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COMPENDIUM ON INTERORGAN CROSSTALK IN HEART FAILURE AND CARDIOMETABOLIC DISEASES

Skeletal Muscle as a Mediator of Interorgan Crosstalk During Exercise: Implications for Aging and Obesity

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ABSTRACT: Physical exercise is critical for preventing and managing chronic conditions, such as cardiovascular disease, type 2 diabetes, hypertension, and sarcopenia. Regular physical activity significantly reduces cardiovascular and all-cause mortality. Exercise also enhances metabolic health by promoting muscle growth, mitochondrial biogenesis, and improved nutrient storage while preventing age-related muscle dysfunction. Key metabolic benefits include increased glucose uptake, enhanced fat oxidation, and the release of exercise-induced molecules called myokines, which mediate interorgan communication and improve overall metabolic function. These myokines and other exercise-induced signaling molecules hold promise as therapeutic targets for aging and obesity-related conditions.

Key Words: cardiovascular diseases ■ epinephrine ■ hypertension ■ muscle, skeletal ■ sarcopenia

Physical exercise is widely recognized as an effective tool for preventing, managing, and treating a variety of chronic conditions, including cardiovascular disease (CVD), type 2 diabetes, hypertension, obesity, and sarcopenia.[1,2,3] A systematic review and meta-analysis of 33 studies involving over 880 000 participants revealed that higher levels of physical activity were linked to a 30% to 50% reduction in cardiovascular mortality and a 20% to 50% reduction in all-cause mortality.[4] In addition, research from the Nurses' Health Study (with nearly 80 000 participants) and the Health Professionals Follow-Up Study (involving 44 000 participants) examined the impact of 5 lifestyle factors, including at least 30 minutes of moderate to vigorous physical activity per day, on life expectancy in the US population. Over a follow-up period of up to 34 years, the most physically active men and women enjoyed an increase in life expectancy of 7 to 8 years.[5]

Exercise enhances metabolic health by inducing adaptations across multiple tissues, including skeletal muscle. In skeletal muscle, regular resistance exercise increases myocyte size[6] and muscle mass[7] and improves the quality and functionality of the muscle.[8] This is due to changes in fiber type and increased mitochondrial content, conferring resistance to atrophy,[9] as well as metabolic adaptations. Endurance exercise results in extensive mitochondrial biogenesis, enhanced glucose and fatty acid transport, and increased capillarization to improve the flux of oxygen delivery and nutrient flux to the skeletal muscle. Nutrient availability is also improved through greater intramuscular lipid and glycogen storage.[10,1] Exercise protects the skeletal muscle from age-associated dysfunction, including decreases in strength and mitochondrial capacity, and increased fat infiltration and insulin resistance.[11,12,13] Moreover, maintaining or beginning physical activity is a well-established way to prevent or improve the effects of aging on skeletal muscle.[14] Exercise results in multiple signals that change skeletal muscle function and metabolism, catecholamine and adrenaline signaling, calcium release, mechanical force, and changes in redox balance that all work to adapt the skeletal muscle to the demands of exercise.[15]

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Nonstandard Abbreviations and Acronyms

ACSL1	acyl-coenzyme-A synthetase long-chain family member 1
ActRII	activin type II receptor
ActRIIA	activin type IIA receptor
ActRIIB	activin type IIB receptor
AKT	protein kinase B
ALK	activity type I receptor
AMPK	AMP-activated protein kinase
ATF2	activating transcription factor 2
ATG7	autophagy-related 7
BAIBA	β-aminoisobutyric acid
BECN1	beclin-1
BMP	bone morphogenic protein
BNP	brain natriuretic peptide
CAD	coronary artery disease
CaMKII	calcium/calmodulin-dependent protein kinase
CDK2	cyclin-dependent kinase 2
CEBPα	CCAAT/enhancer-binding protein-alpha
CoA	coenzyme-A
CPT	carnitine palmitoyltransferase
CREB	cAMP response element-binding protein
CVD	cardiovascular disease
eNOS	endothelial nitric oxide synthase
ERK	extracellular signal-regulated kinase
ERRα	estrogen-related receptor alpha
FABPpm	plasma membrane-associated fatty acid binding protein
FATP	fatty acid transport protein
FBXO32/ Atrogin1/MAFBX	f-box protein 32
FNDC5	fibronectin type III domain-containing protein 5
FOXO	forkhead box O
GLP1	glucagon-like peptide-1
GLP1RA	glucagon-like peptide-1 receptor agonist
GLUT4	glucose transporter type 4
HCAR1	hydroxycarboxylic acid receptor 1
HDAC	histone deacetylase
HF	heart failure
IGF	insulin-like growth factor
IGFBP	insulin-like growth factor-binding protein
IL	interleukin
LDL	low-density lipoprotein
MAPK	mitogen-activated protein kinase
MCT	monocarboxylate transporter
MEF2	myocyte enhancer factor 2
Metrnl	meteorin-like protein
MFN	mitofusin
MOTS-c	mitochondrial open reading frame of the 12S rRNA type-c
mTOR	mammalian target of rapamycin
MuRF1/Trim63	muscle ring-finger protein-1
NFAT	nuclear factor of activated T cells
NFκB	nuclear factor kappa-B
NLRP3	nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 3
NRF1	nuclear respiratory factor 1
OPA1	optic atrophy 1
PGC1α	peroxisome proliferator-activated receptor gamma co-activator 1 alpha
PKA	protein kinase A
PPARγ	peroxisome proliferator-activated receptor gamma
TFEB	transcription factor EB
TGFβ	transforming growth factor beta
TNFα	tumor necrosis factor alpha
TSC2	tuberous sclerosis complex 2
VEGF	vascular endothelial growth factor
β-MHC	beta-myosin heavy chain

With regard to metabolic adaptations to skeletal muscle, exercise improves glucose uptake,[16,17,18,19] increases translocation and expression of GLUT4 (glucose transporter type 4),[20,19] enhances mitochondrial activity,[21] improves the capacity to take up and oxidize fat as fuel,[21] and increases the release of exercise-induced myokines into the bloodstream.[22,23,24,25,26,27,3] These exercise-induced adaptations improve overall metabolic and cardiovascular function.

Exerkines refer to molecules secreted in response to exercise and play a significant role in regulating various bodily functions. These molecules include proteins, metabolites, and noncoding nucleic acids, are secreted by muscles (myokines) or other organs, and can act on the organ itself (autocrine), nearby cells (paracrine), or distant organs (endocrine).[28,29,30] When acting in an endocrine manner, exerkines facilitate communication between different tissues and organs, including the heart, skeletal muscle, liver, and adipose tissue. By promoting this crosstalk, exerkines likely work together to enhance overall metabolic health.[31] Importantly, recent data indicate that endurance training induces molecular

adaptations across 19 different tissues,[32] many associated with mitochondrial or metabolic function.[33] These signaling molecules are of great interest as potential therapeutic targets due to their role in mediating the system-wide benefits of exercise. While initial research focused on myokines, exercise-induced secreted molecules can be produced by various tissues.[31]

In this review, we will focus on the role of skeletal muscle–released myokines in exercise-induced interorgan crosstalk with a specific focus on its role in aging and obesity.

EXERCISE

Exercise refers to intentional physical activity and spans aerobic, resistance, high-intensity interval training, and exercise snacks.[31,34,35,36] Aerobic exercise is the continuous use of large muscle groups, resulting in increased muscle oxygen demand and, therefore, an increase in heart rate,[37] and includes activities such as walking, running, bicycling, and swimming. Resistance training is when resistance, either provided by an external source, such as weights, or by using one's body weight, is used to create progressive overload to the muscles.[38] High-intensity interval training is when repeated bouts of moderate-vigorous work are performed with periods of recovery of easier work or rest in between bouts.[39] Exercise snacks are isolated (≤1 minute) bouts of intense exercise performed periodically throughout one's day.[40]

Repeated exercise, that is, exercise training, confers numerous beneficial effects on multiple tissues, including the skeletal muscle, liver, heart, vasculature, lungs, and adipose tissue.[32,41] Importantly, exercise improves metabolic health independent of weight loss and abrogates age-related changes in glucose disposal and insulin sensitivity.[42,43,44] Exercise is a potent mediator of health, and exercise capacity is the strongest predictor of mortality in humans.[45,46] This is achieved through the complex interplay between various signaling mechanisms that are activated in response to the exercise-induced disruption of homeostasis, ultimately leading to, for example, improved insulin sensitivity,[11,47] anti-inflammatory effects,[48] and improved cardiorespiratory fitness.[15]

EXERCISE AND CARDIOVASCULAR HEALTH

CVD remains the leading cause of morbidity and mortality worldwide,[49] encompassing a spectrum of conditions such as arrhythmias, cardiomyopathies, heart failure (HF), and atherosclerosis.[50] These conditions often culminate in severe pathologies such as stroke, myocardial infarction, or cardiac arrest. The global rise in obesity has significantly contributed to the prevalence of obesity-related CVD,[51] primarily through mechanisms such as hypertension and nutrient overload.[52,53,54,55,56] Obesity-induced hypertension promotes pathological cardiac hypertrophy, which can progress to HF.[57,58] In addition, the increased fatty acid uptake and utilization characteristic of an obesogenic state leads to intramyocardial lipid accumulation, lipotoxicity, and subsequent cardiac dysfunction.[52,59,60] Atherosclerosis, the most common form of CVD, develops gradually due to sedentary lifestyles and obesity and remains a major precursor to fatal cardiovascular events.[50,61,62]

Exercise training offers a powerful means to mitigate the risk and progression of CVD through multiple physiological and metabolic pathways. Regular physical activity decreases cardiovascular risk factors, including obesity, type 2 diabetes, and hypertension,[63,64,65,66] while improving glucose homeostasis, high-density lipoprotein levels, and blood pressure regulation, even without significant weight loss.[67,68,69,70,71] For patients with existing CVD, exercise-based cardiac rehabilitation enhances cardiovascular function and improves exercise tolerance,[72,73] which is critical in conditions such as HF.[74,75,76,77,78,79] Regular exercise induces favorable cardiac and vascular adaptations, including reduced resting heart rate and blood pressure, increased physiological cardiac hypertrophy, and lower circulating lipid levels.[80,81,82,83] Mechanistically, exercise promotes vasodilation, angiogenesis,[84,85,86] and the release of myokines, which mediate anti-inflammatory effects, promote exercise-induced cardiac adaptations, and facilitate intertissue communication,[87,88,89,90,27] fostering cardiovascular health and contributing to enhanced cardiovascular resilience.

EXERCISE-INDUCED ADAPTATIONS TO SKELETAL MUSCLE

Cellular adaptations to skeletal muscle emerge from a complex network of signaling mechanisms triggered by exercise-induced physiological challenges.[1] Various stimuli, including mechanical forces such as shear stress, metabolic shifts in oxygen availability, energy substrate fluctuations, alterations in cellular pH and calcium levels, and temperature changes, collectively initiate a cascade of molecular responses.[85] These intricate cellular perturbations ultimately converge to modulate gene expression patterns and protein dynamics, resulting in enhanced muscular function.

Skeletal Muscle Structural Remodeling With Exercise

Regular exercise induces structural changes in muscles to adapt to the repeated metabolic and mechanical

stresses. When muscles contract, calcium waves are generated within the myofibers due to nerve stimulation and depolarization, resulting in the activation of several signaling pathways that regulate myosin content, mitochondrial function, and muscle capillary growth. The type, intensity, and duration of calcium spikes during exercise are critical for activating calcineurin, a calcium-dependent phosphatase. Endurance exercise maximally activates calcineurin, which dephosphorylates NFAT (nuclear factor of activated T cells) transcription factors, enabling their movement into the nucleus. There, NFATs promote slow myosin expression, triggering muscle fiber-type switching to fatigue-resistant fibers.[91,92]

Calcineurin-NFAT signaling does not induce muscle hypertrophy, which is primarily regulated by the IGF (insulin-like growth factor)-1-AKT (protein kinase B)-mTOR (mammalian target of rapamycin) pathway. However, calcineurin activates TFEB (transcription factor EB), promoting mitochondrial biogenesis and GLUT4 expression. This enhances glucose uptake and ATP production, and supports myofiber contraction.[93,94] TFEB activation sustains β-oxidative metabolism and is partially dependent on PGC1α (PPARγ [peroxisome proliferator-activated receptor gamma] co-activator 1 alpha), a transcription factor that promotes mitochondrial oxidative metabolism,[95] which is upregulated during physical activity. Interestingly, overexpression of TFEB in PGC1α knockout mice can still induce mitochondrial biogenesis and improve exercise performance.[94] PGC1α itself drives several endurance-related changes, such as mitochondrial biogenesis, fiber-type switching, fatty acid oxidation, angiogenesis, and resistance to muscle atrophy.[9,96]

Calcium waves also activate CaMKII (calcium/calmodulin-dependent protein kinase), which, along with calcineurin, converges on cAMP-dependent proteins such as CREB (cAMP response element-binding protein) and ATF2 (activating transcription factor 2). These proteins, when phosphorylated, bind to the promoter of the *PGC1α* gene, inducing its expression. PGC1α activation involves both transcriptional upregulation and posttranslational modifications that regulate protein levels and interactions with coregulators.[97] PGC1α also plays a role in enhancing blood vessel growth by coactivating ERRα (estrogen-related receptor alpha), which stimulates VEGF (vascular endothelial growth factor) expression.[98] Endurance exercise also activates proteolytic systems such as autophagy and the ubiquitin-proteasome pathway to remodel proteins and remove damaged organelles, including mitochondria through mitophagy. This process helps prevent oxidative stress and is mediated by the energy stress sensor, AMPK (AMP-activated protein kinase).[99,100,101] Autophagy activation is critical for training adaptations and improved performance.[102]

In contrast, resistance training induces a specific variant of PGC1α, known as PGC1α4, which promotes muscle hypertrophy.[103] PGC1α4, expressed via an alternative promoter, does not shift muscles to oxidative metabolism but, instead, enhances protein synthesis and blocks myostatin production. The IGF1-AKT-mTOR pathway, which controls protein synthesis and muscle growth, is crucial for resistance training-induced hypertrophy and prevents muscle wasting in catabolic conditions.[104,105,106,107] The increases in hypertrophy as a result of myostatin inhibition on hypertrophy are partly due to its interaction with the AKT-mTOR signaling pathway.

Exercise and Skeletal Muscle Metabolism

Myocytes undergo dynamic changes in metabolism to support both the mass and constant use of skeletal muscle. During periods of fasting and when at rest, the energetic needs are met by the oxidation of fatty acids.[108] Physical activity requires alterations in metabolism to support changes in membrane excitability, calcium handling, myofilament cycling, and other ATP-demanding processes. Exercise alters muscle metabolism, increasing glycogen storage, mitochondrial biogenesis, and β-oxidation.[109,110,111,112] Muscle contractions elevate cytosolic calcium levels, activating CaMKII signaling pathways, promoting glucose uptake,[19,113] and adrenaline-driven glycogenolysis to support energy needs.[114]

At rest, fatty acids in circulation are incorporated into the intramyocellular triglyceride stores before mitochondrial oxidation .[115,116] During exercise, fatty acids from both adipose tissue and the intramyocellular triglyceride stores are oxidized by the muscle .[117–120] These fatty acids are taken up by the skeletal muscle likely via fatty acid transporters such as CD36 (cluster of differentiation 36), FABPpm (plasma membrane-associated fatty acid binding protein), FATP (fatty acid transport protein)-1, and FATP4.[121–124] The mechanism behind increased fatty acid transporter translocation during exercise has not been elucidated but is likely, in part, regulated by AMPK [125] although regulation by other signaling molecules has also been suggested.[126,127] After entering the muscle, fatty acids are modified by ACSL1 (acyl-coenzyme-A synthetase long-chain family member 1), the key isoform in the muscle[128] to their acyl-CoA (coenzyme-A) form. To cross the inner mitochondrial membrane, the fatty acyl-CoAs are then further modified by CPT (carnitine palmitoyl transferase)-1 and CPT2 as part of the carnitine shuttle, after which they oxidized.[127]

Exercise modulates muscle metabolism before, during, and after physical activity. Resting metabolism is altered by exercise training, increasing glycogen muscle content, mitochondrial biogenesis, and promoting β-oxidation.[109,110,111,112] In general, various exercise stimuli alter metabolism to support physical activity and promote health. Muscle contraction increases cytosolic calcium

levels, resulting in CaMKII activation and promoting glucose uptake.[19,113] Adrenaline stimulates glycogenolysis, promoting glycogen oxidation, and activating pyruvate dehydrogenase to promote carbohydrate oxidation.[114]

Exercise Modalities Induce Specific Adaptations to Skeletal Muscle Metabolism

Exercise modality, duration, and intensity contribute to the metabolic response in the skeletal muscle. During intense exercise, the energetic requirements of skeletal muscle increase dramatically, and ATP consumption can increase as much as 100-fold. To support augmented metabolic demand, muscles initially leverage rapid energy sources, including phosphocreatine reserves and anaerobic glycogen breakdown. These initial energy-generating pathways are dynamically regulated by rapid fluctuations in key molecules such as AMP (adenosine monophosphate), ADP (adenosine diphosphate), inorganic phosphate, NAD^+/NADH (nicotinamide adenine dinucleotide) ratios, and intracellular calcium concentrations released from the sarcoplasmic reticulum. Within a brief timeframe, a transition to aerobic metabolism and mobilization of additional molecular energy reserves is necessary.[129,1] Throwing, jumping, and sprinting are examples of short, high-intensity exertions, where ATP is generated primarily by anaerobic metabolism, with anaerobic glycolysis producing lactate,[130,131] which can be secreted, oxidized, and used for gluconeogenesis and muscle glycogenesis.[132,133,134] Skeletal muscle lactate production also regulates cardiovascular and pulmonary function during exercise. Lactate promotes angiogenesis through VEGF,[135] provides the metabolic substrate for cardiac metabolism,[136] and may act as a hypoxia sensor, upregulating breathing during exercise.[137]

Sustained aerobic exercise is fueled by mitochondrial oxidative phosphorylation.[138,130,139] The substrates for oxidative phosphorylation are primarily derived from intramuscular glycogen stores, circulating glucose, and fatty acids from within the muscle and those released into circulation by the adipose tissue.[140,141]

Exercise intensity dictates primary metabolic pathways, with high-intensity activities predominantly relying on carbohydrate metabolism, while moderate-intensity exercise utilizes a mix of carbohydrates and free fatty acids.[141] Secreted lactate can be converted to glucose or metabolized by the gut microbiota Veillonella, which increases in abundance in response to exercise. Higher levels of Veillonella in the gut result in improved exercise capacity in mice, demonstrating the intricate, cross-tissue regulation of metabolism during exercise.[142]

Metabolic adaptations to skeletal muscle are driven by exercise-induced changes in gene expression, protein synthesis, protein activation/inhibition, and release of signaling molecules. Exercise and training lead to extensive remodeling of the skeletal muscle epigenome,[143,144] transcriptomes,[145,146] proteome[147,148,149] and various posttranslational modifications including the phosphoproteome and acetylome.[148,32] Critical mediators of these changes include AMPK, which is activated in skeletal muscle when ATP levels decrease, resulting in suppression of several anabolic pathways and stimulation of catabolic processes, for example, glycogenolysis. AMPK-regulated transcription factors include MEF2 (myocyte enhancer factor 2) and NRF1 (nuclear respiratory factor 1) that are important regulators of mitochondrial biogenesis. CaMKII promotes the activity of CREB, MEF2, and HDACs (histone deacetylases).[1] MAPKs (mitogen-activated protein kinases), mTOR, and PKA (protein kinase A) are other important mediators of the metabolic responses to exercise.[129] Several of these factors also increase the nuclear abundance of the cofactor PGC1α.[1,21] The molecular drivers of the metabolic effects of exercise have been reviewed in detail elsewhere.[129,1,150,127] Importantly, while these central regulators are critical for exercise adaptation in skeletal muscle, the phenotypic and molecular responses demonstrate significant variability, and there is a need for further investigation into how these intricate signaling mechanisms mediate long-term metabolic health benefits of exercise training in various populations.

SKELETAL MUSCLE FACTORS SECRETED DURING EXERCISE AND INTERORGAN CROSSTALK

Skeletal muscle releases a variety of signaling molecules, including myokines and metabolites, in response to exercise (Figure 1; Table). The term myokine was introduced in 2003[185], shortly after the cytokine, IL (interleukin)-6, was identified as a skeletal muscle product released in response to exercise.[186] Myokines are defined as cytokines and other peptides released by the muscle, which exert various effects on the skeletal muscle itself and enter the bloodstream to regulate the function and metabolism of other organs.[187,188, 29,111,30] These secreted factors are differentially regulated by level of activity and intensity, as well as disease state,[189,190,191] with both positive and negative effects on systemic metabolism and cardiovascular health.

