Received: 1 August 2024 | Revised: 21 November 2024 | Accepted: 22 November 2024
DOI: 10.1002/oby.24223

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

REVIEW

Obesity Biology and Integrated Physiology

Skeletal muscle growth to combat diabetes and obesity: the potential role of muscle-secreted factors

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Funding information
Natural Sciences and Engineering Research Council of Canada, Grant/Award Number: RGPGP-2020-06479

Abstract

As the prevalence of obesity and metabolic disease continues to climb, the need for effective therapeutic interventions remains high. The growth of skeletal muscle (SkM) greatly influences systemic metabolism across the whole body, making this tissue an important therapeutic target to combat the rise of metabolic dysfunction. Transgenic rodent models of targeted SkM growth exhibit profound improvements in various remote tissues, including adipose tissue and the liver. It is currently unclear how selective stimulation of SkM growth alters the metabolism of distant tissues; however, evidence suggests that muscle-secreted factors may be involved. Here, we aim to provide basic biomedical researchers with a summary of the current knowledge regarding various muscle-secreted factors regulated by anabolic pathways and proteins in SkM, as well as their systemic metabolic effects, to implicate them in the whole-body metabolic effects of SkM growth. In this review, we also identify several knowledge gaps in this field, future directions of investigation, and implications for therapeutic interventions such as resistance exercise and pharmacology.

INTRODUCTION

The continual rise of obesity and metabolic disease represents a growing epidemic, not only in North America but across the globe. By 2030, type 2 diabetes (T2DM) is predicted to affect 7079 per 100,000 individuals globally, and the prevalence of severe obesity is projected to double in first-world nations by 2035 [1, 2]. As such, it is important to combat metabolic dysfunction caused by lifestyle factors, including physical inactivity and calorically rich environments. Skeletal muscle (SkM) accounts for ∼40% of human body weight, is highly metabolically active, and represents the largest insulin-sensitive tissue in the body [3, 4]. Accordingly, SkM health is an important determinant of systemic metabolic health and should be considered a promising target in the fight against diabetes and obesity. Intriguingly, there is accumulating evidence that the stimulation of SkM growth exhibits antiobesity and antidiabetic effects [5, 6]; however, our current understanding of the mechanisms involved is severely lacking. Furthermore, the role of the secretory function of SkM as an endocrine organ is understudied, especially in the context of muscle growth, obesity, and diabetes.

The purpose of this review is to highlight the potential role of muscle-secreted factors in mediating the whole-body metabolic effects of SkM growth, as well as gaps in our knowledge of these mechanisms. We also summarize various factors that may be secreted from SkM in response to muscle anabolism, along with their metabolic effects in various non-muscle tissues relevant to obesity and diabetes, including adipose tissue, liver, pancreas, and brain. Finally, we discuss implications for therapeutic interventions for obesity and diabetes, such as resistance exercise and pharmacology. As will be discussed, this research area remains vastly understudied and deserves intensive future investigation. As such, this review aims to provide biomedical researchers with a summary of our current knowledge on this topic and potential avenues for further exploration.

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SkM ANABOLIC SIGNALING AND METABOLISM

SkM is highly plastic and exhibits a remarkable capacity for growth in response to various anabolic stimuli, including growth factors (e.g., insulin-like growth factor 1 [IGF-1]) and mechanical overload [7, 8]. It is important to note that SkM size is regulated by the net balance of muscle anabolism/protein synthesis and catabolism/protein breakdown, whereby growth occurs when the rate of muscle protein synthesis is greater than breakdown and vice versa [9]. Although it should be appreciated that muscle protein breakdown, atrophy pathways, and associated proteins (e.g., forkhead box O [FOXO], mothers against decapentaplegic homolog [SMAD], E3 ubiquitin ligases) play an important part in the regulation of SkM growth [8], our review will primarily focus on muscle protein synthesis and positive regulators of SkM anabolism and growth.

Growth factor-stimulated SkM growth primarily works through the phosphoinositide 3-kinase (PI3K)–protein kinase B (Akt1)–mammalian target of rapamycin (mTOR) signaling pathway [10–12]. For example, the binding of IGF-1 to the IGF-1 receptor results in the activation of PI3K, which leads to downstream phosphorylation of Akt1, subsequently inhibiting tuberous sclerosis 1 protein (TSC1) and relieving the inhibitory "brake" on mTORC1 complex to promote protein synthesis and cellular growth (Figure 1) [13, 14].

Conversely, the mechanisms involved in mechanical stress-induced SkM hypertrophy remain unclear and seem to be mediated by mechano-sensing pathways involving proteins associated with components of the extracellular environment and sarcolemma (Figure 1). Roberts et al. highlight various mechanistic candidates thought to play a role in mechano-transduction pathways promoting SkM growth, including focal adhesion kinase (FAK)/integrins, stretch-activated calcium channels, and diacylglycerol (DAG) kinase (we suggest Roberts et al. for a comprehensive review of mechanical overload-induced SkM hypertrophy) [7]. Glycoprotein phospholipase D (PLD) has also been implicated in regulating muscle size following mechanical loading [15]. Importantly, these mechano-sensing pathways lead to the downstream activation of mTOR signaling and protein synthesis. For example, phospholipase D1 (PLD1) and DAG kinase generate phosphatidic acid, which activates mTORC1/2 to promote hypertrophy, via the hydrolysis of phosphatidylcholine and conversion of DAG, respectively [15, 16].

SkM growth is extremely energetically demanding as the process of muscle protein synthesis consumes a significant portion of the intracellular ATP pool [17]. As such, metabolic regulators are important for promoting and sustaining SkM growth. An isoform of peroxisome proliferator-activated receptor coactivator-γ-1α (PGC-1α), PGC-1α4, has been shown to promote hypertrophy and increase anaerobic glycolysis in SkM [18–21]. Although it remains unclear which intracellular events activate PGC-1α4 in SkM and how this promotes SkM growth, PGC-1α4 appears to increase the expression of IGF-1 through G protein-coupled receptor 56 upregulation and decrease the expression of myostatin (MSTN, a negative regulator of muscle mass), thereby promoting anabolic signaling (Figure 1) [17, 18, 22]. PGC-1α4 also increases glucose uptake and anaerobic glycolysis via peroxisome proliferator-activated receptor β (PPARβ) [21]. Indeed, glycolytic metabolism increases to support SkM growth [23, 24]. Although glycolysis may not be an efficient pathway to produce energy, it can rapidly metabolize large amounts of glucose for energy, which is important for energetically demanding cellular growth. mTORC1 activation also increases the expression of glycolytic genes such as hexokinase, glucose transporters (GLUT), phosphofructokinase, and glucose-6-phosphate dehydrogenase via hypoxia-inducible factor 1α to increase glycolysis and pentose phosphate pathway flux [6, 25, 26].

It has recently been shown that muscle fibers undergoing hypertrophy reprogram themselves similarly to cancer cells [23, 24]. Specifically, cancer cells, and possibly hypertrophying muscle cells, increase glucose uptake and metabolism and divert glycolytic intermediates toward anabolic pathways such as the pentose phosphate and serine synthesis pathways to support growth [23]. In support of these observations, the serine synthesis pathway enzyme phosphoglycerate

Study Importance

What is already known?

- Targeted skeletal muscle (SkM) growth in transgenic animal models improves several systemic metabolic parameteres.
- SkM growth alters the metabolism of remote tissues such as the adipose tissue and liver, but the mechanisms by which this occurs are unclear and may involve muscle-secreted factors.

What does this review add?

- This review summarizes our current knowldge of SkM growth-regulated secreted factors and their influence on non-SkM tissues and systemic metabolism.
- Gaps in knowledge in this area, future avenues of investigation, and implications for therapeutic interventions for diabetes and obesity are also discussed.

How might this review change the direction of research or focus of clinical practice?

- This review provides biomedical researchers with areas to be adressed in our understanding of how SkM growth influences systemic metabolism via muscle-sectreted factors, which will promote further research in this area.
- While the focus of current anti-obesity and diabetic treatments is the suppression of appetite and direct effects on adipose tissue and the liver; this review may stimulate interest in the targeting of SkM for the improvement of systemic metabolism.

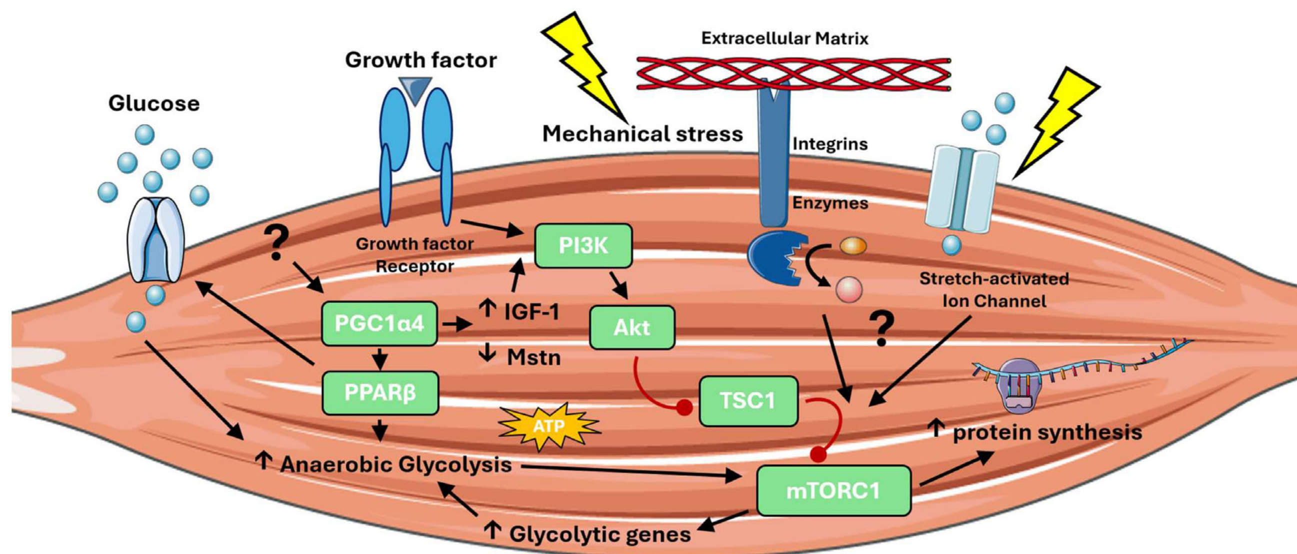

FIGURE 1 Mechanisms of skeletal muscle (SkM) growth. Growth factor binding to the receptor signals through phosphoinositide 3-kinase–protein kinase B (PI3K-Akt) to indirectly activate mammalian target of rapamycin complex 1 (mTORC1) and protein synthesis via tuberous sclerosis 1 protein (TSC1) inhibition. Mechanical stress activates mTORC1 and protein synthesis through various unclear mechano-sensing pathways and proteins associated with the extracellular matrix and sarcolemma, including integrins, kinases, and stretch-activated ion channels. Peroxisome proliferator-activated receptor coactivator-γ-1α4 (PGC-1α4) increases insulin-like growth factor 1 (IGF-1) and decreases myostatin (MSTN) expression, respectively, while signaling through peroxisome proliferator-activated receptor β (PPARβ) to upregulate glucose uptake and anaerobic glycolysis to support cellular growth. mTORC1 also increases genes involved in glucose metabolism to support growth. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. [Color figure can be viewed at wileyonlinelibrary.com]

dehydrogenase (PHGDH) has recently been implicated in promoting muscle cell anabolism and glucose-derived biomass through mTORC1 signaling [27].

SkM GROWTH AND SYSTEMIC METABOLISM

Wackerhage et al. recently highlighted the profound systemic metabolic effects of SkM hypertrophy that combat diabetes and obesity [5]. Indeed, increasing muscle mass, particularly that of fast-twitch glycolytic SkM, has been considered an effective strategy for improving systemic metabolism [6]. Furthermore, data in transgenic animal models strongly support the causative effects of SkM growth on whole-body metabolism (Table 1). For example, the constitutive activity of SkM Akt1 in mice leads to the hypertrophy of fast-twitch glycolytic muscle fibers and increases muscle strength while improving various systemic metabolic parameters [28]. Specifically, SkM-specific Akt1 overactivation counteracts high-fat and -sucrose diet-induced metabolic dysfunction by reducing fat mass, increasing hepatic fatty acid oxidation to prevent hepatic steatosis, reducing hyperglycemia and hyperinsulinemia, and normalizing glucose tolerance and insulin sensitivity [28].

Similarly, SkM-specific knockout of MSTN increases lean muscle mass, reduces fat mass, and improves glucose and insulin tolerance in mice on standard and high-fat diets [29]. Interestingly, MSTN knockout in adipose tissue does not confer the same systemic metabolic effects observed with SkM-specific knockout in mice [29], indicating that these effects are specific to SkM growth.

SkM-specific overexpression of PGC-1α4 prevents age-associated sarcopenia and metabolic dysfunction; induces a lean phenotype; increases muscle strength, muscle weight, and fiber size; reduces fat mass; increases white adipose tissue (WAT) browning; and improves insulin resistance and hepatic steatosis [18, 19].

