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Fighting obesity: When muscle meets fat

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The prevalence of obesity has risen to an unprecedented level. According to World Health Organization, over 500 million adults, equivalent to 10%–14% of the world population, were obese with a body mass index (BMI) of 30 kg/m² or greater in 2008.¹ This rising prevalence and earlier onset of obesity is believed to be resulted from an interplay of genetic factors, over-nutrition and physical inactivity in modern lifestyles. Obesity also increases the susceptibility to metabolic syndromes, hypertension, cardiovascular diseases, Type 2 diabetes mellitus (T2DM) and cancer.^{2–4} The global obesity epidemic has sparked substantial interests in the biology of adipose tissue (fat). In addition, the skeletal muscle and its secretive factors (myokines) have also been shown to play a critical role in controlling body energy balance, adipose homeostasis and inflammation status.⁵ Interestingly, skeletal muscle cells share a common developmental origin with brown adipocytes,^{6,7} which breaks down lipids to generate heat – thus reducing obesity. Here, we provide a brief overview of the basics and recent progress in muscle-fat crosstalk in the context of body energy metabolism, obesity, and diabetes. We summarize the different types of adipocytes, their developmental origins and implications in body composition. We highlight the role of several novel myokines in regulating fat mass and systemic energy balance, and evaluate the potential of skeletal muscles as a therapeutic target to treat obesity.

Characterization and Origin of Brown, White and Beige Adipocytes

White and brown adipocytes are 2 types of commonly known fat cells in mammals.⁸ White adipocytes are characterized by a spherical shape, a large single lipid droplet that takes up to 90% of the total cell volume, and few mitochondria.⁹ White adipocytes constitute the bulky white adipose tissues (WAT) located under the skin (subcutaneous fat), in the muscle (intramuscular fat or “marbling” fat), and in the abdominal cavity attached to the visceral mass (visceral fat).¹⁰ They store excess food intake (or energy surplus) in the form of triglycerides, which can be utilized to generate energy under energy deficit conditions. In contrast, brown adipocytes contain multilocular lipid droplets and numerous mitochondria.⁹ They are found in brown adipose tissues

(BAT) mainly located in the interscapular regions of rodents and human infants.^{10,11} Unlike white adipocytes, brown adipocytes break down lipids to produce heat, thus reducing adiposity. The thermogenesis of brown adipocytes is mediated by uncoupling protein 1 (UCP1) that is uniquely located in their inner mitochondria membrane. Of note, uncoupling activity of UCP1 is under control by sympathetic innervation¹² as well as other factors like free fatty acids from lipolysis.¹³ The thermogenic “energy-leaking” feature of brown adipocytes has made BAT an appealing therapeutic target for treating obesity.¹⁴

Although brown and white adipocytes share multiple morphological and functional similarities, their developmental origins are surprisingly different (Fig. 1). Recent studies have revealed a vascular or perivascular localization of white adipocyte progenitors, and identified several molecular markers of these cells (for example Zfp423, VE-Cad, PDGFR β , and PDGFR α).^{15–18} However, the anatomical localization of brown adipocyte progenitors has not been reported. Interestingly, classic brown fat, but not white fat, shares a developmental origin with the skeletal muscle. Lineage tracing studies demonstrate that muscle and brown fat are from a population of mesodermal progenitors that express myogenic marker genes Myf5, Pax7 and Pax3.^{6,19,20} Furthermore, brown adipocytes and muscle cells share a similar mitochondrial proteomic signature²¹ and both contribute to thermogenesis.^{22,23} In fact, brown fat precursors express a variety of myogenic genes prior to differentiation.²⁴ This is followed by progressive loss of myogenic signature gene expression during brown fat maturation. Recent studies have begun to elucidate factors that diverge brown adipose from muscle development. Particularly, PRDM16 (PRD1-BF-1-RIZ1 homologous domain-containing protein-16) has been shown to be a bidirectional switch that determines BAT versus muscle fate.⁶ Loss of PRDM16 in brown preadipocytes leads to a phenotypic switch to muscle cells, while ectopic expression of PRDM16 in myoblasts switches them back to brown adipocytes.⁶ More recently, it was reported that miR-133 acts as an upstream regulator of PRDM16 to control skeletal muscle vs. BAT fate choice in muscle stem cells (satellite cells).²⁵ Although BAT-specific deletion of PRDM16 does not affect embryonic BAT development, it promotes white fat-specific gene expression in BAT in young mice and attenuates thermogenesis in old mice.²⁶ These lines of evidence suggest that BAT originates differently from WAT, but shares developmental similarities with skeletal muscles.