Myostatin

The myokine myostatin is released from myocytes after acute bouts of exercise[192] and acts within the muscle tissue. Myostatin impairs satellite cell entry into the cell cycle and protein synthesis and alters myoblast cell cycle progression, resulting in reduced muscle size.[193,194] Consistent exercise reduces myostatin levels, and genetic deletion or pharmacological inhibition of myostatin enhances skeletal muscle hypertrophy in

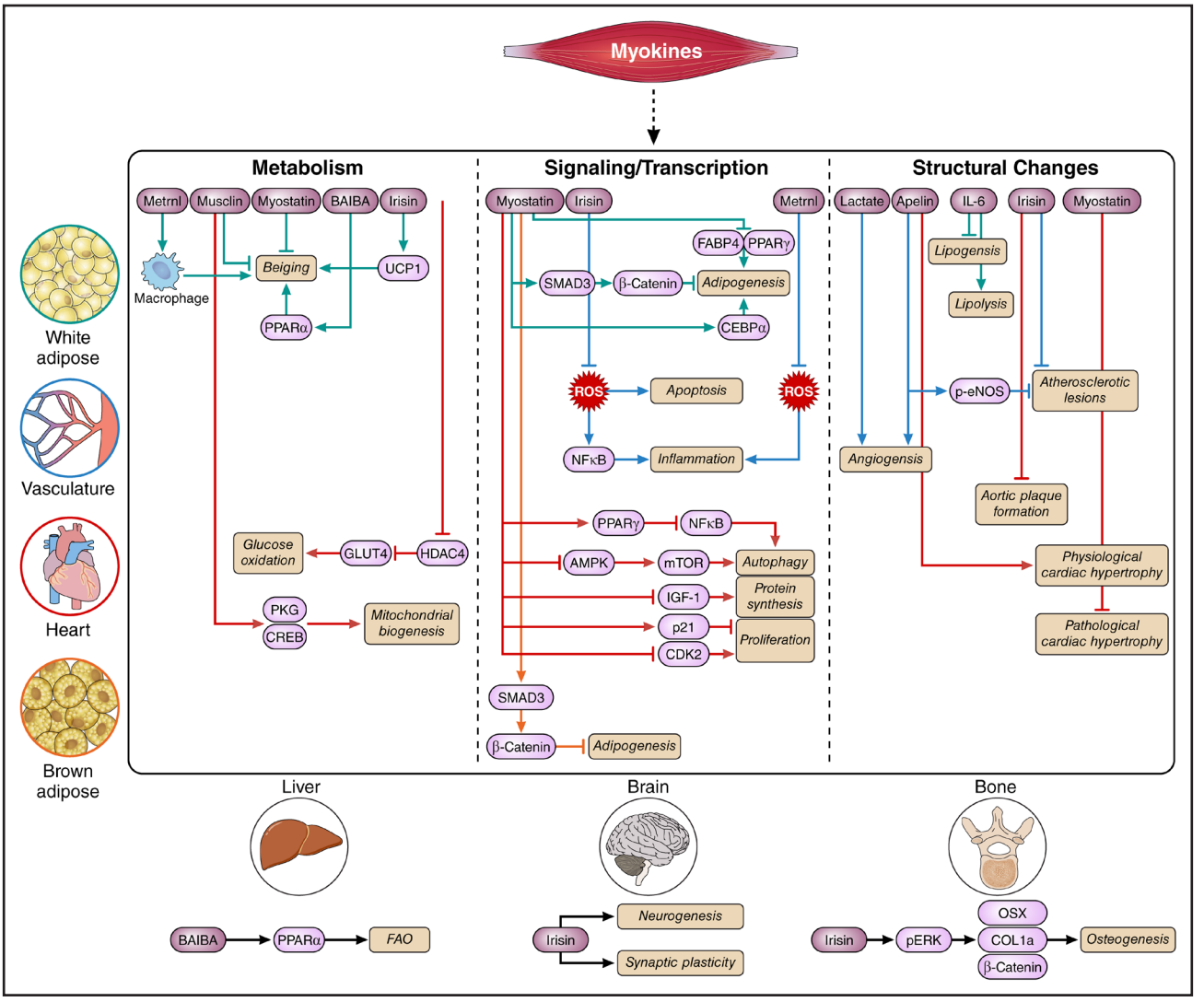

Figure 1. Skeletal muscle releases myokines, cytokines, and metabolites in response to exercise.
These molecules act on other organs and organ systems, such as the white adipose, vasculature, heart, brown adipose, liver, brain, and bone, to regulate changes in metabolism, signaling, transcription, and structure. Illustration credit: Sceyence Studios. AMPK indicates AMP-activated protein kinase; BAIBA, β-aminoisobutyric acid; CDK2, cyclin-dependent kinase 2; CEBPα, CCAAT/enhancer-binding protein-alpha; Col1a, collagen type I alpha 1 chain; CREB, cAMP response element-binding protein; eNOS, endothelial nitric oxide synthase; FABP4, fatty acid binding protein 4; FAO, fatty acid oxidation; GLUT4, glucose transporter type 4; HDAC4, histone deacetylase 4; IGF, insulin-like growth factor; IL, interleukin; mTOR, mammalian target of rapamycin; NFκB, nuclear factor kappa-B; OSX, osterix; pERK, phospho extracellular signal-regulated kinase; PKG, protein kinase g; PPARγ, peroxisome proliferator-activated receptor gamma; p21, wildtype activating factor-1/cyclin-dependent kinase inhibitory protein-1; ROS, reactive oxygen species; SMAD3, Mothers against decapentaplegic homolog 3; UCP1, uncoupling protein 1; and 1PPARa, peroxisome proliferator activated receptor alpha.

mice[195] and humans,[196] demonstrating that myostatin is a negative regulator of exercise-induced skeletal muscle hypertrophy.

Myostatin is part of the TGFβ (transforming growth factor beta) superfamily and binds to ActRIIB (activin type IIB receptor), ActRIIA (activin type IIA receptor), and TGFβ-receptor II, activating ALK (activity type I receptor; 4, 7, 5) to phosphorylate SMAD2/3. This promotes the formation of a complex with SMAD4, leading to nuclear translocation and gene expression regulation.[194] Inhibition of SMAD2/3 promotes muscle growth, targeting genes involved in protein turnover. Myostatin-SMAD2/3 signaling inhibits the anabolic insulin-AKT-mTOR pathway and activates FoxO (forkhead box O) transcription factors, increasing expression of muscle-specific E3 ligases MuRF1/Trim63 (muscle ring-finger protein-1) and FBXO32/Atrogin1/MAFBX (f-box protein 32) and inhibiting protein synthesis, leading to muscle atrophy.[197] The BMP (bone morphogenic protein) signaling pathway also converges on SMAD4 to control muscle mass, with BMP-growth differentiation factor members binding to ActRIIs (activin type II receptors) and activating SMAD1/5/8 in conjunction with SMAD4. Overexpression of the BMP antagonist noggin in myostatin knockout mice suggests genetic interaction between activin-myostatin and BMP pathways. Follistatin-mediated hypertrophy blocks myostatin signaling while stimulating

Table. Effects of myokines on target tissues.

	BAIBA	Irisin	Metrnl	Musclin	Myostatin	Lactate	Apelin	IL-6
White adipose	Promotes beiging			Inhibits beiging	Inhibits beiging and inhibits/promotes adipogenesis			Inhibits lipogenesis and promotes lipolysis
	Roberts et al, 2014[26]	Bostrom et al, 2012,[22] Dong et al, 2016,[23] Wu et al, 2012,[151] and Zhang et al, 2014[152]	Nguyen et al, 2011[153] and Rao et al, 2014[25]	Jin et al, 2023[154]	Artaza et al, 2005,[155] Arataza et al, 2005, Feldman et al, 2006,[156] Guo et al, 2008,[157] Jackson et al, 2012,[158] Kim et al, 2001,[159] Kim et al, 2012,[160] McPherron and Lee, 2002,[161] Rebbapragada et al, 2003,[162] and Shan et al, 2013[163]			Petersen et al, 2005,[164] and Wan et al, 2010[165]
Vasculature		Decreases apoptosis and inflammation, and inhibits atherosclerotic lesions	Decreases inflammation			Promotes angiogenesis	Promotes angiogenesis and inhibits atherosclerotic lesions	
		Lu et al, 2015,[166] Zhang et al, 2016,[167] and Zhang et al, 2016[168]	El-Ashmawy et al, 2019,[169] Javaid et al, 2021,[170] and Liu et al, 2019[171]			Hunt et al, 2008[135]	Helker et al, 2020,[172] and Ishida et al, 2004[173]	
Heart		Inhibits aortic plaque formation	Promotes glucose oxidation	Promotes mitochondrial biogenesis	Inhibits autophagy, protein synthesis, and proliferation, and inhibits pathological cardiac hypertrophy		Promotes physiological cardiac hypertrophy	
		Libby, 2002,[174] and Pober et al, 2009[175]	Wang et al, 2024[176]	Harris et al 2023[95]	Cao et al, 2011,[177] Kamanga-Sollo et al, 2005,[178] Kamanga-Sollo et al, 2003,[179] and Qi et al, 2020[180]		Kilpiö et al, 2024[181]	
Brown adipose					Inhibits adipogenesis			
					Shan et al, 2013[163]			
Liver	Promotes fatty acid oxidation							
	Roberts et al, 2014							
Brain		Promotes neurogenesis and synaptic plasticity						
		Choi et al, 2018,[182] and Lourenco et al, 2019[183]						
Bone		Promotes osteogenesis						
		Colaianni et al, 2017[184]						

BAIBA indicates β-aminoisobutyric acid; IL, interleukin; and Metrnl, meteorin-like protein.

SMAD1/5/8 activation.[198,199,200] Therefore, inhibiting myostatin/activins reduces phosphorylated SMAD2/3, allowing SMAD4 to interact with SMAD1/5/8 and promote muscle growth or counteract atrophy. The BMP pathway helps prevent excessive muscle atrophy by repressing the E3 ligase FBXO30.[200]

Given that myostatin is also expressed in the heart,[201] artificially elevated levels in vivo and in vitro provide insight into the role of myostatin on cardiac function. Like the observations in skeletal muscle, myostatin treatment attenuates cardiac pathological hypertrophy in rats and isolated cardiomyocytes[180] (Figure 1; Table). Myostatin alters the levels of proteins involved in autophagy, a process important for maintaining appropriate cardiac function, but, in excess, autophagy is linked to the development of cardiac hypertrophy.[177] Myostatin downregulates AMPK-mTOR signaling and increases PPARγ, which leads to the silencing of NFκB (nuclear factor kappa-B),[180] a key mediator of autophagy.[202] Myostatin, thus, plays a crucial role in regulating cardiac hypertrophy, exerting significant effects in both in vivo and ex vivo models. Knockout or silencing of myostatin increased cardiac hypertrophy in a rat model and rat cardiomyocytes. This increase in hypertrophy is associated with an increase in key markers, such as BNP (brain natriuretic peptide) and β-MHC (beta-myosin heavy chain), and autophagy markers, such as LC3-II (microtubule-associated protein 1 light chain 3-II) and BECN1 (beclin-1). Furthermore, myostatin blocks cardiomyocyte proliferation by increasing P21 expression, which inhibits cell cycle progression, and reducing CDK2 (cyclin-dependent kinase 2), a critical regulator of the cell cycle. Inhibition of CDK2 availability results in cell cycle arrest. Myostatin also inhibits the proliferation of porcine embryonic myogenic cells, in part through the production of IGFBP (IGF-binding protein)-3 and IGFBP-5, which sequester IGFI outside the cell and may impede the intracellular and nuclear actions required for growth.[203,202,178,179,204,180,205]

Myostatin also regulates adipose tissue function through different mechanisms in vivo and in vitro (Figure 1; Table). In vitro, myostatin inhibits adipogenesis in 3T3-L1 and human mesenchymal stem cells and primary brown adipocytes through the activation of SMAD3 and β-catenin[157,159,160,162] but promotes adipogenic commitment while impairing differentiation in C3H10T1/2 cells.[156] However, when applied after differentiation induction, myostatin enhances adipogenesis,[155] suggesting stage-specific effects. In vivo, myostatin knockout mice show reduced adiposity,[158,161] with decreased expression of adipogenesis markers, CEBPα (CCAAT/enhancer-binding protein-alpha), and PPARγ, indicating impaired adipogenesis. However, this is likely due to glucose diversion from adipose tissue rather than direct effects on adipocyte turnover.[206,207] In high-fat diet-fed mice, adipose-specific loss of myostatin signaling does not significantly affect lean or fat mass, glucose, insulin, or adipokine levels.[206] While myostatin knockout enhances the beiging of subcutaneous white adipose tissue,[163] recombinant myostatin has no direct impact on lipid release or adipose tissue mass, highlighting the context-dependent nature of myostatin's role in adipose regulation.

Irisin

Irisin is a myokine induced during exercise in mice and humans[22,208,209,210] that is secreted primarily from the skeletal muscle.[211] Irisin may regulate beneficial adaptations of exercise, such as improved energy expenditure,[212] glucose homeostasis,[22] and bone health.[213] Acute treatment of irisin on myocytes in vitro increased glucose uptake and glycolysis, and longer treatment induced mitochondrial biogenesis and increased oxygen consumption, suggesting that irisin promotes oxidative metabolism in myocytes.[214] Moreover, irisin-mediated changes in skeletal muscle metabolism may aid in maintaining skeletal muscle integrity in aging.[189] Increased muscle irisin secretion in mice improved glucose tolerance and lowered fasting insulin levels,[22] and levels are decreased in patients with type 2 diabetes. Circulating irisin levels are positively correlated with bone mechanical properties in humans[213] and induce the expression of genes associated with bone formation, such as *Osx*, *Col1a*, and *Ctnnb1*, preventing bone mineral density loss from disuse in mice.[184]

The relationship between irisin and cardiac health remains unclear, with conflicting data in the literature. Some studies report a positive association between serum irisin concentration and CVD, atherosclerosis, and stroke,[215,216,217] while others indicate negative associations and potential cardioprotective effects. For example, several studies have found lower irisin levels in patients with coronary artery disease (CAD).[218,219,220] In contrast, in mouse models of atherosclerosis, irisin treatment reduces the development of carotid and aortic plaques,[166,167,168] indicating a protective role (Figure 1; Table). Irisin also reduced disease severity in both genetic and surgical models of atherosclerosis.[167] In models of atherogenesis, oxidized LDL (low-density lipoprotein) promotes inflammation in endothelial cells, leading to apoptosis and plaque formation.[174,175] In vitro, irisin treatment attenuated oxidized LDL-induced inflammation and apoptosis in endothelial cells by decreasing reactive oxygen species and suppressing inflammation and apoptosis via eNOS (endothelial nitric oxide synthase) phosphorylation and decreased NFκB signaling (Figure 1; Table).[167] These conflicting findings highlight the need for further research to clarify the mechanistic relationship between irisin and CVD.

Irisin may promote the remodeling of adipose tissue by stimulating the browning of white adipocytes and thermogenesis (Figure 1; Table). Acting directly on adipocytes, irisin enhances their thermogenic capacity by activating p38 MAPK and ERK (extracellular signal-regulated kinase) signaling pathways.[152] This molecular signaling cascade facilitates the conversion of white adipocytes into beige, thermogenically active cells.[22,23,151,152] The effects of irisin, stimulating thermogenesis and adipocyte browning, position it as a key factor in modulating

adipose tissue function and combating metabolic disorders.

Exercise has a profound impact on brain health, improving cognitive function and plasticity, particularly in older adults.[221,222] Regular physical activity enhances outcomes in neurodegenerative diseases and stroke.[223,224,225,226] Exercise also promotes neurogenesis in the adult brain, enhancing synaptic plasticity and spatial learning.[227,228] Irisin has been linked to improved cognitive function in various populations. Higher irisin levels correlate with better cognitive performance in older adults at risk for dementia[229] and young athletes.[230] However, elevated irisin levels in obese women have been associated with poorer executive function,[231] suggesting a complex relationship between irisin, cognition, and metabolic health.

Irisin has neuroprotective effects in conditions such as Alzheimer disease, Parkinson disease, stroke, and diabetes. In Alzheimer disease, irisin supports hippocampal neurogenesis and gene regulation,[182] improving memory and synaptic plasticity in mouse models (Figure 1; Table).[183] FNDC5 (fibronectin type III domain-containing protein 5), the precursor to irisin, also enhances memory and synaptic function in Alzheimer disease. In female Alzheimer disease mice, irisin reduced tau protein levels and inflammation although it worsened inflammation in males.[232] In addition, irisin reduces amyloid-beta-induced inflammation in astrocytes and promotes hippocampal cell proliferation.[233]

In Parkinson disease, irisin preserves dopaminergic neurons, improves motor function, and aids stem cell migration and differentiation in rat models.[234] Following ischemic stroke, where irisin levels decline, increasing irisin reduces brain infarct size, inflammation, neurological deficits, and brain edema in mouse models.[235] In vitro irisin reduced oxidative stress and inflammation in neurons under ischemic conditions.[236] In diabetic mouse models, irisin improved cognitive function, preserved synaptic proteins, reduced inflammation, and attenuated NFκB activation in the brain, suggesting its potential to counteract diabetes-associated neurodegeneration.[237] Collectively, these studies highlight the broad interorgan signaling effects of a myokine and demonstrate the therapeutic potential of irisin for various neurological and metabolic disorders.

Meteorin-Like 1

The myokine Metrnl (meteorin-like protein) was identified in primary myotubes overexpressing the PGC1α splice isoform, PGC1α4, which regulates muscle growth and energy expenditure.[103] Metrnl is induced in the skeletal muscle after exercise or cold exposure,[25] suppressing inflammation by inhibiting inflammasome activation.[170] Exogenous Metrnl administration in mice fed a high-fat diet protects from lipid-induced insulin resistance in skeletal muscle and C2C12 cells.[238] Moreover, higher levels of Metrnl in circulation increase energy expenditure and improve glucose homeostasis in mouse models of obesity and diabetes.

Exercise is associated with decreased mortality, increased quality of life, and higher rehabilitation success in patients with CVD.[239,240,241] In a mouse model of HF, Metrnl administration improved cardiac structure and function, whereas Metrnl knockdown eliminated these benefits.[176] Metrnl activates AMPK, which suppresses histone deacetylases such as HDAC4,[242,243] leading to increased GLUT4 expression.[244,245,246] Impaired energy metabolism is a hallmark of HF, and Metrnl-induced GLUT4 expression promotes glucose metabolism, improving mitochondrial function in the hearts of a mouse model of HF (Figure 1; Table).[176] These findings suggest that exercise improves cardiovascular health in HF by altering cellular metabolism via Metrnl.

Exercise also reduces reactive oxygen species and inflammation though the mechanisms remain unclear.[247] Elevated Metrnl levels are associated with a lower risk of CAD and are negatively correlated with LDL and inflammatory cytokines, key mediators of CAD.[169,248] In both a patient study and a mouse model of CAD, exercise increased Metrnl levels, which were associated with reduced LDL and inflammatory cytokines.[170] In addition, exercise-induced Metrnl elevation suppressed oxidative stress and inhibited the NLRP3 (nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 3) inflammasome in obese mice. These findings suggest that exercise-induced Metrnl may improve CAD risk by regulating lipid metabolism and reducing inflammation (Figure 1; Table).

Metrnl plays a critical role in regulating adipose tissue function and systemic energy balance. Increased circulating Metrnl enhanced whole-body energy expenditure, promoted the browning of white adipose tissue, and improved glucose tolerance in obese and diabetic mice.[25] Metrnl does not act directly on adipocytes; instead, it exerts its prothermogenic effects through immune cell modulation. Metrnl recruits eosinophils to adipose, which release IL-4 and IL-13, driving the alternative activation of adipose tissue macrophages. These alternatively activated macrophages are key mediators of cold-induced thermogenesis (Figure 1; Table)[153] and exert anti-inflammatory effects, reducing adipose inflammation and contributing to metabolic health. Through immune regulation, Metrnl establishes a unique mechanism of thermogenic activation and inflammation modulation in adipose tissue.

Mitochondrial Open Reading Frame of the 12S rRNA Type-c

MOTS-c (mitochondrial open reading frame of the 12S rRNA type-c) is a mitochondria-derived peptide that is increased with exercise in humans, expressed in the skeletal muscle,[249] and regulates metabolism.[250,251] MOTS-c targets the folate cycle and increases levels of 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside,

leading to the activation of AMPK.[251] Expression of MOTS-c is age-dependent, circulating levels are negatively correlated with HbA1c levels in patients with type 2 diabetes,[252] and expression of MOTS-c is lower in both skeletal muscle and serum of patients with chronic kidney disease.[248] Genetic variation in MOTS-c has been associated with human longevity,[253] and when given to mice, it reverses age-dependent insulin resistance, suggesting that it may have therapeutic potential in metabolic and aging-associated diseases.[251]

β-Aminosobutyric Acid

β-Aminoisobutyric acid (BAIBA) is a small molecule of myokine that has been shown to promote adipose tissue beiging and fatty acid metabolism in the liver through regulation of PPARα (peroxisome proliferator-activated receptor alpha) (Figure 1; Table).[26] BAIBA has also been implicated in bone health through the prevention of osteocyte apoptosis.[254] BAIBA was identified as a potential myokine through liquid chromatography-mass spectrometry metabolic profiling of human myocytes overexpressing PGC1α. When BAIBA was added to the drinking water of mice, it significantly boosted the expression of beiging-related genes, such as *Ucp1* and *Cidea*, in subcutaneous white adipose tissue.[3] Similarly, when primary stromal-vascular fraction cells isolated from white adipose tissue were incubated with BAIBA, *Ucp1* and *Cidea* expression was increased. Human pluripotent stem cells exposed to BAIBA during differentiation into mature white adipocytes also showed elevated expression of beiging markers. Exercise significantly elevated BAIBA levels in both mice and humans. In mice, 3 weeks of voluntary wheel-cage running led to a notable increase in circulating BAIBA, while, in humans, 20 weeks of supervised submaximal aerobic exercise training[255] in 80 subjects resulted in a significant rise in circulating BAIBA.[256] These findings suggest that exercise significantly boosts circulating BAIBA in both mice and humans, and in rodents and isolated human cells, BAIBA may play a role in promoting the beiging of subcutaneous white adipose tissue. However, the direct involvement of BAIBA in exercise-induced beiging in human subcutaneous white adipose tissue remains to be fully established.

Musclin

Musclin, encoded by the *Ostn* gene, is secreted by skeletal muscle in response to exercise. During exercise, its production is stimulated by calcium-induced activation of AKT1, which removes transcriptional inhibition of the *Ostn* by FOXO1.[257] Musclin has been shown to inhibit proliferation of fibro-adipogenic progenitor cells in skeletal muscle through upregulation of filamin A interacting protein 1 like, which promotes fibro-adipogenic progenitor apoptosis, thereby reducing fibrosis and abnormal fatty infiltration.[258] In mice, when *Ostn* is disrupted and musclin secretion is eliminated, exercise tolerance is diminished; administration of recombinant musclin rescues this phenotype. The reduction in exercise capacity is associated with lower plasma levels of atrial natriuretic peptide and diminished levels of cyclic guanosine monophosphate and PGC1α in skeletal muscles of knockout animals following exercise.[257] Secreted musclin similarly promotes mitochondrial biogenesis in cardiac muscle (Figure 1; Table).[95] However, running capacity remains the same in mice with muscle-specific knockdown of musclin.[154] Paradoxically, obesity is associated with higher circulating levels of musclin. Overexpression of musclin reduces thermogenesis in beige fat (Figure 1; Table), while inactivation has the opposite effect and improves glucose tolerance and insulin sensitivity.[154] Importantly, transient activation of musclin shows many cross-tissue metabolic benefits, while continuous activation appears detrimental to metabolic health.