Transgenic enhancement of glycolysis in SkM alone also promotes increased muscle mass and results in whole-body metabolic adaptations, including the loss of fat mass in mice [26].

Collectively, these findings suggest that targeted SkM hypertrophy influences whole-body metabolic health, alters the metabolism of remote tissues and organs such as adipose tissue and the liver, and prevents or improves metabolic dysfunction associated with obesity and diabetes (Table 1).

The mechanisms mediating these systemic effects of SkM hypertrophy remain unclear; however, some plausible explanations have been proposed. The growth of SkM may promote the "stealing" of substrates such as glucose and fatty acids away from adipose tissue and the liver, preventing fat accretion and hepatic steatosis [23, 29, 30].

Although this mechanism is certainly plausible and warrants further investigation, the potential involvement of systemic cross talk between hypertrophying SkM and distant tissues remains understudied [5].

MUSCLE-SECRETED FACTORS REGULATED BY SkM GROWTH AND ASSOCIATED PATHWAYS

SkM is an endocrine organ that secretes various factors such as myokines and metabolites into circulation to influence the metabolism of

TABLE 1 Phenotypic comparison of transgenic animal models of targeted SkM growth.

Transgenic rodent model	References	SkM mass	Systemic effects	Secreted factors
Constitutive SkM-Akt1	[28, 33, 60, 64, 73, 74]	↑	↓ Fat mass ↑ Hepatic FAO ↓ Hyperglycemia ↓ Hyperinsulinemia ↑ Glucose tolerance/insulin sensitivity	↑ FGF21 ↑ Lactate ↑ EV-miR1, miR133a, miR206 ↑ FSTL1
SkM-MSTN KO	[29]	↑	↓ Fat mass ↑ Glucose tolerance/insulin sensitivity	
SkM-PGC-1α4 overexpression	[18–20]	↑	↓ Fat mass ↑ WAT browning ↑ Insulin sensitivity ↓ Hepatic fat	↑ METRNL
SkM-TSC1 KO/constitutive mTORC1	[14, 41]	↓	↓ Fat mass	↑ FGF21 ↑ GDF15
Synergist ablation (MOV)	[66, 72]	↑		↑ EV-miR1 ↑ Lactate
SkM-GLUT1, HK2, and PFKB3 overexpression	[26]	↑	↓ Fat mass ↑ Insulin sensitivity ↑ Adipose tissue energy expenditure	↑ FGF21

Abbreviations: Akt1, protein kinase B; EV, extracellular vesicle; FAO, fatty acid oxidation; FGF21, fibroblast growth factor 21; FSTL1, follistatin-like 1; GLUT1, glucose transporter 1; HK2, hexokinase 2; KO, knockout; METRNL, meteorin-like; miR, microRNA; MOV, mechanical overload; MSTN, myostatin; mTORC1, mammalian target of rapamycin complex 1; PFKB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; SkM, skeletal muscle; TSC1; tuberous sclerosis complex 1; WAT, white adipose tissue.

remote tissues [31, 32]. Interestingly, many muscle-secreted factors are positively regulated by metabolic and anabolic signaling pathways and proteins involved in promoting SkM hypertrophy (e.g., PI3K-Akt1, mTORC1, PGC-1α4, glycolytic metabolism). This suggests that stimulation and induction of these anabolic pathways and proteins during SkM growth may promote the secretion of factors that influence systemic metabolism.

Here, we summarize these "anabolism-regulated" muscle-secreted factors and their metabolic effects in non-muscle tissues to implicate them in the systemic metabolic effects of SkM growth. This review identified the discussed muscle-secreted factors from preclinical studies involving targeted SkM-specific growth (transgenic or otherwise) and associated whole-body metabolic improvements and/or involving SkM-specific overexpression of anabolism-promoting proteins or pathways.

Fibroblast growth factor 21 and growth and differentiation factor 15

Fibroblast growth factor 21 (FGF21) is an SkM-secreted myokine regulated by Akt1 and mTORC1. Izumiya et al. showed that SkM-specific constitutive Akt1 activity in transgenic mice promoted hypertrophy, significantly upregulated the mRNA transcript and protein expression of FGF21 in the gastrocnemius muscle, and also increased serum concentrations of circulating FGF21 [33]. Furthermore, both Akt1 transduction and insulin stimulation increased FGF21 expression and secretion from cultured SkM cells [33]. Interestingly, the PI3K inhibitor LY294002 prevented the effects of insulin on FGF21, suggesting the important role of PI3K-Akt1 signaling in mediating FGF21 secretion from SkM (Figure 2) [33].

Guridi et al. [14] demonstrated that SkM-specific constitutive mTORC1 activation via TSC1 knockout increased plasma FGF21 and upregulated SkM FGF21 mRNA and protein expression in transgenic mice. The SkM TSC1 knockout-induced increase in FGF21 expression and secretion was subsequently prevented with 3 days of treatment with the mTORC1 inhibitor rapamycin, reinforcing the important role of mTORC1 in the regulation of FGF21 [14]. This suggests that mTORC1 activity, likely through Akt1 activation and TSC1 inhibition, regulates the synthesis of SkM FGF21 and promotes its secretion into the systemic circulation. Specifically, mTORC1 activation appears to promote FGF21 synthesis and secretion through endoplasmic reticulum (ER) stress-mediated activation of the protein kinase RNA-like ER kinase (PERK)–eukaryotic translation initiation factor 2α (eIF2α)–activating transcription factor 4 (ATF4) pathway. To support this mechanism, resolving ER stress with the chemical chaperone 4-phenylbutyric acid (4-PBA) attenuates SkM TSC1 knockout-induced FGF21 expression in SkM [14, 34].

SkM-secreted FGF21 has been shown to enhance whole-body metabolism across various tissues as an endocrine hormone. TSC1 knockout in theSkM of mice, accompanied by FGF21 upregulation, results in a lean phenotype; increased insulin sensitivity; and increased fat oxidation in the liver, WAT, and brown adipose tissue (BAT) [14]. Supporting the role of secreted FGF21 in these systemic metabolic effects, the antibody blockade of FGF21 action prevents many metabolic adaptations observed in SkM-specific TSC1 knockout mice [14].

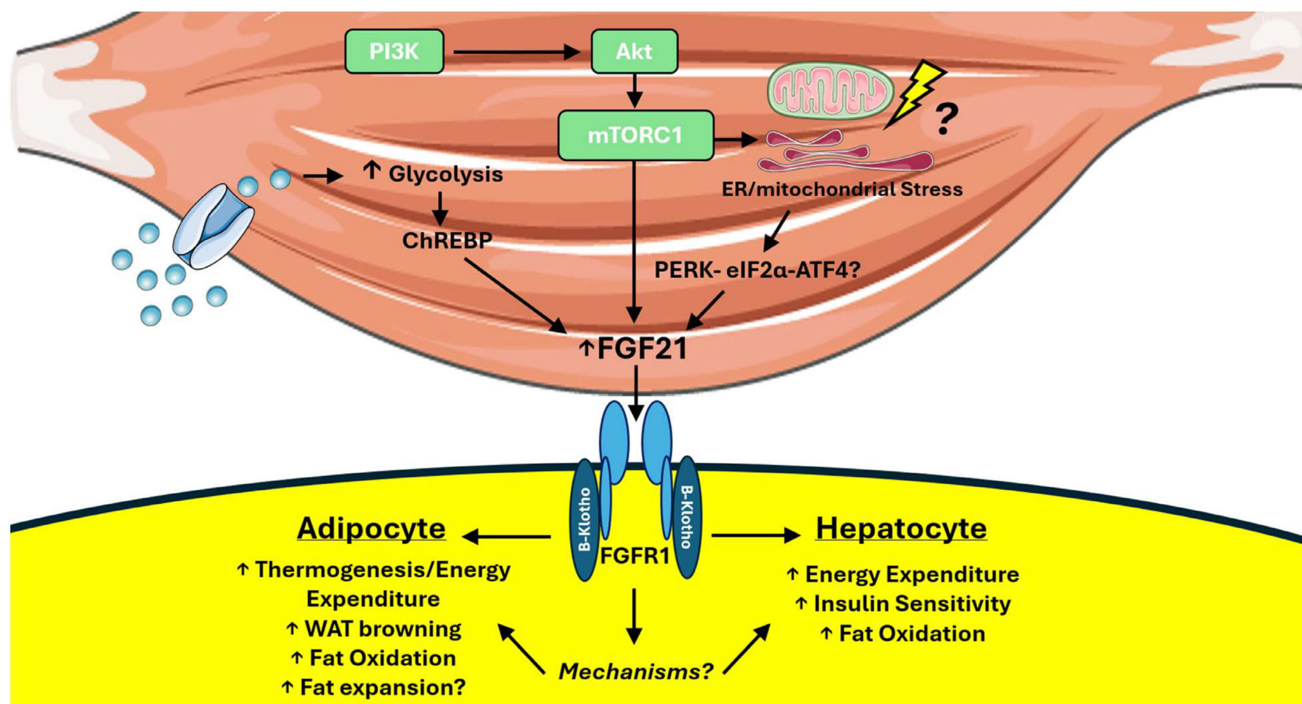

FIGURE 2 Skeletal muscle (SkM) growth regulation of fibroblast growth factor 21 (FGF21). Phosphoinositide 3-kinase–protein kinase B (PI3K-Akt1) signaling activates mammalian target of rapamycin complex 1 (mTORC1) to induce FGF21 expression and secretion. mTORC1-induced endoplasmic reticulum (ER) and mitochondrial stress may induce FGF21 via protein kinase RNA-like ER kinase (PERK)–eukaryotic translation initiation factor 2α (eIF2α)–activating transcription factor 4 (ATF4) signaling; however, the relevance of this pathway to anabolism-regulated FGF21 is unclear. Increased glycolysis with SkM growth may activate carbohydrate-responsive element–binding protein (ChREBP) to induce FGF21 as well. FGF21 acts through the FGF receptor 1 (FGFR1) and β klotho on adipocytes and hepatocytes to influence energy expenditure, lipid metabolism, and insulin sensitivity. The mechanisms governing these effects remain unclear. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. [Color figure can be viewed at wileyonlinelibrary.com]

Similarly, SkM mitochondrial stress induced by respiratory uncoupling strongly induces SkM FGF21 expression and secretion to increase lipid metabolism and WAT browning [35]. The infusion of FGF21 in mice fed a standard and high-fat diet also reduces body weight and fat mass, increases hepatic and SkM insulin sensitivity, and increases energy expenditure in the liver and adipose tissue [36]. Unlike constitutive Akt1, the transgenic mTORC1 and mitochondrial uncoupling rodent models exhibit reductions in muscle mass without myopathy, likely resulting from the enhanced whole-body energy expenditure and largely mediated by FGF21 [14, 35].

Increasing glycolytic metabolism in SkM, as observed with SkM growth, also increases systemic SkM secretion of FGF21. Specifically, SkM overexpression of GLUT1, hexokinase 2 (HK2), and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKB3) (which are increased with SkM growth [23, 24, 37]) in mice (M;G mice) increases relative lean mass and FGF21 secretion from SkM into plasma via glucose-6-phosphate-mediated carbohydrate-responsive element–binding protein (ChREBP) activation [26]. M;G mice also resist diet-induced obesity and insulin resistance via enhanced adipose tissue energy expenditure. Treatment of visceral adipocytes with M;G mice-derived serum induces several genes involved in lipid metabolism and thermogenesis, which was prevented with FGF21 antibody blockade. Importantly, the metabolic governors of FGF21 action, fibroblast growth factor receptor 1 (*Fgfr1*), β klotho (*Klb*), and *Ppar*, are upregulated in adipose tissue of M;G mice, further suggesting that adipose tissue is the target of SkM-secreted FGF21 in this model. These models highlight FGF21 as an SkM-secreted factor likely regulated via Akt1-mTORC1 and ChREBP activation, with profound systemic metabolic effects.

