effects of exercise training to increase capillarization in skeletal muscle and improve oxygen supply and utilization (Hoier and Hellsten 2014). The most important angiogenic factor induced in skeletal muscle on acute exercise is VEGF (Olfert et al. 2016). On a systemic level, plasma VEGF levels are often unaltered in response to exercise, pointing toward primarily local effects (Landers-Ramos et al. 2014). CYR61 or CCN1 and CTGF or CCN2 belong to a family of ECM-associated proteins. Both are localized to capillaries, and CYR61 is also present in myofibers (Kivela et al. 2007). Like VEGF, local increases in CYR61 and CTGF following exercise are well-described, whereas no elevation on the systemic level has been described. Both regulate angiogenesis, in part by promoting VEGF expression, endothe-

lial cell function, and the ECM (Perbal 2004). IL-8 activates endothelial cell proliferation and capillary tube organization (Li et al. 2003); therefore, IL-8 has been proposed to play a role in skeletal muscle angiogenesis. However, a recent study came to an opposite conclusion, showing that elevated IL-8 secretion from human myotubes impairs capillary outgrowth (Amir et al. 2015). Besides the regulation of lipid metabolism, ANGPTL4 also regulates angiogenesis and vascular permeability (Babapoor-Farrokhran et al. 2015). Muscle-specific deficiency or overexpression of follistatin-like 1 (FSTL1) in mice reveals a beneficial effect on vascular repair processes (Miyabe et al. 2014).

Muscle–Bone Interactions

Muscle contraction influences bone mass during development and growth, as well as bone density, risk of fractures, and fracture healing in adults. Mechanical stimuli are considered as driving forces in this relationship (Turner 2006), but there is also evidence that exercise-induced muscle-derived factors regulate bone formation and bone health. Myostatin inhibits bone repair, and consequently myostatin antagonists improve fracture healing (Hamrick et al. 2010). In contrast, IGF-1 (Doorn et al. 2013) and secreted protein rich in cysteine (SPARC) have osteogenic properties and are positively associated with bone mineralization (Breen et al. 2011; Pataquiva-Mateus et al. 2012). Bone mineral content is also increased by muscle-specific oversecretion of IL-15 (Quinn et al. 2009).

Improvement of Cognitive Function

Cognitive function can be improved and preserved by regular physical activity (Duzel et al. 2016). An important factor in that regard is BDNF, which regulates synaptic plasticity, cell survival, and differentiation in the brain (Chao et al. 2006). Elevated systemic levels of BDNF following acute exercise are frequently reported, but increases in BDNF mRNA and protein abundance in skeletal muscle are apparently not associated with a release of the protein (Matthews et al. 2009). However, in mouse models, two muscle-derived factors have been linked to increased BDNF abundance in the hippocampus. Exercise induces the expression of FNDC5 not only in muscle, but also in hippocampus, which leads to increased BDNF levels and neuroprotection in this region (Wrann et al. 2013). This action can also be achieved by elevation of circulating irisin levels. The exercise-induced release of cathepsin B (CTSB) from skeletal muscle in mice was implicated in the improved memory function mediated by enhanced BDNF expression in the hippocampus (Moon et al. 2016). This is supported by human data showing that exercise training increases CTSB mRNA levels in muscle, as well as systemic protein level, which is correlated with cognitive functions (Moon et al. 2016).

Cancer Protection

Regular physical activity is recommended to reduce the risk for developing various tumors. Cytokines derived from exercise-conditioned mouse serum or electrical stimulated muscle cells can inhibit cancer cell proliferation (Hojman et al. 2011). The exercise-dependent mobilization of natural killer cells plays a central role in reducing tumor growth, and the myokines IL-6 and IL-15 regulate maturation and redistribution of natural killer cells (Idorn and Hojman 2016). Moreover, studies in mice support a role of exercise-induced SPARC in suppressing colon tumorigenesis by enhancing apoptosis in colon cells (Aoi et al. 2013).