In cardiac muscle, musclin plays a critical role in promoting mitochondrial biogenesis in response to exercise (Figure 1; Table). Disrupting musclin signaling in mice eliminates exercise's ability to protect against cardiac ischemic injury. The proposed mechanism involves a musclin-induced increase in cyclic guanosine monophosphate signaling, leading to increased protein kinase G and CREB activity that together stimulate the expression of PGC1α. Musclin also elevates cardiac C-type natriuretic peptide levels, which improves cardiomyocyte contractile function.[259] Targeted infusion of musclin reproduced the cardioprotective benefits of exercise in both sedentary wild-type and Ostn-knockout mice.[95] Similarly, skeletal muscle–specific knockout mice were more sensitive to pressure overload, and *Ostn* expression is lower in the skeletal muscle of patients with HF.[259]

Apelin

Apelin is an exercise-induced myokine[260] that is also released from adipose tissue in response to insulin signaling.[261] Apelin affects several organs, including the heart, brown adipose tissue, brainstem, and kidneys.[261,262,263,264,265] It functions by binding to its G-protein coupled receptor, which triggers intracellular signaling that activates AMPK, promoting mitochondrial biogenesis and improving glucose uptake in skeletal muscle.[266]

In obese, insulin-resistant mice, apelin treatment improves insulin sensitivity.[261] In addition, apelin stimulates angiogenesis by activating endothelial cells and promoting glycolytic activity, such as through the activation of c-MYC,[172] and it helps lower arterial blood pressure, potentially via phosphorylation of eNOS (Figure 1; Table).[173] In apelin knockout mice, high-intensity interval training failed to induce insulin-like growth factor 1 and resulted in smaller type I muscle fibers compared with wild-type mice.[181]

In the heart, apelin induces physiological cardiac hypertrophy, enhances mitochondrial gene expression,

and increases ATP production (Figure 1; Table).[181] It also has cardioprotective effects, especially in mice prone to atrial fibrillation.[263] For instance, apelin knockout mice developed eccentric rather than concentric left ventricular hypertrophy in response to high-intensity interval training,[181] highlighting the role of exercise-induced apelin expression in promoting normal cardiac remodeling. Apelin has also been linked to the transgenerational effects of exercise on metabolic health.[265]

Brain Natriuretic Peptide

BNP is primarily secreted by the heart in response to increased cardiac wall stress but is also produced by skeletal muscles. Supraphysiological BNP levels in mice protect against high-fat diet-induced obesity and insulin resistance and stimulate mitochondrial biogenesis in skeletal muscle through upregulation of PGC1α and PPARδ.[267] BNP also has immunomodulatory functions though the exercise-induced benefits from this modulation are unknown.[268]

IL-6

IL-6, an inflammatory cytokine, is released from myocytes during exercise,[24] increasing in concentration with the length of the physical activity.[269] IL-6 is produced during the contraction of skeletal muscle in a TNFα (tumor necrosis factor alpha)–independent manner, uncoupling IL-6 production from the traditional inflammatory cascade.[270] IL-6 secretion has been reported ex vivo in cultured human myotubes[271] and activates AMPK, enhancing energy consumption.[24] IL-6 regulates skeletal muscle fatty acid metabolism and glucose uptake[272,273] and promotes whole-body fatty acid oxidation.[274] IL-6 release is enhanced when glycogen levels are low, suggesting that IL-6 acts as an energy sensor in skeletal muscle rather than a mediator of inflammation.[275,190,276,277]

IL-6 signaling is associated with adipocyte inflammation in obesity,[278,274] but its effects on adipose tissue can vary in different contexts. In obesity, IL-6 plays a role in metabolic programming, particularly in skeletal muscle, and may have similar effects in white adipose tissue. Global IL-6 knockout mice show higher body weight due to increased subcutaneous white adipose mass,[279,280] suggesting IL-6 regulates adipose tissue maintenance and metabolism. IL-6 enhances lipolysis in 3T3-L1 cells[164] and activates AMPK (Figure 1; Table).[281] In IL-6 knockout mice, exercise increases PPARγ expression in subcutaneous white adipose,[279] indicating that IL-6 may influence transcription factors involved in adipogenesis and adipocyte maintenance. However, IL-6 knockout does not alter AMPK activity in subcutaneous white adipose tissue[279] though it impairs exercise-induced AMPK activation in adipocytes,[281] suggesting that IL-6 is required for this process. IL-6 also promotes *Ucp1* expression and thermogenesis in subcutaneous white adipose tissue, contributing to the beiging effect of exercise.[279] In addition, IL-6 dampens the exercise-induced induction of gluconeogenic enzymes such as pyruvate dehydrogenase kinase 4 in white adipose,[165] indicating that IL-6 impairs lipogenesis during exercise.

The role of IL-6 in glucose metabolism is less clear. Some studies show that IL-6 treatment enhances glucose uptake in adipocytes,[272,282] while others find no effect.[283,284] In humans, IL-6 infusion increases glucose uptake in subcutaneous white adipose tissue[285] but does not promote lipolysis or activate IL-6 signaling in adipose tissue from healthy individuals.[273] These findings underscore the complex, context-dependent role of IL-6 in regulating adipose tissue, balancing lipid metabolism, glucose handling, and adipogenesis in response to exercise.

IL-8

Expression of the chemokine IL-8 is increased in skeletal muscle in response to endurance and resistance exercise in humans[286,287] and is predominantly detected after extended physical exertion such as marathon running.[288] Transcription is associated with a reduction in glycogen levels[289] and results in antiapoptotic and proangiogenic signaling through CXCR2 receptor interactions. In endothelial cells, for example, IL-8 increases protein levels of the antiapoptotic factor B-cell lymphoma 2 and matrix metalloproteinases 2 and 9.[290] While IL-8 is induced to a similar extent in young and old individuals, training attenuates the acute IL-8 response in older individuals,[287] potentially reducing the acute, proinflammatory effects of exercise.

Lactate

Lactate is a product of glycolysis under aerobic conditions.[136] Muscle glucose uptake is increased with exercise,[291] increasing lactate production and secretion.[136] Elevated generation of lactate in muscles during exertion regenerates NAD levels, increasing the glycolytic capacity of the cell. Lactate can also modulate skeletal muscle mitochondrial expansion and metabolism. Lactate stimulates mitochondrial biogenesis upstream of PGC1α.[292] Moreover, glycolysis and the production of lactate modulate muscle fatty acid oxidation and uptake. Glycolysis increases the production of the metabolite malonyl-CoA, which inhibits CPT1, and lactate downregulates the expression of CPT2,[136] both of which are important enzymes in fatty acid oxidation.

Outside of the skeletal muscle itself, skeletal muscle lactate production also regulates cardiovascular and pulmonary function during exercise (Figure 1; Table). Lactate promotes angiogenesis through stimulation of VEGF,[135] provides metabolic substrate for cardiac function,[136] and upregulates breathing.[137] Secreted lactate

can also be converted into N-lactoyl-phenylalanine by various immune and endothelial cells, and it increases substantially in blood in response to one bout of exercise. Treatment with N-lactoyl-phenylalanine has been demonstrated to improve glucose metabolism and decrease adiposity in mice.[293]

Skeletal muscle–derived lactate plays a multifaceted role in regulating adipose tissue (Figure 1; Table). High-intensity physical activity results in lactatemia and a corresponding drastic decrease in plasma-free fatty acid concentrations. This is due to the activation of the HCAR1 (hydroxycarboxylic acid receptor 1) on adipocytes by lactate, inhibiting lipolysis in both rodents and humans.[136] Beyond its antilipolytic effects, lactate promotes thermogenic adaptations in adipose tissue. Lactate induces the browning of white adipose, contributing to increased thermogenic capacity. This effect is mediated by proton-linked MCTs (monocarboxylate transporters) present in adipocytes, which facilitate lactate transport into cells.[294] Lactate increases the expression of thermogenic genes, including *Ucp1*, through pathways dependent on PPARγ signaling and intracellular redox modifications.[295] In brown adipose tissue, *Mct1* expression is significantly elevated after exercise, aligning with physiological stimuli of browning and enhancing lactate import for metabolic adaptation.[296] Together, these processes highlight lactate's dual role as both a regulator of lipid mobilization and a potent inducer of thermogenic programming in adipose tissue.

AGING AND LONGEVITY

Increased life expectancy has resulted in older adults becoming the fastest-growing subpopulation in the United States. Aging is the leading driver of disease and mortality,[297] and caring for the aging population presents a significant burden on the health care system.[298] Thus, therapeutic strategies prioritizing the prevention of age-associated decreases in mobility and metabolic decline are of utmost importance. Aging is associated with changes to many metabolic tissues, including the atrophy of skeletal muscle,[299] increase in visceral white adipose tissue depots,[300,301,302] and a decrease in the function of brown adipose tissue (Figure 2; Table).[303] Changes in these depots are both consequences of and drivers for age-associated metabolic dysfunction, emphasizing the importance of how aging disrupts appropriate function in multiple tissues.

Aging is a process of decline in biological function that is mostly irreversible. The causes of decline are multifactorial and driven by the accumulation of stress and damage over an organism's lifetime. Aging increases the risk of many diseases,[304] driven by decreased physical

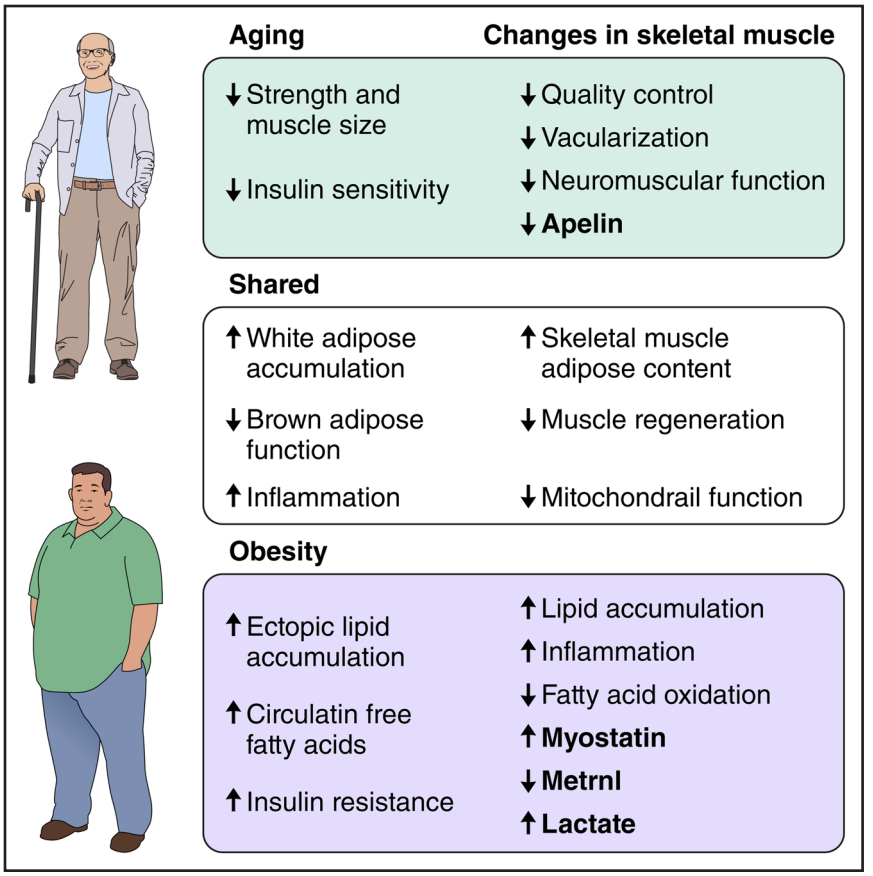

Figure 2. Aging and obesity both induce changes in white adipose accumulation, brown adipose function, and inflammation that can impair metabolism and promote disease pathogenesis.
Obesity promotes changes in muscle lipid metabolism, inflammation, and myokine secretion, and both states increase skeletal muscle adipose content, impair muscle regeneration, and decrease mitochondrial function. Despite the similarities, less is known about how aging alters myokine release and whether the effects differ between sexes. Illustration credit: Sceyence Studios.

activity,[111] increased inflammation,[305,111] muscle atrophy, and increased central adiposity. Increased adiposity caused by energy imbalances, driving metabolic inflexibility and implicating mitochondrial dysfunction in age-associated disease progression.[306,307] Significantly, caloric restriction is one of the only interventions to extend lifespan, implicating systemic energy balance and metabolism in longevity.[308,309]

EXERCISE AND AGING

There is an age-dependent decline in maximal heart rate, reducing the ability to increase cardiac output in response to exercise. The increase in stroke volume is also shifted from enhanced contractility to increased end-diastolic volumes in older individuals. This is due to diminished sensitivity to β-adrenergic signaling, impaired calcium handling and mitochondrial dysfunction, all of which can be improved with exercise training.[310] Exercise, thus, demonstrates promise for prevention and treatment of age-associated decline in cardiac function although further research is needed to establish optimal dose and intensity.

Advanced age is associated with structural alterations that impair muscle function (Figure 2; Table). These include increases in muscle adipose content and decreases in neuromuscular function and vascularization.[311,12,312,313] Aging skeletal muscle also demonstrates a decline in satellite cell number and function[314,315,316] that contributes to delayed[317] or impaired skeletal muscle regeneration after an injury.[318]

The dysfunction of proteostasis and organelle quality control systems plays a major role in bioenergetic defects, fatigue, and reduced force transmission in skeletal muscle as with age. A sedentary lifestyle and reduced physical activity contribute to and accelerate the onset and progression of sarcopenia. This leads to a decrease in mechanotransduction signaling, which affects protein turnover, calcium homeostasis, and mitochondrial function. The impact of reduced physical activity on sarcopenia becomes especially prominent during periods of immobilization, hospitalization, or bed rest in older individuals.[319]

Interestingly, inactivity suppresses mitochondrial fusion protein expression before any changes in mitochondrial mass.[320] However, higher expression of these proteins correlates with muscle force and bioenergetics in the elderly.[321,322] Inhibition of the mitochondrial fusion protein OPA1 (optic atrophy 1) in adult mice leads to premature aging features, including increased oxidative stress, systemic inflammation, sarcopenia, and senescence markers, ultimately causing death.[323,322] Similarly, deletion of the fusion protein MFN (mitofusin)-2 in muscle causes sarcopenia,[324] and double deletion of MFN1 and MFN2 results in severe muscle loss and mitochondrial DNA depletion.[325] On the other hand, deleting the fission protein, dynamin-related protein 1, causes myopathy, with myofiber degeneration due to imbalanced calcium homeostasis and mitochondrial-endoplasmic reticulum tethering.[326]

Gain-of-function experiments further demonstrate the effects of mitochondrial shaping proteins on muscle mass. Overexpression of OPA1 counters muscle loss,[327] while upregulation of fission machinery promotes muscle wasting.[328,329] Mitochondrial dynamics, when altered, profoundly affect mitochondrial function and the onset of sarcopenia, with physical activity playing a key role. Mitochondrial dynamics are interconnected with mitophagy, mitochondrial proteostasis, and the broader mitochondrial quality control system, which adapts mitochondrial bioenergetics to muscle needs.

Inhibition of autophagy, through ATG7 (autophagy-related 7) deletion or TSC2 (tuberous sclerosis complex 2) overexpression in muscle, mimics the pathological features of age-related sarcopenia, such as increased oxidative stress, dysfunctional mitochondria accumulation, myofiber denervation, atrophy, weakness, and premature death.[330,331] Reactivating autophagy in aged mice, either by expressing ATG7 in skeletal muscle or treating with urolithin A (a compound that promotes mitophagy), helps restore muscle mass.[330,332] Overexpression of sestrins, stress-responsive proteins that decline with age, also promotes autophagy and reduces muscle wasting and weakness in older mice.[333] Importantly, failure of autophagy is linked to mitochondrial dysfunction, oxidation of contractile proteins, and impaired force generation.[330] Similarly, urolithin A has been shown to improve muscle strength and performance in middle-aged individuals by restoring genes and proteins involved in mitochondrial metabolism, mass, and PTEN (phosphatase and TENsin homolog)-induced putative kinase 1/Parkin-mediated mitophagy.[334] Importantly, urolithin A demonstrates similar effects in cardiac muscle, and supplementation in humans reduces ceramide levels in plasma, which is predictive of CVD risk.[335]

Mitochondrial dysfunction and impaired mitophagy contribute to sarcopenia through several mechanisms (Figure 2; Table), including reduced mitochondrial ADP sensitivity,[336] increased mitochondrial reactive oxygen species production and DNA damage,[337] activation of an inflammatory response,[323,322] decreased cytosolic calcium due to sequestration,[326] and metabolic crisis.[338] While autophagy is clearly important in sarcopenia, the role of the ubiquitin-proteasome system in this process remains less well understood.

Epigenetic clocks have emerged as a tool to investigate tissue aging and the impact of different antiaging therapies.[339] Endurance exercise training alters the human skeletal muscle genome,[143] and a skeletal muscle–specific epigenetic clock[340] has been used to demonstrate that exercise training can counteract age-related epigenetic changes in skeletal muscle. A comprehensive

meta-analysis of over 3000 human skeletal muscle samples demonstrated that higher aerobic fitness correlated with younger epigenetic and transcriptomic profiles, and exercise training can shift these patterns toward a younger state. Conversely, muscle disuse accelerated molecular aging.[144]

AGING AND SARCOPENIA

Muscle function and metabolism are closely linked to health span and longevity.[12,35] Muscle mass typically begins to decline in the third or fourth decade of life, with the rate accelerating over time, leading to significant loss in later years.[341,342] This decline is driven by changes in muscle structure, function, and regeneration, with strength loss often outpacing size reduction, indicating a decline in muscle quality (Figure 2; Table).[343,342,312,344] When muscle aging results in excessive force loss, fatigue, and exercise intolerance, it is considered sarcopenia, a disease that predicts frailty, poor quality of life, and increased morbidity and mortality.[345,346]

Sarcopenia affects 15% of individuals at the age of 65 years and up to 50% by the age of 80 years.[347,319] While the mechanisms behind sarcopenia are not fully understood, genetic factors and lifestyle-related epigenetic changes play a significant role. Parabiosis experiments in mice suggest that serum factors from young blood can influence muscle cell senescence, indicating that hormonal, metabolic, and gene expression changes affect key determinants of muscle function, including calcium ions, ATP production, and contractile protein quality and assembly.[348]

In addition to reduced strength and mobility, sarcopenia also disrupts whole-body metabolism, contributing to impaired glycemic regulation and insulin resistance, which are common with age.[349,350,351]

AGING ALTERS MYOKINES

Exercise continues to be an effective intervention for counteracting the effects of aging, delaying the development of disability and dependence in older adults.[352,2,353] The beneficial effects of exercise are, in part, mediated by secreted factors, including myokines. There are well-established, sex-based differences in many parameters in response to exercise[354,355,356,357,358,359,360] including in myokine release.[361,362,363,364,365] However, how aging alters myokine release, and the significance of age-associated disease, remains unclear (Figure 2; Table).[366,367] In young subjects, increased myostatin levels are associated with decreased muscle mass. However, in elderly men, low serum levels of myostatin are associated with lowered skeletal muscle mass but not in older women.[367] In response to endurance training, older individuals demonstrate a greater skeletal muscle induction of interferon-induced inflammatory genes,[145] while single-cell transcriptional profiling showed exercise reversed aging-induced inflammatory changes in many skeletal muscle cell types.[368] In addition, little work has been done, which examines changes in the myokine profile in postmenopausal women. On average, women live longer than men but experience higher rates of disability and have an increased risk of age-related comorbidities that cannot be attributed solely to life span.[369,370]

OBESITY

Obesity is a disease characterized by increased pathological adiposity and ectopic lipid accumulation and is considered an accelerated state of aging.[371,372] There is increasing evidence suggesting that the increase in and the redistribution of adiposity is the driver of insulin resistance with age, rather than age itself.[11,373,374] Accumulation of visceral white adipose tissue is associated with the development of insulin resistance and cardiometabolic disease,[375] while subcutaneous adiposity is thought to be more metabolically protective.[376] Increased visceral white adipose tissue promotes dyslipidemia and inflammation in the liver, skeletal, and cardiac muscle.[377,378] Moreover, white adipose tissue accumulation leads to a decrease in brown adipose tissue, which also occurs with increasing age (Figure 2; Table).[379,380]

Visceral adiposity also has detrimental effects on the heart, primarily through higher circulating blood volume and increased levels of proinflammatory factors, resulting in elevated stroke volume, cardiac wall stress and injury, and left ventricular hypertrophy.[381] Obesity is, therefore, a major risk factor for developing HF, with each 1-unit increase in body mass index raising the risk of HF by 5% in men and 7% in women,[382] and obesity accounts for ≈20% of atrial fibrillation cases. Accumulation of epicardial fact is of particular importance in the pathogenicity of arrhythmias. Similar body mass indexes may have different CVD risk profiles depending on fat distribution and fitness levels, demonstrating the complex relationship across cardiac, skeletal, and adipose tissues.

OBESITY AND SKELETAL MUSCLE FUNCTION

Unsurprisingly, energy imbalance worsens skeletal muscle dysfunction in aging. Increased adiposity in older subjects worsened skeletal muscle function independent of age-related decreases in muscle mass, referred to as sarcopenic obesity.[341] Aging and obesity are characterized by chronic inflammation[383,384,385]; therefore elderly individuals with obesity have worsened age-related decreases in muscle strength and mass.[350] These findings are replicated in mouse models, in which both ob/ob and db/db mice have significantly less muscle mass

relative to body mass compared with controls.[386,387,388] Both in vitro and in vivo lipolysis rates are higher in the visceral white adipose leading to increased circulating lipid levels,[389] and these differences are more pronounced in centralized obesity.[390] Increased circulating free fatty acids and adipose-mediated inflammation suppress skeletal muscle fatty acid oxidation and hinder insulin signaling, further impairing systemic glucose homeostasis (Figure 2; Table).[391,392,393]

OBESITY ALTERS RELEASE OF MYOKINES

Obesity significantly disrupts the production and regulation of myokines, which contributes to metabolic dysfunction. Physical inactivity, a major contributor to obesity, leads to the dysregulation of myokine production, impacting various tissues and metabolic pathways (Figure 2; Table). The changes in myokine levels associated with obesity are complex and often contradictory. For instance, circulating irisin levels are typically lower in individuals with obesity and those with type 2 diabetes,[394,395] but, paradoxically, some studies report elevated irisin under these conditions.[396,215] Exogenous irisin treatment in obese mice has improved glucose tolerance and mitochondrial gene expression,[22] suggesting that elevated irisin levels may, in some cases, reflect compensatory mechanisms or irisin resistance.

