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Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis

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ABSTRACT

Sarcopenia, an age-associated decline in skeletal muscle mass coupled with functional deterioration, may be exacerbated by obesity leading to higher disability, frailty, morbidity and mortality rates. In the combination of sarcopenia and obesity, the state called sarcopenic obesity (SOB), some key age- and obesity-mediated factors and pathways may aggravate sarcopenia. This review will analyze the mechanisms underlying the pathogenesis of SOB. In obese adipose tissue (AT), adipocytes undergo hypertrophy, hyperplasia and activation resulted in accumulation of pro-inflammatory macrophages and other immune cells as well as dysregulated production of various adipokines that together with senescent cells and the immune cell-released cytokines and chemokines create a local pro-inflammatory status. In addition, obese AT is characterized by excessive production and disturbed capacity to store lipids, which accumulate ectopically in skeletal muscle. These intramuscular lipids and their derivatives induce mitochondrial dysfunction characterized by impaired β-oxidation capacity and increased reactive oxygen species formation providing lipotoxic environment and insulin resistance as well as enhanced secretion of some pro-inflammatory myokines capable of inducing muscle dysfunction by auto/paracrine manner. In turn, by endocrine manner, these myokines may exacerbate AT inflammation and also support chronic low grade systemic inflammation (inflammaging), overall establishing a detrimental vicious circle maintaining AT and skeletal muscle inflammation, thus triggering and supporting SOB development. Under these circumstances, we believe that AT inflammation dominates over skeletal muscle inflammation. Thus, in essence, it redirects the vector of processes from "sarcopenia → obesity" to "obesity → sarcopenia". We therefore propose that this condition be defined as "obese sarcopenia", to reflect the direction of the pathological pathway.

Abbreviations: ActR, activin type receptor; ALM, appendicular lean mass; AMPK, AMP-activated protein kinase; ALST, appendicular lean soft tissue; AT, adipose tissue; ATGL, adipose triglyceride lipase; BAT, brown adipose tissue; BIA, bioelectrical impedance analysis; BMD, bone mineral density; BMPs, bone morphogenic proteins; BMI, body mass index; CAF, terminal agrin fragment; CRP, C-reactive protein; DAG, diacylglycerol; DXA, dual-energy x-ray absorptiometry; DC, dendritic cells; DMD, duchenne muscular dystrophy; FDF-21, fibroblast growth factor 21; FNDC5, fibronectin type III domain containing protein 5; FA, fatty acid; FST, follistatin; GLUT4, glucose transporter type 4; HFD, high-fat diets; HSL, hormone-sensitive lipase; HOMA-IR, homeostasis model assessment of insulin resistance; IKK, IκB kinase; IL, interleukin; IFNγ, interferon γ; IR, insulin resistance; IS, insulin sensitivity; IMAT, intermuscular adipose tissue; IMCL, sintramyocellular lipids; iNKT, invariant natural killer T cell; LPS, lipopolysaccharide; LNK, c-jun N-terminal kinase; LD, lipid drop; MAG, monoacylglycerol lipase; MCP-1, monocyte-chemoattractant protein-1; MAIT, mucosal-associated invariant T cell; MHO, metabolically healthy obesity; MONW, metabolically obese normal weight; mTOR, mammalian target of rapamycin; MyoD, myogenic differentiation factor; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer cell; NMJ, neuromuscular junction; OPN, osteopontin; OSO, osteosarcopenic obesity; PEDF, pigment epithelium-derived factor; PKC, protein kinase C; p38-MAPK, p38-mitogen-activated protein kinase; p75NTR, p75 neurotrophin receptor; PI3K, phosphatidylinositide 3-kinases; PKB, protein kinase B; PLIN, perilipin; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; ROS, reactive oxygen species; perf-DCs, DCs enriched with perforin-containing granules; PPARγ, peroxisome proliferator-activated receptor γ; RA, rheumatoid arthritis; SASP, senescence-associated secretory phenotype; SAT, subcutaneous adipose tissue; SMM, skeletal muscular mass; sTnT, skeletal muscle-specific troponin T; SOB, sarcopenic obesity; TAG, triacylglycerol; TCR, T-cell receptor; TGFβ, transforming growth factor beta; Th, T-helper cell; Treg, T-regulatory cell; TNFα, tumor necrosis factor alpha; T2DM, type 2 diabetes mellitus; TrkBR, tropomyosin-related kinase-B receptor; UCP1, uncoupling protein 1; VAT, visceral adipose tissue; WAT, white adipose tissue.

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Contents

1. Introduction

The two greatest public health concerns in developed countries are the aging of the population and the obesity widespread. Currently, it became clear that the demographic trends in which both the size and proportion of the older and obese population are increasing at unprecedented rates would have a major challenge for the health system in the near future (Kaeberlein et al., 2015). Each of these trends has important effects on body composition, functional disability, morbidity, and mortality (Fabbri et al., 2015). Aging is accompanied with a progressive loss of muscle mass and strength, called sarcopenia (Rosenberg, 1989) that affects dramatically health status and quality of life (Beaudart et al., 2014; Cesari et al., 2014; Evans et al., 2010). Depending on the criteria used for its definition, the estimates of sarcopenia prevalence is reported as from <10% to >70% in individuals older than 60 years (Batsis et al., 2013, 2015; Cruz-Jentoft et al., 2014; Dam et al., 2014). Even with a conservative estimate of prevalence, sarcopenia affects >50 million people today and will affect >200 million in the next 40 years (Santilli et al., 2014).