PHYSIOLOGICAL RELEVANCE OF ENDOCRINE EFFECTS OF MYOKINES

The importance of exercise-induced myokines in the regulation of immunomodulatory processes, in angiogenesis, and in remodeling the ECM in muscle is well established. Exercise-induced myokines play a central role in orchestrating the interaction of myofibers, immune cells, fibroblasts, and endothelial cells (Fig. 1). In addition, the release of neurotrophic factors such as BNDF and neurotrophic factor-4 have been proposed to be involved in promoting survival and function of motoneurons (Nishimune et al.

2014). Thus, myokines are of crucial importance for the adaptation of skeletal muscle to an increased physical workload. Moreover, as described above, there are several exercise-regulated muscle-derived factors with proposed endocrine effects (summarized in Fig. 2). The biological effects attributed to myokines comprise more or less all beneficial consequences of regular physical activity. However, the extent to which endocrine effects of muscle-derived factors contribute to the health-promoting effects of exercise in humans is still unclear. First of all, for many myokines, whether the increase in transcript and protein abundance in muscle is translated into increased systemic levels is uncertain. The studies of Steensberg provide evidence that skeletal muscle accounts for a major part of the systemic elevation in IL-6 following exercise (Steensberg et al. 2000; Toft et al. 2011), but data for many other myokines is lacking. Fibroblast growth factor 21 (FGF-21) has been classified as a myokine, because its expression in skeletal muscle is increased several-fold in mouse models with mitochondrial disorders (Kim et al. 2013a; Keipert et al. 2014). Moreover, serum levels of FGF-21 are elevated after acute exercise (Kim et al. 2013b). However, analyzing the flux of FGF-21 over the exercising muscle and over the hepatosplanchnic bed in humans reveals liver, rather than skeletal muscle, is the main contributor to exercise-induced systemic increases in FGF-21 (Hansen et al. 2015a). Other myokines showed a pronounced up-regulation following exercise in other organs—for example, exercise also induces a marked ANGPTL4 expression in liver (Kersten et al. 2009)—and the contribution of skeletal muscle to systemic ANGPTL4 levels following exercise requires further clarification.

To elucidate the relevance of individual myokines for a role in exercise adaptations, it turned out to be a challenge to generate appropriate animal models. Muscle-specific overexpression of myokines in mice needs to be fine-tuned to yield a physiologically relevant local and systemic concentration and should ideally mimic the transient changes. Because of the expression and release of most myokines from several tissues and their pleiotropic functions, whole-body knockout mice are less helpful in this context. There is the need for convincing transgenic mouse models specifically targeting the exercise-regulated release of myokines from skeletal muscle. This proved to be more challenging than expected. Skeletal muscle–specific IL-6 knockout mice appear to have higher systemic IL-6 levels following exercise (Gudiksen et al. 2016), which again shows the tight regulation and importance of feedback control mechanisms in the cytokine network.

FURTHER PERSPECTIVES

Role of the Extracellular Matrix in Exercise Adaptations

Structural proteins of the ECM are released by their cellular sources within skeletal muscle and are highly abundant in the supernatant of cultured skeletal muscle cells (Weigert et al. 2014). Moreover, transcriptional and proteomics profiling of the skeletal muscle following acute exercise and training revealed a large number of regulated ECM proteins, including several collagens, proteoglycans, and modulators of the ECM such as cathepsins and matrix metalloproteinases (Rullman et al. 2007; Norheim et al. 2011; Heinemeier et al. 2013; Catoire et al. 2014b; Hjorth et al. 2015; Hyldahl et al. 2015).