It has long been known that when rodents are exposed to cold stress or β -adrenergic stimulating drugs, certain depots of WAT undergo a “browning” process, giving rise to brown adipocyte-like

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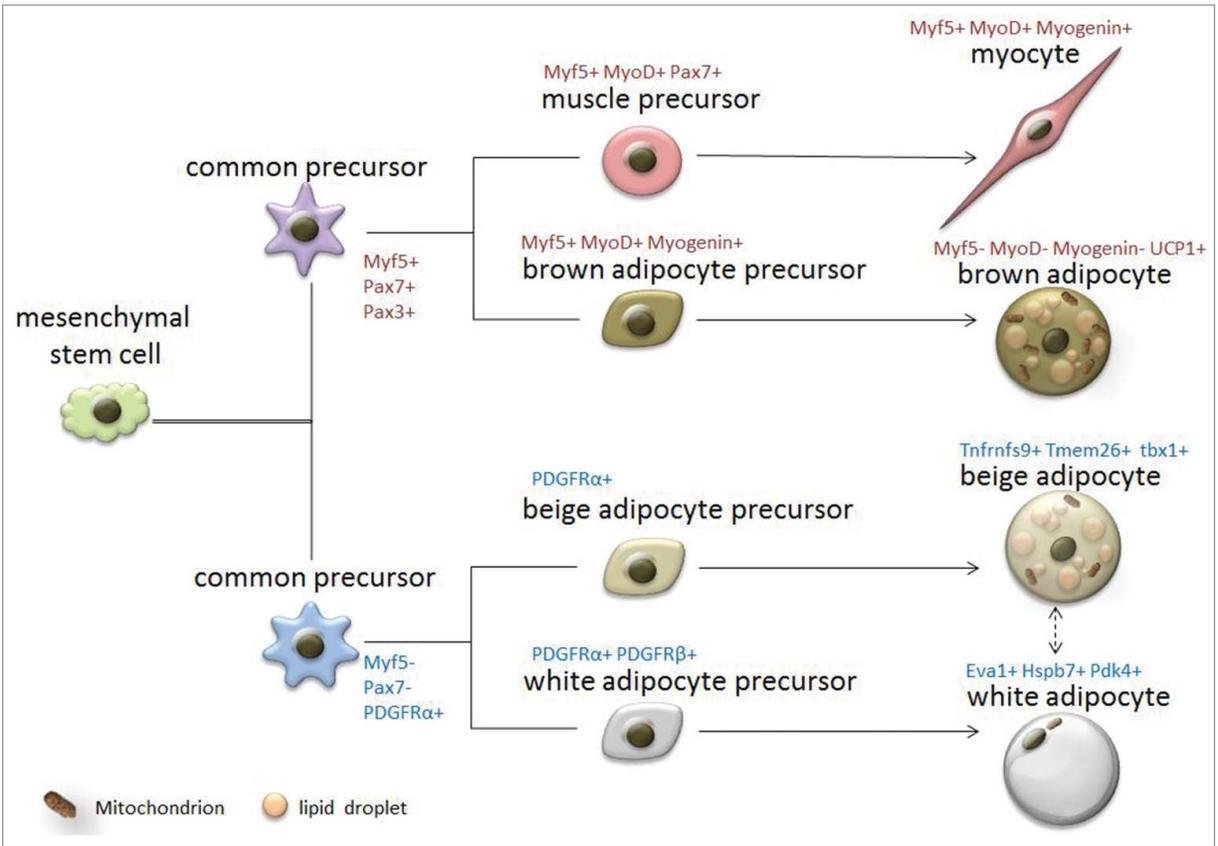


Figure 1. Origin of brown, white and beige adipocytes. Two types of common precursors of muscle/fat lineage are derived from mesenchymal stem cells. These 2 types of common precursors are distinguished by Myf5, Pax7, Pax3 and PDGFR α expression. Myf5 $^{+}$, Pax7 $^{+}$ and Pax3 $^{+}$ common precursors give rise to specified muscle or brown adipose precursors that differentiate into either mature myocytes (Myf5 $^{+}$, MyoD $^{+}$, Myogenin $^{+}$) or brown adipocytes (UCP1 $^{+}$), respectively. Myf5 $^{-}$, Pax3 $^{-}$, Pax7 $^{-}$ and PDGFR α $^{+}$ common precursors give rise to specified beige or white adipose precursors that differentiate into either mature beige adipocytes (Tnfrnf9 $^{+}$, Tmem26 $^{+}$, Tbx1 $^{+}$) or white adipocytes (Eva1 $^{+}$, Hspb7 $^{+}$, Pdk4 $^{+}$), respectively. The interconversion of mature beige and white adipocytes may occur under environmental stimulus.