An aging-dependent increase of fat mass (obesity) is associated with the onset of other pathologies, such as metabolic syndrome. It represents a cluster of risk factors, including insulin resistance (IR), dyslipidemia and hypertension that together culminate in the increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular disorders, as well as sleep apnea, arthritis, and some types of cancer (Allott and Hursting, 2015; Kopelman, 2000; O'Neill and O'Driscoll, 2015). Coexistence of sarcopenia and obesity, called sarcopenic obesity, SOB (Baumgartner, 2000; Roubenoff, 2000), and meaning a concomitant overriding of abnormal age-dependent muscle loss and fat accumulation, may act synergistically thus maximizing their health threatening effects (Bouchard et al., 2009; Lee et al., 2016; Stenholm et al., 2008; Zamboni et al., 2008). Importantly, SOB has been reported to increase the risk of metabolic impairment and physical disability more than either sarcopenia or obesity alone (Dominguez and Barbagallo, 2007; Rolland et al., 2009).

Despite immense attempts to decipher the mechanisms of sarcopenia and obesity (and thus, SOB) this issue remains unclear. Among the reasons for this failure is the pleiotropic function of the molecules and pathways presumably involved in the development of sarcopenia and obesity (Kob et al., 2015; Sakuma et al., 2015) as well as a high level of age-associated co-morbidities, which often leads to confounding results (Schelbert, 2009). Moreover, sarcopenia and obesity are considered as the multifactorial syndromes with various overlapping causes and feedback mechanisms supposed to be strongly interconnect and aggravate each other (Biolo et al., 2014; Blüher and Mantzoros, 2015; Goisser et al., 2015; Kohara, 2014; Lavie et al., 2009; McGregor et al., 2014; Tyrovolas et al., 2015).

With regard to sarcopenia, we have previously proposed that normal muscle mass and function maintenance is dependent on the dynamic balance between several positive and negative regulators of muscle growth, and that the shift of this balance to muscle growth inhibitors is one of the key mechanisms involved in the pathogenesis of sarcopenia (Kalinkovich and Livshits, 2015). In addition, neuromuscular junction (NMJ) dysfunction characterized by the appearance of the C-terminal agrin fragment (CAF) in the NMJs is also proposed to be most crucial in sarcopenia pathogenesis (Kalinkovich and Livshits, 2015). Contractile insufficiency followed by the appearance of tropomyosin-binding subunit troponin – skeletal muscle-specific troponin T (sTnT), playing an important role in the control of striated muscle contraction, is also suggested as a key element in sarcopenia pathogenesis (Kalinkovich and Livshits, 2015).

Concerning SOB, in this review we focused on several mechanisms regulating muscle and fat metabolism, and divided them into a number of clusters (Fig. 1). Fat accumulation induces dysregulated production of array of adipokines and infiltration of macrophages and other immune cells in AT (Esser et al., 2014) producing variety of pro-inflammatory cytokines and chemokines, thus establishing a local as well as a systemic, chronic low-grade inflammation, "inflammaging" (Florez and Troen, 2008; Franceschi et al., 2000; Lackey and Olefsky, 2016; Schrager et al., 2007; Tateya et al., 2013). This inflammation is shown to contribute to the development and progression of sarcopenia (Beyer et al., 2012) as well as to affect insulin sensitivity (IS) (Chang et al., 2015). Since insulin is a central anabolic signal, and IR is considered to be the main factor that controls the development of T2DM (Cleasby et al., 2016), these observations connect obesity-associated metabolic

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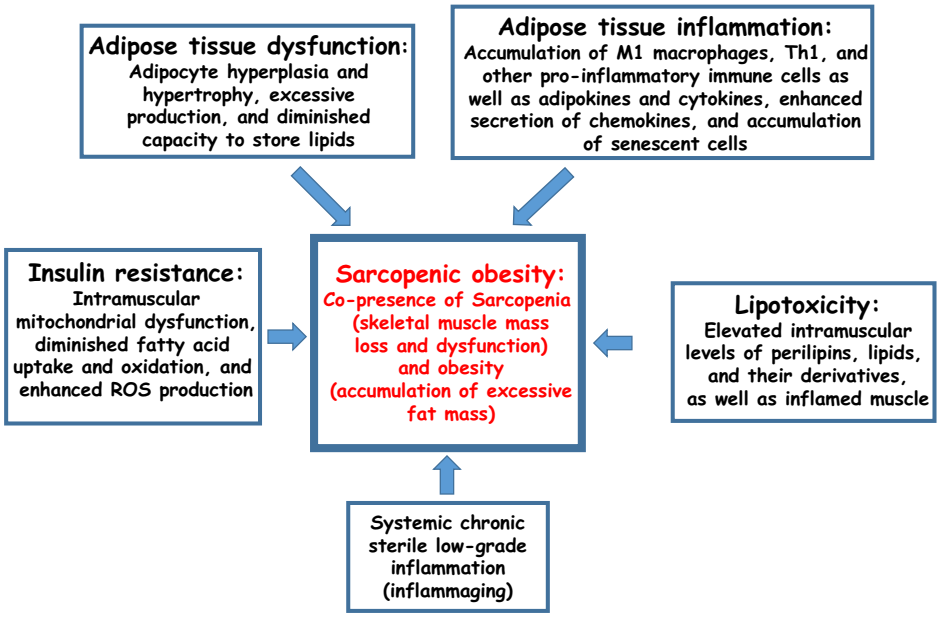