Similarly, myostatin, a negative regulator of muscle growth, is elevated in skeletal muscle and serum in obesity, contributing to metabolic dysfunction.[397,398] On the other hand, decreased levels of Metrnl, a myokine linked to cardiac health, are associated with impaired cardiac GLUT4 expression and maladaptive cardiac function in hypertrophic and failing hearts[246,399,400]

In addition, BAIBA, a myokine involved in metabolism, enhances fatty acid oxidation and reduces fat synthesis, showing potential for improving obesity outcomes in mouse models.[401] These findings highlight the complex and context-dependent roles of myokines in regulating metabolism, illustrating their significant impact on the pathophysiology of obesity and related metabolic disorders.

BARRIERS TO EXERCISE ADHERENCE

Exercise is a cornerstone of health promotion and disease prevention, but, despite its well-documented benefits, adherence to regular physical activity remains a persistent challenge. Barriers to exercise are multifaceted, ranging from personal and psychological to social and systemic influences, highlighting the intricate relationship between these obstacles and overall health.

Exercise is a widely recommended therapeutic intervention to improve health at all stages of life.[402] Despite extensive efforts to promote this message,[403,404] sedentary lifestyles remain a concern[405,406,407] and contribute to poor health outcomes.[14,408] Poor adherence to an exercise regimen is often due to a variety of barriers, encompassing personal, social, and systemic factors. Common obstacles include lack of perceived time, especially among patients with aging-related conditions,[409,410,411] and limited social support, such as disinterest from friends and family.[409,412] Motivation, energy, and access to resources are often hindered by financial or logistical challenges.[406] Feelings of discomfort, embarrassment, or intimidation in gym settings, particularly among individuals with obesity, further impede participation.[410,413,414] Health issues including chronic diseases, pain, and fatigue, as well as treatments for cancer or autoimmune disease, also reduce adherence.[415,416,417,418] Mental health challenges, including depression, are linked to higher dropout rates, especially in older adults.[419,420,421,422] Socioeconomic constraints, such as inflexible work schedules and cultural norms, also impact exercise adherence.[420,421 423, 424] Collectively, these barriers underscore the complex interplay of factors influencing exercise behaviors. Therefore, addressing factors that contribute to poor exercise adherence is also an essential part of promoting overall global health.

Emerging therapeutic aids may provide additional support for individuals facing exercise adherence challenges. GLP1 (glucagon-like peptide-1) is an exerkine secreted from the gut.[425] In humans, higher cardiorespiratory fitness is associated with lower fasting levels of GLP1 but a higher induction in response to glucose intake.[426] Prescription of GLP1RA (GLP1 receptor agonist) has increased dramatically in recent years due to their effective induction of weight loss. One of the side effects of GLP1RAs is loss of skeletal muscle mass,[427] and exercise could, therefore, be an effective co-adjuvant therapy for obesity by counteracting muscle loss and further stimulating metabolic health.

SUMMARY AND FUTURE PERSPECTIVES

The significant evidence for the health benefits of exercise highlights its critical role in preventing and managing chronic conditions, enhancing cardiovascular and metabolic health, and improving overall quality of life, particularly as populations age. With a deeper understanding of the intricate mechanisms governing skeletal muscle adaptations and the role of exercise-induced signaling molecules, we have an opportunity to develop targeted therapeutic strategies that harness these insights to combat CVD and obesity and promote healthy aging. Future research will be essential in translating these findings into precision exercise interventions that further improve health outcomes across diverse populations.

ARTICLE INFORMATION

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REFERENCES

1. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab*. 2013;17:162–184. doi: 10.1016/j.cmet.2012.12.012
2. Haskell WL, Lee I-M, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007;39:1423–1434. doi: 10.1249/mss.0b013e3180616b27
3. Stanford KI, Goodyear LJ. Muscle-adipose tissue crosstalk. *Cold Spring Harb Perspect Med*. 2018;8:a029801. doi: 10.1101/cshperspect.a029801
4. Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil*. 2008;15:239–246. doi: 10.1097/HJR.0b013e3282f55e09
5. Li Y, Pan A, Wang DD, Liu X, Dhana K, Franco OH, Kaptoge S, Di Angelantonio E, Stampfer M, Willett WC, et al. Impact of healthy lifestyle factors on life expectancies in the US Population. *Circulation*. 2018;138:345–355. doi: 10.1161/CIRCULATIONAHA.117.032047
6. Bamman MM, Hill VJ, Adams GR, Haddad F, Wetzstein CJ, Gower BA, Ahmed A, Hunter GR. Gender differences in resistance-training-induced myofiber hypertrophy among older adults. *J Gerontol A Biol Sci Med Sci*. 2003;58:108–116. doi: 10.1093/gerona/58.2.b108
7. Harridge SD, Kryger A, Stensgaard A. Knee extensor strength, activation, and size in very elderly people following strength training. *Muscle Nerve*. 1999;22:831–839. doi: 10.1002/(sici)1097-4598(199907)22:7<831::aid-mus4>3.0.co;2-3
8. Da Boit M, Sibson R, Meakin JR, Aspden RM, Thies F, Mangoni AA, Gray SR. Sex differences in the response to resistance exercise training in older people. *Physiol Rep*. 2016;4:e12834. doi: 10.14814/phy2.12834
9. Lin J, Wu H, Tarr PT, Zhang C-Y, Wu Z, Boss O, Michael LF, Puigserver P, Isotani E, Olson EN, et al. Transcriptional coactivator PGC-1 alpha drives formation of slow-twitch muscle fibres. *Nature*. 2002;418:797–801. doi: 10.1038/nature00904
10. Coffey VG, Hawley JA. The molecular bases of training adaptation. *Sports Med*. 2007;37:737–763. doi: 10.2165/00007256-200737090-00001
11. Amati F, Dube JJ, Coen PM, Stefanovic-Racic M, Toledo FGS, Goodpaster BH. Physical inactivity and obesity underlie the insulin resistance of aging. *Diabetes Care*. 2009;32:1547–1549. doi: 10.2337/dc09-0267
12. Goodpaster BH, Chomentowski P, Ward BK, Rossi A, Glynn NW, Delmonico MJ, Kritchevsky SB, Pahor M, Newman AB. Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. *J Appl Physiol (1985)*. 2008;105:1498–1503. doi: 10.1152/japplphysiol.90425.2008
13. Safdar A, Hamadeh MJ, Tarnopolsky MA. Aberrant mitochondrial homeostasis in the skeletal muscle of sedentary older adults. *PLoS One*. 2010;5:e10778. doi: 10.1371/journal.pone.0010778
14. Booth FW, Laye MJ, Roberts MD. Lifetime sedentary living accelerates some aspects of secondary aging. *J Appl Physiol (1985)*. 2011;111:1497–1504. doi: 10.1152/japplphysiol.00420.2011
15. Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative biology of exercise. *Cell*. 2014;159:738–749. doi: 10.1016/j.cell.2014.10.029
16. Howlett KF, Andrikopoulos S, Proietto J, Hargreaves M. Exercise-induced muscle glucose uptake in mice with graded, muscle-specific GLUT-4 deletion. *Physiol Rep*. 2013;1:e00065. doi: 10.1002/phy2.65
17. Hussey SE, McGee SL, Garnham A, McConell GK, Hargreaves M. Exercise increases skeletal muscle GLUT4 gene expression in patients with type 2 diabetes. *Diabetes Obes Metab*. 2012;14:768–771. doi: 10.1111/j.1463-1326.2012.01585.x
18. Look Ahead Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2014;2:801–809. doi: 10.1016/S2213-8587(14)70156-1
19. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiol Rev*. 2013;93:993–1017. doi: 10.1152/physrev.00038.2012
20. Higashida K, Hyun Kim S, Higuchi M. Normal adaptations to exercise despite protection against oxidative stress. *Am J Physiol Endocrinol Metab*. 2011;301:E779–E784. doi: 10.1152/ajpendo.00655.2010
21. Little JP, Gillen JB, Percival ME, Safdar A, Tarnopolsky MA, Punthakee Z, Jung ME, Gibala MJ. Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *J Appl Physiol (1985)*. 2011;111:1554–1560. doi: 10.1152/japplphysiol.00921.2011
22. Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye Li, Lo JC, Rasbach KA, Boström EA, Choi JH, Long JZ, et al. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481:463–468. doi: 10.1038/nature10777
23. Dong J, Dong Y, Dong Y, Chen F, Mitch WE, Zhang L. Inhibition of myostatin in mice improves insulin sensitivity via irisin-mediated cross talk between muscle and adipose tissues. *Int J Obes (Lond)*. 2016;40:434–442. doi: 10.1038/ijo.2015.200
24. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol Rev*. 2008;88:1379–1406. doi: 10.1152/physrev.90100.2007
25. Rao R, Long JZ, White JP. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. *Cell*. 2014;157:1279–1291. doi: 10.1016/j.cell.2014.03.065
26. Roberts LD, Bostrom P, O'Sullivan JF, Schinzel RT, Lewis GD, Dejam A, Lee Y-K, Palma MJ, Calhoun S, Georgiadi A, et al. B-aminoisobutyric acid induces browning of white fat and hepatic B-oxidation and is inversely correlated with cardiometabolic risk factors. *Cell Metab*. 2014a;19:96–108. doi: 10.1016/j.cmet.2013.12.003
27. Seldin MM, Peterson JM, Byerly MS, Wei Z, Wong GW. Myonectin (CTRP15), a novel myokine that links skeletal muscle to systemic lipid homeostasis. *J Biol Chem*. 2012;287:11968–11980. doi: 10.1074/jbc.m111.336834
28. Guidice J, Taylor JM. Muscle as a paracrine and endocrine organ. *Curr Opin Pharmacol*. 2017;34:49–55. doi: 10.1016/j.coph.2017.05.005
29. Han Lee J, Jun, H-S. Role of myokines in regulating skeletal muscle mass and function. *Front Physiol*. 2019;10:42. doi: 10.3389/fphys.2019.00042
30. Severinsen MCK, Pedersen BK. Muscle-organ crosstalk: the emerging roles of myokines. *Endocr Rev*. 2020;41:594–609. doi: 10.1210/endrev/bnaa016
31. Chow LS, Gerszten RE, Taylor JM, Pedersen BK, van Praag H, Trappe S, Febbraio MA, Galis ZS, Gao Y, Haus JM, et al. Exerkines in health, resilience and disease. *Nat Rev Endocrinol*. 2022;18:273–289. doi: 10.1038/s41574-022-00641-2
32. MoTrPAC Study Group. Temporal dynamics of the multi-omic response to endurance exercise training. *Nature*. 2024;629:174–183. doi: 10.1038/s41586-023-06877-w
33. Amar D, Gay NR, Jimenez-Morales D, Beltran PMJ, Ramaker ME, Raja AN, Zhao B, Sun Y, Marwaha S, Gaul DA, et al; MoTrPAC Study Group. The mitochondrial multi-omic response to exercise training across rat tissues. *Cell Metab*. 2024;36:1411–1429. doi: 10.1016/j.cmet.2023.12.021
34. Jones MD, Clifford BK, Stamatakis E, Gibbs MT. Exercise snacks and other forms of intermittent physical activity for improving health in adults and older adults: a scoping review of epidemiological, experimental and qualitative studies. *Sports Med*. 2024;54:813–835. doi: 10.1007/s40279-023-01983-1
35. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The physical activity guidelines for Americans. *JAMA*. 2018;320:2020–2028. doi: 10.1001/jama.2018.14854
36. Vollaard NB, Metcalfe RS. Research into the health benefits of sprint interval training should focus on protocols with fewer and shorter sprints. *Sports Med*. 2017;47:2443–2451. doi: 10.1007/s40279-017-0727-x
37. Aerobic Exercise. *American Academy of Orthopaedic Surgeons*. 2019. Accessed October 1, 2024. https://orthoinfo.aaos.org/en/staying-healthy/aerobic-exercise/

38. Phillips SM, Winett RA. Uncomplicated resistance training and health-related outcomes: evidence for a public health mandate. *Curr Sports Med Rep*. 2010;9:208–213. doi: 10.1249/JSR.0b013e3181e7da73
39. Coates AM, Joyner MJ, Little JP, Jones AM, Gibala MJ. A perspective on high-intensity interval training for performance and health. *Sports Med*. 2023;53:85–96. doi: 10.1007/s40279-023-01938-6
40. Islam H, Gibala MJ, LIttle JP. Exercise snacks: a novel strategy to improve cardiometabolic health. *Exerc Sport Sci Rev*. 2022;50:31–37. doi: 10.1249/JES.0000000000000275
41. Thyfault JP, Bergouignan A. Exercise and metabolic health: beyond skeletal muscle. *Diabetologia*. 2020;63:1464–1474. doi: 10.1007/s00125-020-05177-6
42. Bienso RS, Olesen J, Gliemann L, Schmidt JF, Matzen MS, Wojtaszewski JFP, Hellsten Y, Pilegaard H. Effects of exercise training on regulation of skeletal muscle glucose metabolism in elderly men. *J Gerontol A Biol Sci Med Sci*. 2015;70:866–872. doi: 10.1093/gerona/glv012
43. Dube JJ, Amati F, Stefanovic-Racic M, Toledo FGS, Sauers SE, Goodpaster BH. Exercise-induced alterations in intramyocellular lipids and insulin resistance: the athlete's paradox revisited. *Am J Physiol Endocrinol Metab*. 2008;294:E882–E888. doi: 10.1152/ajpendo.00769.2007
44. Lanza IR, Short DK, Short KR, Raghavakaimal S, Basu R, Joyner MJ, McConnell JP, Nair KS. Endurance exercise as a countermeasure for aging. *Diabetes*. 2008;57:2933–2942. doi: 10.2337/db08-0349
45. Korpelainen R, Lämsä J, Kaikkonen KM, Korpelainen J, Laukkanen J, Palatsi I, Takala TE, Ikäheimo TM, Hautala AJ. Exercise capacity and mortality-a follow up study of 3033 subjects referred to clinical exercise testing. *Ann Med*. 2016;48:359–366. doi: 10.1080/07853890.2016.1178856
46. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793–801. doi: 10.1056/NEJMoa011858
47. Amati F, Pennant M, Azuma K, Dubé JJ, Toledo FGS, Rossi AP, Kelley DE, Goodpaster BH. Lower thigh subcutaenous and high visceral abdominal adipose tissue content both contribute to insulin resistance. *Obesity*. 2012;20:1115–1117. doi: 10.1038/oby.2011.401
48. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. 2011;11:607–615. doi: 10.1038/nri3041
49. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Barone Gibbs B, Beaton AZ, Boehme AK, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. 2024 Heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. 2024;149:e347–e913. doi: 10.1161/CIR.0000000000001209
50. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Woo YJW. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933–944. doi: 10.1161/CIR.0b013e31820a55f5
51. Kivimaki M, Kuosma E, Ferrie JE, Luukkonen R, Nyberg ST, Alfredsson L, Batty GD, Brunner EJ, Fransson E, Goldberg M, et al. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120,813 adults from 16 cohort studies from the USA and Europe. *Lancet Public Health*. 2017;2:e277–e285. doi: 10.1016/S2468-2667(17)30074-9
52. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol Rev*. 2008;88:389–419. doi: 10.1152/physrev.00017.2007
53. Briones AM, Nguyen Dinh Cat A, Callera GE, Yogi A, Burger D, He Y, Corrêa JW, Gagnon AM, Gomez-Sanchez CE, Gomez-Sanchez EP, et al. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction. *Hypertension*. 2012;59:1069–1078. doi: 10.1161/HYPERTENSIONAHA.111.190223
54. DeMarco VG, Aroor AR, Sowers JR. The pathophysiology of hypertension in patients with obesity. *Med Clin North Am*. 2017;101:129–137. doi: 10.1038/nrendo.2014.44.
55. Harte A, McTernan P, Chetty R, Coppack S, Katz J, Smith S, Kumar S. Insulin-mediated upregulation of the renin angiotensin system in human subcutaneous adipocytes is reduced by rosiglitazone. *Circulation*. 2005;111:1954–1961. doi: 10.1161/01.CIR.0000161954.17870.5D
56. Lopaschuk GD, Folmes CD, Stanley WC. Cardiac energy metabolism in obesity. *Circ Res*. 2007;101:335–347. doi: 10.1161/CIRCRESAHA.107.150417
57. Aurigemma GP, de Simone G, Fitzgibbons TP. Cardiac remodeling in obesity. *Circ Cardiovasc Imaging*. 2013;6:142–152. doi: 10.1161/CIRCIMAGING.111.964627
58. Halade GV, Kain V. Obesity and cardiometabolic defects in heart failure pathology. *Compr Physiol* 2017;7:1463–1477. doi: 10.1002/cphy.c170011
59. Fukushima A, Lopaschuk GD. Cardiac fatty acid oxidation in heart failure associated with obesity and diabetes. *Biochim Biophys Acta*. 2016;1861:1525–1534. doi: 10.1016/j.bbalip.2016.03.020
60. Harmancey R, Wilson CR, Taegtmeyer H. Adaptation and maladaptation of the heart in obesity. *Hypertension*. 2008;52:181–187. doi: 10.1161/HYPERTENSIONAHA.108.110031
61. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol*. 2009;6:399–409. doi: 10.1038/nrcardio.2009.55
62. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, et al; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551–2567. doi: 10.1093/eurheartj/ehs184
63. Ashor AW, Lara J, Siervo M, Celis-Morales C, Oggioni C, Jakovljevic DG, Mathers JC. Exercise modalities and endothelial function: a systematic review and dose-response meta-analysis of randomized controlled trials. *Sports Med*. 2015;45:279–296. doi: 10.1007/s40279-014-0272-9
64. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Schoene N, Schuler G. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med*. 2000;342:454–460. doi: 10.1056/NEJM200002173420702
65. Laughlin MH, Bowles DK, Duncker DJ. The coronary circulation in exercise training. *Am J Physiol Heart Circ Physiol*. 2012;302:H10–H23. doi: 10.1152/ajpheart.00574.2011
66. Platt C, Houstis N, Rosenzweig A. Using exercise to measure and modify cardiac function. *Cell Metab*. 2015;21:227–236. doi: 10.1016/j.cmet.2015.01.014
67. Carnelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension*. 2005;46:667–675. doi: 10.1161/01.HYP.0000184225.05629.51
68. Church TS, Blair SN, Cocreham S, Johannsen N, Johnson W, Kramer K, Mikus CR, Myers V, Nauta M, Rodarte RQ, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2010;304:2253–2262. doi: 10.1001/jama.2010.1710
69. Kodama S, Tanaka S, Saito K, Shu M, Sone Y, Onitake F, Suzuki E, Shimano H, Yamamoto S, Kondo K, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol. *Arch Intern Med*. 2007;167:999–1008. doi: 10.1001/archinte.167.10.999
70. Sigal RJ, Kenny GP, Boule NG, Wells GA, Prud'homme D, Fortier M, Reid RD, Tulloch H, Coyle D, Phillips P, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes—a randomized trial. *Ann Intern Med*. 2007;147:357–369. doi: 10.7326/0003-4819-147-6-200709180-00005
71. Swift DL, Johannsen NM, Lavie CJ, Earnest CP, Church TS. The role of exercise and physical activity in weight loss and maintenance. *Prog Cardiovasc Dis*. 2014;56:441–447. doi: 10.1016/j.pcad.2013.09.012
72. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2016;1:CD001800.
73. Vega RB, Konhilas JP, Kelly DP, Leinwand LA. Molecular mechanisms underlying cardiac adaptation to exercise. *Cell Metab*. 2017;25:1012–1026. doi: 10.1016/j.cmet.2017.04.025
74. Alvarez P, Hannawi B, Guha A. Exercise and heart failure: advancing knowledge and improving care. *Methodist Debakey Cardiovasc J*. 2016;12:110–115. doi: 10.14797/mdcj-12-2-110
75. Gudmundsdottir HL, Raja AA, Rossing K, Rasmusen H, Snoer M, Andersen LJ, Gottlieb R, Christensen AH, Bundgaard H, Gustafsson F, et al. Exercise training in patients with hypertrophic cardiomyopathy without left ventricular outflow tract obstruction: a randomized clinical trial. *Circulation*. 2025;151:132–144. doi: 10.1161/CIRCULATIONAHA.124.070064
76. Haykowsky MJ, Daniel KM, Bhella PS, Sarma S, Kitzman DW. Heart failure: exercise-based cardiac rehabilitation: who, when, and how intense? *Can J Cardiol*. 2016;32(10 Suppl. 2):S382–S387. doi: 10.1016/j.cjca.2016.06.001
77. Kamiya K, Tanaka S, Saito H, Yamashita M, Yonezawa R, Hamazaki N, Matsuzawa R, Nozaki K, Endo Y, Kazuki W, et al. Effects of acute phase intensive exercise training in patients with acute decompensated heart failure. *JACC Heart Failure*. 2025;2213–1779:00869–2. doi: 10.1016/j.jchf.2024.11.006.
78. Tang WHW, Liu Y, Butler J, Del Prato S, Ezekowitz JA, Ibrahim NE, Lam CSP, Marwick TH, Perfetti R, Rosenstock J, et al. Impaired exercise capacity in high-risk diabetic cardiomyopathy: the ARISE-HF cardiopulmonary exercise testing subanalysis. *Circ Heart Failure*. 2025;18:e012200. doi: 10.1161/CIRCHEARTFAILURE.124.012200