cells (called beige or brite adipocytes) with multilocular lipid droplets, UCP1 expression and thermogenic activity.²⁷ However, whether adult humans have a similar capacity to form inducible BAT (iBAT) has been unclear. Recently, advanced imaging analysis using positron emission tomography (PET) revealed that in cold conditions, active “brown-like” adipocytes form along the cervical-supraclavicular area in human adults.^{28–31} These cells retain radioactive fluorodeoxyglucose, suggesting that they actively uptake and utilize glucose. Different from classic WAT and BAT, iBAT is characterized by the presence of beige adipocytes.³² Beige cells specifically express several marker genes (for example, Tnfrnf9, Tmem26 and Tbx1 in mice and HOXC8, HOXC9 and CITED1 in humans) that are not expressed by white or brown adipocytes. In contrast, brown adipocytes uniquely express several marker genes (for example, Eva1, Hspb7 and Pdk4 in mouse and EPST11, LHX8 and ZIC1 in human) that are not shared by beige or white cells.³³ Notably, genetic analysis of human iBAT suggests it contains both brown and beige adipocytes.^{34,35}

Beige adipocytes can be differentiated *de novo* from precursors or transdifferentiate from mature white adipocytes (Fig. 1). Beige cell precursors are believed to be enriched in Pax3 $^{+}$ cell

lineage.³⁶ A study using Adiponectin-Cre combined with Tert inducible lacZ mice (named Adipo-chaser mice) shows that in response to cold stimulation, preadipocytes in subcutaneous fat undergo *de novo* differentiation to form beige cells, while abdominal beige fat cells accumulate through proliferation.³⁷ Using EdU labeling combined with β 3-adrenergic receptor stimulation, it was shown that the mitotic index was 7.5 times higher in epididymal WAT than inguinal WAT. Interestingly, UCP1 co-localizes with a fraction of the proliferating cells.³⁸ Together, these studies suggest the existence of beige preadipocytes. It is worth mentioning that an independent study identified a population of beige precursors within skeletal muscle that respond to bone morphogenetic protein 7 (BMP7) stimulation.⁷ On the other hand, interconversion of white and beige adipocytes has also been observed. Even before the characterization of beige cells, it was reported that white adipose precursors do not increase in response to cold acclimation, and iBAT formation is predominantly due to β 3-adrenergic receptor-dependent transdifferentiation of white adipocytes.³⁹ Indeed, murine perivascular Pdgfra $^{+}$ cells differentiate into beige adipocytes upon β -adrenergic receptor stimulation, but become white adipocytes in

response to high fat diet (HFD) feeding.⁴⁰ Based on these studies, cold can induce de novo formation of beige adipocytes from a population of beige precursor cells. These beige adipocytes are plastic: they can become white adipocytes upon warm adaption and switch back to beige adipocytes after additional cold stimulation. Beige cell formation is regulated by many factors. Among these, inhibition of Prdm16 blocks the function of beige adipose and induces redistribution of subcutaneous white fat to unfavorable visceral fat, resulting in obesity and metabolic disorders.⁴¹ On the contrary, inhibition of Notch signaling dramatically promotes “browning” of white adipocyte through activating Prdm16 and Pparg (Peroxisome proliferator-activated receptor gamma). Importantly, the Notch inhibitor dibenzazepine (DBZ) effectively reduces adiposity and improves glucose metabolism in ob/ob mice.⁴² Further understanding of mechanisms underlying beige cell development and adipose “browning” will have a huge impact in the treatment of obesity.

Adipose depots at different anatomical locations not only differ in the relative composition of brown, beige and white adipocytes,⁸ but are also heterogeneous in developmental origins.⁴³⁻⁴⁶

Classic brown adipose depots include interscapular BAT (isBAT), subscapular BAT (sBAT), cervical BAT (cBAT), peri-aortic BAT (paBAT) and renal BAT (rBAT), whereas white adipose depots include anterior subcutaneous WAT (asWAT), inguinal WAT (inWAT), retroperitoneal WAT (rWAT), gonadal WAT (gWAT), mesenteric WAT (mWAT), and intramuscular fat (IMAT)^{8,44,45,47,48} (Fig. 2). The white adipose depots can also be broadly divided into subcutaneous WAT (asWAT and inWAT) and visceral WAT (sWAT, rWAT and gWAT). IMAT refers to adipocytes located in muscle interstitium and is different from the intramyocellular triglycerides, which refer to cellular lipid droplets within muscle cells. Developmentally, visceral WAT develops from the lateral plate mesoderm Wnt⁺ cells whereas no subcutaneous or BAT were found to come from the Wnt⁺ population.⁴⁶ A recent in vivo lineage tracing experiment employing the Myf5-Cre, Myod-Cre, Pax3-Cre mice models combined with mTmG dual reporter mice shows that while isBAT depot contains 99% Myf5 lineage adipocytes, cBAT had only ~60% Myf5 lineage adipocytes. Myf5 lineage cells also contribute to 25% and 50% of asWAT and rWAT progenitors,