Fig. 1. Schematic representation of the mechanisms presumably involved in sarcopenic obesity (SOB) pathogenesis.
Age-associated obesity and sarcopenia are suggested to be mutually connected (thus, establishing SOB) and are reciprocally regulated by dysfunctional adipose tissue (AT) and skeletal muscle. Obese AT, especially visceral AT (VAT), is characterized by adipocyte hyperplasia (increased cell number) and hypertrophy (increased cell size), excessive production and diminished capacity to store lipids (Rutkowski et al., 2015). Excessive lipids in the form of free fatty acids (FAs) outflow the AT and accumulate ectopically in skeletal muscle, where they and their derivatives accumulate both inter- and intra-myocellularly and induce mitochondrial dysfunction, disturbed β-oxidation of FAs, and enhanced reactive oxygen species (ROS) production, leading to lipotoxicity and insulin resistance (Kob et al., 2015; Stinkens et al., 2015). Moreover, intramuscular lipids are supposed to attract immune cells capable of producing pro-inflammatory myokines and cytokines (Rivas et al., 2016), thus providing local inflammation and, by their leakage to the circulation, they support general and AT inflammation. In addition, adipocyte activation lead to excessive accumulation in AT of various immune cells possessing pro-inflammatory activity such as M1-type macrophages, mast cells, Th1, Th17 and other cells secreting pro-inflammatory cytokines (Apostolopoulos et al., 2016; Exley et al., 2014; Tateya et al., 2013). Furthermore, activated adipocytes by themselves produce pro-inflammatory adipokines, such as leptin, osteopontin, chemerin and some others. In parallel, chemokines recruit immune cells to already inflamed AT (Raschke and Eckel, 2013; Rodríguez et al., 2015) generating a pro-inflammatory vicious circle. Moreover, age-associated accumulation of senescent cells leads to the creation of senescence-associated secretory phenotype (SASP) (LeBrasseur et al., 2015). Taken together, they establish a profound pro-inflammatory milieu exacerbating AT inflammation and affecting skeletal muscle functionality (Kelley and Goodpaster, 2015; Pellegrinelli et al., 2015). In addition to this AT-skeletal muscle pro-inflammatory interconnection, a systemic chronic sterile low-grade inflammation (inflammaging) is also proposed to be closely associated with SOB (Macaulay et al., 2013; Michaud et al., 2015). All these factors and events are suggested to be key elements in SOB triggering and development.

syndrome, immunity and sarcopenia (Chen et al., 2015; Johnson and Olefsky, 2013; Minihane et al., 2015).

Obesity is characterized by enhanced production of fatty acids (FAs) that are stored not only in AT, but can also spill over to several other tissues including skeletal muscle. They accumulate there as intermuscular AT (IMAT) and as intramyocellular lipids (IMCLs) containing triacylglycerol (TAG) or FA derivatives such as diacylglycerol (DAG), long chain acyl CoA, and ceramide (Adams et al., 2004; Coen and Goodpaster, 2012; Ritter et al., 2015; Stinkens et al., 2015). IMCLs induce muscle lipotoxic effect characterized by impaired single-fiber contractility leading to lower muscle strength and power in elderly (Tumova et al., 2015; Unger et al., 2010) in association with decreased IS (Corcoran et al., 2007; Crane et al., 2010; Johannsen et al., 2012; Krssak et al., 1999). IMCLs are found mostly in lipid droplets (LDs) containing perilipins (PLINs), which are believed to be involved in some important aspects of muscle physiology/pathology such as breakdown of stored lipids and IS (Bosma et al., 2012; Robenek et al., 2005). Moreover, IMCLs are found in mitochondria where they impair FA β-oxidation (Bosma et al., 2013) and increase reactive oxygen species (ROS) formation resulted in the apoptosis/autophagy of muscle cells, thus considered as one of the potential mechanisms of obesity-mediated sarcopenia pathogenesis (Marzetti et al., 2013). This review provides an analysis of the mechanisms of the mentioned above molecules and their interrelationships in the pathogenesis of SOB. Several additional mechanisms supposed to be involved in SOB development like genetic and epigenetic regulation, the roles of muscle stem (satellite) cells, growth and sex hormones, and gut micriobiota have not been considered in the present paper but they have been comprehensively discussed by others (Arner and Kulyté, 2015; Bischoff, 2016; Blau et al., 2015; Liu and Lim, 2015; Maynard et al., 2015; Sousa-Victor and Muñoz-Cánoves, 2016).

2. Definition of SOB

As mentioned, SOB is associated with augmented risks for disability, poor quality of life and higher morbidity and mortality, thus representing an increasing public health challenge and emphasizing the urgency in clearly defining the SOB cutoff points. Although this issue attracts a lot of intention, as reflected in numerous recent reviews (Buch et al., 2016; Budui et al., 2015; Cauley, 2015; Goisser et al., 2015; Kob et al., 2015; Kohara, 2014; Molino et al., 2016; Prado et al., 2016), it remains controversial and unclear. One of the most important concerns is that although obesity is officially considered as a disease per se, requiring doctors to treat obese patients for weight loss (Bosello et al., 2016), surprisingly, to date there has been no accepted definition of obesity (Blundell et al., 2014; Casazza et al., 2013). An additional complexity in this issue arose from the different effects of obesity occurring at different ages. For example, the “obesity paradox”, in which overweight or obese individuals display a survival advantage compared with lean adults (Allison et al., 1999), is very controversial regarding the effect of obesity in the elderly (Wannamethee and Atkins, 2015; Zamboni et al., 2005). Another example is the “athlete’s paradox” (Goodpaster et al., 2001), in which chronically exercised humans are markedly insulin-sensitive despite having high IMCLs, which, in turn, was shown to play a major role in obesity-associated skele-

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tal muscle IR and is crucial for the development of T2DM (Marzetti et al., 2013; Samuel and Shulman, 2016; Stinkens et al., 2015).

In attempting to clarify this problem, several descriptive conditions have been introduced. One of them is "metabolically healthy obesity (MHO)" – a body-mass index (BMI) >30 kg/m^2 phenotype but without any metabolic syndrome component and which has a homeostasis model assessment of IR (HOMA) <2.5 (Rey-López et al., 2014; Stefan et al., 2008). However, in this "healthy" phenotype, a significant proportion (up to 24%) of individuals was found to be at cardiometabolic risk (Roberson et al., 2014) with an additional increase in the elderly (Oreopoulos et al., 2009). Moreover, meta-analysis of eight studies (>61,000 obese individuals) led to the conclusion that, compared with metabolically healthy normal-weight individuals, obese persons are at increased risk for adverse long-term outcomes even in the absence of metabolic abnormalities, suggesting that there is no healthy pattern of increased weight (Kramer et al., 2013). A similar conclusion has been reached in a more recent meta-analysis of twenty-two prospective studies concerning cardiovascular risk (Eckel et al., 2016). The second phenotype is "metabolically obese normal weight (MONW)" – normal weight individuals displaying obesity-related phenotypic characteristics (Ruderman et al., 1981; Lopez-Miranda and Perez-Martinez, 2013), which is just the opposite of the obesity paradox. As expected, meta-analysis of fourteen perspective studies (almost 300,000 participants) of MONW individuals revealed that they have a substantial cardiovascular and mortality risk (Fan et al., 2013).