79. Upadhya B, Haykowsky MJ, Eggebeen J, Kitzman DW. Exercise intolerance in heart failure with preserved ejection fraction: more than a heart problem. *J Geriatr Cardiol*. 2015;12:294–304. doi: 10.11909/j.issn.1671-5411.2015.03.013
80. Hambrecht R, Adams V, Erbs S, Linke A, Kränkel N, Shu Y, Baither Y, Gielen S, Thiele H, Gummert JF, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation*. 2003;107:3152–3158. doi: 10.1161/01.CIR.0000074229.93804.5C
81. Leung FP, Yung LM, Laher I, Yao X, Chen ZY, Huang Y. Exercise, vascular wall and cardiovascular diseases an update (part 1). *Sports Med*. 2008;38:1009–1024. doi: 10.2165/00007256-200838120-00005
82. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu W-C, Liu S, Song Y. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4:e002014. doi: 10.1161/JAHA.115.002014
83. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. *Front Cardiovasc Med*. 2018;5:135. doi: 10.3389/fcvm.2018.00135
84. Hoier B, Hellsten Y. Exercise-induced capillary growth in human skeletal muscle and the dynamics of VEGF. *Microcirculation*. 2014;21:301–314. doi: 10.1111/micc.12117
85. Olver TD, Ferguson BS, Laughlin MH. Chapter ten- molecular mechanisms for exercise training-induced changes in vascular structure and function: skeletal muscle, cardiac muscle, and the brain. *Prog Mol Biol Transl Sci*. 2015;135:227–257. doi: 10.1016/bs.pmbts.2015.07.017
86. Tao L, Bei Y, Zhang H, Xiao J, Li X. Exercise for the heart: signaling pathways. *Oncotarget*. 2015;6:20773–20784. doi: 10.18632/oncotarget.4770
87. Joki Y, Ohashi K, Yuasa D, Shibata R, Kataoka Y, Kambara T, Uemura Y, Matsuo K, Hiramatsu-Ito M, Kanemura N, et al. Neuron-derived neurotrophic factor ameliorates adverse cardiac remodeling after experimental myocardial infarction. *Circ Heart Fail*. 2015;8:342–351. doi: 10.1161/CIRCHEARTFAILURE.114.001647
88. Ogura Y, Ouchi N, Ohashi K, Shbata R. Therapeutic impact of follistatin-like 1 on myocardial ischemic injury in preclinical models. *Circulation*. 2012;126:1728–1738. doi: 10.1161/CIRCULATIONAHA.112.115089
89. 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
90. Pedersen BK, Fischer CP. Beneficial health effects of exercise- the role of IL-6 as a myokine. *Trends Pharmacol Sci*. 2007;28:152–156. doi: 10.1016/j.tips.2007.02.002
91. Calabria E, Cicilliot S, Moretti I. NFAT isoforms control activity-dependent muscle fiber type specification. *Proc Natl Acad Sci USA*. 2009;106:13335–13340. doi: 10.1073/pnas.0812911106
92. McCullagh KJA, Calabria E, Pallafacchina G. NFAT is a nerve activity sensor in skeletal muscle and controls activity-dependent myosin switching. *Proc Natl Acad Sci USA*. 2004;101:10590–10595. doi: 10.1073/pnas.0308035101
93. Erlich AT, Brownlee DM, Beyfuss K, Hood DA. Exercise induces TFEB expression and activity in skeletal muscle in a PGC-1a dependent manner. *Am J Physiol Cell Physiol*. 2018;314:C62–C72. doi: 10.1152/ajpcell.00162.2017
94. Mansueto G, Armani A, Viscomi C, D'Orsi L, De Cegli R, Polishchuk EV, Lamperti C, Di Meo I, Romanello V, Marchet S, et al. Transcription factor EB controls metabolic flexibility during exercise. *Cell Metab*. 2017;25:182–196. doi: 10.1016/j.cmet.2016.11.003
95. Harris MP, Zeng S, Zhu Z, Zingman LV. Myokine musclin is critical for exercise-induced cardiac conditioning. *Int J Mol Sci* . 2023;24:6525. doi: 10.3390/ijms24076525
96. Sandri M, Lin J, Handschin C, Yang W, Arany ZP, Lecker SH, Goldberg AL, Spiegelman BM. PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. *Proc Natl Acad Sci USA*. 2006;103:16260–16265. doi: 10.1073/pnas.0607795103
97. Kupr B, Handschin C. Complex coordination of cell plasticity by a PGC-1a-controlled transcriptional network in skeletal muscle. *Front Physiol*. 2015;6:325. doi: 10.3389/fphys.2015.00325
98. Arany Z, Foo S-Y, Ma Y, Ruas JL, Bommi-Reddy A, Spiegelman BM. HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1alpha. *Nature*. 2008;451:1008–1012. doi: 10.1038/nature06613
99. Franco-Romero A, Sandri M, Schiaffino S. Autophagy in skeletal muscle. *Cold Spring Harbor Perspect Biol*. 2024;a041565. doi: 10.1101/cshperspect.a041565
100. Grumati P, Coletto L, Schiavinato A, Castagnaro S, Bertaggia E, Sandri M, Bonaldo P. Physical exercise stimulates autophagy in normal skeletal muscles but is detrimental for collagen VI-deficient muscles. *Autophagy*. 2011;7:1415–1423. doi: 10.4161/auto.7.12.17877
101. Lo Verso F, Carnio S, Vainshtein A, Sandri M. Autophagy is not required to sustain exercise and PRKAA1/AMPK activity but is important to prevent mitochondrial damage during physical activity. *Autophagy*. 2014;10:1883–1894. doi: 10.4161/auto.32154
102. Lira VA, Okutsu M, Zhang M, Greene NP, Laker RC, Breen DS, Hoehn KL, Yan Z. Autophagy is required for exercise training-induced skeletal muscle adaptation and improvement of physical performance. *FASEB J*. 2013;27:4184–4193. doi: 10.1096/fj.13-228486
103. Ruas JL, White JP, Rao RR, Kleiner S, Brannan KT, Harrison BC, Greene NP, Wu J, Estall JL, Irving BA, et al. PGC-1alpha isoform induced by resistance training regulates skeletal muscle hypertrophy. *Cell*. 2012;151:1319–1331. doi: 10.1016/j.cell.2012.10.050
104. Bodine SC, Stitt TN, Gonzalez M, Kine WO, Stover GL, Bauerlein R, Zlotchenko E, Scrimgeour A, Lawrence JC, Glass DJ, et al. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. *Nat Cell Biol*. 2001;3:1014–1019. doi: 10.1038/ncb1101-1014
105. Musarò A, McCullagh K, Paul A, Houghton L, Dobrowolny G, Molinaro M, Barton ER, Sweeney HL, Rosenthal N. Localized Igf-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. *Nat Genet*. 2001;27:195–200. doi: 10.1038/84839
106. Pallafacchina G, Calabria E, Serrano AL, Kalhovde JM, Schiaffino SA. A protein kinase B-dependent and rapamycin-sensitive pathway controls skeletal muscle growth but not fiber type specification. *Proc Natl Acad Sci USA*. 2002;99:9213–9218. doi: 10.1073/pnas.142166599
107. Sandri M, Sandri C, Gilbert A, Skurk C, Calabria E, Picard A, Walsh K, Schiaffino S, Lecker SH, Goldberg AL. Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell*. 2004;117:399–412. doi: 10.1016/s0092-8674(04)00400-3
108. Bülow J, Simonsen L. Determination of local energy expenditure and local metabolism: methodological considerations. *Int J Obes Relat Metab Disord*. 1993;17:S14–7; discussion S22.
109. Hood DA, Memme JM, Oliveira AN, Triolo M. Maintenance of skeletal muscle mitochondria in health, exercise, and aging. *Annu Rev Physiol*. 2019;81:19–41. doi: 10.1146/annurev-physiol-020518-114310
110. Hoppeler H, Baum O, Lurman G, Mueller M. Molecular mechanisms of muscle plasticity with exercise. *Compr Physiol*. 2011;1:1383–1412. doi: 10.1002/cphy.c100042
111. Pedersen BK. Exercise-induced myokines and their role in chronic diseases. *Brain Behav Immun*. 2011;25:811–816. doi: 10.1016/j.bbi.2011.02.010
112. Phillips SM, Green HJ, Tarnopolsky MA, Heigenhauser GF, Hill RE, Grant SM. Effects of training duration on substrate turnover and oxidation during exercise. *J Appl Physiol (1985)*. 1996;81:2182–2191. doi: 10.1152/jappl.1996.81.5.2182
113. Rose AJ, Hargreaves M. Exercise increases Ca2+-calmodulin-dependent protein kinase II activity in human skeletal muscle. *J Physiol*. 2009;553:303–309. doi: 10.1113/jphysiol.2003.054171
114. Watt MJ, Howlett KF, Febbraio MA, Spriet LL, Hargreaves M. Adrenaline increases skeletal muscle glycogenolysis, pyruvate dehydrogenase activation and carbohydrate oxidation during moderate exercise in humans. *J Physiol*. 2001;534:269–278. doi: 10.1111/j.1469-7793.2001.t01-1-00269.x
115. Dagenais GR, Tancredi RG, Zierler KL. Free fatty acid oxidation by forearm muscle at rest, and evidence for an intramuscular lipid pool in the human forearm. *J Clin Invest*. 1976;58:421–431. doi: 10.1172/JCI108486
116. Daskalopoulou SS, Cooke AB, Gomez YH, Mutter AF, Filippaios A, Mesfum ET, Mantzoros CS. Plasma irisin levels progressively increase in response to increasing exercise workloads in young, heathy, active subjects. *Eur J Endocrinol*. 2014;171:343–352. doi: 10.1530/EJE-14-0204
117. Ahlborg G, Felig P, Hagenfeldt L, Hendler R, Wahren J. Substrate turnover during prolonged exercise in man. Splanchnic and leg metabolism of glucose, free fatty acids, and amino acids. *J Clin Invest*. 1974;53:1080–1090. doi: 10.1172/JCI107645
118. Horowitz JF, Klein S. Oxidation of nonplasma fatty acids during exercise is increased in women with abdominal obesity. *J Appl Physiol*. 2000;89:2276–2282. doi: 10.1152/jappl.2000.89.6.2276
119. van Loon LJ, Thomason-Hughes M, Constantin-Teodosiu D, Koopman R, Greenhaff PL, Hardie DG, Keizer HA, Saris WHM, Wagenmakers AJM. Inhibition of adipose tissue lipolysis increases intramuscular lipid and glycogen use in vivo in humans. *Am J Physiol Endocrinol Metab*. 2005;289:E482–E493. doi: 10.1152/ajpendo.00092.2005

120. Watt MJ, Heigenhauser GJ, Stellingwerff T, Hargreaves M, Spriet LL. Carbohydrate ingestion reduces skeletal muscle acetylcarnitine availability but has no effect on substrate phosphorylation at the onset of exercise in man. *J Physiol*. 2002;544:949–956. doi: 10.1113/jphysiol.2002.026757
121. Glatz JF, Luiken JJ, Bonen A. Membrane fatty acid transporters as regulators of lipid metabolism: implications for metabolic disease. *Physiol Rev*. 2010;90:367–417. doi: 10.1152/physrev.00003.2009
122. Ibrahimi A, Bonen A, Blinn WD, Hajri T, Li X, Zhong K, Cameron R, Abumrad NA. Muscle-specific overexpression of FAT/CD36 enhances fatty acid oxidation by contracting muscle, reduces plasma triglycerides and fatty acids, and increases plasma glucose and insulin. *J Biol Chem*. 1999;274:26761–26766. doi: 10.1074/jbc.274.38.26761
123. Jain SS, Chabowski A, Snook LA, Schwenk RW, Glatz JFC, Luiken JJFP, Bonen A. Additive effects of insulin and muscle contraction on fatty acid transport and fatty acid transporters, FAT/CD36, FABPpm, FATP1, 4 and 6. *FEBS Lett*. 2009;583:2294–2300. doi: 10.1016/j.febslet.2009.06.020
124. Nickerson JG, Alkhateeb H, Benton CR, Lally J, Nickerson J, Han X-X, Wilson MH, Jain SS, Snook LA, Glatz JFC, et al. Greater transport efficiencies of the membrane fatty acid transporters FAT/CD36 and FATP4 compared with FABPpm and FATP1 and differential effects on fatty acid esterification and oxidation in rat skeletal muscle. *J Biol Chem*. 2009;284:16522–16530. doi: 10.1074/jbc.M109.004788
125. Bonen A, Chabowski A, Luiken JJ, Glatz JF. Is membrane transport of FFA mediated by lipid, protein, or both? Mechanisms and regulation of protein-mediated cellular fatty acid uptake: molecular, biochemical, and physiological evidence. *Physiology (Bethesda)*. 2007;22:15–29. doi: 10.1152/physiologyonline.2007.22.1.15
126. Dzamko N, Schertzer JD, Ryall JG, Steel R, Macaulay SL, Wee S, Chen Z-P, Michell BJ, Oakhill JS, Watt MJ, et al. AMPK-independent pathways regulate skeletal muscle fatty acid oxidation. *J Physiol*. 2008;586:5819–5831. doi: 10.1113/jphysiol.2008.159814
127. Smith JAB, Murach KA, Dyar KA, Zierath JR. Exercise metabolism and adaptation in skeletal muscle. *Nat Rev Mol Cell Biol*. 2023;24:607–632. doi: 10.1038/s41580-023-00606-x
128. Li LO, Grevengoed TJ, Paul DS, Ilkayeva O, Koves TR, Pascual F, Newgard CB, Muoio DM, Coleman RA. Compartmentalized acyl-CoA metabolism in skeletal muscle regulates systemic glucose homeostasis. *Diabetes*. 2015;64:23–35. doi: 10.2337/db13-1070
129. Ashcroft SP, Stocks B, Egan B, Zierath JR. Exercise induces tissue-specific adaptations to enhance cardiometabolic health. *Cell Metab*. 2024;36:278–300. doi: 10.1016/j.cmet.2023.12.008
130. Medbo JI, Tabata I. Anaerobic energy release in working muscle during 30 s to 3 min of exhausting bicycling. *J Appl Physiol (1985)*. 1993;75:1654–1660. doi: 10.1152/jappl.1993.75.4.1654
131. Parolin ML, Chesley A, Matsos MP, Spriet LL, Jones NL, Heigenhauser GJ. Regulation of skeletal muscle glycogen phosphorylase and PDH during maximal intermittent exercise. *Am J Physiol*. 1999;277:E890–E900. doi: 10.1152/ajpendo.1999.277.5.E890
132. Brooks GA. The lactate shuttle during exercise and recovery. *Med Sci Sports Exerc*. 1986;18:360–368. doi: 10.1249/00005768-198606000-00019
133. Medbo JJ, Jebens E, Noddeland H. Lactate elimination and glycogen resynthesis after intense bicycling. *Scand J Clin Lab Invest*. 2006;66:211–226. doi: 10.1080/00365510600570599
134. Miller BF, Fattor JA, Jacobs KA, Horning MA, Navazio F, Lindinger MI, Brooks GA. Lactate and glucose interactions during rest and exercise in men: effect of exogenous lactate infusion. *J Physiol*. 2002;544:963–975. doi: 10.1113/jphysiol.2002.027128
135. Hunt TK, Aslam R, Hussain Z, Beckert S. Lactate, with oxygen, incites angiogenesis. *Adv Exp Med Biol*. 2008;614:73–80. doi: 10.1007/978-0-387-74911-2_9
136. Brooks GA. The science and translation of lactate shuttle theory. *Cell Metab*. 2018;27:757–785. doi: 10.1016/j.cmet.2018.03.008
137. Chang AJ, Ortega FE, Riegler J, Madison DV, Krasnow MA. Oxygen regulation of breathing through an olfactory receptor activated by lactate. *Nature*. 2015;527:240–244. doi: 10.1038/nature15721
138. Hawley JA, Leckey JJ. Carbohydrate dependent during prolonged, intense endurance exercise. *Sports Med*. 2015;45:5–12. doi: 10.1007/s40279-015-0400-1
139. O'Brien MJ, Viguie CA, Mazzeo RS, Brooks GA. Carbohydrate dependence during marathon running. *Med Sci Sports Exerc*. 1993;25:1009–1017.
140. Romijn JA. Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. *Am J Physiol*. 1993;265:E380–E391. doi: 10.1152/ajpendo.1993.265.3.E380
141. van Loon LJ, Greenhaff PL, Cnstantin-Teodosiu D. The effects of increasing exercise intensity on muscle fuel utilization in humans. *J Physiol*. 2001;536:295–304. doi: 10.1111/j.1469-7793.2001.00295.x
142. Sales KM, Reimer RA. Unlocking a novel determinant of athletic performance: the role of the gut microbiota, short-chain fatty acids, and "biotics" in exercise. *J Sport Health Sci*. 2023;12:36–44. doi: 10.1016/j.jshs.2022.09.002
143. Lindholm ME, Marabita F, Gomez-Cabrero D, Rundqvist H, Sundberg CJ. An integrative analysis reveals coordinated reprogramming of the epigenome and the transcriptome in human skeletal muscle after training. *Epigenetics*. 2014;9:1557–1569. doi: 10.4161/15592294.2014.982445
144. Voisin S, Seale K, Jacques M, Eynon N. Exercise is associated with younger methylome and transcriptome profiles in human skeletal muscle. *Aging Cell*. 2024;23:e13859. doi: 10.1111/acel.13859
145. Amar D, Lindholm ME, Norrbom J, Ashley EA. Time trajectories in the transcriptomic response to exercise—a meta-analysis. *Nat Commun*. 2021;12:3471. doi: 10.1038/s41467-021-23579-x
146. Lindholm ME, Giacomello S, Solnestam BW, Sundberg CJ. The impact of endurance training on human skeletal muscle memory, global isoform expression and novel transcripts. *PLoS Genet*. 2016;12:e1006294. doi: 10.1371/journal.pgen.1006294
147. Deshmukh AS, Steenberg DE, Hostrup M, Birk JB, Larsen JK, Santos A, Kjøbsted R, Hingst JR, Schéele CC, Murgia M, et al. Deep muscle-proteomic analysis of freeze-dried human muscle biopsies reveals fiber-type-specific adaptations to exercise training. *Nat Commun*. 2021;12:304. doi: 10.1038/s41467-020-20556-8
148. Hostrup M, Lemming AK, Stocks B, Deshmukh AS. High-intensity interval training remodels the proteome and acetylome of human skeletal muscle. *eLife*. 2022;11:e69802. doi: 10.7554/eLife.69802
149. Robinson MM, Dasari S, Konopka AR, Johnson ML, Sreekumaran Nair K. Enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young and old humans. *Cell Metab*. 2017;25:581–592. doi: 10.1016/j.cmet.2017.02.009
150. Katz DH, Lindholm ME, Ashley EA. Charting the molecular terrain of exercise: the power of multi-omic mapping. *Physiology*. 2023;40:185–202. doi: 10.1152/physiol.00024.2024
151. Wu J, Bostrom P, Sparks LM, Ye Li, Choi JH, Giang A-H, Khandekar M, Virtanen KA, Nuutila P, Schaart G, et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell*. 2012;150:366–376. doi: 10.1016/j.cell.2012.05.016
152. Zhang Y, Li R, Meng Y, Li S, Donelan W, Zhao Y, Qi L, Zhang M, Wang X, Cui T, et al. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. *Diabetes*. 2014;63:514–525. doi: 10.2337/db13-1106
153. Nguyen KD, Qiu Y, Cui X, Goh YPS, Mwangi J, David T, Mukundan L, Brombacher F, Locksley RM, Chawla A. Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis. *Nature*. 2011;480:104–108. doi: 10.1038/nature10653
154. Jin L, Han S, Lv X, Li X, Meng Z-X. The muscle-enriched myokine musclin impairs beige fat thermogenesis and systemic energy homeostasis via Tfr1/PKA signaling in male mice. *Nat Commun*. 2023;14:4257. doi: 10.1038/s41467-023-39710-z
155. Artaza JN, Bhasin S, Magee TR, Reisz-Porszasz S, Shen R, Groome NP, Meerasahib MF, Gonzalez-Cadavid NF. Myostatin inhibits myogenesis and promotes adipogenesis in C3H10T1/2 mesenchymal multipotent cells. *Endocrinology*. 2005;146:3547–3557. doi: 10.1210/en.2005-0362
156. Feldman BJ, Streeper RS, Farese RV, Yamamoto KR. Myostatin modulates adipogenesis to generate adipocytes with favorable metabolic effects. *Proc Natl Acad Sci USA*. 2006;103:15675–15680. doi: 10.1073/pnas.0607501103
157. Guo W, Flanagan J, Jasuja R, Bhasin S. The effects of myostatin on adipogenic differentiation of human bone marrow-derived mesenchymal stem cells are mediated through cross-communication between Smad3 and Wnt/beta-catenin signaling pathways. *J Biol Chem*. 2008;238:9136–9145. doi: 10.1074/jbc.M708968200
158. Jackson MF, Luong D, Vang DD, Rodgers BD. The aging myostatin null phenotype: reduced adiposity, cardiac hypertrophy, enhanced cardiac stress response, and sexual dimorphism. *J Endocrinol*. 2012;213:263–275. doi: 10.1530/JOE-11-0455
159. Kim HS, Liang L, Dean RG, Hausman DB, Hartzell DL, Baile CA. Inhibition of pre-adipocyte differentiation by myostatin treatment in 3T3-L1 cultures. *Biochem Biophys Res Commun*. 2001;281:902–906. doi: 10.1006/bbrc.2001.4435