Although FGF21 may increase the expression of lipolysis and thermogenesis-related genes in adipose tissue, it may also improve insulin sensitivity via the β klotho–dependent expansion of subcutaneous fat [38]. The FGF21-induced subcutaneous fat expansion allows for systemic insulin sensitivity, possibly through increased insulin-stimulated glucose uptake, adiponectin upregulation, and anti-inflammatory signaling via M2 macrophage polarization [38]. Additionally, BonDurant et al. reported that, although β klotho–mediated signaling to adipose tissue, particularly BAT, is required for the acute insulin-sensitizing effects of FGF21, it appears to be unnecessary for the chronic effects of FGF21 on weight loss and energy expenditure [39]. This suggests that chronic exposure to FGF21 may be mediated by non-adipose tissues such as the brain; however, this remains unclear. Although the metabolic effects of FGF21 have been and continue to be studied, it remains unclear whether many of these mechanisms are relevant to muscle-derived FGF21 in the context of SkM growth. Future research is required to understand the

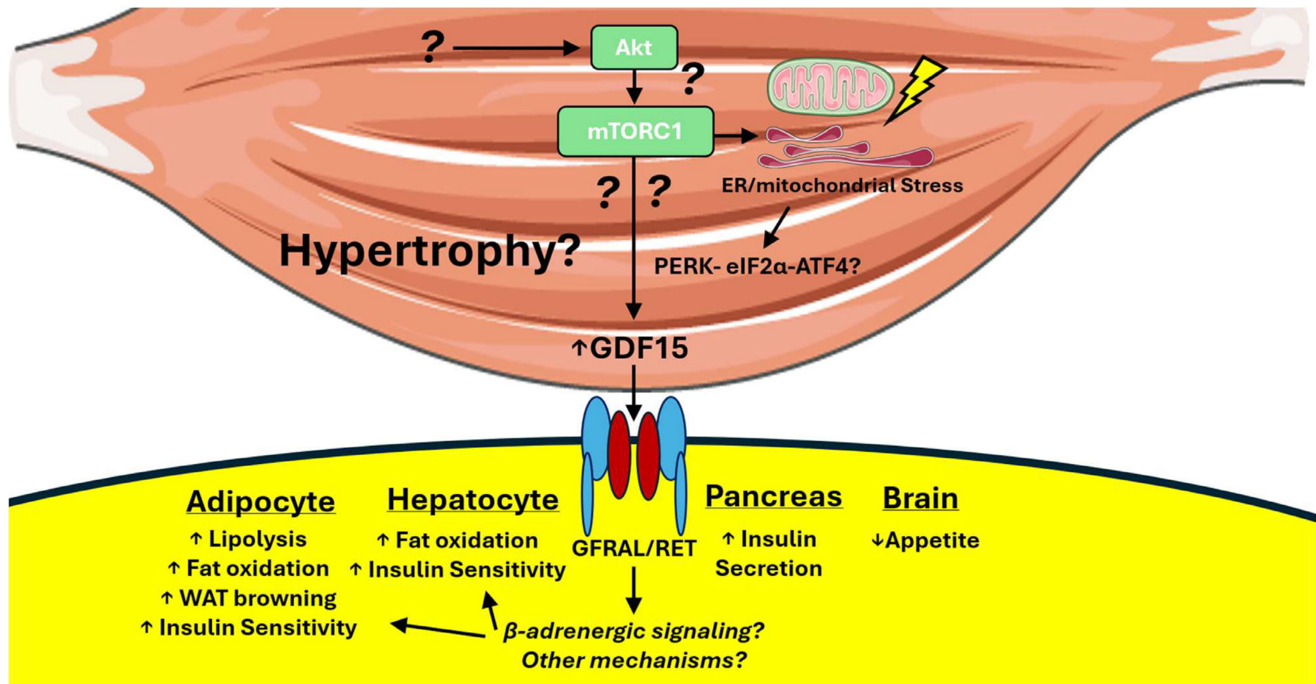

FIGURE 3 Skeletal muscle (SkM) growth regulation of growth and differentiation factor 15 (GDF15). mammalian target of rapamycin complex 1 (mTORC1) activation leads to the induction and secretion of GDF15; however, it is unclear whether this is initiated by upstream protein kinase B (Akt1) signaling. mTORC1 may activate protein kinase RNA-like ER kinase (PERK)– eukaryotic translation initiation factor 2α (eIF2α)–activating transcription factor 4 (ATF4) signaling; however, this pathway is unclear in the context of SkM growth and GDF15 secretion. It is also unclear whether GDF15 is secreted from SkM with growth. GDF15 acts through glial cell-derived neurotrophic factor family receptor α-like (GFRAL)/rearranged during transfection (RET) axis on adipocytes, hepatocytes, the pancreas, and the brain to influence lipid metabolism, insulin sensitivity, insulin secretion, and appetite. β-adrenergic signaling may mediate some of these effects, particularly in adipose tissue and the liver; however; the mechanisms governing these effects remain unclear. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. [Color figure can be viewed at wileyonlinelibrary.com]

mechanisms mediating the metabolic effects of SkM-secreted FGF21 in tissues such as the liver and adipose tissue with SkM growth in models of obesity and diabetes.

Growth differentiation factor 15 (GDF15) is another cellular stress-regulated protein secreted from SkM as a systemic hormone [34, 40]. Similar to FGF21, GDF15 is regulated by mTORC1 activation, and its mRNA and protein expression is induced in SkM of TSC1 knockout mice and other models of SkM-specific mTORC1 overactivity [41–43]. The increased synthesis and secretion of GDF15 also appears to be regulated by the PERK–eIF2α–ATF4 pathway in response to ER and mitochondrial stress in SkM following increased mTORC1 activity in these models (Figure 3) [34]. Indeed, SkM knockout of CR6-interacting factor 1 (CRIF1; an essential protein for the synthesis of oxidative phosphorylation proteins in the mitochondria) induces mitochondrial stress, GDF15 expression, and elevated circulating levels of GDF15 in serum [44].

GDF15 has recently been shown to be secreted from SkM in vitro and in vivo, exerting effects on non-SkM tissues in an endocrine fashion [44–47]. Laurens et al. showed that the contraction of SkM cells increases the expression and secretion of GDF15 [45]. Furthermore, the GDF15-rich conditioned media collected from contracting SkM cells increases lipolysis in adipocytes via GDNF family receptor α-like (GFRAL)/rearranged during transfection (RET) receptors, which was prevented following treatment with anti-GDF15 antibodies [45]. GDF15 also enhances glucose-stimulated insulin secretion in pancreatic β cells [46]. The 16-h pretreatment of cultured human β cells with GDF15-rich conditioned media (derived from electric pulse stimulation of isolated myotubules) increases insulin secretion by 30% in β-TC-6 (rodent) cells and 150% in mouse insulinoma (MIN6; human) cells compared with untreated cells [46]. This increase in insulin secretion appears to occur by increasing glycolytic flux. The treatment of β cells with isolated GDF15 was noted to increase the cytosolic ATP to ADP ratio and intracellular calcium influx compared with cells treated with a vehicle, which was reversed with the treatment of anti-GDF15 neutralizing antibody. In addition, no significant changes in gene expression of proteins regulating insulin secretion were observed, indicating that GDF15 enhances insulin secretion by increasing activation of the canonical insulin secretion pathway. Beyond its lipolytic and insulin-stimulating effects, GDF15 exhibits appetite-suppressing properties, reducing food intake and body weight through GFRAL/RET-mediated signaling in the hindbrain [48, 49]. Interestingly, GFRAL expression is predominantly observed in the hindbrain of both rodents and primates, whereas RET is highly expressed in the hindbrain and hypothalamus [48]. This suggests that GDF15 influences metabolism via peripheral and central mechanisms, with the latter likely predominating.

SkM-specific induction of GDF15 governs whole-body metabolism. Chung et al. showed that induction of mitochondrial stress in SkM via oxidative phosphorylation-respiratory uncoupling induced the secretion of GDF15, which improved systemic metabolism by increasing insulin sensitivity, reducing fat mass, and elevating fat oxidation in adipose tissue and the liver [44]. Ost et al. also showed that the upregulation of SkM-secreted GDF15 reduced appetite and food intake and increased metabolic flexibility and WAT browning [47]. GDF15-mediated increases in lipid metabolism, insulin sensitivity, and glucose uptake in adipose tissue and the liver appear to be governed by increased sympathetic nervous activity and β-adrenergic receptor signaling [49, 50]. This evidence suggests that GDF15 may act as a myokine regulated by mTORC1 activation, which influences the metabolism of tissues such as adipose tissue, liver, pancreas, and brain. More work is required to understand how SkM-secreted GDF15 signals to the brain and periphery to influence food intake and systemic metabolism, particularly in the context of muscle hypertrophy, diabetes, and obesity.

Although these data in transgenic animal models support the systemic role of SkM-secreted FGF21 and GDF15, more work is required to understand the mechanisms that regulate these myokines in SkM during growth. For example, SkM-mTORC1 overactivity in the TSC1 knockout model results in a lean phenotype without muscular hypertrophy. It is unclear whether the lean phenotype and enhanced energy expenditure in this model are a result of the high energetic costs of inducing constitutive protein synthesis via mTORC1, thereby leading to ER and mitochondrial stress, which promotes FGF21 and GDF15 secretion. Whether these mechanisms are relevant to physiological SkM growth has yet to be elucidated and requires further investigation. Similarly, it remains unclear whether GDF15 is secreted from SkM as a result of SkM growth, as is the case with FGF21. Considering that GDF15 and FGF21 appear to be regulated through similar pathways downstream of mTORC1 activation, future work should investigate SkM-secreted GDF15 in hypertrophy models such as the constitutive SkM Akt1 model. As such, more work is required to understand how SkM hypertrophy influences the synthesis and secretion of FGF21 and GDF15, as well as their metabolic properties in remote tissues.

Meteorin-like protein

Meterorin-like (METRNL) is a novel PGC-1α4-regulated secreted protein that has been identified as a myokine involved in tissue cross talk and systemic metabolism [51]. Ruas et al. reported that PGC-1α4 induces SkM growth in vitro and in vivo in cultured myotubes and SkM-specific PGC-1α4 (Myo-PGC-1α4) transgenic mice, respectively [20]. Recently, Guo et al. reported that gastrocnemius muscle-specific PGC-1α4 overexpression in aged mice alleviates sarcopenia by increasing strength and promoting SkM growth [18]. PGC-1α4 overexpression in sarcopenic mice also increased gastrocnemius muscle METRNL mRNA and protein expression and circulating serum levels of METRNL, thereby suggesting secretion from theSkM into circulation [18]. Similarly, METRNL mRNA and protein levels were significantly upregulated in the quadriceps of Myo-PGC-1α4 mice and culture media of PGC-1α4-overexpressing myotubes [19].

METRNL is shown to mediate SkM-adipose tissue cross talk and induce the lipolysis and browning of WAT, potentially through the induction of interleukins 4 and 13 (IL-4 and -13) and M2 macrophage activation (Figure 4) [19, 51–53]. Specifically, METRNL appears to activate eosinophils to produce IL-4 and IL-13 and activate M2 macrophages through signal transducer and activator of transcription 6 (STAT6) signaling, which increases the production of catecholamines to induce the browning of adipocytes [53, 54].

Rao et al. reported that Myo-PGC-1α4 mice exhibit a lean phenotype, reductions in epididymal and subcutaneous fat depots, and increased browning of WAT [19]. Supporting the endocrine effect of SkM-secreted METRNL on adipose tissue, Guo et al. reported a reduction in fat mass and the induction of several genes involved in IL-4 and -13-mediated macrophage activation and thermogenesis in the WAT of aged mice following PGC-1α4 overexpression in the gastrocnemius muscle [18]. Importantly, the induction of these genes in WAT was prevented following antibody-mediated METRNL inhibition [18]. Furthermore, systemic delivery of METRNL in mice using adenoviral vectors induces a lean phenotype, reductions in fat mass, increases in whole-body glucose tolerance and energy expenditure, and an upregulation in genes involved in browning and thermogenesis in WAT and subcutaneous adipose tissue depots [19].

The mechanisms governing METRNL's effects on insulin signaling appear to involve the activation of PPAR signaling [54–56]. Adipocyte-METRNL overexpression increases insulin-stimulated Akt1 phosphorylation in WAT and insulin sensitivity in mice [56]. METRNL overexpression in adipocytes also increases PPARγ, and inhibition or knockdown of PPARγ blocks the insulin-sensitizing effects of METRNL, suggesting that PPARγ mediates METRNL-induced insulin sensitivity in adipocytes [56]. However, these effects are unknown in the context of SkM-derived METRNL and hypertrophy.

METRNL also significantly increases lipase activity, lipid disposal, and triglyceride turnover in WAT [56], which likely contributes to insulin sensitization with METRNL injection and overexpression in rodent models. Furthermore, METRNL increases the expression of several genes relating to adipocyte differentiation (adipogenesis) and lipolysis in WAT [56]. Interestingly, METRNL also expands adipocytes (adipocyte area) [56]. This suggests that METRNL may simultaneously promote lipogenesis and lipolysis by enhancing adipocyte storage capacity (i.e., area), lipid uptake, and lipid metabolism to increase the turnover of triglycerides. However, more work is required to understand the tissue-specific effects of SkM-derived METRNL, such as in adipose tissue, and how they contribute to systemic metabolism.