Notably, both MHO and MONW conditions are based only on the measurement of BMI, which, as is widely accepted now (Hruschka and Hadley, 2016) has its intrinsic limitations as a measure of obesity. BMI does not appropriately determine major components of body mass, in particular, body fat, fat distribution, lean body mass, and body fluid content. This could potentially introduce serious limitations when analyzing the relationship of body composition to health outcomes. As such, MHO and MONW cannot be referred to as biological entities since they merely reflect the limited accuracy of BMI in risk prediction, making their clinical value doubtful (Müller et al., 2016). However, surprisingly, in predicting disease risks, fat mass and fat-free mass, as assessed by validated techniques, i.e., densitometry, dual energy X ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA), do not exceed the value of BMI (Bosello et al., 2016; Müller et al., 2016; Wannamethee and Atkins, 2015).

In a recent cross-sectional study, including 4984 subjects (≥60 years), conducted within the framework of the National Health and Nutrition Examination Surveys (1999–2004) (Batsis et al., 2015), DXA, BIA and BMI were used for evaluation of body composition parameters. Sarcopenia was defined using appendicular lean mass (ALM) (men <19.75 kg, women <15.02 kg) and ALM adjusted for BMI, ALM/BMI (men <0.789 kg/m^2, women <0.512 kg/m^2). SOB was defined as subjects fulfilling the criteria for sarcopenia and obesity by% body fat (%BF) (men ≥25%, women ≥35%) (Deurenberg et al., 2001). It was found that ALM is significantly higher in men than in women, but fat mass was lower. By using the ALM and ALM/BMI criteria, respectively, sarcopenia prevalence in men was 16.0% and 27.8%, and 40.5% and 19.3%, thus revealing a pronounced difference depending on the applied measures and between men and women. In addition, sarcopenia was found to be associated with a risk of physical limitations also depending on applied criteria. Although prevalence of sarcopenia and SOB varied greatly, they agreeably correlated with each other in both sexes (Batsis et al., 2015). In a longitudinal study (more than 2 years follow-up in 379 Korean individuals, mean age 51.9 ± 14.6 years, from the Korean Sarcopenic Obesity Study), appendicular lean soft tissue (ALST) mass was calculated using DXA, and visceral adipose tissue (VAT) fat area was measured using computed tomography (Kim et al., 2014a). It was shown that while ALST mass significantly decreased, VAT and total body fat mass increased in most studied men and women. However, baseline muscle mass was unable to predict the development of obesity. The authors suggested that VAT enlargement is associated with future loss of skeletal muscle mass providing a novel insight into SOB obesity in an aging society.

This prospective study is the first to support the existence of the "obesity to skeletal muscle route" in SOB development, suggesting that there may be a causal component in this association. However, in both studies (Batsis et al., 2015; Kim et al., 2014a), the criteria used for defining sarcopenia did not include functional muscle components such as handgrip strength and/or walking abilities, which were shown to be reduced faster than muscle mass was in ageing and they contributed significantly to age-related frailty (Mitchell et al., 2012).

A further challenge to the definition and assessment of SOB arose from the suggestion that sarcopenia and osteoporosis might be almost the same disease simply expressed in muscle and bone, respectively (Sjöblom et al., 2013). Indeed, a substantially higher correlation has been observed between the bone mineral density and lean mass, as compared with the fat body mass (Ho-Pham et al., 2014; Livshits et al., 2007; Korostishevsky et al., 2016). Moreover, SOB was found to be associated with the development of osteoporosis among the middle-aged and elderly Korean population (Chung et al., 2016), thus being in line with the suggestion of the existence of an "osteosarcopenic obesity" (OSO) syndrome proposed as triad of osteoporosis, sarcopenia and adiposity (Ilich et al., 2014; Ormsbee et al., 2014). However, recent data from this group revealed an association of OSO with obesity and the functional features of sarcopenia (reduced handgrip strength and walking abilities) but not with osteoporosis in postmenopausal women (Ilich et al., 2015).

In going beyond BMI and descriptive body composition analysis, the concept of functional body composition was introduced (Müller et al., 2009, 2016). It refers to the masses of body components, organs, and tissues as well as to their inter-relationships within the context of endocrine, metabolic, and immune functions. Thus, it provides suitable physiological criteria for future definitions of a metabolically healthy or unhealthy body composition potentially including obesity, sarcopenia, and thus, SOB. Correspondingly, we provide here evidence supporting the notion that joint age- and obesity-associated AT and skeletal muscle inflammation constitute the main mechanism underlying the development of SOB and therefore, they could be used in an accurate and complete definition of SOB.