160. Kim WK, Choi HR, Park SG, Ko Y, Bae K-H, Lee SC. Myostatin inhibits brown adipocyte differentiation via regulation of Smad3-mediated-beta-catenin stabilization. *Int J Biochem Cell Biol*. 2012;44:327–334. doi: 10.1016/j.biocel.2011.11.004
161. McPherron AC, Lee S-J. Suppression of body fat accumulation in myostatin-deficient mice. *J Clin Invest*. 2002;109:595–601. doi: 10.1172/JCI13562
162. Rebbapragada A, Benchabane H, Wrana JL. Myostatin signals through a transforming growth factor beta-life signaling pathway to block adipogenesis. *Mol Cell Biol*. 2003;23:7230–7242. doi: 10.1128/MCB.23.20.7230-7242.2003
163. Shan T, Liang X, Bi P, Kuang S. Myostatin knockout drives browning of white adipose tissue through activating the AMPK-PGC1alpha-Fndc6 pathway in muscle. *FASEB J*. 2013;27:1981–1989. doi: 10.1096/fj.12-225755
164. Petersen EW, Carey AL, Sacchetti M, Steinberg GR, Macaulay SL, Febbraio MA, Pedersen BK. Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro. *Am J Physiol Endocrinol Metab*. 2005;288:E155–E162. doi: 10.1152/ajpendo.00257.2004
165. Wan Z, Thrush AB, Legare M, Frier BC, Sutherland LN, Williams DB, Wright DC. Epinephrine-mediated regulation of PDK4 mRNA in rat adipose tissue. *Am J Physiol Cell Physiol*. 2010;299:C1162–C1170. doi: 10.1152/ajpcell.00188.2010
166. Lu J, Xiang G, Liu M, Dong J. Irisin protects against endothelial injury and ameliorates atherosclerosis in apolipoprotein E-null diabetic mice. *Atherosclerosis*. 2015;243:438–448. doi: 10.1016/j.atherosclerosis.2015.10.020
167. Zhang Y, Mu Q, Zhou Z, Tang D. Protective effect of irisin on atherosclerosis via suppressing oxidized low density lipoprotein induced vascular inflammation and endothelial dysfunction. *PLoS One*. 2016;11:e0158038. doi: 10.1371/journal.pone.0158038
168. Zhang Y, Song H, Zhang Y, Tang D. Irisin inhibits atherosclerosis by promoting endothelial proliferation through microRNA126-5p. *J Am Heart Assoc*. 2016;5:e004031. doi: 10.1161/JAHA.116.004031
169. El-Ashmawy HM, Selim FO, Hosny TAM, Almassry HN. Association of low serum Meteorin like (Metrnl) concentrations with worsening of glucose tolerance, impaired endothelial cell function and atherosclerosis. *Diabetes Res Clin Pract*. 2019;150:57–63. doi: 10.1016/j.diabres.2019.02.026
170. Javaid HMA, Sahar NE, ZhuGe DL, Huh JY. Exercise inhibits NLRP3 inflammasome activation in obese mice via the anti-inflammatory effect of meteorin-like. *Cells*. 2021;10:3480. doi: 10.3390/cells10123480
171. Liu ZH, Ji HH, Yao MP. Serum Metrnl is associated with presence and severity of coronary artery disease. *J Cell Mol Med*. 2019;23:271–280. doi: 10.1111/jcmm.13915
172. Helker CS, Eberlein J, Willhelm K, Sugino T, Stainier DY. Apelin signaling drives vascular endothelial cells toward a pro-angiogenic state. *eLife*. 2020;9:e55589. doi: 10.7554/eLife.55589
173. Ishida J, Hashimoto T, Hashimoto Y, Nishiwaki S, Fukamizu A. Regulatory roles for APJ, a seven-transmembrane receptor related to angiotensin-type 1 receptor in blood pressure in vivo. *J Biol Chem*. 2004;279:26274–26279. doi: 10.1074/jbc.M404149200
174. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868–874. doi: 10.1038/nature01323
175. Pober JS, Min W, Bradley JR. Mechanisms of endothelial dysfunction, injury, and death. *Annu Rev Pathol*. 2009;4:71–95. doi: 10.1146/annurev.pathol.4.110807.092155
176. Wang Y, Yuan J, Huadong L. Elevated meteorin-like protein from high-intensity interval training improves heart function via AMPK/HDAC4 pathway. *Genes Dis*. 2024;11:101100. doi: 10.1016/j.gendis.2023.101100
177. Cao DJ, Wang ZV, Battiprolu PK, Hill JA. Histone deacetylase (HDAC) inhibitors attenuate cardiac hypertrophy by suppressing autophagy. *Proc Natl Acad Sci USA*. 2011;108:4123–4128. doi: 10.1073/pnas.1015081108
178. Kamanga-Sollo E, Pampusch MS, White ME, Hathway MR, Dayton WR. Insulin-like growth factor binding protein (IGFBP)-3 and IGFBP-5 mediate TGF-beta- and myostatin-induced suppression of proliferation in porcine embryonic myogenic cell cultures. *Exp Cell Res*. 2005;311:167–176. doi: 10.1016/j.yexcr.2005.09.003
179. Kamanga-Sollo E, Papmusch MS, White ME, Dayton WR. Role of insulin-like growth factor binding protein (IGFBP)-3 in TGF-beta- and GDF-8 (myostatin)-induced suppression of proliferation in porcine embryonic myogenic cell cultures. *J Cell Physiol*. 2003;197:225–231. doi: 10.1002/jcp.10362
180. Qi H, Ren J, Ba L, Song C, Sun H. MSTN attenuates cardiac hypertrophy through inhibition of excessive cardiac autophagy by blocking AMPK/mTOR and miR-128/PPARγ/NF-kB. *Mol Ther Nucleic Acids*. 2020;19:507–522. doi: 10.1016/j.omtn.2019.12.003
181. Kilpiö T, Skarp S, Perjés A, Swan J, Kerkelä R. Apelin regulates skeletal muscle adaptation to exercise in a high-intensity interval training model. *Am J Physiol Cell Physiol*. 2024;326:C1437–C1450. doi: 10.1152/ajpcell.00427.2023
182. Choi SH, Bylybashi E, Chatila ZK, Lee SW, Pulli B, Clemenson GD, Kim E, Rompala A, Oram MK, Asselin C, et al. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science*. 2018;361:eaan8821. doi: 10.1126/science.aan8821
183. Lourenco MV, Frozza RL, de Freitas GB, De Felice FG. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat Med*. 2019;25:165–175. doi: 10.1038/s41591-018-0275-4
184. Colaianni G, Mongelli T, Cuscito C, Pignataro P, Lippo L, Spiro G, Notarnicola A, Severi I, Passeri G, Mori G, et al. Irisin prevents and restores bone loss and muscle atrophy in hind-limb suspended mice. *Sci Rep*. 2017;7:2811. doi: 10.1038/s41598-017-02557-8
185. Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, Febbraio M, Saltin B. Searching for the exercise factor: is IL-6 a candidate? *J Muscle Res Cell Motil*. 2003;24:113–119. doi: 10.1023/a:1026070911202
186. Steensberg A, van Hall G, Osada T, Sacchetti M, Saltin B, Klarlund Pedersen B. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. *J Physiol*. 2000;529 Pt 1:237–242. doi: 10.1111/j.1469-7793.2000.00237.x
187. Eckel J. Myokines in metabolic homeostasis and diabetes. *Diabetologia*. 2000;62:1523–1528. doi: 10.1007/s00125-019-4927-9
188. Trayhurn P, Drevon CA, Eckel J. Secreted proteins from adipose tissue and skeletal muscle - adipokines, myokines and adipose/muscle cross-talk. *Arch Physiol Biochem*. 2011;117:47–56. doi: 10.3109/13813455.2010.535835
189. Kim H-J, So B, Choi M, Kang D, Song W. Resistance exercise training increases the expression of irisin concomitant with improvement of muscle function in aging mice and humans. *Exp Gerontol*. 2015;70:11–17. doi: 10.1016/j.exger.2015.07.006
190. Pedersen BK. Muscular IL-6 and its role as an energy sensor. *Med Sci Sports Exerc*. 2012;44:392–396. doi: 10.1249/MSS.0b013e31822f94ac
191. Schnyder S, Handschin C. Skeletal muscle as an endocrine organ: PGC-1a, myokines and exercise. *Bone*. 2015;80:115–125. doi: 10.1016/j.bone.2015.02.008
192. Rodgers B, Garikipati D. Clinical, agricultural, and evolutionary biology of myostatin: a comparative review. *Endocr Rev*. 2008;29:513–534. doi: 10.1210/er.2008-0003
193. McCroskery S, Thomas M, Maxwell L, Sharma M, Kambadur R. Myostatin negatively regulates satellite cell activation and self-renewal. *J Cell Biol*. 2003;162:1135–1147. doi: 10.1083/jcb.200207056
194. Sartori R, Romanello V, Sandri M. Mechanisms of muscle atrophy and hypertrophy: implications in health and disease. *Nat Commun*. 2021;12:330. doi: 10.1038/s41467-020-20123-1
195. McPherron A, Lawler A, Lee S. Regulation of skeletal muscle mass in mice by a new TGF-B superfamily member. *Nature*. 1997;387:83–90. doi: 10.1038/387083a0
196. Schuelke M, Wagner KR, Stolz LE, Hübner C, Riebel T, Kömen W, Braun T, Tobin JF, Lee S-J. Myostatin mutation associated with gross muscle hypertrophy in a child. *N Engl J Med*. 2004;350:2682–2688. doi: 10.1056/NEJMoa040933
197. Sartori R, Gregorevic P, Sandri M. TGFB and BMP signaling in skeletal muscle: potential significance for muscle-related disease. *Trends Endocrinol Metab*. 2014;25:464–471. doi: 10.1016/j.tem.2014.06.002
198. Davey JR, Watt KI, Parker LB, Chaudhuri R, Ryall JG, Gregorevic P. Integrated expression analysis of muscle hypertrophy identifies Asb2 as a negative regulator of muscle mass. *JCI Insight*. 2016;1:e85477. doi: 10.1172/jci.insight.85477
199. Sartori R, Schirwis E, Blaauw B, Bortolanza S, Sandri M. BMP signaling controls muscle mass. *Nat Genet*. 2013;45:1309–1318. doi: 10.1038/ng.2772
200. Winbanks CE, Chen JL, Qian H, Gregorevic P. The bone morphogenetic protein axis is a positive regulator of skeletal muscle mass. *J Cell Biol*. 2013;203:345–357. doi: 10.1083/jcb.201211134
201. Sharma M, Kambadur R, Matthews KG, Somers WG, Devlin GP, Bass JJ. Myostatin, a transforming growth factor-beta superfamily member, is expressed in heart muscle and is upregulated in cardiomyocytes after infarct. *J Cell Physiol*. 1999;180:1–9. doi: 10.1002/(SICI)1097-4652(199907)180:1<1::AID-JCP1>3.0.CO;2-V
202. Johansen T, Lamark T. Selective autophagy mediated by autophagic adapter proteins. *Autophagy*. 2011;7:279–296. doi: 10.4161/auto.7.3.14487

203. Harper JW, Elledge SJ, Keyomarsi K, Swindell E. Inhibition of cyclin-dependent kinases by p21. *Mol Biol Cell*. 1995;6:387–400. doi: 10.1091/mbc.6.4.387
204. Pampusch MS, Xi G, Kamanga-Sollo E, Loseth KJ, Hathway MR, Dayton WR, White ME. Production of recombinant porcine IGF-binding protein-5 and its effect on proliferation of porcine embryonic myoblast cultures in the presence and absence of IGF-I and Long-R3-IGF-I. *J Endocrinol*. 2005;185:197–206. doi: 10.1677/joe.1.06037
205. Tsai LH, Lees E, Harlow E, Riabowol K. The cdk2 kinase is required for the G1-to-S transition in mammalian cells. *Oncogene*. 1993;8:1593–1602.
206. Guo T, William J, Chanturiya T, McPherron AC. Myostatin inhibition in muscle, but not adipose tissue, decreases fat mass and improves insulin sensitivity. *PLoS One*. 2009;4:e4937. doi: 10.1371/journal.pone.0004937
207. Mehta RH, Jain SP, Nanda NC, Sanyal R. Isolated partial anomalous pulmonary venous connection: echocardiographic diagnosis and a new color Doppler method to assess shunt volume. *Am Heart J*. 1991;122:870–873. doi: 10.1016/0002-8703(91)90544-r
208. Daskalopoulou SS, Cooke AB, Gomez YH, Mutter AF, Filippaios A, Mesfum ET, Mantzoros CS. Plasma irisin levels progressively increase in response to increasing exercise workloads in young, healthy, active subjects. *Eur J Endocrinol*. 2014;171:343–352. doi: 10.1530/EJE-14-0204
209. Jedrychowski MP, Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM, Nair KS, Gygi SP, Spiegelman BM. Detection and quantitation of circulating human irisin by tandem mass spectrometry. *Cell Metab*. 2015;22:734–740. doi: 10.1016/j.cmet.2015.08.001
210. Kim H, Lee HJ, So B, Son JS, Yoon D, Song W. Effects of aerobic training and resistance training on circulating irisin level and their association with change of body composition in overweight/obese adults: a pilot study. *Physiol Res*. 2016;65:271–279. doi: 10.33549/physiolres.932997
211. Aydin S. Three new players in energy regulation: preptin, adropin and irisin. *Peptides*. 2014;56:94–110. doi: 10.1016/j.peptides.2014.03.021
212. Kelly DP. Irisin, light my fire. *Science*. 2012;336:42–43. doi: 10.1126/science.1221688
213. Zhang J, Huang X, Yu R, Wang Y, Gao C. Circulating irisin is linked to bone mineral density in geriatric Chinese men. *Open Med*. 2020;15:763–768. doi: 10.1515/med-2020-0215
214. Vaughan RA, Gannon NP, Barberena MA, Garcia-Smith R, Bisoffi M, Mermier CM, Conn CA, Trujillo KA. Characterization of the metabolic effects of irisin on skeletal muscle in vitro. *Diabetes Obes Metab*. 2014;16:711–718. doi: 10.1111/dom.12268
215. Park KH, Zaichenko L, Brinkoetter M, Thakkar B, Sahin-Efe A, Joung KE, Tsoukas MA, Geladari EV, Huh JY, Dincer F, et al. Circulating irisin in relation to insulin resistance and the metabolic syndrome. *J Clin Endocrinol Metab*. 2013;98:4899–4907. doi: 10.1210/jc.2013-2373
216. Sesti G, Andreozzi F, Fiorentino TV, Mannino GC, Sciacqua A, Marini MA, Perticone F. High circulating irisin levels are associated with insulin resistance and vascular atherosclerosis in a cohort of nondiabetic adult subjects. *Acta Diabetol*. 2014;51:705–713. doi: 10.1007/s00592-014-0576-0
217. Wu H, Guo P, Jin Z, Ke J. Serum levels of irisin predict short-term outcomes in ischemic stroke. *Cytokine*. 2019;122:154303. doi: 10.1016/j.cyto.2018.02.017
218. Anastasilakis AD, Koulaxis D, Kefala N, Mantzoros CS. Circulating irisin levels are lower in patients with either stable coronary artery disease (CAD) or myocardial infarction (MI) versus healthy controls, whereas follistatin and activin A levels are higher and can discriminate MI from CAD with similar to CK-MB accuracy. *Metabolism*. 2017;73:1–8. doi: 10.1016/j.metabol.2017.05.002
219. Deng W. Association of serum irisin concentrations with presence and severity of coronary artery disease. *Med Sci Monitor*. 2016;22:4193–4197. doi: 10.12659/msm.897376
220. Guo W, Zhang B, Wang X. Lower irisin levels in coronary artery disease: a meta-analysis. *Minerva Endocrinol*. 2020;45:61–69. doi: 10.23736/S0391-1977.17.02663-3
221. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. 2003;14:125–130. doi: 10.1111/1467-9280.t01-1-01430
222. Mattson MP. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. *Cell Metab*. 2012;16:706–722. doi: 10.1016/j.cmet.2012.08.012
223. Ahlskog JE. Does vigorous exercise have a neuroprotective effect in Parkinson disease? *Neurology*. 2011;77:288–294. doi: 10.1212/WNL.0b013e318225ab66
224. Buchman AS, Boyle PA, Yu L, Shah RC, Bennet DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology*. 2012;78:1323–1329. doi: 10.1212/WNL.0b013e3182535d35
225. Corrochano S, Blanco G, Acevedo-Arozena A. Skeletal muscle modulates Huntington's disease pathogenesis in mice: role of physical exercise. *J Exp Neurosci*. 2018;12:1179069518809059. doi: 10.1177/1179069518809059
226. Quaney BM, Boyd LA, McDowd JM, Macko RF. Aerobic exercise improves cognition and motor function poststroke. *Neurorehabil Neural Repair*. 2009;23:879–885. doi: 10.1177/1545968309338193
227. van Praag H, Christie BR, Senjowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci USA*. 1999b;96:13427–13431. doi: 10.1073/pnas.96.23.13427
228. van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci*. 1999a;2:266–270. doi: 10.1038/6368
229. Küster OC, Laptinskaya D, von Arnim CAF. Novel blood-based biomarkers of cognition, stress, and physical or cognitive training in older adults at risk of dementia: preliminary evidence for a role of BDNF, irisin, and the kynurenine pathway. *J Alzheimers Dis*. 2017;59:1097–1111. doi: 10.3233/JAD-170447
230. Belviranli M, Okudan N, Kabak B, Karanfilci M. The relationship between brain-derived neurotrophic factor, irisin and cognitive skills of endurance athletes. *Phys Sportsmed*. 2016;44:290–296. doi: 10.1080/00913847.2016.1196125
231. Fagundo AB, Jiménez-Murcia S, Giner-Bertolomé C, Agüera Z, Sauchelli S, Pardo M, Crujeiras AB, Granero R, Baños R, Botella C, et al. Modulation of irisin and physical activity on executive functions in obesity and morbid obesity. *Sci Rep*. 2016;6:30820. doi: 10.1038/srep30820
232. Bretland KA, Lin L, Bretland KM, Smith MA, Fleming SM, Dengler-Crish CM. Irisin treatment lowers levels of phosphorylated tau in the hippocampus of pre-symptomatic female but not male htau mice. *Neuropathol Appl Neurobiol*. 2021;47:967–978. doi: 10.1111/nan.12711
233. Wang K, Li H, Wang H, Wang J-H, Song F, Sun Y. Irisin exerts neuroprotective effects on cultured neurons by regulating astrocytes. *Mediators Inflamm*. 2018;2018:9070341. doi: 10.1155/2018/9070341
234. Zarbakhsh S, Safari M, Aldaghi MR, Parsaie H. Irisin protects the substantia nigra dopaminergic neurons in the rat model of Parkinson's disease. *Iran J Basic Med Sci*. 2019;22:722–728. doi: 10.22038/ijbms.2019.33444.7987
235. Li D-J, Li Y-H, Yuan H-B, Qu L-F, Wang P. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metabolism*. 2017;68:31–42. doi: 10.1016/j.metabol.2016.12.003
236. Peng J, Deng X, Huang W, Xu F-Y. Irisin protects against neuronal injury induced by oxygen-glucose deprivation in part depends on the inhibition of ROS-NLRP3 inflammatory signaling pathway. *Mol Immunol*. 2017;91:185–194. doi: 10.1016/j.molimm.2017.09.014
237. Wang K, Song F, Xu K, Liu Z, Han S, Li F, Sun Y. Irisin attenuates neuroinflammation and prevents the memory and cognitive deterioration in streptozotocin-induced diabetic mice. *Mediators Inflamm*. 2019;2019:1567179. doi: 10.1155/2019/1567179
238. Jung TW, Lee SH, Kim HC, Bang JS, Abd El-Aty AM, Hacımüftüoğlu A, Shin YK, Jeong JH. METRNL attenuates lipid-induced inflammation and insulin resistance via AMPK or PPARdelta-dependent pathways in skeletal muscle of mice. *Exp Mol Med*. 2018;50:1–11. doi: 10.1038/s12276-018-0147-5
239. Aggarwal M, Bozkurt B, Panjrath G. Lifestyle modifications for preventing and treating heart failure. *J Am Coll Cardiol*. 2018;72:2391–2405. doi: 10.1016/j.jacc.2018.08.2160
240. Akyuz A. Exercise and coronary artery disease. *Adv Exp Med Biol*. 2020;1228:169–179. doi: 10.1007/978-981-15-1792-1_11
241. Patti A, Merlo M, Ambrosetti M. Execise-based cardiac rehabilitation programs in heart failure patients. *Heart Fail Clin*. 2021;17:263–271. doi: 10.1016/j.hfc.2021.01.007
242. Lee JO, Byun WS, Kang MJ, Han JA, Moon J, Shin M-J, Lee HJ, Chung JH, Lee J-S, Son C-G, et al. The myokine meteorin-like (metrnl) improves glucose tolerance in both skeletal muscle cells and mice by targeting AMPKa2. *FEBS J*. 2020;287:2087–2104. doi: 10.1111/febs.15301
243. Xu L, Cai Y, Wang Y. Meteorin-like (METRNL) attenuates myocardial ischemia/reperfusion injury-induced cardiomyocytes apoptosis by alleviating endoplasmic reticulum stress via activation of AMPK-PAK2 signaling in H9C2 cells. *Med Sci Monitor*. 2020;26:e924564.
244. Feng T, Szabo E, Dziak E, Opas M. Cytoskeletal disassembly and cell rounding promotes adipogenesis from ES cells. *Stem Cell Rev Rep*. 2010;6:74–85. doi: 10.1007/s12015-010-9115-8
245. Helmstadter KG, Ljubojevic-Holzer S, Wood BM, Taheri KD, Sedej S, Erickson JR, Bossuyt J, Bers DM. CaMKII and PKA-dependent phosphorylation