METRNL also works to protect the β cells of the pancreas. In T2DM mice, METRNL injection inhibits and increases β-cell apoptosis and proliferation, respectively, via proto-oncogene Wnt/β-catenin signaling [57]. Intravenous injection of METRNL also delays the onset of type 1 diabetes mellitus in nonobese, diabetic mice by reducing pancreatic leukocyte infiltration and altering the T-cell response and cytokine secretion [58]. Once again, the pancreatic effects of SkM-derived

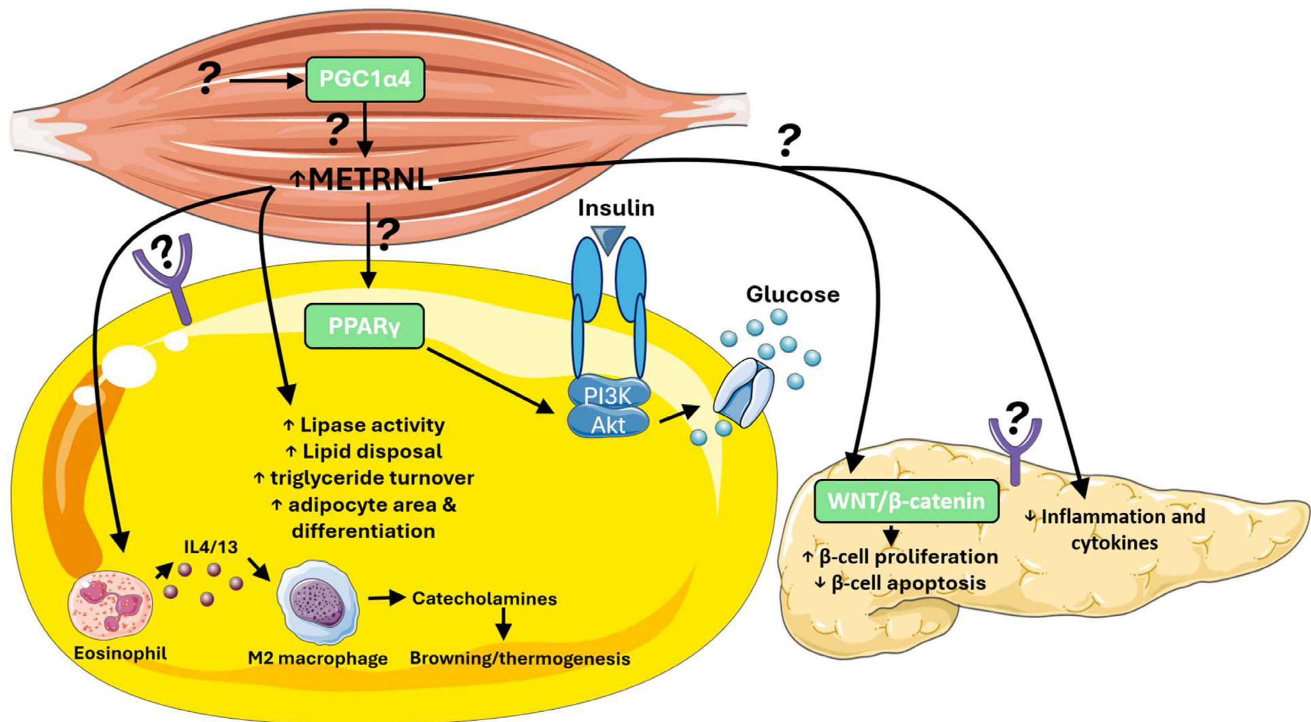

FIGURE 4 Skeletal muscle (SkM) growth regulation of meteorin-like (METRNL). PGC-1α4 induces METRNL. It is unknown what initiates proliferator-activated receptor coactivator-γ-1α (PGC-1α4) with SkM growth. METRNL activates eosinophils to produce interleukin (IL)-4 and -13 to activate M2 macrophages resulting in catecholamine production and white adipose tissue (WAT) browning and thermogenesis. METRNL also influences adipocyte lipid handling and size/differentiation; however, this is unknown for muscle-derived METRNL. In the pancreas, METRNL is protective of β cells via Wnt/β-catenin signaling and reduces inflammation. These effects in the pancreas are unknown for muscle-derived METRNL with growth. The receptors through which METRNL acts in different tissues are also unclear. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. [Color figure can be viewed at wileyonlinelibrary.com]

METRNL have not been examined and represent an avenue for future investigation. The exact mechanisms mediating the protective and insulin-secretory effects of METRNL on the pancreas also remain unclear and warrant further exploration. Finally, the receptor interaction mediating SkM-derived METRNL signaling in different tissues is not yet clear and should be investigated for future agonism of these pathways [54].

This evidence supports the role of METRNL as a PGC-1α4-regulated myokine that may be associated with the systemic metabolic effects of SkM hypertrophy, including WAT browning, increased insulin sensitivity and secretion, and improved adipocyte lipid handling.

Follistatin-like 1

Follistatin-like 1 (FSTL1) is an Akt1-regulated myokine that exhibits direct endocrine effects on adipose tissue to regulate lipid metabolism [59, 60]. Ouchi et al. reported that overexpression of Akt1 in SkM of transgenic mice induced muscle hypertrophy and upregulated the serum concentration of FSTL1, as well as the mRNA and protein expression of FSTL1 in SkM, suggesting systemic secretion [59].

Nam et al. have shown that FSTL1 induces cyclic GMP (cGMP) production, hormone-sensitive lipase (HSL) activity, and lipolysis in adipocytes (Figure 5) [61]. These effects were partly mediated through disco-interacting protein 2 homolog A (DIP2a) as DIP2a knockdown attenuates these effects, possibly suggesting alternative receptor interactions/signaling [61]. Although epinephrine co-treatment of adipocytes did not increase FSTL1-stimulated lipolysis, treatment with atrial natriuretic peptide (ANP) and FSTL1 showed synergistic effects for cGMP, HSL activation, and lipolysis [61]. This suggests that FSTL1 enhances ANP-induced lipolysis in adipocytes. Furthermore, FSTL1 attenuates both basal and insulin-stimulated Akt1 activation in adipocytes, suggesting that FSTL1 inhibits lipogenesis while enhancing lipolysis [61]. These effects have yet to be investigated for SkM-derived FSTL1 in the context of muscle growth and systemic metabolism. Glycosylated FSTL1 has also been shown to activate BAT thermogenesis via β3-adrenergic signaling, generating cyclic AMP (cAMP) and activating protein kinase A (PKA), PPARγ, and thermogenic genes [62]. However, this is also unclear in the context of muscle-derived FSTL1. Furthermore, limited work has been done to determine the endocrine effects of SkM-secreted FSTL1 in tissues such as adipose tissue and the liver with muscular growth in models of obesity and diabetes, and, as such, more work is warranted in this area.

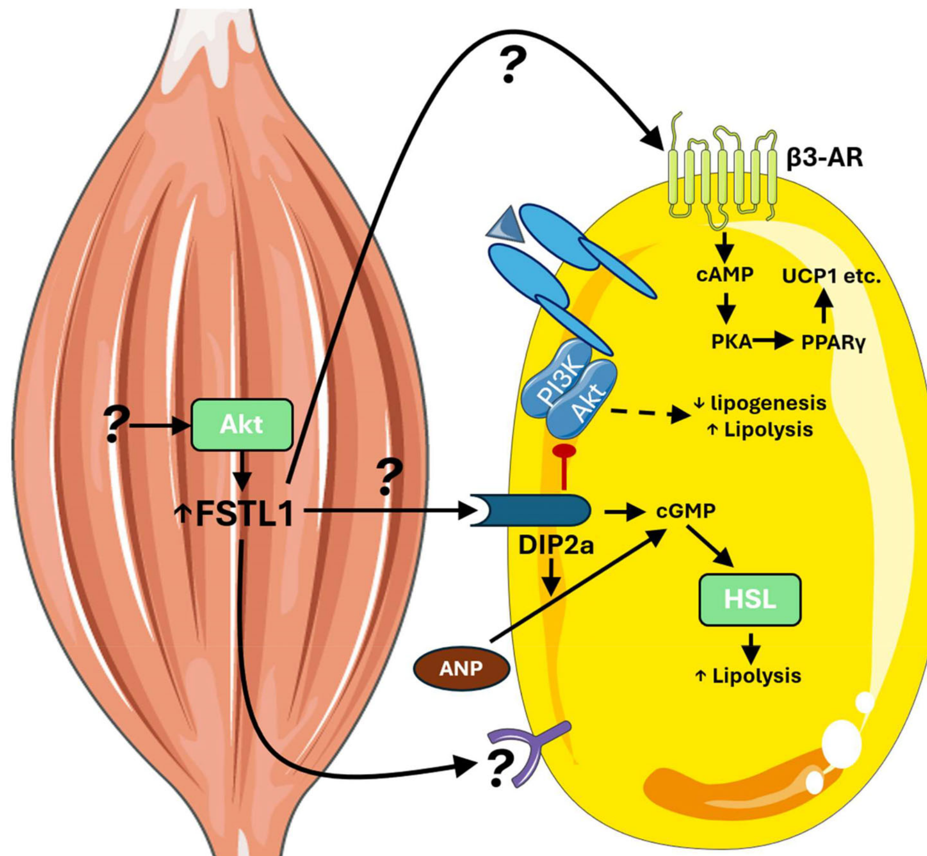

FIGURE 5 Skeletal muscle (SkM) growth regulation of follistatin-like 1 (FSTL1). Protein kinase B (Akt1) induces FSTL1. It is unknown what upstream signaling initiates Akt1-mediated FSTL1 expression with growth. FSTL1 acts through the disco-interacting protein 2 (DIP2a) receptor on adipocytes to increase cyclic GMP (cGMP) production and activate hormone-sensitive lipase (HSL) and lipolysis. It is unclear whether these mechanisms apply to muscle-derived FSTL1. Additional receptors may mediate the effects of FSTL1 in adipocytes; however, they remain unclear. The effects of FSTL1 on lipolysis are synergistic with atrial natriuretic peptide (ANP). Glycosylated FSTL1 acts through β-adrenergic signaling to induce cyclic adenosine monophosphate (cAMP), activate protein kinase A (PKA) and peroxisome proliferator-activated receptor γ (PPARγ), and increase browning/thermogenesis-related genes. These mechanisms are unclear for muscle-secreted FSTL1. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. [Color figure can be viewed at wileyonlinelibrary.com]

Extracellular vesicles and microRNAs

Extracellular vesicles (EVs) have been recognized as SkM-secreted factors with the potential to mediate tissue cross talk [63]. EVs contain various molecular cargo capable of influencing cellular metabolism, including bioactive proteins (e.g., myokines) and noncoding microRNAs (miRNAs).

SkM growth has been shown to upregulate the secretion of EVs and miRNAs (Figure 6). Hayashi et al. recently demonstrated that SkM hypertrophy in muscle-specific Akt1 transgenic mice increases the serum concentration of EV-associated miRNAs, specifically miR1, miR133a, and miR206, independent of total EV concentration [64]. Furthermore, stimulation of cultured myotubes with IGF-1 increased Akt1 activation and the secretion of miR206 in culture medium [64]. This evidence is corroborated by the synergist ablation model of SkM mechanical overload-induced hypertrophy in mice. Ablation of the soleus and gastrocnemius in mice results in functional overload of the plantaris, which induces SkM hypertrophy [65]. In response to this overload-induced hypertrophy, intramuscular levels of miR1 and miR133a are depleted through increased systemic EV-contained secretion [66, 67]. It is currently unknown which cellular pathways are involved in mechanical overload-induced SkM EV secretion. However, these observations point to miR1 and miR133a, likely among other miRNAs, as SkM-secreted factors in response to anabolism. Although the fate of SkM-secreted EVs and miRNAs in response to muscle growth remains unclear, they appear to influence the metabolism of adipose tissue.

Mechanical overload-induced SkM EVs and miR1 are shown to preferentially target WAT [66]. Intriguingly, GW4869-mediated blockage of EV release abolished the decrease in SkM miR1 expression and decreased serum EV miR1 abundance and miR1 uptake into WAT following mechanical overload [66]. This reinforces that mechanical overload-induced WAT miR1 uptake is mediated by SkM export of miR1 in EVs. In WAT, SkM-derived miR1 upregulates genes involved in adrenergic signaling and lipolysis [66]. Specifically, miR1 may indirectly activate CCAAT/enhancer binding protein α (Cebpα) via transcription factor AP-2 α (Tfap2α) repression, which activates adrenergic receptor β3 and increases the expression of the lipolytic enzymes adipose tissue triglyceride lipase, HSL, and perilipin [66].