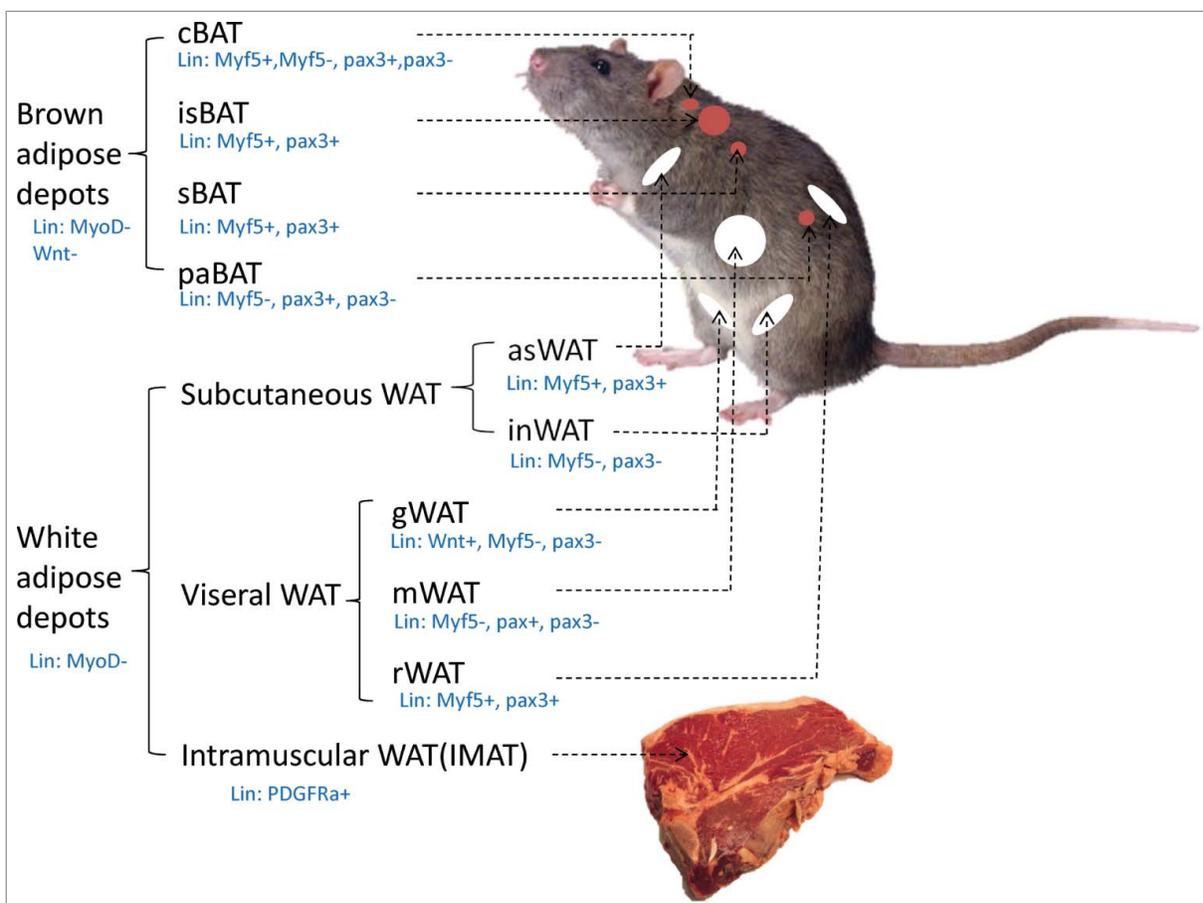


Figure 2. Distribution of various adipose depots Adipose tissues are generally divided into brown adipose depots and white adipose depots. Brown adipose depots include interscapular BAT (isBAT), subscapular BAT (sBAT), cervical BAT (cBAT), peri-aortic BAT (paBAT) and renal BAT (rBAT). White adipose depots include anterior subcutaneous WAT (asWAT), inguinal WAT (inWAT), retroperitoneal WAT (rWAT), gonadal WAT (gWAT), mesenteric WAT (mWAT), and intramuscular fat (IMAT).

respectively. Pax3 lineage tracing shows similar results, but interestingly, shows gender differences in various depots especially in rBAT and gWAT.⁴⁵ These experiments together suggest that depot-specific origin of adipose tissues is under combined influences of genetic, breeds, age, gender and even seasons.