3. Age- and obesity-associated skeletal muscle lipid metabolism

Being a complex multifaceted phenomenon, sarcopenia involves a variety of molecular, structural and physiological factors changing with age (Kalinkovich and Livshits, 2015). Recent data clearly demonstrated that sarcopenia could be caused also by lipid metabolic products infiltrated into muscles (Fig. 2). Thus, lipids ectopically accumulated between muscle fibres, IMAT, found beneath the fascia of a muscle, are shown to impose a significant risk of muscle dysfunction in older adults and across a wide variety of comorbid conditions (Addison et al., 2014). Moreover, IMCLs, in the form of lipid droplets (LDs), which are dynamic energy organelles functioning to store neutral lipids, are found in most tissue types including AT and skeletal muscle (Badin et al., 2013). Coated with a phospholipid monolayer, LDs accumulate predominantly TAG, but also DAG, sterol esters, long-chain acetyl coenzyme A and sphingolipids including ceramides that used as substrates for the formation of intracellular membranes and/or

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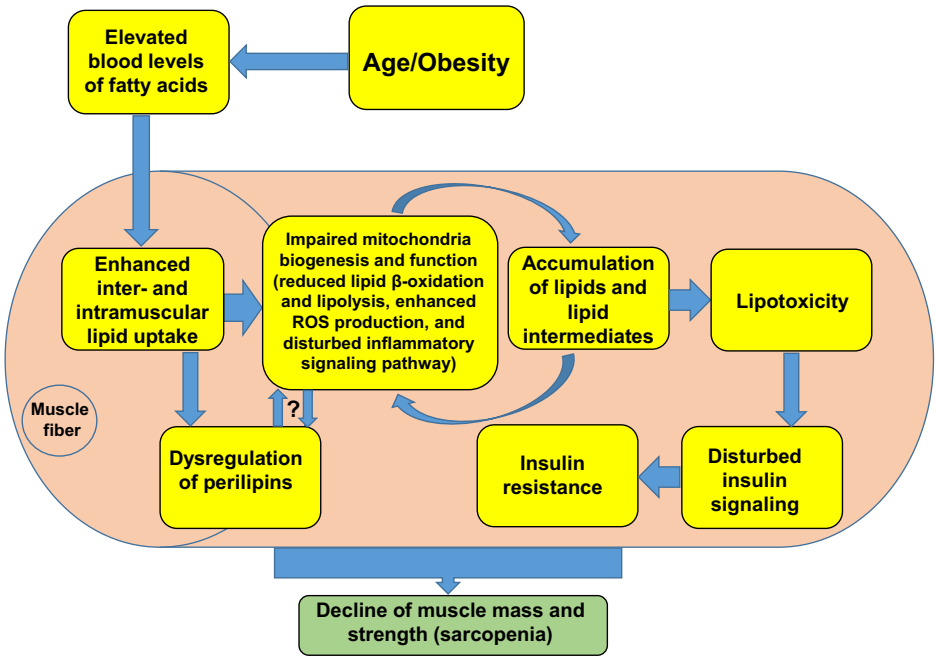

Fig. 2. A model of the proposed major obese/age-inducing factors contributing to skeletal muscle insufficiency resulting in sarcopenia.
Obesity in aged individuals is accompanied by elevated free FA blood levels resulted in their enhanced ectopic accumulation in the form of intermuscular adipose tissue (IMAT) as well as intra-muscular triglycerides (IMCLs) in the lipid droplets (LDs) (Badin et al., 2013). Excessive FA accumulation in the LDs, mainly in the form of triglycerides (TG), diacylglycerols (DAG) and ceramides may lead to some pathological conditions, finally leading to muscle fiber insufficiency. The main effect is the marked impairment of muscle mitochondria characterized by their reduced biogenesis along with dramatic function disturbances, such as reduced lipid β-oxidation and lipolysis, resulting in the accumulation of TG and their derivatives (Akhmedov and Berdeaux, 2013; Romanello and Sandri, 2016). In addition, dysfunctional mitochondria reveal enhanced ROS production (oxidative stress) (Marzetti et al., 2013), and a disturbed inflammatory signaling pathway (mainly, mTOR blockage) (Sakuma et al., 2015) also occur. In parallel, dysfunction of perilipins (PLINs), which are a major component of LDs, is also occurs as a consequence of excessive accumulation of lipids and their derivatives (Bosma, 2016), all leading to lipotoxic effect, which targets the insulin signaling pathway, resulting in an IR state (Muoio, 2012). The main outcome of these events is muscle fiber insufficiency, leading to decline in muscle mass and function (sarcopenia).

energy production in the form of ATP (Bosma et al., 2012; Pol et al., 2014; Watt and Hoy, 2012).

In skeletal muscle, lipolysis of FAs from IMCL stores in LDs is mediated by lipoprotein lipases mainly by adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), and some others (Badin et al., 2013). HSL and ATGL work in concert to regulate lipolysis in skeletal muscle, and their discordant phosphorylation and activity are suggested to be responsible for impaired lipolysis in skeletal muscle of obese and T2DM individuals, associated with lipotoxicity and IR (Badin et al., 2013; Kase et al., 2015).

3.1. Insulin resistance (IR) links fat accretion and muscle mass diminution

IR typically develops in conditions of excessive fat mass, leading to a compensatory increase of insulin secretion by pancreatic β-cells and hyperinsulinemia. However, when β-cells are no longer able to compensate for IR, hyperglycemia develops (Samuel and Shulman, 2016; Tuomi et al., 2014). Insulin acts through a tyrosine kinase receptor, which phosphorylates the insulin receptor substrates (IRS-1 and IRS-2), leading to successive PI3K and protein kinase B (PKB)/Akt activation. The main postprandial actions of insulin include the translocation of glucose transporter GLUT4 to the membrane of myocytes and adipocytes, activation of glucokinase in hepatocytes, and inhibition of lipolysis and gluconeogenesis (Samuel and Shulman, 2016; Tuomi et al., 2014).

Such processes are compromised in 2TDM, due to the development of IR, which is mainly based on the desensitization of the insulin receptor and impaired phosphorylation of its substrates. Skeletal muscle, comprising a system that represents the largest organ of the human body and consisting of over 600 separate muscles, is the major reservoir of the postprandial glucose (Lenk et al., 2010). One of the major mechanisms to cause IR is the accumulation in myocytes of the secondary products of lipid metabolism such as DAG, ceramides and others. This in turn leads to activation of serine/threonine kinases like c-jun N-terminal kinase (JNK), IκB kinase (IKK), and protein kinase C (PKC), conducting to serine phosphorylation and consequent inactivation of the insulin receptor and its substrates (Boura-Halfon and Zick, 2009). IR was also shown to correlate with impaired lipid oxidation in mitochondria in obesity (Dela and Helge, 2013; Hafizi Abu Bakar et al., 2015) and during aging (Carter et al., 2015; Hepple, 2016; Konopka and Sreekumaran, 2013; Leduc-Gaudet et al., 2015; Marzetti et al., 2013; Romanello and Sandri, 2016).