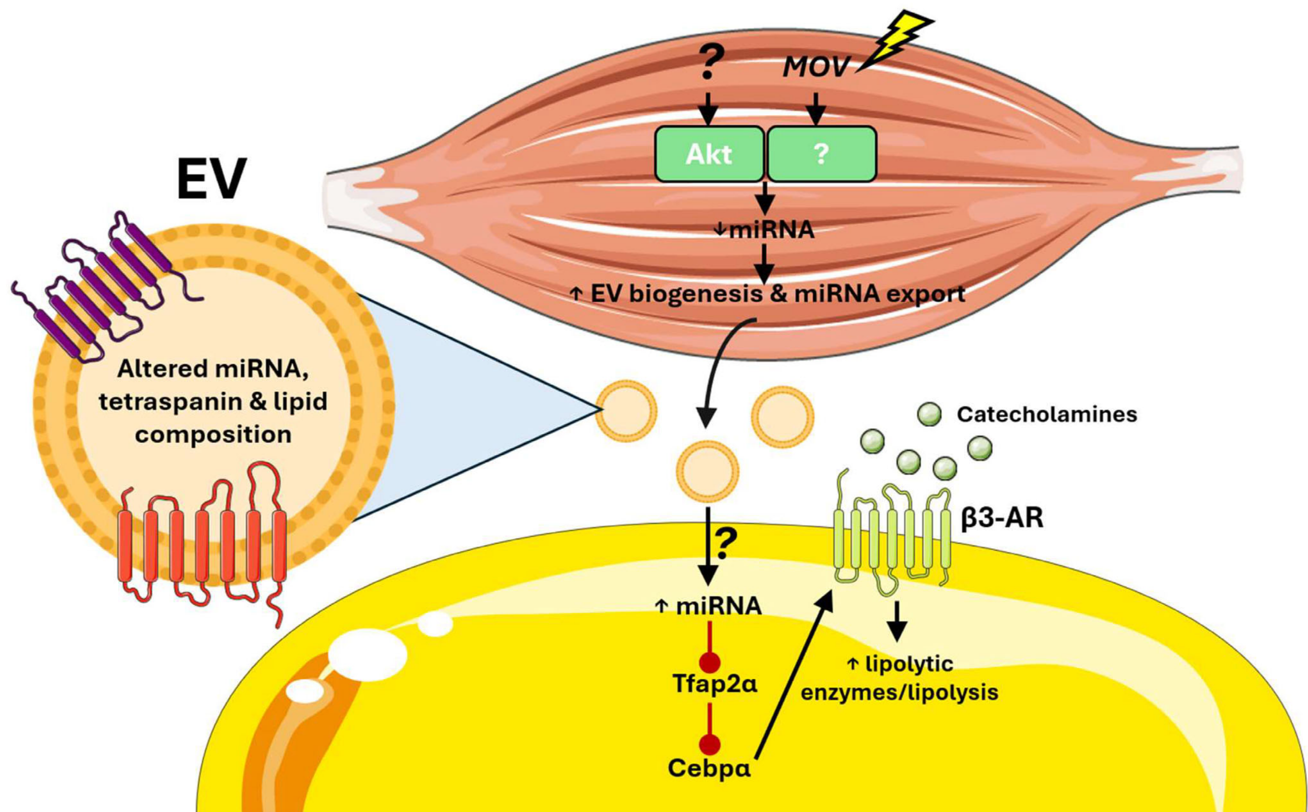

FIGURE 6 Skeletal muscle (SkM) growth regulation of extracellular vesicles (EVs) and microRNAs (miRNAs). Protein kinase B (Akt1) activation and mechanical overload (MOV) induce EV-mediated miRNA secretion. It is unknown what upstream pathways activate Akt1 or mediate MOV-induced secretion. Growth alters the composition of EVs secreted from skeletal muscle. EVs and miRNAs target white adipose tissue (WAT), where they increase lipolysis through Tfap2α-Cebpα and β-adrenergic signaling. It is unclear how muscle-derived EVs transfer miRNAs to WAT in the context of growth. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. [Color figure can be viewed at wileyonlinelibrary.com]

Accordingly, SkM-derived miR following mechanical overload also enhances catecholamine sensitivity in WAT [66].

Valentino et al. reported growth-induced alterations in the composition of EVs derived from SkM [68]. Specifically, IGF-1–treated myotubes exhibited a greater abundance of EV CD63 and CD81 tetraspanins than nontreated myotube EVs. [68] Tetraspanins such as CD81 may mediate muscle cross talk with other tissues such as WAT to increase de novo beige adipogenesis and energy expenditure to improve cardiometabolic health [69, 70]. Furthermore, IGF-1 treatment altered the composition of diacylglycerol, ceramide, and other lipid species in SkM-derived EVs [68]. It is unclear how changing the lipid composition of EVs may influence tissue cross talk; however, this may help increase the stability of EVs for interaction with target cells [68]. Future work should also investigate the interactions mediating cargo transfer of SkM growth-induced EVs to other tissue types.

Further investigation is required to understand how SkM growth alters the secretion, composition, and cargo of SkM-derived EVs, as well as their interaction with remote tissues to influence metabolism. Additionally, the contributions of SkM to systemically circulating EVs remain highly debated and unclear. As such, more work is required to determine the systemic fate of SkM-secreted EVs during periods of growth.

Lactate

Lactate is a metabolic product of glycolysis, produced by the reduction of pyruvate via lactate dehydrogenase (LDH) [71]. Although lactate has incorrectly been thought of as a "waste product," it is now recognized as an important metabolic fuel and signaling molecule in health and disease [71]. Importantly, in the context of this review, lactate is an SkM-secreted metabolite that enters systemic circulation during periods of energetic demand (e.g., elevated SkM glycolysis; Figure 7).

As previously discussed, hypertrophying SkM upregulates glucose uptake and glycolysis to support growth [23, 24]. Treatment of myotubes with IGF-1 stimulates growth and significantly increases glycolysis and lactate concentrations [23, 24]. Similarly, mechanical overloading of the plantaris muscle significantly increases lactate secretion [72]. In vivo, SkM constitutive Akt1 transgenic mice and other models of SkM hypertrophy exhibit increased expression of SkM LDH and blood and SkM lactate concentrations [26, 73, 74].

Once in circulation, lactate exerts numerous effects on multiple tissues, as highlighted by Brooks et al. [71]. Of major importance in the context of diabetes and obesity is the role of lactate in appetite

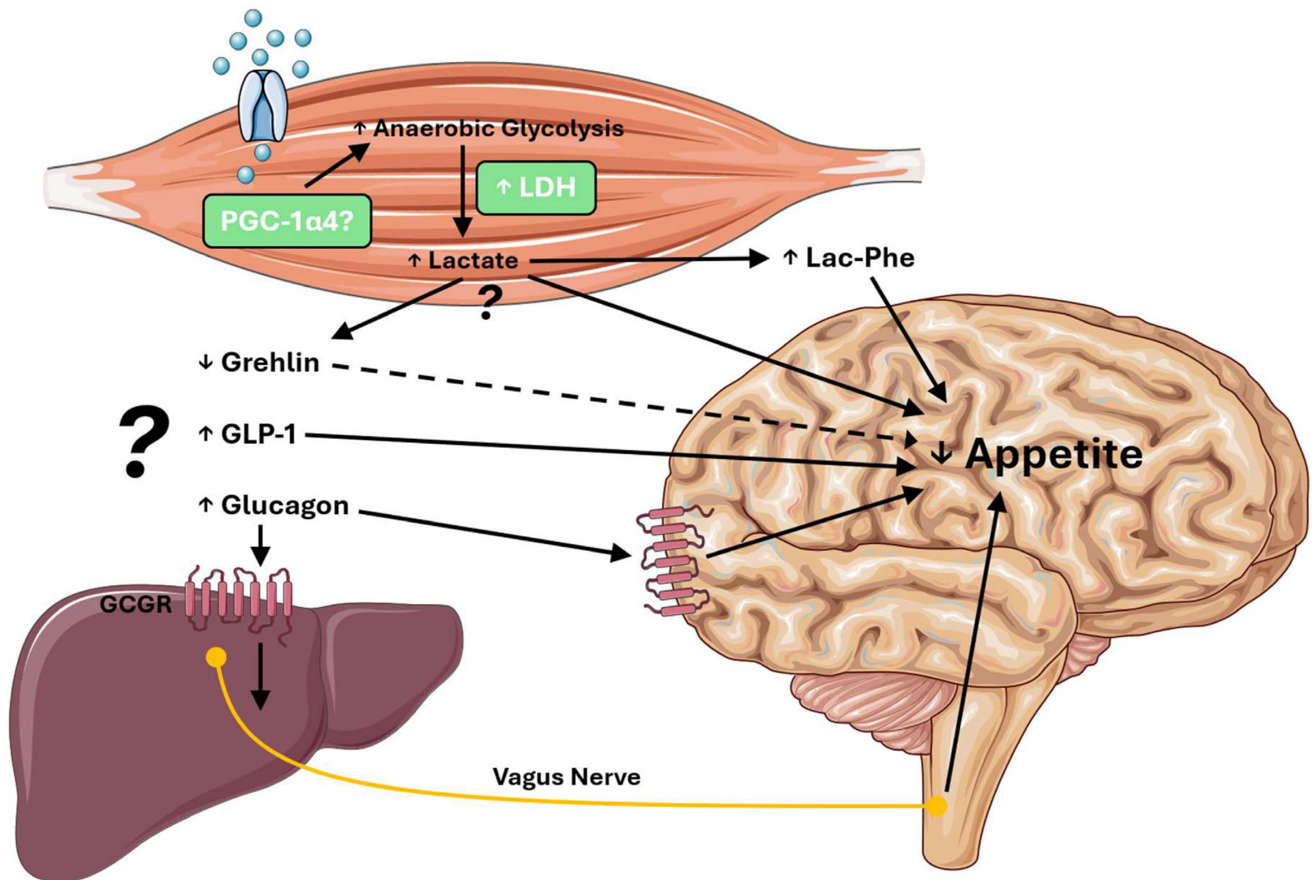

FIGURE 7 Skeletal muscle (SkM) growth regulation of lactate. Anaerobic glycolysis is likely upregulated by peroxisome proliferator-activated receptor coactivator-γ-1α (PGC-1α4; possibly among other regulators) and produces lactate via lactate dehydrogenase (LDH). Lactate reduces ghrelin and increases glucose-like peptide-1 (GLP-1) and glucagon to reduce appetite by various unclear mechanisms. Lac-Phe is also generated from lactate and suppresses appetite. The degree of lactate secretion and its effects with skeletal muscle growth remain unclear. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. [Color figure can be viewed at wileyonlinelibrary.com]

regulation. Indirectly, lactate reduces appetite by suppressing the secretion and growth hormone secretagogue receptor-mediated signaling of the "hunger hormone," ghrelin [71]. Lactate also influences the secretion of other appetite-regulating hormones. For example, oral lactate administration in healthy male adults reduces plasma ghrelin while elevating plasma glucagon and glucagon-like peptide1 (GLP-1) concentrations [75]. It appears that glucagon suppresses appetite indirectly by glucagon receptor (GCGR)-mediated action on the liver, which then conveys satiety signals to the hypothalamus via the hepatic branch of the vagus nerve [76]. Glucagon may also directly bind the hypothalamus via the GCGR after crossing the blood–brain barrier [76]. Although the mechanisms governing GLP-1-mediated satiation are multifaceted and complex, GLP-1 appears to act peripherally (e.g., enteric and vagal neurons) and centrally (e.g., hypothalamus) to reduce food intake [77].

Lactate crosses the blood–brain barrier through monocarboxylate transporters to influence the hypothalamus [71], the major brain region responsible for governing hunger and satiation. Indeed, exogenous lactate infusion drastically reduces appetite in healthy adults [71, 75]. Recent evidence has also suggested profound appetite-suppressing effects of N-lactoyl-phenylalanine (Lac-Phe), a complex of lactate and phenylalanine catalyzed by the enzyme carnosine dipeptidase 2 (CNDP2), within $CNDP2^{+}$ cells such as macrophages, monocytes, and epithelial cells [71]. Although the site(s) of Lac-Phe action have yet to be elucidated, administration of Lac-Phe in diet-induced obese mice reduces food intake and adiposity while improving glucose homeostasis, without affecting energy expenditure [78].

Although there is evidence for the effects of lactate and its associated metabolites on appetite and consequently adiposity and glucose homeostasis, it is unknown whether these are relevant to SkM-secreted lactate with muscle growth. Additionally, the extent to which lactate is secreted into systemic circulation with physiological (i.e., non-transgenic) SkM growth is unclear. Specifically, it is unclear whether periods of SkM anabolism and growth in humans increase lactate secretion to the levels required for the appetite-suppressive effects seen in lactate infusion studies. Additionally, work in humans and transgenic models of hypertrophy (e.g., constitutive Akt1) should investigate the effects of SkM growth on food intake and the involvement of endogenously produced lactate to better understand the mechanisms governing these effects in vivo.

IMPLICATIONS FOR RESISTANCE EXERCISE TRAINING AND PHARMACOLOGIC INTERVENTIONS

Resistance exercise (RE) and pharmacology are two options that can target SkM growth and improve metabolic dysfunction in humans [6, 7, 79–83]. However, it is unclear whether these SkM-targeted therapies elevate the secretion of myokines, EVs, miRNAs, metabolites, and other factors into the systemic circulation to concentrations that are physiologically and clinically relevant to induce improvements in whole-body metabolism. Here, we discuss our current knowledge of these two therapeutic interventions in the context of SkM growth, systemic metabolism, and muscle-secreted factors.

RE

RE training is an effective exercise modality to stimulate the growth of SkM via mechanical and metabolic stress [7, 84]. Importantly, RE training is often associated with improved whole-body metabolism, including improved glycemic control, insulin sensitivity, and reduced body fat mass, as has been demonstrated in both experimental and clinical studies [85–88]. A commonly used noninvasive method for dynamic RE in rodent models is weighted climbing, whereby rodents pull an external load vertically up a ladder, resulting in mechanical overload of SkM [89]. Although this differs from the RE training that humans engage in, this model of RE has been validated to produce the canonical human adaptations to RE training such as increased muscle strength, muscle size, and fiber cross-sectional area [89].