Role of Skeletal Muscle in Body Energy Balance

Obesity results from an energy surplus (i. e. greater energy intake than expenditure). As the largest organ in the body, the skeletal muscle comprises ~40% of body mass⁴⁹ and serves as one of the major regulators of body energy homeostasis. Even under severe obese conditions, skeletal muscles still account for ~25% of body mass and remain metabolically active to a certain extent. In order to satisfy the structural and functional needs for skeletal muscle, massive amounts of energy are utilized for muscle protein synthesis and motor function under both resting and exercise conditions. Skeletal muscles mainly utilize glucose as the energy source, but can also utilize free fatty acids (FFA) and amino acids (AA) as fuels or structural “building blocks.” Thus, the skeletal muscle can affect not only glucose, but also fat and protein homeostasis in the body.

Skeletal muscles uptake ~75% of ingested carbohydrate from meals.⁵⁰ Postprandial plasma glucose is primarily taken up through glucose transporter 4 (GLUT4) facilitated infusion, and then subjected to glycolysis, oxidative phosphorylation, or glycogen synthesis depending on individual activity levels. The process of glucose uptake and catabolism during muscle activity contributes to a negative energy balance. Contraction and insulin stimulation are 2 main activators of muscle glucose uptake.⁵¹

Muscle contraction directly stimulates glucose uptake predominantly through activation of AMP-activate protein kinase (AMPK), which increases GLUT4 translocation to the muscle cell membrane (sarcolemma).^{52,53} Briefly, muscle contraction increases the ratio of AMP/ATP, which is detected by energy sensor AMPK. The activated AMPK then phosphorylates TBC1 (Tre-2/USP6, BUB2, Cdc16) domain family member 4 and 1 (TBC1D4 and TBC1D1), leading to the release of GLUT4 from cytoplasmic storage vesicles to the sarcolemma.⁵² Differential phenotypes of mice lacking AMPK α , β , or γ subunit suggest that each subunit has a unique role in regulating muscle glucose uptake.⁵⁴⁻⁵⁸ AMPK-independent mechanisms may also be involved in skeletal muscle glucose uptake. For example, the antioxidant N-acetyl-L-cysteine (NAC) and the nitric oxide synthase (NOS) inhibitor N(G)-monomethyl-L-arginine (l-NMMA) can attenuate contraction stimulated glucose uptake in both wild type and muscle specific AMPK α 2 knockout mice.⁵⁹ As an energy “sensor” and regulatory molecule, AMPK also inhibits glycogen synthesis, promotes fatty acid oxidation, and enhances mitochondria oxidation in contracting muscle cells. AMPK also promotes exercise-mediated improvements in insulin sensitivity through mechanisms involving interleukin 6 (IL-6), adiponectin, IR, IRS, and mTOR.⁵² Human studies indicate that AMPK mRNA and protein levels are down-regulated in obese subjects

but elevated by exercise, suggesting the potential of AMPK mimetic as therapeutic agents to treat obesity and insulin resistance. In fact, metformin, an AMPK activating compound, has been used as the first-line drug in current clinical treatments of diabetes.^{60,61} The most updated meta-analyses also indicate that metformin also reduces colorectal, liver, pancreatic and stomach cancer risks in diabetic patients.⁶²

Insulin stimulates muscle glucose uptake and disposal through the IR-IRS-PI3K pathway. Insulin binding to the insulin receptor (IR) activates the intrinsic tyrosine kinase of IR β -subunit, which phosphorylates insulin receptor substrate 1 (IRS-1). Phospho-IRS-1 docks class I phosphatidylinositol-3-kinase (PI3K), which phosphorylates Akt and atypical protein kinase C zeta (aPKC ζ), leading to GLUT4 translocation. Insulin resistance commonly associated with obesity and T2DM describes the condition of reduced cellular responsiveness to circulating insulin, resulting in the hyperinsulinemia, hyperglycemia and hyperlipidemia. Insulin resistance dampens insulin signaling transduction without damaging the structures needed for glucose uptake, since insulin resistant human skeletal muscles exhibit normal GLUT4 translocation when stimulated by contraction or hypoxia.^{63,64} As ~80% of body insulin stimulated glucose uptake is mediated by the skeletal muscle,⁵² skeletal muscle insulin resistance can be devastating, and can lead to a vicious circle of insulin resistance and metabolic disorders. Thus, exercise therapies and pharmaceutical compounds that improve muscle insulin sensitivity represent a promising direction to treat Type 2 diabetes and other metabolic syndromes.