Although most of the regulated ECM components may not have direct signaling properties, the importance of the dynamic nature of the ECM of skeletal muscle for mechanotransduction, force transmission to tendons, protection against force-induced injury, exercise-induced angiogenesis, and ECM-residing progenitor cells is well-acknowledged (Kjaer 2004; Gustafsson 2011). Notably, skeletal muscle insulin resistance is accompanied by increased collagen content (Berria et al. 2006) and decreased desmin and actinin-2 content (Hwang et al. 2010). Alterations in the ECM, such as the content of hyaluronan, have been proposed to act as a physical barrier and influence glucose and insulin delivery (Kang et al. 2013; Williams et al. 2015), whereas alterations in desmin or actinin can influence mechanosignal transduction and translocation of glucose transporter-4 (Coletta

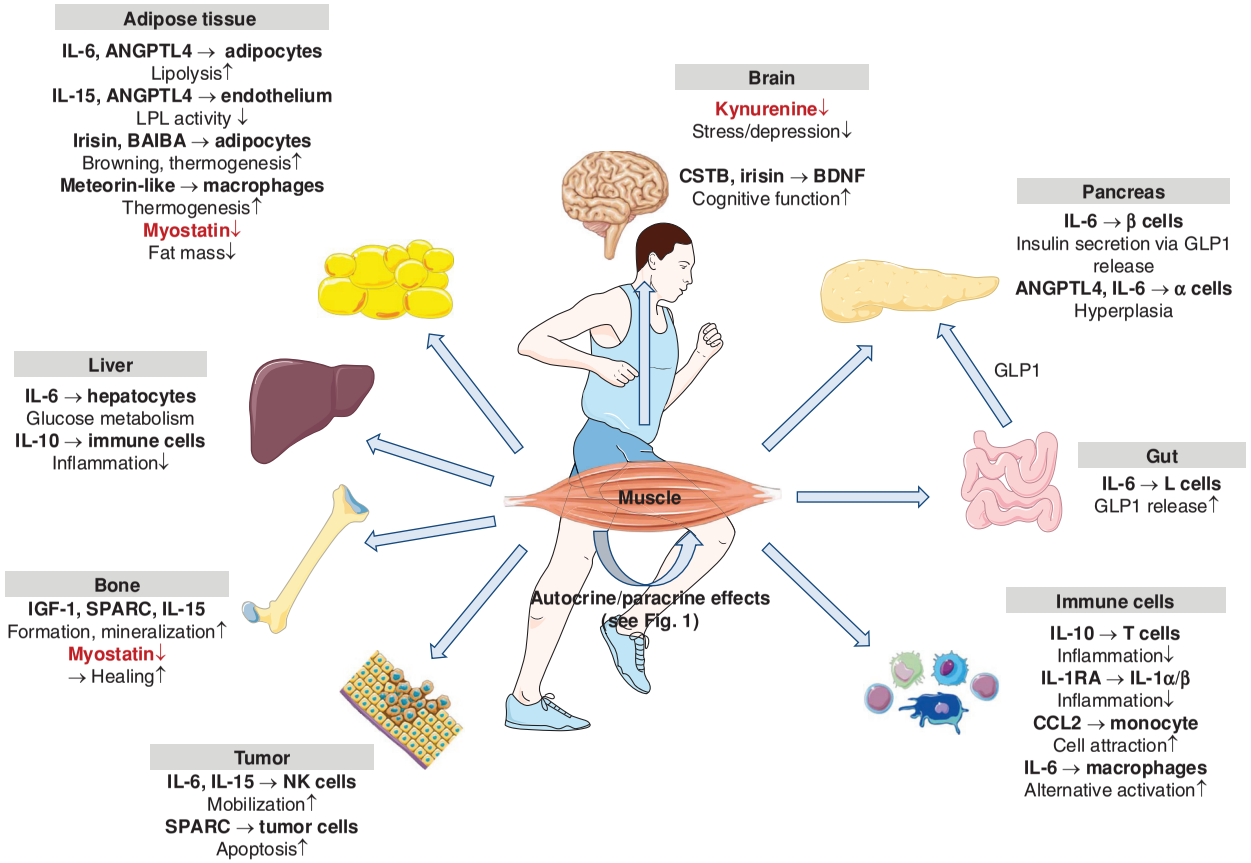

Figure 2. Endocrine effects of exercise-regulated human myokines and metabolites. In addition to their autocrine and paracrine effects, myokines act on adipose tissue, liver, gut, brain, pancreas, bone, circulating and resident immune cells, and tumors. In most cases, exercise stimulates the release of myokines and metabolites (shown in black; BAIBA, β-amino isobutyric acid). Notable exceptions are myostatin and kynurenine, which are reduced after regular exercise (shown in red). (Figure created using illustrations provided by Servier Medical Art.)