Previously mentioned proteins involved in SkM anabolic signaling (e.g., Akt1, mTORC1, PGC-1α4) are induced with RE training. As previously discussed, RE-induced mechanical overload is thought to be sensed by various proteins associated with components of the extracellular environment and sarcolemma in SkM, which subsequently activate mTORC1, increasing protein synthesis [90]; see Roberts et al. for a comprehensive review [7]. Cumulative spikes in Akt1-mTORC1 activation and protein synthesis with chronic RE result in SkM growth [7, 91]. Furthermore, PGC-1α4 is induced in SkM 48 h after an acute bout of RE, and basal levels are increased after 12 weeks of chronic RE training in humans [20, 21].

Importantly, the secreted factors highlighted in this review may be increased in SkM and/or systemic circulation with RE. FGF21 and GDF15 are associated with cellular stress and are often upregulated with chronic diseases such as T2DM [92]. As such, conflicting data exist regarding the effects of RE on these myokines. FGF21 expression increases in SkM following RE training in Zucker diabetic rats [93], whereas many studies in humans have reported a reduction in circulating FGF21 with RE [94]. This discrepancy may be due to differences in exercise intensity, species, and populations studied, as many studies have investigated states of metabolic dysfunction. Additionally, the observed low-grade chronic elevations of these factors in states of metabolic dysfunction may represent desensitization of these pathways, similar to insulin resistance and hyperinsulinemia, which differs from the transient elevations that may occur with RE [95–97]. As such, future work should determine the effects of RE on FGF21 secretion in a metabolically healthy state to avoid confounding cellular stress resulting from metabolic disease. Conversely, circulating GDF15 increases immediately following RE in humans [98]; however, few, if any, studies have assessed the effects of RE on GDF15 expression and regulation in SkM.

The expression of METRNL at the mRNA level is increased in SkM after an acute bout of RE in humans and rodents and following chronic RE training in rodents [99]. RE training promotes SkM hypertrophy while increasing basal levels of circulating METRNL at rest in individuals with T2DM and rodents [100, 101]. Chronic RE training also increases FSTL1 expression in SkM and secretion into the plasma in rats with myocardial infarction [102, 103]. Unfortunately, clinical work regarding RE, SkM hypertrophy, and FSTL1 is lacking.

Recently, it has been shown that acute RE alters circulating EVs and miRNA profiles in humans [104, 105]. An acute bout of RE alters several SkM miRNAs targeting mRNA of signaling pathways related to tumor protein p53, IGF-1, STAT3, PPAR, Janus kinase (JAK)/STAT, growth hormone, WNT/β-catenin, extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK), AMP-activated protein kinase (AMPK), mTOR, PI3K/Akt1, transforming growth factor-beta (TGF-β), and ILs [105]. However, the systemic relevance of these SkM miRNAs is unclear. Acute RE also increases plasma CD9, CD36, and vesicle-associated membrane protein 3 (VAMP3)-positive EV concentrations, CD81-positive EV size, and EV surface protein density in healthy adults [104, 106]. In humans, an acute bout of RE also reduces SkM miR1 while increasing circulating EV and adipose tissue miR1, suggesting SkM secretion of miR1 and uptake into adipose [66, 106]. Recently, Burke et al. identified CD63-positive EVs as predictors of the increased adipose tissue miR1, as well as increased adipose tissue EV uptake gene expression and catecholamine-induced lipolysis following RE, suggesting EV-mediated cross talk between SkM and adipose tissue with RE [106]. Furthermore, 12 weeks of RE training increases proteins involved in miRNA and exosome biogenesis in SkM and circulating muscle health-associated miRNAs in exosome-like vesicles in older adults [107].

RE training upregulates glycolysis and increases the glycolytic capacity of SkM in rodents and humans [6, 21, 108]. Acutely, RE significantly increases plasma lactate, whereas chronic RE training increases the basal activity and expression of SkM LDH [21]. Despite the increased glycolytic metabolism of hypertrophying SkM, it remains unclear whether this influences basal lactate secretion to any physiologically meaningful extent following RE training. Considering that plasma lactate levels return to baseline ~1 h after exercise [21], increased basal systemic lactate secretion seems unlikely to occur with SkM growth in humans. Additionally, it is plausible that lactate-related metabolites such as Lac-Phe may be upregulated following acute and chronic RE; however, these questions have yet to be examined and certainly warrant investigation. Furthermore, although research in humans has reported weight loss concomitant with reductions in food intake following

RE [109, 110], a causative relationship with SkM-derived lactate has yet to be determined.

The molecular regulators of RE-induced SkM anabolism and growth in humans are still unclear and are the topic of extensive study. Recent work has supported the role of several newly identified regulators of muscle mass in response to RE [111, 112]. Future work should also focus on novel and understudied governors of RE/mechanical overload-induced SkM anabolism (e.g., DAG kinase, integrins, stretch-induced channels, PLD) and their regulation of SkM-secreted factors that may influence systemic metabolism.

Although RE promotes SkM growth and may increase the expression of various factors in SkM and their concentration in the systemic circulation, this area remains understudied. As such, our knowledge of how RE-induced SkM growth influences the regulation and secretion of myokines, EVs, and miRNAs is based on few studies. For example, although some myokines such as FGF21 and GDF15 are regulated by cellular stress pathways induced by mTORC1 activity, it is unclear whether such pathways are involved in RE-induced expression and secretion [34]. Future work is required to ascertain the molecular mechanisms regulating myokine and EV expression and biogenesis in SkM with RE-induced hypertrophy. Additionally, many previously conducted studies investigating RE have failed to determine the tissue of origin of circulating factors. Determining whether SkM is responsible for increased secretion can be challenging, especially in humans; however, future studies should aim to incorporate molecular data in SkM with measures from the systemic circulation (i.e., plasma). Finally, most reports of RE and SkM-secreted factors are not investigated in the context of systemic metabolic health. More work should focus on how SkM hypertrophy and secreted factors following RE may be used as a therapeutic intervention to improve the health of different clinical populations.

Pharmacology

The activin type II receptor (ActRII) inhibitor bimagrumab represents a promising antiobesity pharmacological treatment. Unlike current appetite-suppressive weight loss drugs, bimagrumab blocks the actions of MSTN and activin A, which are negative regulators of muscle mass [113, 114]. A clinical trial showed that injection of bimagrumab over 48 weeks significantly increased lean mass, reduced fat mass, and improved glycemic control in individuals with T2DM, highlighting the hypertrophic and systemic metabolic effects of this agent [115]. Additionally, Nunn et al. showed that the addition of bimagrumab to GLP-1 agonist therapy results in superior reductions in fat mass and preserved muscle mass despite reduced food intake compared to GLP-1 agonism alone in diet-induced obese mice [83]. Interestingly, the deletion of SkM Akt1 only modestly attenuated the hypertrophy induced by ActRII inhibition, suggesting the involvement of Akt1-independent mechanisms [83]. Taken together, this suggests that bimagrumab-induced SkM hypertrophy promotes whole-body metabolic effects, namely reductions in adiposity. Although direct effects of ActRII inhibition on BAT and energy expenditure are plausible [116], the relative contribution of adipose tissue ActRII signaling to these metabolic changes remains unclear [29]. Alternatively, alterations in myokine secretion following bimagrumab-induced SkM hypertrophy may mediate some of these changes in fat mass and systemic metabolism [83, 117]. Further research should work to investigate the effects of ActRII inhibition and other pharmacological inductions of SkM hypertrophy on myokine regulation and secretion, as well as the influence on whole-body metabolism.

GLP-1 agonists offer a promising therapeutic option for the treatment of obesity by modulating satiety signaling, among other mechanisms [118]. However, a controversial and highly debated concern associated with the rapid weight loss that is associated with GLP-1 agonist therapy is the loss of lean muscle mass [119, 120], an important metric for physical function [121], metabolic health [122], and mortality [123, 124], especially in older adults. Consequently, this possible drawback of current antiobesity medications has initiated the call for the investigation of therapeutic interventions targeting SkM health [5]. Although the interest and use of GLP-1 agonists in different clinical populations continue to surge, their direct and indirect effects on SkM mass and metabolism are unclear. Some evidence has suggested that GLP-1 and GLP-1 agonists may augment SkM metabolism [125–127]. However, it is still unknown how anabolic pathways regulating SkM anabolism and myokine secretion are influenced by GLP-1 agonism [119]. Future work is needed to understand how this robust weight loss following GLP-1 agonist therapy alters SkM anabolism, myokine secretion, and systemic metabolic health in different organ systems.

Interaction between RE and pharmacology

As previously mentioned, a potential concern of GLP-1 agonist therapy is the loss of lean muscle mass in certain populations such as older adults [119, 120]. As such, the addition of RE training with incretin mimetics is gaining attention as a strategy to preserve SkM health following rapid weight loss [119, 128]. Although RE helps preserve lean mass following caloric restriction in humans [119], no data exist regarding lean mass preservation with the combination of RE and GLP-1 agonist therapy. Future research is not only required to understand how pharmacologically induced weight loss alters anabolic signaling in SkM and muscle-secreted factors but also whether and how the addition of RE augments or attenuates these effects in SkM and systemic metabolism. Additionally, considering that ActRII inhibition-based therapies such as bimagrumab may involve Akt1-independent mechanisms, this may suggest potential synergistic effects of these therapies with RE [83, 129, 130].

CONCLUSION

In transgenic rodent models, targeted SkM hypertrophy induces whole-body metabolic changes such as reduced adiposity, WAT browning, increased glycemic control and insulin sensitivity, and enhanced

fat oxidation in remote tissues such as the liver and adipose tissue. Although mechanisms mediating this effect remain unclear, secreted factors from growing SkM may play an important role. Several proteins involved in anabolic and metabolic signaling in SkM such as Akt1, mTORC1, and PGC-1α4 regulate several endocrine factors (e.g., myokines, EVs, miRNAs, metabolites) that are known to target non-SkM tissues and influence systemic metabolism. As such, it is plausible that activation of these signaling proteins and pathways in SkM during periods of anabolism and growth promotes the expression and secretion of endocrine-like factors that improve whole-body metabolic health. Furthermore, RE training and pharmacological agents such as ActRII inhibitors (e.g., bimagrumab) are interventions that promote SkM hypertrophy and systemic metabolic improvements, potentially mediated by secreted factors. Future work is required to expand our knowledge of the role of SkM hypertrophy in promoting the secretion of circulating factors, their effects on metabolism, and implications for therapeutic interventions such as RE training and pharmaceuticals in populations with metabolic disease.

FUNDING INFORMATION

This study was supported by Natural Sciences and Engineering Council Discovery Grant 16 (RGPGP-2020-06479).

CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest.