Increased ROS levels, consequent to lipotoxicity and impaired mitochondrial function, further augment development of IR. As a result, the imbalance between oxidant and antioxidant compounds leads to the activation of stress pathways, such as JNK, IKK, and p38-mitogen-activated protein kinase (p38-MAPK). In addition, ROS also inhibits mitochondria function, leading to further intracellular FA accumulation, thus creating a vicious cycle of lipotoxicity and IR (Aon et al., 2014; Stinkens et al., 2015). Elevated production of ROS in muscle mitochondria was found in aged individuals leading to local oxidative stress generation and inducing post-translational modifications, which compromise muscle protein function (Claflin et al., 2015; Javadov et al., 2015). Notably, high-fat diets (HFD) result in increased IMCL stores and a concomitant development of IR (Boden, 2011), highlighting an important role of lipid supply in FA acid-induced IR (Rivas et al., 2016). Moreover, in obese, IR and T2DM patients, elevated IMCL levels have been linked to a reduced oxidative capacity (Bruce et al., 2003). This suggests that muscle fat turnover (lipolysis/oxidation) leading to accumulation of bioactive lipid metabolites such as DAG and others is critical in FA-induced IR

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(Samuel and Shulman, 2016; Stinkens et al., 2015), and to skeletal muscle inflammation (see below).

3.2. PLIN family of proteins is related to muscle strength and atrophy

An immanent part of muscle lipid metabolism are PLIN family of proteins (PLINs1-5), bound to and embedded in the LD membrane and involved in the breakdown of LD stored lipids (Robenek et al., 2005; Sztalryd and Kimmel, 2014). PLIN2, PLIN5, and, probably, PLIN3 are the most abundant muscle PLINs (Badin et al., 2013; Coen and Goodpaster, 2012; Harris et al., 2015; MacPherson and Peters, 2015; Sztalryd and Kimmel, 2014), but their participation in muscle physiology and pathology seems to be different. For example, age and physical inactivity or immobilization are found to be associated with elevated PLIN2 and PLIN3 expression and decreased PLIN5 expression in humans and in animal models (Conte et al., 2013, 2015; Vigelso et al., 2015). Moreover, in old individuals, only PLIN2 was associated with the decrease in muscle strength and the expression of factors related to muscle atrophy (atrogenes *MuRF1, Atrogin* and *p53*). In addition, PLINs (2, 3 and 5) and ATGL were found to be co-located within LDs indicating a close association between the key lipolytic effectors in resting skeletal muscle (MacPherson et al., 2013). In addition, PLIN5 ablation was found to be accompanied by reduced TAG stores but increased sphingolipids including ceramide and sphingomyelin, leading to skeletal muscle-specific IR and suggesting that PLIN5 is required to match lipolysis of skeletal muscle TAG to metabolic demands, which helps to maintain IS in skeletal muscle (Bosma, 2016). It was also shown that some PLINs are expressed not only in the muscle LDs but also in mitochondria (Ramos et al., 2014). Furthermore, overexpression experiments demonstrated that only PLIN5, but not PLIN2, promoted the expression of a cluster of genes involved in FA catabolism and mitochondrial β-oxidation (Bosma et al., 2013), suggesting that the role of PLIN5 is not limited to the regulation of lipolysis, but also includes driving of FAs into the mitochondria for their β-oxidation. Overall, these findings imply an existence of a close link between obesity-induced lipid turnover within skeletal muscle (in addition to the role of increased lipid supply and uptake fat accumulation), IR and lypotoxicity leading to sarcopenia (Fig. 2).

In support to this notion, several observations demonstrated that various types of exercise and training lead to improvements in IS mechanistically linked to increased muscle levels of ATGL both in rat model (Stephenson et al., 2014) and human subjects (Kiens et al., 2011; Yao-Borengasser et al., 2011). Similarly, exercises resulted in elevated muscle oxidative capacity, IMCL breakdown (utilization) and increased content of PLIN2, PLIN3 and PLIN5 in type I and type II fibres, both in normal (Mason et al., 2014; Shepherd et al., 2013; Vigelso et al., 2015) and obese individuals (Bosma et al., 2012; Louche et al., 2013; Peters et al., 2012). Accordingly, an enhancement in intramuscular lipid turnover resulting in accelerated lipolysis may serve as a basis for the beneficial metabolic effects of exercise in obesity, namely decreased lipotoxicity and increased IS leading to prevention of sarcopenia.

4. Adipose tissue inflammation: mechanisms and cross talk with skeletal muscle

4.1. Mechanisms of AT inflammation

As proposed in the previous chapter, disturbed age- and obesity-associated skeletal muscle lipid metabolism might be one of the mechanisms leading to sarcopenia. In addition, cumulated evidence exists to support the idea that inflammation, both local (in AT and skeletal muscle) and systemic (inflammaging) has a main role in the development of sarcopenia and, as we hypothesize, in SOB pathogenesis. AT covers much of the human body and has several distinct adipose depots, including omental, mesenteric, subcutaneous and VAT surrounding the organs (Wronska and Kmiec, 2012). They all could be involved in a variety of age/obesity-associated abnormalities, such as dyslipidemia (impaired lipogenesis and lipolysis), compromised glucose metabolism, elevated cardiovascular risk, and premature death (Gaggini et al., 2015). Remarkably, AT retains also a substantial and unique immune system, which has been appreciated only recently mainly in the context of its emergent and significant role in both local and systemic homeostasis, especially in the development of inflammaging, IR and T2DM (Febbraio, 2014; Ferrante, 2013; Osborn and Olefsky, 2012; Smitka and Marešová, 2015; Tsai et al., 2015a; Wensveen et al., 2015). Main participants and their apparent interrelationships in AT inflammation are depicted in Fig. 3.