and Mandarino 2011). Mutations in collagen VI lead to defective muscle microfibril formation and mitochondrial dysfunction (Bushby et al. 2014; Zamurs et al. 2015). Furthermore, ECM–integrin receptor interaction is involved in diet-induced insulin resistance in mouse models (Kang et al. 2016). Another regulatory level of signal transduction in skeletal muscle is the binding, release, and presentation of growth factors such as VEGF and transforming growth factor β (TGF-β) by the ECM (Hynes 2009), which can be directly influenced by the exercise-dependent remodeling of the ECM. Thus, several modes of interaction exist between the ECM and myofibers within skeletal muscle that can be involved in exercise-induced adaptations including improved metabolism and exercise capacity.

TGF-β as Potential Regulator of Metabolic Adaptations

The TGF-β protein family is of great importance for muscle development and regeneration (Kollias and McDermott 2008). TGF-β is an inhibitor of myogenic differentiation (Massague et al. 1986) and plays an important role in inflammatory process after muscle injury and fibrosis (Mann et al. 2011). After acute exercise or training, mRNA abundance of TGF-β1 and TGF-β receptor 2 is increased (Heinemeier et al. 2013). Moreover, TGF-β signaling can be enhanced by release of active TGF-β protein from a large latent complex in the ECM by exercise-activated metalloproteinases or mechanical force-mediated activation via integrin signaling (Hynes 2009), but the contribution of these mechanisms to the enhanced TGF-β signaling following exercise needs to be clarified. Numerous TGF-β target transcripts, such as the TGF-β inducible protein and other ECM proteins, are increased after exercise and training (Heinemeier et al. 2013; Neubauer et al. 2014). Thus, TGF-β contributes to the adaptation of the ECM to exercise. Recently, TGF-β has also been implicated in the exercise-dependent regulation of PGC1α and substrate oxidation capacity of skeletal muscle (Tiano et al. 2015; Bohm et al. 2016). TGF-β1 down-regulates several mitochondrial key regulators and enzymes in primary human skeletal muscle cells and activated TGF-β signaling may account for the failure to enhance insulin sensitivity in some subjects after training (Bohm et al. 2016). This effect of TGF-β is not restricted to skeletal muscle, because whole-body blockade of TGF-β signaling in obese mice improves mitochondrial respiration in adipocytes, hepatic steatosis, glucose tolerance, and energy homeostasis (Yadav et al. 2011). Thus, TGF-β appears to be relevant not only for the ECM composition and inflammatory processes but also for improvements in glycemic control after exercise training.

FUTURE DIRECTIONS

Myometabokines

The secretome of skeletal muscle not only comprises proteins and peptides but also metabolites and lipids. These factors can contribute to the health-promoting effects of exercise not only caused by altered substrate fluxes between organs but also based on the potential of some metabolites and lipids to activate surface or intracellular receptors (Schoonjans et al. 1996; Itoh et al. 2003; Hashimoto et al. 2007; Cao et al. 2008). These factors can act as muscle-derived paracrine or endocrine factors and are termed "myometabokines." Metabolomics and lipidomics analyses of arterial and venous plasma samples of the exercising leg enable the identification of a wide range of metabolites and lipids released from skeletal muscle (Xu et al. 2016). In rodent studies, two interesting candidates with endocrine function have been identified. β-Amino isobutyric acid is released from cultured muscle cells and increased in plasma of exercising mice and trained humans. β-Amino isobutyric acid contributes to the browning of white fat and hepatic fat oxidation (Roberts et al. 2014). Exercise training increases kynurenine aminotransferase in skeletal muscle, inducing a shift in circulating kynurenine to kynurenic acid in both mice and humans, which is proposed to be involved in the protection from stress-induced depressive disorders (Agudelo et al. 2014; Schlittler et al. 2016).