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REFERENCES

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes – global burden of disease and forecasted trends. *J Epidemiol Glob Health*. 2019;10:107-111. doi:10.2991/jegh.k.191028.001
2. Koliaki C, Dalamaga M, Liatis S. Update on the obesity epidemic: after the sudden rise, is the upward trajectory beginning to flatten? *Curr Obes Rep*. 2023;12:514-527. doi:10.1007/s13679-023-00527-y
3. Stump CS, Henriksen EJ, Wei Y, Sowers JR. The metabolic syndrome: role of skeletal muscle metabolism. *Ann Med*. 2006;38:389-402. doi:10.1080/07853890600888413
4. Frontera WR, Ochala J. Skeletal muscle: a brief review of structure and function. *Calcif Tissue Int*. 2015;96:183-195.
5. Wackerhage H, Hinrichs A, Wolf E, Hrabě De Angelis M. Turning fat into muscle: can this be an alternative to anti-obesity drugs such as semaglutide? *J Physiol*. 2024;602:1655-1658. doi:10.1113/JP286430
6. LeBrasseur NK, Walsh K, Arany Z. Metabolic benefits of resistance training and fast glycolytic skeletal muscle. *Am J Physiol Endocrinol Metab*. 2011;300:E3-E10. doi:10.1152/ajpendo.00512.2010
7. Roberts MD, McCarthy JJ, Hornberger TA, et al. Mechanisms of mechanical overload-induced skeletal muscle hypertrophy: current understanding and future directions. *Physiol Rev*. 2023;103:2679-2757. doi:10.1152/physrev.00039.2022
8. Schiaffino S, Dyar KA, Ciciliot S, Blaauw B, Sandri M. Mechanisms regulating skeletal muscle growth and atrophy. *FEBS J*. 2013;280:4294-4314. doi:10.1111/febs.12253
9. Kumar V, Atherton P, Smith K, Rennie MJ. Human muscle protein synthesis and breakdown during and after exercise. *J Appl Physiol*. 2009;106:2026-2039. doi:10.1152/japplphysiol.91481.2008
10. Schiaffino S, Mammucari C. Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: insights from genetic models. *Skelet Muscle*. 2011;1:4. doi:10.1186/2044-5040-1-4
11. Vainshtein A, Sandri M. Signaling pathways that control muscle mass. *Int J Mol Sci*. 2020;21:4759.
12. Adegoke OAJ, Abdullahi A, Tavajohi-Fini P. mTORC1 and the regulation of skeletal muscle anabolism and mass. *Appl Physiol Nutr Metab*. 2012;37:395-406. doi:10.1139/h2012-009
13. Ballou LM, Lin RZ. Rapamycin and mTOR kinase inhibitors. *J Chem Biol*. 2008;1:27-36. doi:10.1007/s12154-008-0003-5
14. Guridi M, Tintignac LA, Lin S, Kupr B, Castets P, Rüegg MA. Activation of mTORC1 in skeletal muscle regulates whole-body metabolism through FGF21. *Sci Signal*. 2015;8:ra113. doi:10.1126/scisignal.aab3715
15. Jaafar R, De Larichaudy J, Chanon S, et al. Phospholipase D regulates the size of skeletal muscle cells through the activation of mTOR signaling. *Cell Commun Signal*. 2013;11:55. doi:10.1186/1478-811X-11-55
16. You J-S, Lincoln HC, Kim C-R, et al. The role of diacylglycerol kinase ζ and phosphatidic acid in the mechanical activation of mammalian target of rapamycin (mTOR) signaling and skeletal muscle hypertrophy. *J Biol Chem*. 2014;289:1551-1563.
17. Sartori R, Romanello V, Sandri M. Mechanisms of muscle atrophy and hypertrophy: implications in health and disease. *Nat Commun*. 2021;12:330.
18. Guo M, Zhang J, Ma Y, et al. AAV-mediated nuclear localized PGC1α4 delivery in muscle ameliorates sarcopenia and aging-associated metabolic dysfunctions. *Aging Cell*. 2023;22:e13961. doi:10.1111/acel.13961
19. Rao RR, Long JZ, White JP, et al. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. *Cell*. 2014;157:1279-1291.
20. Ruas JL, White JP, Rao RR, et al. A PGC-1α isoform induced by resistance training regulates skeletal muscle hypertrophy. *Cell*. 2012;151:1319-1331.
21. Koh J-H, Pataky MW, Dasari S, et al. Enhancement of anaerobic glycolysis–a role of PGC-1α4 in resistance exercise. *Nat Commun*. 2022;13:2324.
22. White JP, Wrann CD, Rao RR, et al. G protein-coupled receptor 56 regulates mechanical overload-induced muscle hypertrophy. *Proc Natl Acad Sci*. 2014;111:15756-15761. doi:10.1073/pnas.1417898111
23. Wackerhage H, Vechetti IJ, Baumert P, et al. Does a hypertrophying muscle fibre reprogramme its metabolism similar to a cancer cell? *Sports Med*. 2022;52:2569-2578.
24. Baumert P, Mäntyselkä S, Schönfelder M, et al. Skeletal muscle hypertrophy rewires glucose metabolism: an experimental investigation and systematic review. *J Cachexia Sarcopenia Muscle*. 2024;15:989-1002. doi:10.1002/jcsm.13468
25. Szwed A, Kim E, Jacinto E. Regulation and metabolic functions of mTORC1 and mTORC2. *Physiol Rev*. 2021;101:1371-1426. doi:10.1152/physrev.00026.2020
26. Xiang C, Zhang Y, Chen Q, et al. Increased glycolysis in skeletal muscle coordinates with adipose tissue in systemic metabolic homeostasis. *J Cell Mol Med*. 2021;25:7840-7854. doi:10.1111/jcmm.16698
27. Mäntyselkä S, Kolari K, Baumert P, et al. Serine synthesis pathway enzyme PHGDH is critical for muscle cell biomass, anabolic metabolism, and mTORC1 signaling. *Am J Physiol Endocrinol Metab*. 2024;326:E73-E91. doi:10.1152/ajpendo.00151.2023
28. Izumiya Y, Hopkins T, Morris C, et al. Fast/glycolytic muscle fiber growth reduces fat mass and improves metabolic parameters in obese mice. *Cell Metab*. 2008;7:159-172.
29. Guo T, Jou W, Chanturiya T, Portas J, Gavrilova O, McPherron AC. Myostatin inhibition in muscle, but not adipose tissue, decreases fat mass and improves insulin sensitivity. *PLoS One*. 2009;4:e4937.

30. Thyfault JP, Rector RS. Exercise combats hepatic steatosis: potential mechanisms and clinical implications. *Diabetes*. 2020;69:517-524.
31. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol*. 2012;8:457-465.
32. Schnyder S, Handschin C. Skeletal muscle as an endocrine organ: PGC-1α, myokines and exercise. *Bone*. 2015;80:115-125.
33. Izumiya Y, Bina HA, Ouchi N, Akasaki Y, Kharitonenkov A, Walsh K. FGF21 is an Akt-regulated myokine. *FEBS Lett*. 2008;582:3805-3810.
34. Allard C, Miralpeix C, López-Gambero AJ, Cota D. mTORC1 in energy expenditure: consequences for obesity. *Nat Rev Endocrinol*. 2024;20:1-13.
35. Keipert S, Ost M, Johann K, et al. Skeletal muscle mitochondrial uncoupling drives endocrine cross-talk through the induction of FGF21 as a myokine. *Am J Physiol-Endocrinol Metab*. 2014;306:E469-E482. doi:10.1152/ajpendo.00330.2013
36. Camporez JPG, Jornayvaz FR, Petersen MC, et al. Cellular mechanisms by which FGF21 improves insulin sensitivity in male mice. *Endocrinology*. 2013;154:3099-3109.
37. Gaster M, Handberg A, Beck-Nielsen H, Schrøder HD. Glucose transporter expression in human skeletal muscle fibers. *Am J Physiol-Endocrinol Metab*. 2000;279:E529-E538. doi:10.1152/ajpendo.2000.279.3.E529
38. Li H, Wu G, Fang Q, et al. Fibroblast growth factor 21 increases insulin sensitivity through specific expansion of subcutaneous fat. *Nat Commun*. 2018;9:1-16.
39. BonDurant LD, Ameka M, Naber MC, et al. FGF21 regulates metabolism through adipose-dependent and-independent mechanisms. *Cell Metab*. 2017;25:935-944.
40. Johann K, Kleinert M, Klaus S. The role of GDF15 as a myomitokine. *Cells*. 2021;10:2990.
41. Tang H, Inoki K, Brooks SV, et al. mTORC1 underlies age-related muscle fiber damage and loss by inducing oxidative stress and catabolism. *Aging Cell*. 2019;18:e12943. doi:10.1111/acel.12943
42. Khan NA, Nikkanen J, Yatsuga S, et al. mTORC1 regulates mitochondrial integrated stress response and mitochondrial myopathy progression. *Cell Metab*. 2017;26:419-428.
43. Yasuda T, Ishihara T, Ichimura A, Ishihara N. Mitochondrial dynamics define muscle fiber type by modulating cellular metabolic pathways. *Cell Rep*. 2023;42:112434.
44. Chung HK, Ryu D, Kim KS, et al. Growth differentiation factor 15 is a myomitokine governing systemic energy homeostasis. *J Cell Biol*. 2017;216:149-165.
45. Laurens C, Parmar A, Murphy E, et al. Growth and differentiation factor 15 is secreted by skeletal muscle during exercise and promotes lipolysis in humans. *JCI Insight*. 2020;5:5.
46. Zhang H, Mulya A, Nieuwoudt S, et al. GDF15 mediates the effect of skeletal muscle contraction on glucose-stimulated insulin secretion. *Diabetes*. 2023;72:1070-1082.
47. Ost M, Igual Gil C, Coleman V, et al. Muscle-derived GDF15 drives diurnal anorexia and systemic metabolic remodeling during mitochondrial stress. *EMBO Rep*. 2020;21:e48804. doi:10.15252/embr.201948804
48. Wang D, Day EA, Townsend LK, Djordjevic D, Jørgensen SB, Steinberg GR. GDF15: emerging biology and therapeutic applications for obesity and cardiometabolic disease. *Nat Rev Endocrinol*. 2021;17:592-607.
49. Wang D, Townsend LK, DesOrmeaux GJ, et al. GDF15 promotes weight loss by enhancing energy expenditure in muscle. *Nature*. 2023;619:143-150.
50. Sjøberg KA, Sigvardsen CM, Alvarado-Diaz A, et al. GDF15 increases insulin action in the liver and adipose tissue via a β-adrenergic receptor-mediated mechanism. *Cell Metab*. 2023;35:1327-1340.
51. Alizadeh H. Myokine-mediated exercise effects: the role of myokine meteorin-like hormone (Metrnl). *Growth Factors*. 2021;39:71-78. doi:10.1080/08977194.2022.2032689
52. de A, de B, Miola VFB, et al. Adipokines, myokines, and hepatokines: crosstalk and metabolic repercussions. *Int J Mol Sci*. 2021;22:2639.
53. Li Z, Gao Z, Sun T, et al. Meteorin-like/Metrnl, a novel secreted protein implicated in inflammation, immunology, and metabolism: a comprehensive review of preclinical and clinical studies. *Front Immunol*. 2023;14:1098570.
54. Dong W, Hu C, Hu M, et al. Metrnl: a promising biomarker and therapeutic target for cardiovascular and metabolic diseases. *Cell Commun Signal*. 2024;22:389. doi:10.1186/s12964-024-01767-8
55. Jung TW, Lee SH, Kim H-C, et al. METRNL attenuates lipid-induced inflammation and insulin resistance via AMPK or PPARδ-dependent pathways in skeletal muscle of mice. *Exp Mol Med*. 2018;50:1-11.
56. Li Z-Y, Song J, Zheng S-L, et al. Adipocyte Metrnl antagonizes insulin resistance through PPARγ signaling. *Diabetes*. 2015;64:4011-4022.
57. Hu W, Wang R, Sun B. Meteorin-like ameliorates β cell function by inhibiting β cell apoptosis of and promoting β cell proliferation via activating the WNT/β-catenin pathway. *Front Pharmacol*. 2021;12:627147.
58. Yao Z, Lin P, Wang C, Wang K, Sun Y. Administration of metrnl delays the onset of diabetes in non-obese diabetic mice. *Endocr J*. 2021;68:179-188.
59. Ouchi N, Oshima Y, Ohashi K, et al. Follistatin-like 1, a secreted muscle protein, promotes endothelial cell function and revascularization in ischemic tissue through a nitric-oxide synthase-dependent mechanism. *J Biol Chem*. 2008;283:32802-32811.
60. Oshima Y, Ouchi N, Sato K, Izumiya Y, Pimentel DR, Walsh K. Follistatin-like 1 is an Akt-regulated Cardioprotective factor that is secreted by the heart. *Circulation*. 2008;117:3099-3108. doi:10.1161/CIRCULATIONAHA.108.767673
61. Nam JS, Park S, Ahn CW, Cho E, Kim H, Kim Y. Follistatin-like 1 is a myokine regulating lipid mobilization during endurance exercise and recovery. *Obesity*. 2024;32:352-362. doi:10.1002/oby.23949
62. Fang D, Shi X, Lu T, Ruan H, Gao Y. The glycoprotein follistatin-like 1 promotes brown adipose thermogenesis. *Metabolism*. 2019;98:16-26.
63. Vechetti IJ, Valentino T, Mobley CB, McCarthy JJ. The role of extracellular vesicles in skeletal muscle and systematic adaptation to exercise. *J Physiol*. 2021;599:845-861. doi:10.1113/JP278929
64. Hayashi H, Izumiya Y, Ishida T, et al. Exosomal miR206 secreted from growing muscle promotes Angiogenic response in endothelial cells. *Circ J*. 2024;88:425-433.
65. Burke BI, Ismaeel A, McCarthy JJ. The utility of the rodent synergist ablation model in identifying molecular and cellular mechanisms of skeletal muscle hypertrophy. *Am J Physiol Cell Physiol*. 2024;327:C601-C606. doi:10.1152/ajpcell.00362.2024
66. Vechetti IJ Jr, Peck BD, Wen Y, et al. Mechanical overload-induced muscle-derived extracellular vesicles promote adipose tissue lipolysis. *FASEB J*. 2021;35:e21644.
67. McCarthy JJ, Esser KA. MicroRNA-1 and microRNA-133a expression are decreased during skeletal muscle hypertrophy. *J Appl Physiol*. 2007;102:306-313. doi:10.1152/japplphysiol.00932.2006
68. Valentino TR, Rule BD, Mobley CB, Nikolova-Karakashian M, Vechetti IJ. Skeletal muscle cell growth alters the lipid composition of extracellular vesicles. *Membranes*. 2021;11:619.
69. Easterday DS, Lark DS. Circulating tetraspanins: from markers to mechanisms driving systemic exercise adaptation. *Function (Oxf)*. 2023;4:zqad048.
70. Oguri Y, Shinoda K, Kim H, et al. CD81 controls beige fat progenitor cell growth and energy balance via FAK signaling. *Cell*. 2020;182:563-577.