In addition to glucose, skeletal muscle also utilizes fatty acids and proteins depending on availability of substrates. This adaptive process is known as “metabolic flexibility.” During fasting, fatty acid oxidation (FAO) accounts for up to 90% of muscle energy supply. Healthy human skeletal muscle actively catabolizes non-esterified fatty acid (NEFA) via hormone-sensitive lipoprotein lipase (LPL), while muscles of obese or T2DM patients show nearly diminished NEFA uptake and deficiency in FAO.⁶⁵ The impaired FFA metabolism potentially causes ectopic lipid accumulation in skeletal muscle, liver, and heart; increasing the risk of insulin resistance and metabolic disorders. The impaired FFA metabolism may be associated with mitochondrial mass reduction or functional disruption, such as inhibition of carnitine palmitoyltransferase 1 (CPT-1) mediated lipid transport and ROS inactivation of mitochondrial membrane enzymes.^{65,66}

The skeletal muscle is also highly active in protein metabolism since it requires rapid protein synthesis and degradation for maintaining muscle turnover. Proteins also serve as a source of energy for muscle contraction under extreme fasting conditions. Increased levels of plasma amino acids (AA) and decreased skeletal muscle protein synthesis were evident in obese animal models.⁶⁷ Skeletal muscle protein metabolism is regulated by complex mechanisms. Mammalian target of rapamycin (mTOR), especially the mTOR complex 1 (mTORC1), is the most important regulator of skeletal muscle mass and protein synthesis in response to high plasma AA concentration. Activation of mTOR initiates canonical muscle protein synthesis

pathways, and interestingly, partially decreases autophagic influx that facilitates protein degradation.⁴⁹

Myokines Regulate Body Fat Composition and Inflammation Status

Skeletal muscle is not only a motor organ but also an endocrine organ releasing small secretive molecules known as myokines. Broadly speaking, “peptides or proteins that are produced, expressed and released by muscle fibers and exert a paracrine or endocrine effect” are referred to as myokines.⁶⁸⁻⁷¹ Myokines often alter body energy utilization and inflammatory status, therefore affecting weight gain and fat composition. Common myokines include irisin, myostatin, interleukins (IL6, 7, 8, 15), Leukemia Inhibitory Factor (LIF), among others.⁵

Irisin is a short peptide cleaved from the extracellular domain of the *Fndc5* (fibronectin domain-containing 5). *Fndc5* mRNA is abundantly expressed in the heart, brain, rectum and skeletal muscle and moderately in the intracranial artery, tongue and optic nerve.⁷²⁻⁷⁴ The expression pattern implies that irisin may exert functions on multiple tissues. One example is that exercising mice have elevated *Fndc5* in their hippocampus, suggesting that *Fndc5* positively regulates neural activities.⁷⁵ Another example is the original discovery demonstrating irisin as an “exercise hormone” secreted by skeletal muscle. Once secreted, irisin circulates through the bloodstream to fat tissues, where it promotes browning of white adipocytes.⁷⁶ The irisin mediated “browning” of WAT depends on proliferator-activated receptor γ coactivator 1 α (PGC1- α).⁷⁷ The “browning” can be synergistically enhanced by fibroblast growth factor21 (FGF21), a cold-induced myokine.⁷⁸⁻⁸⁰ Irisin also serves as a focal regulator of muscle cell metabolism through promoting mitochondria biogenesis and metabolic gene expression.⁸¹ Besides its hormonal function, *Fndc5* may serve as a transmembrane signaling protein.⁸² However, contradictory results regarding association between plasma irisin levels and insulin sensitivity have been reported in human studies.⁸³ For example, obesity and T2DM are reported to be negatively correlated with irisin/ *FNDC5* secretion and mRNA expression.^{84,85} In contrast, high levels of baseline plasma irisin are correlated with insulin resistance in obese patients, implying the possibility of “irisin resistance”.⁸⁶ In cell culture experiments, palmitate and glucose treatments that partially mimics diabetic and obese situations decrease muscle cell *FNDC5* mRNA expression.⁸⁵ Other studies show that neither acute nor long term exercise significantly improves circulating irisin level or brown fat gene expression, despite elevated irisin/*Fndc5* expression in muscle.^{84,85} Another independent study reports that the human *FNDC5* gene start codon is mutated, and irisin treatment does not increase human brite cell formation *in vitro*.⁸⁷ Although the majority of studies support the idea that irisin/*Fndc5* mediates the “crosstalk” of skeletal muscles to other tissues in rodents,^{80,88} whether the effect of irisin can be translated to humans remains to be confirmed.