MyomiRs

Other recently discovered components of the muscle's secretome include regulatory, noncoding RNA molecules (micro-RNA [miRNA], long noncoding RNA [lncRNA]) (Coenen-Stass et al. 2016). Exercise and training regulates the plasma miRNA profile in humans (Baggish et al. 2011; Nielsen et al. 2014), which differs from the miRNA signature in exercised or trained muscle (Nielsen et al. 2010; Russell et al. 2013). Muscle-enriched miRNA (referred to as myomiRs) are involved in the regulation of myogenic processes and circulating miRNAs responding to exercise are associated with angiogenesis, inflammation, and mitochondrial dynamics, and a role in the adaptation to exercise is discussed (Russell and Lamon 2015). MyomiRs are also found in exosomes, interesting new players of the muscle's secretome, because they can carry a whole array of exercise-regulated factors, thereby transporting the health-promoting information of exercise to other tissues (Safdar et al. 2016).

Therapeutic Potential of Exercise-Regulated Myokines

Although future research will provide more insight into the relevance of endocrine effects of single myokines or other muscle-derived factors, the increasing knowledge about the biological function of exercise-regulated muscle-derived factors is a valuable source for novel therapeutic options to treat chronic diseases. However, the transient regulation of most myokines by exercise—a sharp increase in systemic levels, followed by a decline within hours—is a very important aspect when considering the therapeutic potential of myokines, because chronically elevated systemic concentrations of most cytokines and ECM-regulating growth factors are associated with conditions of prolonged and uncontrolled inflammation and are found in many diseases, including autoimmune diseases, cancer, and obesity-related metabolic disorders, or muscular dystrophies (Akira et al. 1993; Gabay 2006; Hoene and Weigert 2008; Burks and Cohn 2011).

In the case of myostatin with its clear function in regulating muscle mass and body fat content, a soluble form of the activin receptor type IIB, which blocks myostatin (Lee et al. 2016), was tested in a double-blind, placebo-controlled study in 48 healthy women and was shown to increase total lean body mass and muscle volume (Attie et al. 2013). Based on the multiple potential beneficial effects of IL-6, current research is also focusing on the development of novel gp130 ligands. IL-6 and other cytokines share signaling via a gp130/α-receptor complex (Heinrich et al. 2003). Among them is CNTF, which has weight-lowering effects in mice (Watt et al. 2006) and humans (Ettinger et al. 2003). The design of new gp130 ligands, by combining the beneficial signaling properties and abolishing the negative effects, which in the case of IL-6 is triggering proinflammatory reactions, has been proposed to be a promising future goal (Cron et al. 2016).

CONCLUDING REMARKS

Based on the current state of knowledge, the major physiological function of the secretory capability of skeletal muscle is to protect and improve the functionality of the working muscle by regulating the intramuscular cross talk of myofibers, immune cells, fibroblasts, the vasculature, and the bone. Furthermore, there is convincing evidence that factors secreted by skeletal muscle act as endocrine signaling mediators and are involved in the beneficial effects of exercise on almost all cell types and organs. The entire secretome of exercising skeletal muscle has not yet been described. Thus, novel components, including metabolites, lipids, and RNA molecules, will add additional regulatory levels to the interorgan cross talk. Because of the complexity of not only the muscle's secretome, an "exercise mimetic" might not be possible, and efforts to motivate people to increase their daily physical activity should even be intensified. But research has started to develop modified myokines that combine the beneficial effects and omit the undesired side effects, aiming to support the treatment of chronic diseases.

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