71. Brooks GA, Osmond AD, Arevalo JA, et al. Lactate as a myokine and exerkine: drivers and signals of physiology and metabolism. *J Appl Physiol*. 2023;134:529-548. doi:10.1152/japplphysiol.00497.2022
72. Weyrauch LA, McMillin SL, Witczak CA. Insulin resistance does not impair mechanical overload-stimulated glucose uptake, but does alter the metabolic fate of glucose in mouse muscle. *Int J Mol Sci*. 2020;21:4715.
73. Cheng K-K, Akasaki Y, Lecommandeur E, et al. Metabolomic analysis of Akt1-mediated muscle hypertrophy in models of diet-induced obesity and age-related fat accumulation. *J Proteome Res*. 2015;14:342-352. doi:10.1021/pr500756u
74. Akasaki Y, Ouchi N, Izumiya Y, Bernardo BL, LeBrasseur NK, Walsh K. Glycolytic fast-twitch muscle fiber restoration counters adverse age-related changes in body composition and metabolism. *Aging Cell*. 2014;13:80-91. doi:10.1111/acel.12153
75. Pedersen MGB, Søndergaard E, Nielsen CB, et al. Oral lactate slows gastric emptying and suppresses appetite in young males. *Clin Nutr*. 2022;41:517-525.
76. Al-Massadi O, Fernø J, Diéguez C, Nogueiras R, Quiñones M. Glucagon control on food intake and energy balance. *Int J Mol Sci*. 2019;20:3905.
77. Dailey MJ, Moran TH. Glucagon-like peptide 1 and appetite. *Trends Endocrinol Metab*. 2013;24:85-91.
78. Li VL, He Y, Contrepois K, et al. An exercise-inducible metabolite that suppresses feeding and obesity. *Nature*. 2022;606:785-790.
79. Croymans DM, Paparisto E, Lee MM, et al. Resistance training improves indices of muscle insulin sensitivity and β-cell function in overweight/obese, sedentary young men. *J Appl Physiol*. 2013;115:1245-1253.
80. Bandy WD, Lovelace-Chandler V, McKitrick-Bandy B. Adaptation of skeletal muscle to resistance training. *J Orthop Sports Phys Ther*. 1990;12:248-255.
81. Pesta DH, Goncalves RL, Madiraju AK, Strasser B, Sparks LM. Resistance training to improve type 2 diabetes: working toward a prescription for the future. *Nutr Metab*. 2017;14:1-10.
82. Klickstein L, Flynt A, Edgerton D, Dole K, Nguyen K. RF28|PSUN198 the dramatic fat mass loss caused by Bimagrumab is similar in diabetic and non-diabetic patients. *J Endocr Soc*. 2022;6:A37-A38.
83. Nunn E, Jaiswal N, Gavin M, et al. Antibody blockade of activin type II receptors preserves skeletal muscle mass and enhances fat loss during GLP-1 receptor agonism. *Mol Metab*. 2024;80:101880.
84. Schoenfeld BJ. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. *Sports Med*. 2013;43:179-194. doi:10.1007/s40279-013-0017-1
85. Dunstan DW, Daly RM, Owen N, et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care*. 2002;25:1729-1736.
86. Castaneda C, Layne JE, Munoz-Orians L, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care*. 2002;25:2335-2341.
87. Ibañez J, Izquierdo M, Argüelles Ĩ, et al. Twice-weekly progressive resistance training decreases abdominal fat and improves insulin sensitivity in older men with type 2 diabetes. *Diabetes Care*. 2005;28:662-667.
88. Kim HJ, Kim YJ, Kim IY, Seong JK. Resistance exercise training-induced skeletal muscle strength provides protective effects on high-fat-diet-induced metabolic stress in mice. *Lab Anim Res*. 2022;38:36. doi:10.1186/s42826-022-00145-0
89. Lourenço Í, Krause W, dos L, et al. Muscle hypertrophy and ladder-based resistance training for rodents: a systematic review and meta-analysis. *Physiol Rep*. 2020;8:8. doi:10.14814/phy2.14502
90. Hajj-Boutros G, Karelis AD, Cefis M, et al. Potential mechanisms involved in regulating muscle protein turnover after acute exercise: a brief review. *Front Physiol*. 2023;13:1106425.
91. Bodine SC. The role of mTORC1 in the regulation of skeletal muscle mass. *Fac Rev*. 2022;11:32.
92. Post A, Dam WA, Sokooti S, et al. Circulating FGF21 concentration, fasting plasma glucose, and the risk of type 2 diabetes: results from the PREVEND study. *J Clin Endocrinol Metab*. 2023;108:1387-1393.
93. Kim H, Song W. Resistance training increases fibroblast growth factor-21 and irisin levels in the skeletal muscle of Zucker diabetic fatty rats. *J Exerc Nutr Biochem*. 2017;21:50-54.
94. Kim H, Jung J, Park S, et al. Exercise-induced fibroblast growth factor-21: a systematic review and meta-analysis. *Int J Mol Sci*. 2023;24:7284.
95. Fisher FM, Chui PC, Antonellis PJ, et al. Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. *Diabetes*. 2010;59:2781-2789.
96. Markan KR. Defining "FGF21 resistance" during obesity: controversy, criteria and unresolved questions. *F1000Res*. 2018;7:289.
97. Eddy AC, Trask AJ. Growth differentiation factor-15 and its role in diabetes and cardiovascular disease. *Cytokine Growth Factor Rev*. 2021;57:11-18.
98. Klein AB, Nicolaisen TS, Ørtenblad N, et al. Pharmacological but not physiological GDF15 suppresses feeding and the motivation to exercise. *Nat Commun*. 2021;12:1041.
99. Alizadeh H. Meteorin-like protein (Metrnl): a metabolic syndrome biomarker and an exercise mediator. *Cytokine*. 2022;157:155952.
100. Tayebi SM, Golmohammadi M, Eslami R, Shakiba N, Costa PB. The effects of eight weeks of circuit resistance training on serum METRNL levels and insulin resistance in individuals with type 2 diabetes. *J Diabetes Metab Disord*. 2023;22:1151-1158. doi:10.1007/s40200-023-01225-1
101. Amano Y, Nonaka Y, Takeda R, Kano Y, Hoshino D. Effects of electrical stimulation-induced resistance exercise training on white and brown adipose tissues and plasma meteorin-like concentration in rats. *Physiol Rep*. 2020;8:8. doi:10.14814/phy2.14540
102. Xi Y, Hao M, Tian Z. Resistance exercise increases the regulation of skeletal muscle FSTL1 consequently improving cardiac angiogenesis in rats with myocardial infarctions. *J Sci Sport Exerc*. 2019;1:78-87. doi:10.1007/s42978-019-0009-4
103. Xi Y, Hao M, Liang Q, Li Y, Gong D-W, Tian Z. Dynamic resistance exercise increases skeletal muscle-derived FSTL1 inducing cardiac angiogenesis via DIP2A–Smad2/3 in rats following myocardial infarction. *J Sport Health Sci*. 2021;10:594-603.
104. Conkright WR, Beckner ME, Sterczala AJ, et al. Resistance exercise differentially alters extracellular vesicle size and subpopulation characteristics in healthy men and women: an observational cohort study. *Physiol Genomics*. 2022;54:350-359. doi:10.1152/physiolgenomics.00171.2021
105. Conkright W, Kargl C, Hubal M, et al. Acute resistance exercise modifies extracellular vesicle miRNAs targeting anabolic gene pathways: a prospective cohort study. *Med Sci Sports Exerc*. 2024;56:1225-1232.
106. Burke BI, Ismaeel A, Long DE, et al. Extracellular vesicle transfer of miR-1 to adipose tissue modifies lipolytic pathways following resistance exercise. *JCI Insight*. 2024;9:e182589.
107. Xhuti D, Nilsson MI, Manta K, Tarnopolsky MA, Nederveen JP. Circulating exosome-like vesicle and skeletal muscle microRNAs are altered with age and resistance training. *J Physiol*. 2023;601:5051-5073. doi:10.1113/JP282663
108. Evans PL, McMillin SL, Weyrauch LA, Witczak CA. Regulation of skeletal muscle glucose transport and glucose metabolism by exercise training. *Nutrients*. 2019;11:2432.
109. Tavassoli H, Tofighi A, Panah FH, Hedaytai M. Appetite and exercise; influence of 12 weeks of circuit resistance training on the nesfatin-1 to acylated ghrelin ratio of plasma in overweight adolescents. 2014.

110. Liu H-W, Cheng H-C, Tsai S-H, Shao Y-T. Effects of acute resistance exercise with different loads on appetite, appetite hormones and autonomic nervous system responses in healthy young men. *Appetite*. 2023;182:106428.
111. Edman S, Jones RG III, Jannig PR, et al. The 24-hour time course of integrated molecular responses to resistance exercise in human skeletal muscle implicates MYC as a hypertrophic regulator that is sufficient for growth. *bioRxiv*. 2024. (preprint).
112. Zhu W, Thomas A, Wilson G, et al. Identification of a Resistance Exercise-Specific Signaling Pathway that Drives Skeletal Muscle Growth. Research Square 2024. (preprint).
113. Morvan F, Rondeau J-M, Zou C, et al. Blockade of activin type II receptors with a dual anti-ActRIIA/IIB antibody is critical to promote maximal skeletal muscle hypertrophy. *Proc Natl Acad Sci*. 2017;114:12448-12453. doi:10.1073/pnas.1707925114
114. Latres E, Mastaitis J, Fury W, et al. Activin A more prominently regulates muscle mass in primates than does GDF8. *Nat Commun*. 2017;8:15153.
115. Heymsfield SB, Coleman LA, Miller R, et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. *JAMA Netw Open*. 2021;4:e2033457.
116. Fournier B, Murray B, Gutzwiller S, et al. Blockade of the activin receptor IIB activates functional Brown Adipogenesis and thermogenesis by inducing mitochondrial oxidative metabolism. *Mol Cell Biol*. 2012;32:2871-2879. doi:10.1128/MCB.06575-11
117. Lee S-J, Bhasin S, Klickstein L, Krishnan V, Rooks D. Challenges and future prospects of targeting myostatin/activin a signaling to treat diseases of muscle loss and metabolic dysfunction. *J Gerontol A Biol Sci Med Sci*. 2023;78:32-37.
118. Collins L, Costello RA. Glucagon-like peptide-1 receptor agonists. 2019.
119. Neeland IJ, Linge J, Birkenfeld AL. Changes in lean body mass with GLUCAGON-LIKE PEPTIDE −1-based therapies and mitigation strategies. *Diabetes Obes Metab*. 2024;26:dom.15728. doi:10.1111/dom.15728
120. Prado CM, Phillips SM, Gonzalez MC, Heymsfield SB. Muscle matters: the effects of medically induced weight loss on skeletal muscle. *Lancet Diabetes Endocrinol*. 2024;12:785-787.
121. Tan LF, Chan YH, Denishkrshna A, Merchant RA. Association between different skeletal muscle mass indices, physical function, and inflammation in obese pre-frail older adults. *Arch Gerontol Geriatr*. 2024;118:105289.
122. Haines MS, Dichtel LE, Santoso K, Torriani M, Miller KK, Bredella MA. Association between muscle mass and insulin sensitivity independent of detrimental adipose depots in young adults with overweight/obesity. *Int J Obes*. 2020;44:1851-1858.
123. Srikanthan P, Karlamangla AS. Muscle mass index as a predictor of longevity in older adults. *Am J Med*. 2014;127:547-553.
124. Wang Y, Luo D, Liu J, Song Y, Jiang B, Jiang H. Low skeletal muscle mass index and all-cause mortality risk in adults: a systematic review and meta-analysis of prospective cohort studies. *PLoS One*. 2023;18:e0286745.
125. Abdulla H, Phillips BE, Wilkinson DJ, et al. Glucagon-like peptide 1 infusions overcome anabolic resistance to feeding in older human muscle. *Aging Cell*. 2020;19:e13202. doi:10.1111/acel.13202
126. Ren Q, Chen S, Chen X, et al. An effective glucagon-like Peptide-1 receptor agonists, Semaglutide, improves Sarcopenic obesity in obese mice by modulating skeletal muscle metabolism. *Drug Des Devel Ther*. 2022;16:3723-3735. doi:10.2147/DDDT.S381546
127. Wu L, Zhou M, Li T, et al. GLP-1 regulates exercise endurance and skeletal muscle remodeling via GLP-1R/AMPK pathway. *Biochim Biophys Acta, Mol Cell Res*. 2022;1869:119300.
128. Locatelli JC, Costa JG, Haynes A, et al. Incretin-based weight loss pharmacotherapy: can resistance exercise optimize changes in body composition? *Diabetes Care*. 2024;47:1718-1730.
129. Dreyer HC, Drummond MJ, Glynn EL, et al. Resistance exercise increases human skeletal muscle AS160/TBC1D4 phosphorylation in association with enhanced leg glucose uptake during postexercise recovery. *J Appl Physiol*. 2008;105:1967-1974. doi:10.1152/japplphysiol.90562.2008
130. Thomas AC, Stead CA, Burniston JG, Phillips SM. Exercise-specific adaptations in human skeletal muscle: molecular mechanisms of making muscles fit and mighty. *Free Radic Biol Med*. 2024;223:341-356.

How to cite this article: Sammut MJ, Thorne BR, Melling CWJ. Skeletal muscle growth to combat diabetes and obesity: the potential role of muscle-secreted factors. *Obesity (Silver Spring)*. 2025;1-17. doi:10.1002/oby.24223