Myostatin (Mstn), also called growth/differentiation factor 8 (GDF8), is another extensively studied and well-established

myokine. Mstn belongs to the highly conserved TGF- β family and its absence causes dramatic increases of muscle cell size (hypertrophy) in humans, mice, cattle and other mammals.⁸⁹⁻⁹² Mstn also affects other tissues such as adipose and bone.⁹³ In addition to muscle hypertrophy, reduced adiposity and adipose browning were observed in muscle-specific and whole body Mstn knockout, but not in adipose-specific Mstn knockout mice.⁹³⁻⁹⁵ Mechanistically, whole body deletion of Mstn robustly induces *Fndc5* expression in skeletal muscle, which in turn increases serum irisin levels and promotes formation of beige fat cells.⁹⁶ Although Mstn and one of its receptors – activin receptor IIB (ActRIIB) – are expressed by adipocytes, the expression level may be too low to provide physiological relevance,⁹⁷⁻⁹⁹ explaining the lack of phenotype in adipose-specific knockout mice. Consistently, Mstn treatment has no effect on cultured adipocytes.⁹⁶ Together these lines of evidence suggest that Mstn reduces body fat composition and induces “browning” of WAT likely through an indirect mechanism mediated by the skeletal muscle. In both human and rodents, Mstn is expressed at higher levels in obese individuals and lower levels in exercised subjects.^{5,99-101} As Mstn seems to partially explain the beneficial effect of exercise, targeting Mstn signaling pathway using soluble ActRIIB decoy receptor ACE-031 is currently in clinical trial.¹⁰²

The IL family members (IL-4, 6, 7, 8 and 15) are regarded as myokines for their versatile functions in regulating energy homeostasis, immune responses and cell movements.⁹⁴ They are produced in muscle cells, though some, such as IL-8, are mainly produced by other cell types. Of these IL family myokines, IL-6 appears to have the most promising clinical value. IL6 production is low when cellular glucose import is high, but increases during exercise¹⁰³ or when skeletal muscle glycogen content is low¹⁰³. IL-6 also promotes muscle growth and regeneration^{104,105} in addition to its function in improving muscle glucose metabolism.¹⁰⁶ Recombinant IL-6 improves glucose metabolism and insulin sensitivity in humans, and helps to shift the source of skeletal muscle energy from glucose to fat.⁵ However, IL-6 is also produced by adipocytes and has been shown to induce insulin resistance¹⁰⁷⁻¹⁰⁹ and inflammation in adipose tissues.¹¹⁰ Moreover, elevation of the long-term effect of IL-6 seems to suggest some adverse effects.¹¹¹ Other IL family members IL-7, 8 and 15 are all involved in immune responses that play a key role in adipose tissue function.⁵ Although they are not yet well-characterized, they do seem to facilitate the maintenance of energy homeostasis or inflammation status. Notably, IL-15 mediates muscle-fat interaction by negatively regulating lipid metabolism.¹¹²

Other myokines and potential myokines include LIFs,⁵ FGF2,⁵ brain-derived neurotrophic factor,^{70,113,114} follistatin,⁵ insulin-like growth factor 1,^{5,115,116} monocyte chemoattractant protein,^{117,118} and myonectin^{119,120} (Table 1). Myokines are secreted in different amounts and combinations depending on various physical activity levels. Some of the myokines are also produced in adipose tissue and are known as adipomyokines.⁷⁰ The adipomyokines are key players involved in bidirectional muscle-fat cross talk.

Table 1. Potential myokines, their secretion and target sites, and functions

	Production site	Target site	Function
BDNF	muscle, brain, gastrointestinal sites, others	muscle, brain	fatty acid oxidation, cognition
FGF2	various	muscle-bone interphase, central nervous system, heart, blood vessels	muscle-bone interaction, neurogenesis
FGF21	muscle, liver, others	muscle, adipose tissue	anti-obese, browning of WAT
Fstl	Liver, muscle	muscle, liver	Antagonizes myostatin
IL4	muscle, mast cells, Th2 cells, eosinophils, and basophils	muscle, leukocytes and other immune cells, brain	immunity regulation, satellite cell proliferation, muscle hypertrophy and myogenesis, cognition
IL6	muscle, adipose, liver, pancreas	muscle, adipose, liver, pancreas	glucose production, fatty acid oxidation, hepatic glucose production, anti-inflammation
IL7	muscle	muscle, immune cells	satellite cell differentiation, T/B cell development
IL8	muscle, liver	muscle, liver	chemokine, angiogenic factor
IL15	muscle	muscle	fat metabolism, muscle-fat interaction
Irisin/Fndc5	muscle, brain, liver, heart, intracranial artery, tongue, and nerve	muscle, brain	oxidative metabolism, browning of WAT
LIFs	various	muscle, blood, bone, liver, nerve	cell proliferation, muscle hypertrophy and regeneration
MCP1	Muscle, adipose, blood and etc.	various	recruiting monocytes, neutrophils, lymphocytes, and inducing chemotaxis
Mstn	muscle, adipose, bone	muscle, adipose	muscle mass, fatty acid oxidation, browning of WAT
Myonectin	muscle	muscle, adipose	metabolic control

More Muscle, Less Fat?