Two keystone findings, namely, TNFα overexpression in the VAT of obese mice capable of affecting IS (Hotamisligil, 1999) and increased accumulation of macrophages in AT (Weisberg et al., 2003; Xu et al., 2003) have linked obesity and immunity, specifically, obesity-related inflammation. Macrophages emerged as an important player in AT inflammation. Comprising ~10% of all AT cells in lean subjects, their number may extent up to 50% in obese individuals (Weisberg et al., 2003). This elevation is presumably caused by increased levels of free FAs, cholesterol, and circulating lipopolysaccharide (LPS) (due to the changes in the gut microbiota) (Chakraborti, 2015; Kraakman et al., 2014; Pereira and Alvarez-Leite, 2014). Macrophages are found in crown-like structures surrounding dying adipocytes, rendering them to capture and cleave proteolytically adipocyte-derived antigens as well as present to and activate antigen-specific $CD4^+$ T cells (Morris et al., 2013). In the steady state lean conditions, there is a prevalence of M2 macrophage subtype in AT. M2 macrophages are associated with anti-inflammatory responses, helminth infection and tumor progression. After activation by T-helper type 2 (Th2) mediators, such as IL-4 and IL-13, M2 macrophages produce anti-inflammatory cytokines including IL-10 and IL-1 receptor antagonist (IL1Ra) (Gordon and Taylor, 2015; Odegaard et al., 2007). Notably, M2 macrophages might promote IS through IL-10 by antagonizing TNFα-induced IR (Tateya et al., 2013). During weight gain, a "phenotypic switch" of AT macrophages from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 state is suggested as one of the key AT inflammation events (Lumeng et al., 2007). M1 macrophages play a significant role in bacterial and viral infections; being activated by Th1 mediators, such as IFNγ, they secrete pro-inflammatory molecules like TNFα, IL1-β, IL-6, and monocyte-chemoattractant protein-1 (MCP-1/CCL2) (Bing, 2015; Castoldi et al., 2016; Olefsky and Glassm, 2010). Moreover, a M2-to-M1 switch is linked to the emergence of systemic IR (Lumeng et al., 2007).

Recently, an alternative type of AT macrophage activation based on increased lipid metabolism has been described (Calay and Hotamisligil, 2013; Mathis and Shoelson, 2011; Xu et al., 2013). Upon the exposure to a mixture of glucose, insulin, and palmitate ("metabolic activation"), macrophages accept a complex phenotype (i.e., secretion of classical pro-inflammatory cytokines and expression of uncommon cell surface proteins ABCA1, CD36, and PLIN2, but not M1 or M2 surface markers), indicating that metabolic pathways trigger macrophage inflammation via the mechanisms that are different from those operative during infection (Kratz et al., 2014). It has been also suggested that this unusual phenotype is due to continuous and excessive exposure of AT macrophages to free FAs, such as palmitate, in a microenvironment that is saturated with glucose and insulin, thus causatively connecting AT inflammation and IR (Kratz et al., 2014). Altogether, these findings suggest that obesity-promoting accumulation of macrophages in

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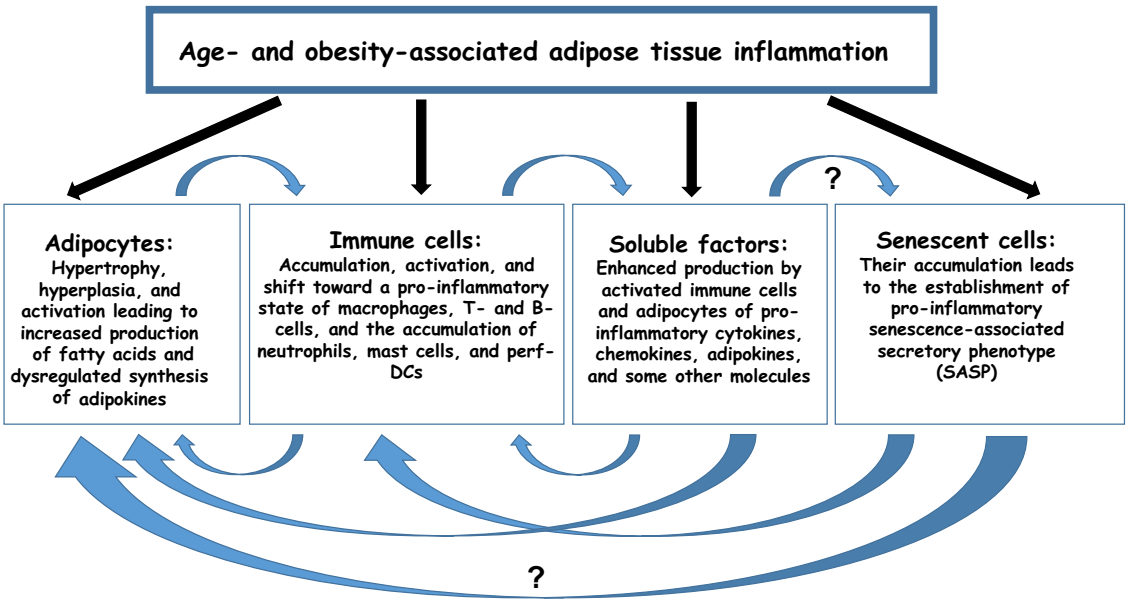