co-regulate nuclear localization of HDAC4 in adult cardiomyocytes. *Basic Res Cardiol*. 2021;116:11. doi: 10.1007/s00395-021-00850-2
246. Szablewski L. Glucose transporters in healthy heart and in cardiac disease. *Int J Cardiol*. 2016;230:70–75. doi: 10.1016/j.ijcard.2016.12.083
247. Yang J, Cao RY, Gao R, Mi Q, Dai Q, Zhu F. Physical exercise is a potential "medicine" for atherosclerosis. *Adv Exp Med Biol*. 2017;999:269–286. doi: 10.1007/978-981-10-4307-9_15
248. Liu C, Gidlund E-K, Witasp A, Qureshi AR, Söderberg M, Thorell A, Nader GA, Barany P, Stenvinkel P, von Walden F. Reduced skeletal muscle expression of mitochondrial-derived peptides humanin and MOTS-c and Nrf2 in chronic kidney disease. *Am J Physiol Renal Physiol*. 2019;317:F1122–F1131. doi: 10.1152/ajprenal.00202.2019
249. Reynolds JC, Lai RW, Woodhead JST, Joly JH, Mitchell CJ, Cameron-Smith D, Lu R, Cohen P, Graham NA, Benayoun BA, et al. MOTS-c is an exercise-induced mitochondria-encoded regulator of age-dependent physical decline and muscle homeostasis. *Nat Commun*. 2021;12:470. doi: 10.1038/s41467-020-20790-0
250. Lee C, Kim KH, Cohen P. MOTS-c: a novel mitochondrial-derived peptide regulating muscle and fat metabolism. *Free Radic Biol Med*. 2016;100:182–187. doi: 10.1016/j.freeradbiomed.2016.05.015
251. Lee C, Zeng J, Drew BG, Sallam T, Martin-Montalvo A, Wan J, Kim S-J, Mehta H, Hevener AL, de Cabo R, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metab*. 2015;21:443–454. doi: 10.1016/j.cmet.2015.02.009
252. Ramanjaneya M, Bettahi I, Jerobin J, Chandra P, Khalil CA, Skarulis M, Atkin SL, Abou-Samra A-B. Mitochondrial-derived peptides are down regulated in diabetes subjects. *Front Endocrinol (Lausanne)*. 2019;10:331. doi: 10.3389/fendo.2019.00331
253. Fuku N, Pareja-Galeano H, Zempo H, Alis R, Arai Y, Lucia A, Hirose N. The mitochondrial-derived peptide MOTS-c: a player in exceptional longevity. *Aging Cell*. 2015;14:921–923. doi: 10.1111/acel.12389
254. Kitase Y, Vallejo JA, Gutheil W, Vemula H, Bonewald LF. B-aminoisobutyric acid, I-BAIBA, is a muscle-derived osteocyte survival factor. *Cell Rep*. 2018;22:1531–1544. doi: 10.1016/j.celrep.2018.01.041
255. Sarzynski MA, Rice TK, Després J-P, Bouchard C. The HERITAGE Family Study: a review of the effects of exercise training on cardiometabolic health, with insights into molecular transducers. *Med Sci Sports Exerc*. 2022;54:S1–S43. doi: 10.1249/MSS.0000000000002859
256. Roberts LD, Bostrom P, O'Sullivan JF, Schinzel RT, Lewis GD, Dejam A, Lee Y-K, Palma MJ, Calhoun S, Georgiadi A, et al. Beta-aminoisobutyric acid induces browning of white fat and hepatic beta-oxidation and is inversely correlated with cardiometabolic risk factors. *Cell Metab*. 2014b;19:96–108. doi: 10.1016/j.cmet.2013.12.003
257. Subbotina E, Sierra A, Zhu Z, Gao Z, Zingman LV. Musclin is an activity-stimulated myokine that enhances physical endurance. *Proc Natl Acad Sci USA*. 2015;112:16042–16047. doi: 10.1073/pnas.1514250112
258. Kang X, Qian J, Shi Y-X, Miao H-M. Exercise-induced musclin determines the fate of fibro-adipogenic progenitors to control muscle homeostasis. *Cell Stem Cell*. 2024;31:212–226. doi: 10.1016/j.stem.2023.12.011
259. Szaroszyk M, Kattih B, Martin-Garrido A, Heineke J. Skeletal muscle derived Musclin protects the heart during pathological overload. *Nat Commun*. 2022;13:149. doi: 10.1038/s41467-021-27634-5
260. Vinel C, Lukjanenko L, Batut A, Dray C. The exerkine apelin reverses age-associated sarcopenia. *Nat Med*. 2018;24:1360–1371. doi: 10.1038/s41591-018-0131-6
261. Castan-Laurell I, Dray C, Knauf C, Kunduzova O, Valet P. Apelin, a promising target for type 2 diabetes treatment? *Peptides*. 2022;147:170697. doi: 10.1016/j.tem.2012.02.005.
262. de Oliveira AA, Vergara A, Wang X, Vederas JC, Oudit GY. Therapeutic role of apelin analogs and apelin receptor agonists. *Peptides*. 2022;147:170697. doi: 10.1016/j.peptides.2021.170697
263. Kim YM, Lakin R, Zhang H, Ashley EA. Apelin increases atrial conduction velocity, refractoriness, and prevents inducibility of atrial fibrillation. *JCI Insight*. 2020;5:e126525. doi: 10.1172/jci.insight.126525
264. Parikh VN, Liu J, Shang C, Woods C, Ashley EA. Apelin and APJ orchestrate complex tissue-specific control of cardiomyocyte hypertrophy and contractility in the hypertrophy-heart failure transition. *Am J Physiol Heart Circ Physiol*. 2018;315:H348–H356. doi: 10.1152/ajpheart.00693.2017
265. Son JS, Chae SA, Wang H, Du M. Maternal inactivity programs skeletal muscle dysfunction in offspring mice by attenuating apelin signaling and mitochondrial biogenesis. *Cell Rep*. 2020;33:108461. doi: 10.1016/j.celrep.2020.108461
266. Attané C, Foussal C, Le Gonidec S, Benani A, Daviaud D, Wanecq E, Guzmán-Ruiz R, Dray C, Bezaire V, Rancoule C, et al. Apelin treatment increases complete fatty acid oxidation, mitochondrial oxidative capacity, and biogenesis in muscle of insulin-resistant mice. *Diabetes*. 2012;61:310–320. doi: 10.2337/db11-0100
267. Miyashita K, Itoh H, Tsujimoto H, Nakao K. Natriuretic peptides/cGMP/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. *Diabetes*. 2009;58:2880–2892. doi: 10.2337/db09-0393
268. Leuchtmann AB, Adak V, Dilbaz S, Handschin C. The role of the skeletal muscle secretome in mediating endurance and resistance training adaptations. *Front Physiol*. 2021;12:709807. doi: 10.3389/fphys.2021.709807
269. Addison O, Drummond MJ, LaStayo PC, Dibble LE, Wende AR, McClain DA, Marcus RL. Intramuscular fat and inflammation differ in older adults: the impact of frailty and inactivity. *J Nutr Health Aging*. 2014;18:532–538. doi: 10.1007/s12603-014-0019-1
270. Keller C, Hellsten Y, Steensberg A, Pedersen BK. Differential regulation of IL-6 and TNF-alpha via calcineurin in human skeletal muscle cells. *Cytokine*. 2006;36:141–147. doi: 10.1016/j.cyto.2006.10.014
271. Haugen F, Norheim F, Lian H, Wensaas AJ, Dueland S, Berg O, Funderud A, Skålhegg BS, Raastad T, Drevon CA. IL-7 is expressed and secreted by human skeletal muscle cells. *Am J Physiol Cell Physiol*. 2010;298:C807–C816. doi: 10.1152/ajpcell.00094.2009
272. Carey A, Steinberg G, Macaulay S. IL-6 increases insulin-stimulated glucose disposal in humans glucose uptake and fatty acid oxidation in vitro via AMPK. *Diabetes*. 2006;55:2688–2697. doi: 10.2337/db05-1404
273. Wolsk E, Mygind H, Grondahl T. IL-6 selectively stimulates fat metabolism in human skeletal muscle. *Am J Physiol Endocrinol Metab*. 2010;299:E832–E840. doi: 10.1152/ajpendo.00328.2010
274. van Hall G, Steensberg A, Sacchetti M, Fischer C, Keller C, Schjerling P, Hiscock N, Møller K, Saltin B, Febbraio MA, et al. Interleukin-6 stimulates lipolysis and fat oxidation in humans. *J Clin Endocrinol Metab*. 2003;88:3005–3010. doi: 10.1210/jc.2002-021687
275. Keller C, Steensberg A, Hansen AK, Fischer CP, Plomgaard P, Pedersen BK. Effect of exercise, training, and glycogen availability on IL-6 receptor expression in human skeletal muscle. *J Appl Physiol (1985)*. 2005;99:2075–2079. doi: 10.1152/japplphysiol.00590.2005
276. Ruderman NB, Keller C, Richard A-M, Saha AK, Luo Z, Xiang X, Giralt M, Ritov VB, Menshikova EV, Kelley DE, et al. Interleukin-6 regulation of AMP-activated protein kinase. Potential role in the systemic response to exercise and prevention of the metabolic syndrome. *Diabetes*. 2006;55:S48–S54. doi: 10.2337/db06-s007
277. Steensberg A, Febbraio MA, Osada T, Schjerling P, van Hall G, Saltin B, Pedersen BK. Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. *J Physiol*. 2001;537:633–639. doi: 10.1111/j.1469-7793.2001.00633.x
278. Trujillo ME, Sullivan S, Harten I, Schneider SH, Greenberg AS, Fried SK. Interleukin-6 regulates human adipose tissue lipid metabolism and leptin production in vitro. *J Clin Endocrinol Metab*. 2004;89:5577–5582. doi: 10.1210/jc.2004-0603
279. Brandt C, Jakobsen AH, Adser H, Olesen J, Iversen N, Kristensen JM, Hojman P, Wojtaszewski JFP, Hidalgo J, Pilegaard H. IL-6 regulates exercise and training-induced adaptations in subcutaneous adipose tissue in mice. *Acta Physiol (Oxf)*. 2012;205:224–235. doi: 10.1111/j.1748-1716.2011.02373.x
280. Wallenius V, Wallenius K, Ahrén B, Jansson J-O. Interleukin-6-deficient mice develop mature-onset obesity. *Nat Med*. 2002;8:75–79. doi: 10.1038/nm0102-75
281. Kelly M, Keller C, Avilucea PR, Ruderman NB. AMPK activity is diminished in tissues of IL-6 knockout mice: the effect of exercise. *Biochem Biophys Res Commun*. 2004;320:449–454. doi: 10.1016/j.bbrc.2004.05.188
282. Stouthard JM, Oude Elferink RP, Sauerwein HP. Interleukin-6 enhances glucose transport in 3T3-L1 adipocytes. *Biochem Biophys Res Commun*. 1996;220:241–245. doi: 10.1006/bbrc.1996.0389
283. Lagathu C, Bastard JP, Auclair M, Maachi M, Capeau J, Caron M. Chronic interleukin-6 (IL-6) treatment increased IL-6 secretion and induced insulin resistance in adipocyte: prevention by rosiglitazone. *Biochem Biophys Res Commun*. 2003;311:372–379. doi: 10.1016/j.bbrc.2003.10.013
284. Rotter V, Nagaev I, Smith U. Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem*. 2003;278:45777–45784. doi: 10.1074/jbc.M301977200
285. Lyngsø D, Simonsen L, Bülow J. Interleukin-6 production in human subcutaneous abdominal adipose tissue: the effect of exercise. *J Physiol*. 2002;543:373–378. doi: 10.1113/jphysiol.2002.019380

286. Akerstrom T, Steensberg A, Keller P, Keller C, Penkowa M, Pedersen BK. Exercise induces interleukin-8 expression in human skeletal muscle: exercise and IL-8. *J Physiol*. 2005;563:507–516. doi: 10.1113/jphysiol.2004.077610
287. Della Gatta PA, Garnham AP, Peake JM, Cameron-Smith D. Effect of exercise training on skeletal muscle cytokine expression in the elderly. *Brain Behav Immun*. 2014;39:80–86. doi: 10.1016/j.bbi.2014.01.006
288. Suzuki K, Nakaji S, Yamada M, Sugawara K. Impact of a competitive marathon race on systemic cytokine and neutrophil responses. *Med Sci Sports Exerc*. 2003;35:348–355. doi: 10.1249/01.MSS.0000048861.57899.04
289. Chan MHS, Carey AL, Watt MJ, Febbraio MA. Cytokine gene expression in human skeletal muscle during concentric contraction: evidence that IL-8, like IL-6, is influenced by glycogen availability. *Am J Physiol Regul Integr Comp Physiol*. 2004;287:R322–R327. doi: 10.1152/ajpregu.00030.2004
290. Li A, Dubey S, Varney ML, Dave BJ, Singh RK. IL-8 directly enhanced endothelial cell survival, proliferation, and matrix metalloproteinases production and regulated angiogenesis. *J Immunol*. 2003;170:3369–3376. doi: 10.4049/jimmunol.170.6.3369
291. Hargreaves M. Skeletal muscle metabolism during exercise in humans. *Clin Exp Pharmacol Physiol*. 2000;27:225–228. doi: 10.1046/j.1440-1681.2000.03225.x
292. Hashimoto T, Hussien R, Oommen S, Gohil K, Brooks GA. Lactate sensitive transcription factor network in L6 cells: activation of MCT1 and mitochondrial biogenesis. *FASEB J*. 2007;21:2602–2612. doi: 10.1096/fj.07-8174com
293. Li VL, He Y, Contrepois K, Long JZ. An exercise-inducible metabolite that suppresses feeding and obesity. *Nature*. 2022;606:785–790. doi: 10.1038/s41586-022-04828-5
294. Halestrap AP. The SLC16 gene family- structure, role and regulation in health and disease. *Mol Aspects Med*. 2013;34:337–349. doi: 10.1016/j.mam.2012.05.003
295. Carriere A, Jeanson Y, Berger-Muller S, André M, Chenouard V, Arnaud E, Barreau C, Walther R, Galinier A, Wdziekonski B, et al. Browning of white adipose cells by intermediate metabolites: an adaptive mechanism to alleviate redox pressure. *Diabetes*. 2014;63:3253–3265. doi: 10.2337/db13-1885
296. De Matteis R, Lucertini F, Guescini M, Polidori E, Zeppa S, Stocchi V, Cinti S, Cuppini R. Exercise as a new physiological stimulus for brown adipose tissue activity. *Nutr Metab Cardiovasc Dis*. 2013;23:582–590. doi: 10.1016/j.numecd.2012.01.013
297. López-Aramda MJ, Riveiro-Naveira RR, Vaamonde-Garcia C, Valcárcel-Ares MN. Mitochondrial dysfunction and the inflammatory response. *Mitochondrion*. 2013;13:106–118. doi: 10.1016/j.mito.2013.01.003
298. Kennedy KM, Scarbrough PM, Ribeiro A, Richardson R, Yuan H, Sonveaux P, Landon CD, Chi J-T, Pizzo S, Schroeder T, et al. Catabolism of exogenous lactate reveals it is a legitimate metabolic substrate in breast cancer. *PLoS One*. 2013;8:e75154. doi: 10.1371/journal.pone.0075154
299. McCormick R, Vasilaki A. Age-related changes in skeletal muscle. *Biogerontology*. 2018;19:519–536. doi: 10.1007/s10522-018-9775-3
300. Ahima RS. Connecting obesity, aging, and diabetes. *Nat Med*. 2009;15:996–997. doi: 10.1038/nm0909-996
301. Schwartz RS, Shuman WP, Bradbury VL, Cain KC, Fellingham GW, Beard JC, Kahn SE, Stratton JR, Cerqueira MD, Abrass IB. Body fat distribution in healthy young and older men. *J Gerontol*. 1990;45:M181–M185. doi: 10.1093/geronj/45.6.m181
302. Shimokata H, Tobin JD, Muller DC, Elahi D, Coon PJ, Andres R. Studies in the distribution of body fat: I. effects of age, sex, and obesity. *J Gerontol*. 1989;44:M66–M73. doi: 10.1093/geronj/44.2.m66
303. Nirengi S, Stanford KI. Brown adipose tissue and aging: a potential role for exercise. *Exp Gerontol*. 2023;178:112218. doi: 10.1016/j.exger.2023.112218
304. Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, Li J. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. *Signal Transduct Target Ther*. 2022;7:391. doi: 10.1038/s41392-022-01251-0
305. Li X, Li C, Zhang W, Wang Y, Qian P, Huang H. Inflammation and aging: signaling pathways and intervention therapies. *Signal Transduct Target Ther*. 2023;8:239. doi: 10.1038/s41392-023-01502-8
306. Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes*. 2002;51:2944–2950. doi: 10.2337/diabetes.51.10.2944
307. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science*. 2003;300:1140–1142. doi: 10.1126/science.1082889
308. Lamming DW, Latorre-Esteves M, Medvedik O, Wong SN, Tsang FA, Wang C, Lin S-J, Sinclair DA. HST2 mediates SIR2-independent lifespan extension by calorie restriction. *Science*. 2005;309:1861–1864. doi: 10.1126/science.1113611
309. Lin SJ, Defossez PA, Guarente L. Requirement of NAD and SIR2 for lifespan extension by calorie restriction in Saccharomyces cerevisiae. *Science*. 2000;289:2126–2128. doi: 10.1126/science.289.5487.2126
310. Roh J, Rhee J, Chaudhari V, Rosenzweig A. The role of exercise in cardiac aging: from physiology to molecular mechanisms. *Circ Res*. 2017;118:279–295. doi: 10.1161/circresaha.115.305250
311. Gonzalez-Freire M, de Cabo R, Studenski SA, Ferrucci L. The neuromuscular junction: aging at the crossroad between nerves and muscle. *Front Aging Neurosci*. 2014;6:208. doi: 10.3389/fnagi.2014.00208
312. Lexell J, Henriksson-Larsen K, Winblad B, Sjöström M. Distribution of different fiber types in human skeletal muscles: effects of aging studied in whole muscle cross sections. *Muscle Nerve*. 1983;6:588–595. doi: 10.1002/mus.880060809
313. Mendonca GV. Impact of aging on endurance and neuromuscular physical performance. *Sports Med*. 2016;47:583. doi: 10.1007/s40279-016-0596-8..
314. Alway SE, Myers MJ, Mohamed JS. Regulation of satellite cell function in sarcopenia. *Front Aging Neurosci*. 2014;6:246. doi: 10.3389/fnagi.2014.00246
315. Brack AS, Bildsoe H, Hughes SM. Evidence that satellite cell decrement contributes to preferential decline in nuclear number from large fibres during murine age-related muscle atrophy. *J Cell Sci*. 2005;118:4813–4821. doi: 10.1242/jcs.02602
316. Chakkalakal JV, Jones KM, Basson MA, Brack AS. The aged niche disrupts muscle stem cell quiescence. *Nature*. 2012;490:355–360. doi: 10.1038/nature11438
317. Shavlakadze T, McGeachie J, Grounds MD. Delayed by excellent myogenic stem cell response of regenerating geriatric skeletal muscles in mice. *Biogerontology*. 2010;11:363–376. doi: 10.1007/s10522-009-9260-0
318. Joanisse S, Nederveen JP, Baker JM, Snijders T, Iacono C, Parise G. Exercise conditioning in old mice improves skeletal muscle regeneration. *FASEB J*. 2016;30:3256–3268. doi: 10.1096/fj.201600143RR
319. Sayer AA, Cooper R, Arai H, Cruz-Jentoft AJ. Sarcopenia. *Nat Rev Dis Primers*. 2024;10:68. doi: 10.1038/s41572-024-00550-w
320. Murgia M, Cicillot S, Nagaraj N, Mann M. Signatures of muscle disuse in spaceflight and bed rest revealed by single muscle fiber proteomics. *PNAS Nexus*. 2022;1,:pgac086. doi: 10.1093/pnasnexus/pgac086
321. Coen PM, Huo Z, Tranah GJ, Barnes HN, Zhang X, Wolff CA, Wu K, Cawthon PM, Hepple RT, Toledo FGS, et al. Autophagy gene expression in skeletal muscle of older individuals is associated with physical performance, muscle volume and mitochondrial function in the study of muscle, mobility and aging (SOMMA). *Aging Cell*. 2024;23:e14118. doi: 10.1111/acel.14118
322. Tezze C, Romanello V, Desbats MA, Fadini GP, Sandri M. Age-associated loss of OPA1 in muscle impacts muscle mass, metabolic homeostasis, systemic inflammation, and epithelial senescence. *Cell Metab*. 2017;25:1374–1389. doi: 10.1016/j.cmet.2017.04.021
323. Taylor JW, Kaiser ET. Structure-function analysis of proteins through the design, synthesis, and study of peptide models. *Methods Enzymol*. 1987;154:473–498. doi: 10.1016/0076-6879(87)54091-5
324. Sebastían D, Sorianello E, Segalés J, Zorzano A. Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. *EMBO J*. 2016;35:1677–1693. doi: 10.15252/embj.201593084
325. Chen H, Vermulst M, Wang YE, Chomyn A, Prolla TA, McCaffery JM, Chan DC. Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. *Cell*. 2010;141:280–289. doi: 10.1016/j.cell.2010.02.026
326. Favaro G, Romanello V, Varanita T, Desbats MA, Morbidoni V, Tezze C, Albiero M, Canato M, Gherardi G, De Stefani D, et al. DRP1-mediated mitochondrial shape controls calcium homeostasis and muscle mass. *Nat Commun*. 2019;10:2576. doi: 10.1038/s41467-019-10226-9
327. Varanita T, Soriano ME, Romanello V, Zaglia T, Quintana-Cabrera R, Scorrano L. The OPA1-dependent mitochondrial cristae remodeling pathway controls atrophic, apoptotic, and ischemic tissue damage. *Cell Metab*. 2015;21:834–844. doi: 10.1016/j.cmet.2015.05.007
328. Romanello V, Guadagnin E, Gomes L, Roder I, Sandri M. Mitochondrial fission and remodelling contributes to muscle atrophy. *EMBO J*. 2010;29:1774–1785. doi: 10.1038/emboj.2010.60
329. Touvier T, De Palma C, Rigamonti E, Scagliola A, Brunelli S. Muscle-specific Drp1 overexpression impairs skeletal muscle growth via translational attenuation. *Cell Death Dis*. 2015;6:e1663. doi: 10.1038/cddis.2014.595