Obesity and sarcopenia (age related loss of muscle) represent 2 typical situations in which fat mass and muscle mass are negatively correlated. Obesity is generally accompanied by increased fat and lean mass, but the fat mass increases at a larger scale, resulting in a smaller lean muscle to fat ratio. The overall increased body mass in obese individuals also leads to skeletal muscle overload, resulting in greater leg and trunk muscle strength but not handgrip or arm strength.¹²¹ Sarcopenic obesity, which affects 5–10% of the elderly, is a type of obesity in which patients have normal body mass but little lean mass. Sarcopenic obesity is difficult to detect and treat, because subjects have a normal body weight.¹²² In addition to sarcopenic obesity, aging is naturally accompanied by sarcopenia and fat deposition,^{123–125} together with redistribution of body fat from appendicular to stomach and ectopic sites such as liver and muscle.⁴⁸

Individuals who exercise regularly gain more muscle mass, have better muscle function, and lower risks of obesity and T2DM. In contrast, physical inactivity is associated with decreased muscle mass, increased visceral adiposity, and increased macrophage infiltration, chronic systemic inflammation, insulin resistance, obesity, and T2DM.⁵ As discussed previously, skeletal muscle exercise increases energy expenditure, stimulates secretion of beneficial myokines, and increases insulin sensitivity. Muscle exercise also attenuates adipogenesis of mesenchymal stem cells through Akt-mediated mechanical signal responses.^{126,127} An increase in skeletal muscle mass may directly lead to reduced body fat composition, manifested by the fact that body builders

often find themselves stuck in an extremely lean condition.¹²⁸ Consistently, animals with enhanced muscle growth, such as Mstn knockout mice and Callipyge sheep, often have little body fat deposition.^{95,129} However, moderate to high intensity exercise training increases intramyocellular triglycerides,^{130–132} a lipid store within muscle cells.¹³³ This phenomenon is referred to as “athlete’s paradox”¹³⁴ and is likely associated with an increase in oxidative metabolism in exercised muscle. The intramyocellular triacylglycerol droplets act as a FFA fuel source for muscle contraction.¹³⁵ Interestingly, diabetic individuals also have elevated levels intramyocellular triglycerides.^{132,134}

Body fat deposition in turn affects skeletal muscle function. It is widely accepted that inflammatory adipokines secreted by ectopic accumulation of fat leads to muscle insulin resistance.^{136,137} It was also reported that FFA and exercise mimetics (such as AICAR) impact the secretion of myokines, especially the IL family members.¹³⁸ Importantly, fat deposition affects muscle homeostasis. Decreases of muscle mass were consistently reported in obese rodents and humans. In accordance, mice with ectopic fat accumulation exhibit impaired muscle regeneration possibly due to lipid toxicity, pro-inflammatory cytokines and compromised muscle stem cell or satellite cell function.¹³⁹ Adipocytes are nevertheless necessary for muscle regeneration, and in the absence of adipocytes skeletal muscles cannot regenerate after injury.¹⁹ This observation suggests that adipocytes or their “crosstalk” to muscle cells may facilitate muscle recovery. Indeed, adiponectin, an adipokine secreted by adipocytes, has been reported to improve skeletal muscle regeneration by promoting satellite cell proliferation and differentiation.¹⁴⁰

Summary and Future Trends

Muscle-fat interaction is a complicated process acting at multiple levels. (1) Developmental origin. Muscle and fat both develop from mesenchymal precursors; brown fat and skeletal muscle share surprisingly similar origins, suggesting a close relationship, even interconversion between adipocytes and muscle cells. (2) Energy balance. Muscle affects global energy balance and inflammatory status through its active metabolism of nutrients. In these processes, muscle substrates and metabolites intricately “talk” to adipose and other tissues. (3) Body composition. Increased muscle mass and muscle exercise reduces fat deposition and increases insulin sensitivity through secretion of beneficial myokines. (4) Adipose tissue affects muscle inflammation, insulin sensitivity and regeneration possibly through adipokine secretion and physical infiltration, providing a novel target to regulate muscle function.

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In conclusion, regulating skeletal muscle function represents a potential strategy to counteract obesity and T2DM. Understanding muscle-fat interaction may lead to the development of exercise therapies and molecular targets for obesity treatment. It is also critical to understand how muscle reacts to fat accumulation in order to minimize loss of muscle mass and function in obesity. Areas that need further exploration include the research of beneficial myokines, individually tailored training programs, and mechanisms underlying muscle-fat interactions that can be employed for developing drugs. It is critical to carry out human studies in order to translate animal data into novel therapeutic approaches to benefit mankind.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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