330. Carnio S, LoVerso F, Baraibar MA, Longa E, Khan MM, Maffei M, Reischl M, Canepari M, Loefler S, Kern H, et al. Autophagy impairment in muscle induces neuromuscular junction degeneration and precocious aging. *Cell Rep*. 2014;8:1509–1521. doi: 10.1016/j.celrep.2014.07.061
331. Castets P, Lin S, Rion N, Di Fulvio S, Romanino K, Guridi M, Frank S, Tintignac LA, Sinnreich M, Rüegg MA. Sustained activation of mTORC1 in skeletal muscle inhibits constitutive and starvation-induced autophagy and causes a severe, late-onset myopathy. *Cell Metab*. 2013;17:731–744. doi: 10.1016/j.cmet.2013.03.015
332. Ryu D, Mouchiroud L, Andreux PA, Katsyuba E, Auwerx J. Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. *Nat Med*. 2016;22:879–888. doi: 10.1038/nm.4132
333. Segalés J, Perdiguero E, Serrano AL, Muñoz-Cánoves P. Sestrin prevents atrophy of disused and aging muscles by integrating anabolic and catabolic signals. *Nat Commun*. 2020;11:189. doi: 10.1038/s41467-019-13832-9
334. Singh A, D'Amico D, Andreux PA, Rinsch C. Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. *Cell Rep Med*. 2022;3:100633. doi: 10.1016/j.xcrm.2022.100633
335. Liu S, Faitg J, Tissot C, Konstantopoulos D, Laws R, Bourdier G, Andreux PA, Davey T, Gallart-Ayala H, Ivanisevic J, et al. Urolithin A provides cardioprotection and mitochondrial quality enhancement preclinically and improves human cardiovascular health biomarkers. *iScience*. 2025;28:111814. doi: 10.1016/j.isci.2025.111814
336. Holloway GP, Holwerda AM, Miotto PM, Dirks ML, Verdijk LB, van Loon LJC. Age-associated impairments in mitochondrial ADP sensitivity contribute to redox stress in senescent human skeletal muscle. *Cell Reports*. 2018;22:2837–2848. doi: 10.1016/j.celrep.2018.02.069
337. Park S-J, Gavrilova O, Brown AL, Soto JE, Chung JH. DNA-PK promotes the mitochondrial, metabolic, and physical decline that occurs during aging. *Cell Metab*. 2017;26:447. doi: 10.1016/j.cmet.2017.04.008
338. Migliavacca E, Tay SKH, Patel HP, Sonntag T, Civiletto G, McFarlane C, Feige JN. Mitochondrial oxidative capacity and NAD+ biosynthesis are reduced in human sarcopenia across ethnicities. *Nat Commun*. 2019;10:5808. doi: 10.1038/s41467-019-13694-1
339. Bell CG, Lowe R, Adams PD, Baccarelli AA, Beck S, Bell JT, Christensen BC, Gladyshev VN, Heijmans BT, Horvath S, et al. DNA methylation aging clocks: challenges and recommendations. *Genome Biol*. 2019;20:249. doi: 10.1186/s13059-019-1824-y
340. Voisin S, Harvey NR, Haupt LM, Griffiths LR, Eynon N. An epigenetic clock for human skeletal muscle. *J. Cachexia Sarcopenia Muscle*. 2020;11:887–898. doi: 10.1002/jcsm.12556
341. Koster A, Ding J, Stenholm S. Does the amount of fat mass predict age-related loss of lean muscle mass, strength, and muscle quality in older adults? *J Gerontol A Biol Sci Med Sci*. 2011;66:888–895. doi: 10.1093/gerona/glr070
342. Lexell J, Downham D. What is the cause of the aging atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci*. 1988;72:275–294. doi: 10.1016/0022-510x(88)90132-3
343. Forsberg AM, Nilsson E, Werneman J, Bergström J, Hultman E. Muscle composition in relation to age and sex. *Clin Sci (Lond)*. 1991;81:249–256. doi: 10.1042/cs0810249
344. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr*. 1997;127:990S–991S. doi: 10.1093/jn/127.5.990s
345. Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. *J Cachexia Sarcopenia Muscle*. 2016;7:512–514. doi: 10.1002/jcsm.12147
346. Westbury LD, Beaudart C, Bruyère O, Cauley JA, Cawthon P, Cruz-Jentoft AJ, Curtis EM, Ensrud K, Fielding RA, Johansson H, et al; International Musculoskeletal Ageing Network. Recent sarcopenia definitions-prevalence, agreement and mortality associations among men: findings from population-based cohorts. *J Cachexia Sarcopenia Muscle*. 2023;14:565–575. doi: 10.1002/jcsm.13160
347. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. *J Cachexia Sarcopenia Muscle*. 2014;5:253–259. doi: 10.1007/s13539-014-0161-y
348. Lagunas-Rangel FA. Aging insights from heterochronic parabiosis models. *NPJ Aging*. 2024;10:38. doi: 10.1038/s41514-024-00166-0
349. Janssen I, Ross R. Linking age-related changes in skeletal muscle mass and composition with metabolism and disease. *J Nutr Health Aging*. 2005;9:408–419.
350. Schaap LA, Plujm SM, Deeg DJ. Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength. *J Gerontol A Biol Sci Med Sci*. 2009;64:1183–1189. doi: 10.1093/gerona/glp097
351. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the US. *Diabetes Care*. 2006;29:2415–2419. doi: 10.2337/dc06-1058
352. Di Raimondo D, Musiari G, Miceli G, Arnao V, Pinto A. Preventive and therapeutic role of muscle contraction against chronic disease. *Curr Pharm Des*. 2016;22:4686–4699. doi: 10.2174/1381612822666160510125011
353. Izquierdo M, Merchant RA, Morley JE, Anker SD, Singh MF. International exercise recommendations in older adults (ICFSR): expert consensus guidelines. *J Nutr Health Aging*. 2021;25:824–853. doi: 10.1007/s12603-021-1665-8
354. Ivey FM, Tracy BL, Lemmer JT, NessAiver M, Metter EJ, Fozard JL, Hurley BF. Effects of strength training and detraining on muscle quality: age and gender comparisons. *J Gerontol A Biol Sci Med Sci*. 2000;55:B152–7; discussion B158. doi: 10.1093/gerona/55.3.b152
355. Lindle RS, Metter EJ, Lynch NA, Fleg JL, Fozard JL, Tobin J, Roy TA, Hurley BF. Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. *J Appl Physiol (1985)*. 1997;83:1581–1587. doi: 10.1152/jappl.1997.83.5.1581
356. Roepstorff C, Thiele M, Hillig T, Pilegaard H, Richter EA, Wojtaszewski JFP, Kiens B. Higher skeletal muscle alpha2AMPK activation and lower energy charge and fat oxidation in men than in women during submaximal exercise. *J Physiol*. 2006;574:125–138. doi: 10.1113/jphysiol.2006.108720
357. Simoneau JA, Bouchard C. Human variation in skeletal muscle fiber-type proportion and enzyme activities. *Am J Physiol*. 1989;257:E567–E572. doi: 10.1152/ajpendo.1989.257.4.E567
358. Staron RS, Hagerman FC, Hikida RS, Murray TF, Hostler DP, Crill MT, Ragg KE, Toma K. Fiber type composition of the vastus lateralis muscle of young men and women. *J Histochem Cytochem*. 2000;48:623–629. doi: 10.1177/002215540004800506
359. Tarnopolsky MA. Sex differences in exercise metabolism and the role of 17-beta estradiol. *Med Sci Sports Exerc*. 2008;40:648–654. doi: 10.1249/MSS.0b013e31816212ff
360. Welle S, Tawil R, Thornton CA. Sex-related differences in gene expression in human skeletal muscle. *PLoS One*. 2008;3:e1385. doi: 10.1371/journal.pone.0001385
361. Ferguson L, Giza CC, Serpa RO, Greco T, Robert H, Folkerts M, Prins ML. Sex differences in neurophysiological changes following voluntary exercise in adolescent rats. *Front Neurol*. 2021;12:685822. doi: 10.3389/fneur.2021.685822
362. Ghimire PS, Eckart A, Al-Makhzoomy IK, Stavitz J. Sex differences in bone, muscle, and inflammatory markers and their associations with muscle performance variables. *Sports (Basel)*. 2023;11:215. doi: 10.3390/sports11110215
363. Norton A, Thieu K, Baumann CW, Lowe DA, Mansky KC. Estrogen regulation of myokines that enhance osteoclast differentiation and activity. *Sci Rep*. 2022;12:15900. doi: 10.1038/s41598-022-19438-4
364. Raafat F, Castro R, Booth IW. Eosinophilic proctitis with giant cells: a manifestation of cow's milk protein intolerance. *J Pediatr Gastroenterol Nutr*. 1990;11:128–132. doi: 10.1097/00005176-199007000-00025
365. Yang X, Brobst D, Chan WS, Tse MCL, Chan CB. Muscle-generated BDNF is a sexually dimorphic myokine that controls metabolic flexibility. *Sci Signal*. 2019;12:eaau1468. doi: 10.1126/scisignal.aau1468
366. Parker L, Caldow MK, Watts R, Levinger I. Age and sex differences in human skeletal muscle fibrosis markers and transforming growth factor-beta signaling. *Eur J Appl Physiol*. 2017;117:1463–1472. doi: 10.1007/s00421-017-3639-4
367. Peng L-N, Lee W-J, Liu L-K, Lin M-H, Chen L-K. Healthy community-living older men differ from women in associations between myostatin levels and skeletal muscle mass. *J Cachexia Sarcopenia Muscle*. 2018;9:635–642. doi: 10.1002/jcsm.12302
368. Liu L, Kim S, Buckley MT, Reyes JM, Rando TA. Exercise reprograms the inflammatory landscape of multiple stem cell compartments during mammalian aging. *Cell Stem Cell*. 2023;30:689–705. doi: 10.1016/j.stem.2023.03.016
369. Hubbard RE, Rockwood K. Frailty in older women. *Maturitas*. 2011;69:203–207. doi: 10.1016/j.maturitas.2011.04.006
370. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, Rockwood K. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *J Am Geriatr Soc*. 2005;53:2184–2189. doi: 10.1111/j.1532-5415.2005.00506.x

371. Santos AL, Sinha S. Obesity and aging: molecular mechanisms and therapeutic approaches. *Ageing Res Rev*. 2021;67:101268. doi: 10.1016/j.arr.2021.101268
372. Van Herper NA, Schrauwen-Hinderling VB. Lipid accumulation in non-adipose tissue and lipotoxicity. *Physiological Behav*. 2008;94:231–241. doi: 10.1016/j.physbeh.2007.11.049
373. Karakelides H, Irving BA, Short KR, O'Brien P, Nair KS. Age, obesity, and sex effects on insulin sensitivity and skeletal muscle mitochondrial function. *Diabetes*. 2010;59:89–97. doi: 10.2337/db09-0591
374. Lalia AZ, Dasari S, Johnson ML, Robinson MM, Konopka AR, Distelmaier K, Port JD, Glavin MT, Esponda RR, Nair KS, et al. Predictors of whole-body insulin sensitivity across ages and adiposity in adult humans. *J Clin Endocrinol Metab*. 2016;101:626–634. doi: 10.1210/jc.2015-2892
375. Tandon P, Wafer R, Minchin JEN. Adipose morphology and metabolic disease. *J Exp Biol*. 2018;221:jef164970. doi: 10.1242/jeb.164970.
376. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes (Lond)*. 2010;34:949–959. doi: 10.1038/ijo.2009.286
377. Liuzzi A, Savia G, Tagliaferri M, Lucantoni R, Berselli ME, Petroni ML, De Medici C, Viberti GC. Serum leptin concentration in moderate and severe obesity: relationship with clinical, anthropomorphic and metabolic factors. *Int J Obes Relat Metab Disord*. 1999;23:1066–1073. doi: 10.1038/sj.ijo.0801036
378. Tai E, Lau TN, Ho SC, Fok ACK, Tan CE. Body fat distribution and cardiovascular risk in normal weight women. Associations with insulin resistance, lipids, and plasma leptin. *Int J Obes*. 2000;24:751–757. doi: 10.1038/sj.ijo.0801220
379. Pfannenberg C, Werner MK, Ripkens S, Stef I, Deckert A, Schmadl M, Reimold M, Häring H-U, Claussen CD, Stefan N. Impact of age on the relationship of brown adipose tissue with sex and adiposity in humans. *Diabetes*. 2010;59:1789–1793. doi: 10.2337/db10-0004
380. Yoneshiro T, Aita S, Matsushita M, Okamatsu-Ogura Y, Kameya T, Kawai Y, Miyagawa M, Tsujisaki M, Saito M. Age-related decrease in cold-activated brown adipose tissue and accumulation of body fat in healthy humans. *Obesity*. 2011;19:1755–1760. doi: 10.1038/oby.2011.125
381. Powell-Wiley TM, Poirier P, Burke LE, Després J-P, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, et al; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e984–e1010. doi: 10.1161/CIR.0000000000000973
382. Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–313. doi: 10.1056/NEJMoa020245
383. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci*. 2017;13:851–863. doi: 10.5114/aoms.2016.58928
384. Park SW, Goodpaster BH, Strotmeyer ES, Kuller LH, Broudeau R, Kammerer C, de Rekeneire N, Harris TB, Schwartz AV, Tylavsky FA, et al; Health, Aging, and Body Composition Study. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the health, aging, and body composition study. *Diabetes Care*. 2007;30:1507–1512. doi: 10.2337/dc06-2537
385. Schrager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F, Ferrucci L. Sarcopenic obesity and inflammation in the InCHIANTI study. *J Appl Physiol (1985)*. 2007;102:919–925. doi: 10.1152/japplphysiol.00627.2006
386. Almond RE, Enser M. A histochemical and morphological study of skeletal muscle from obese and hyperglycaemic ob/ob mice. *Diabetologia*. 1984;27:407–413. doi: 10.1007/BF00304859
387. Aoyama H, Ohara H, Oze Y, Itani T. Recent trends in research on occupational cervicobrachial disorder. *J Hum Ergol (Tokyo)*. 1979;8:39–45. doi: 10.11183/JHE1972.8.39.
388. Stickland NC, Batt RA, Crook AR, Sutton CM. Inability of muscles in the obese mouse (ob/ob) to respond to changes in body weight and activity. *J Anat*. 1994;184 (Pt 3):527–533.
389. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. *Eur J Clin Invest*. 2002;32(Suppl. 3):14–23. doi: 10.1046/j.1365-2362.32.s3.3.x
390. Arner P. Differences in lipolysis between human subcutaneous and omental adipose tissue. *Ann Med*. 1995;27:435–438. doi: 10.3109/07853899709002451
391. Adams JM, Pratipanawatr T, Berria R, Wang E, DeFronzo RA, Sullards MC, Mandarino LJ. Ceramide content in increased in skeletal muscle from obese insulin-resistant humans. *Diabetes*. 2004;53:25–31. doi: 10.2337/diabetes.53.1.25
392. Pang S, Tang H, Zhuo S, Zang YQ, Le Y. Regulating of fasting fuel metabolism by toll-like receptor 4. *Diabetes*. 2010;59:3041–3048. doi: 10.2337/db10-0418
393. Straczkowski M, Kowalska I, Nikolajuk A, Dzienis-Straczkowska S, Kinalska I, Baranowski M, Zendzian-Piotrowska M, Brzezinska Z, Gorski J. Relationship between insulin sensitivity and sphingomyelin signaling pathway in human skeletal muscle. *Diabetes*. 2004;53:1215–1221. doi: 10.2337/diabetes.53.5.1215
394. Han F, Zhang S, Hou N, Wang D, Sun X. Irisin improves endothelial function in obese mice through the AMPK-eNOS pathway. *Am J Physiol Heart Circ Physiol*. 2015;309:H1501–H1508. doi: 10.1152/ajpheart.00443.2015
395. Hou N, Han F, Sun X. The relationship between circulating irisin levels and endothelial function in lean and obese subjects. *Clin Endocrinol (Oxf)*. 2015;83:339–343. doi: 10.1111/cen.12658
396. Huh JH, Ahn SV, Choi JH, Koh SB, Chung CH. High serum irisin level as an independent predictor of diabetes mellitus: a longitudinal population-based study. *Medicine (Baltimore)*. 2016;95:e3742. doi: 10.1097/MD.0000000000003742
397. Allen DL, Hittel DS, McPherron AC. Expression and function of myostatin in obesity, diabetes, and exercise adaptation. *Med Sci Sports Exerc*. 2011;43:1828–1835. doi: 10.1249/MSS.0b013e3182178bb4
398. Hittel DS, Berggren JR, Shearer J, Boyle K, Houmard JA. Increased secretion and expression of myostatin in skeletal muscle from extremely obese women. *Diabetes*. 2009;58:30–38. doi: 10.2337/db08-0943
399. Tran DH, Wang ZV. Glucose metabolism in cardiac hypertrophy and heart failure. *J Am Heart Assoc*. 2019;8:e012673. doi: 10.1161/JAHA.119.012673
400. Wende AR, Kim J, Holland WL. Glucose transporter 4-deficient hearts develop maladaptive hypertrophy in response to physiological or pathological stress. *Am J Physiol Heart Circ Physiol*. 2017;313:H1098–H1108. doi: 10.1152/ajpheart.00101.2017
401. Begriche K, Massart J, Abbey-Toby A, Igoudjil A, Lettéron P, Fromenty B. Beta-aminoisobutyric acid prevents diet-induced obesity in mice with partial leptin deficiency. *Obesity (Silver Spring)*. 2008;16:2053–2067. doi: 10.1038/oby.2008.337
402. World Health Organization. *WHO Guidelines on Physical Activity and Sedentary Behavior: At a Glance*. World Health Organization; 2020.
403. Blair S, Sallis R, Hutber A, Archer E. Exercise therapy—the public health message. *Scand J Med Sci Sports*. 2012;22:e22–e28. doi: 10.1111/j.1600-0838.2012.01462.x
404. Thomas MM, Phongsavan P, McGill B, O'Hara BJ, Bauman AE. A review of the impact of physical activity mass media campaigns on low compared to high socioeconomic groups. *Health Educ Res*. 2018;33:429–446. doi: 10.1093/her/cyy032
405. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012;2:1143–1211. doi: 10.1002/cphy.c110025
406. Collado-Mateo D, Lavín-Pérez AM, Peñacoba C, Del Coso J, Leyton-Román M, Luque-Casado A, Gasque P, Fernández-Del-Olmo MA, Amado-Alonso D. Key factors associated with adherence to physical exercise in patients with chronic diseases and older adults: an umbrella review. *Int J Environ Res Public Health*. 2023;18:2023. doi: 10.3390/ijerph18042023
407. Rodulfo JIA. Sedentarism, a disease from xxi century. *Clin Investig Arterioscler*. 2019;31:233–240. doi: 10.1016/j.arteri.2019.04.004
408. Young DR, Hivert MF, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT, Lewis CE, Owen N, Perry CK, Siddique J, et al; Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Stroke Council. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. *Circulation*. 2016;134:e262–e279. doi: 10.1161/CIR.0000000000000440
409. American Heart Association. *Breaking Down Barriers to Fitness*. Heart.Org; 2024. Accessed October 1, 2024. https://www.heart.org/en/healthy-living/fitness/getting-active/breaking-down-barriers-to-fitness
410. Burgess E, Hassmén P, Pumpa KL. Determinants of adherence to lifestyle interventions in adults with obesity: a systematic review. *Clin. Obes*. 2017;7:123–135. doi: 10.1111/cob.12183
411. Rodrigues IB, Armstrong JJ, Adachi JD, MacDermid JC. Facilitators and barriers to exercise adherence in patients with osteopenia and

osteoporosis: a systematic review. *Osteoporos Int*. 2017;28:735–745. doi: 10.1007/s00198-016-3793-2
412. Ozbay F, Johnson DC, Dimoulas E, Morgan CA, Charney D, Southwick S. Social support and resilience to stress: from neurobiology to clinical practice. *Psychiatry (Edgmont)*. 2007;4:35–40.
413. Leone LA, Ward DS. A mixed methods comparison of perceived benefits and barriers to exercise between obese and nonobese women. *J Phys Act Health*. 2013;10:461–469. doi: 10.1123/jpah.10.4.461
414. Morgan F, Battersby A, Weightman AL, Searchfield L, Turley R, Morgan H, Jagroo J, Ellis S. Adherence to exercise referral schemes by participants-what do providers and commissioners need to know? A systemic review of barriers and facilitators. *BMC Public Health*. 2016;16:227. doi: 10.1186/s12889-016-2882-7
415. Catala P, Lopez-Roig S, Ecija C, Suso-Ribera C, Peñacoba Puente C. Why do some people with severe chronic pain adhere to walking prescriptions whilst others won't? A cross-sectional study exploring clinical and psychosocial predictors in women with fibromyalgia. *Rheumatol Int*. 2020;41:1–6. doi: 10.1007/s00296-020-04719-w
416. Craike M, Gaskin CJ, Courneya KS, Fraser SF, Salmon J, Owen PJ, Broadbent S, Livingston PM. Predictors of adherence to a 12-week exercise program among men treated for prostate cancer: ENGAGE study. *Cancer Med*. 2016;5:787–794. doi: 10.1002/cam4.639
417. Gatt K, Schembri J, Katsanos KH, Christodoulou D, Karmiris K, Kopylov U, Pontas C, Koutroubakis IE, Foteinogiannopoulou K, Fabian A, et al. Inflammatory Bowel disease [IBD] and physical activity: a study on the impact of diagnosis on the level of exercise amongst patients with IBD. *J Crohns Colitis*. 2019;13:686–692. doi: 10.1093/ecco-jcc/jjy214
418. Midtgaard J, Baadsgaard MT, Møller T, Rasmussen B, Quist M, Andersen C, Rørth M, Adamsen L. Self-reported physical activity behaviour; exercise motivation and information among Danish adult cancer patients undergoing chemotherapy. *Eur J Oncol Nurs*. 2009;13:116–121. doi: 10.1016/j.ejon.2009.01.006
419. Bachmann C, Oesch P, Bachmann S. Recommendations for improving adherence to home-based exercise: a systematic review. *Phys Med Rehabil*. 2017;28:20–31.
420. Helgadóttir B, Hallgren M, Kullberg CL, Forsell Y. Sticking with it? Factors associated with exercise adherence in people with mild to moderate depression. *Psychol Sport Exerc*. 2018;35:104–110. doi: 10.1016/j.psychsport.2017.11.011
421. Picorelli AMA, Pereira LSM, Pereira DS, Felício D, Sherrington C. Adherence to exercise programs for older people is influenced by program characteristics and personal factors: a systematic review. *J Physiother*. 2014;60:151–156. doi: 10.1016/j.jphys.2014.06.012
422. Stubbs B, Vancampfort D, Rosenbaum S, Ward PB, Richards J, Soundy A, Veronese N, Solmi M, Schuch FB. Dropout from exercise randomized controlled trials among people with depression: a meta-analysis and meta regression. *J Affect Disord*. 2016;190:457–466. doi: 10.1016/j.jad.2015.10.019
423. Horne M, Tierney S. What are the barriers and facilitators to exercise and physical activity uptake and adherence among South Asian older adults: a systematic review of qualitative studies. *Prev Med*. 2012;55:276–284. doi: 10.1016/j.ypmed.2012.07.016
424. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, Raposeiras S, van 't Hof A, Meindersma E, Bossano Prescott EI, González-Juanatey JR. Participation and adherence to cardiac rehabilitation programs. A systematic review. *Int J Cardiol*. 2016;223:436–443. doi: 10.1016/j.ijcard.2016.08.120
425. Holliday A, Blannin A. Appetite, food intake and gut hormone responses to intense aerobic exercise of different duration. *J Endocrinol*. 2017;235:193–205. doi: 10.1530/JOE-16-0570
426. Janus C, Vistisen D, Amadid H, Witte DR, Lauritzen T, Brage S, Torekov SS. Habitual physical activity is associated with lower fasting and greater glucose-induced GLP-1 response in men. *Endocr Connect*. 2019;8:1607–1617. doi: 10.1530/EC-19-0408
427. Wilding JPH, Batterham RL, Calanna S; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384:989–1002. doi: 10.1056/NEJMoa2032183