Fig. 3. Schematic representation of the main participants and their apparent interrelationships in adipose tissue (AT) inflammation.
Adipocytes, immune and senescent cells, and soluble factors secreted by these cells are proposed to be the key players in age- and obesity-associated AT inflammation. However, the interrelationships between these components, especially causal relationships during AT inflammation remain unclear. Upon fat accumulation, adipocytes expand their number, size, and activation. This results in enhanced release of free fatty acids (FAs) and dysregulated production of adipokines, in particular, a shift from adiponectin to leptin/MCP-1(CCL2) production (Romacho et al., 2015). Along with other adipokines, they can activate and recruit macrophages in AT via binding CCR2, CD36 and/or toll-like receptor 4 (Castoldi et al., 2016), as well as other immune cells via activation of adhesion molecules and triggering chemotaxis (Exley et al., 2014; Tateya et al., 2013). Most importantly, the main feature of these cells is their pronounced pro-inflammatory status. Macrophages undergo polarization from an anti-inflammatory (M2) to a pro-inflammatory (M1) phenotype, apparently under the influence of accumulating Th1 and Th17 $CD4^+$ cells, and $CD8^+$ cells (Wensveen et al., 2015). B-lymphocytes, neutrophils, mast cells and some other immune cells are also accumulated and undrgo activation in obese AT contributing to its inflammation (Apostolopoulos et al., 2016; Grant and Dixit., 2015; Huh et al., 2014a,b; Magalhaes et al., 2015a; Zlotnikov-Klionsky et al., 2015). All these pro-inflammatory, polarized activated cells secrete a variety of soluble substances such as cytokines, chemokines, and many others (Castoldi et al., 2016; Exley et al., 2014; Makki et al., 2013), capable of inducing, supporting, or exacerbating AT inflammation. In addition, accumulating in AT, various senescent cells are shown to support ongoing AT inflammation via establishment of senescence-associated secretory phenotype (SASP) (Acosta et al., 2013; Lasry and Ben-Neriah, 2015). Excessively synthesized, soluble pro-inflammatory factors lead to further activation of the immune cells producing these factors, and thus amplifying immune response. This self-generating scenario appears to be a main mechanism maintaining and aggravating an ongoing AT inflammation. However, a key question – whether obesity by itself induces these events (and if so, what are the mechanisms?) or they only concomitant to obesity, remains open. Blue arrows reflect scientifically established relationships between AT inflammation components; Perf-DCs – perforin-granule containing dendritic cells;? – The link is not yet confirmed.

AT, mainly in VAT, is associated with sterile inflammation resulted in inhibition of insulin signaling, thus supporting the existence of emerging status termed "immunometabolism" combining both detrimental and beneficial functions of macrophages in AT inflammation (Beenakker et al., 2013; Fitzgibbons and Czech, 2016; Loftus and Finlay, 2016; Mathis and Shoelson, 2011; Schipper et al., 2012; Torres et al., 2016). For example, it has been shown that macrophages regulate positively efferocytosis – removing of apoptotic cells by phagocytic cells (Martin et al., 2014). Moreover, supporting and/or activation of macrophage autophagy capacity, the process by which cytoplasmic contents are delivered to the lysosome for degradation, was found to prevent pro-inflammatory M1 macrophage polarization (Liu et al., 2015a) and IR. This effect is presumably occurs via abrogation of the mammalian target of rapamycin (mTOR) activation (Jiang et al., 2014), thus linking macrophage autophagy and obesity-associated inflammation (Fitzgibbons and Czech, 2016).

Obesity-associated AT inflammation has recently been designated as having an innate and adaptive immune components (Andersen et al., 2016; Chng et al., 2015; DiSpirito and Mathis, 2015; Seijkens et al., 2014; Travers et al., 2015). Among them, T lymphocytes were found to play a major role in AT inflammatory status. In lean steady state conditions, AT is enriched in anti-inflammatory $CD4^+$ Th2 and T-regulatory cells (Tregs) that suppress the expansion of pro-inflammatory Th1 cells by secreting IL-10 and inducing IL-10 synthesis in M2 macrophages (Harford et al., 2011; McLaughlin et al., 2014; Rodríguez et al., 2015). Importantly, the shift from anti-inflammatory Th2 and Tregs toward the pro-inflammatory Th1 and Th17 cells, particularly in the VAT, may trigger AT inflammation, in close association with IR (Eljaafari et al., 2015; Kintscher et al., 2008). Th1 and Th17 secrete IFNγ and IL-17, respectively, stimulating the release of TNFα and IL-6 from M1 macrophages (Sell et al., 2012). Notably, adipocytes themselves exhibit immune cell-like functions that lead to Th1 cell activation, triggering inflammation independently on macrophage infiltration (Meijer et al., 2011). In addition, AT from metabolically abnormal IR obese individuals was found to contain increased numbers of IL-22 producing Th22 cells, capable of causing metabolic dysfunction in liver and muscle (Fabbrini et al., 2013) as well as to amplify IL-1β-driven inflammation in human AT with a clear relevance to obesity-induced T2DM (Dalmas et al., 2014). These data support the idea on the existence of a close link between AT inflammation and glucose metabolism.

In addition to $CD4^+$ T lymphocytes, infiltration of $CD8^+$ T cells to obese AT was shown to lead the macrophage influx and M1 polarization. An adoptive transfer of $CD8^+$ T cells led to the establishment of IR in CD8-deficient mice and, in contrast, depletion of $CD8^+$ T cells in obese mice improved IS (Nishimura et al., 2009). Moreover, $CD8^+$ T cells from HFD-obese mice more efficiently stimulated TNFα production by VAT macrophages than $CD8^+$ T cells from lean mice (Nishimura et al., 2009). In line with the reports on increased production of IFNγ, granzyme B and/or perforin by $CD8^+$ T cells (Ghazarian et al., 2015), these data suggest a major role of $CD8^+$ T cells in AT inflammation.

Recent findings deciphered participation of non-MHC-restricted unconventional T cells in obesity-associated AT inflammation. These cells are less diverse in terms of antigen recognition (Exley

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et al., 2014; Kohlgruber and Lynch, 2015; Tard et al., 2015; Wensveen et al., 2015) and are present at relatively high frequency in lean AT. They recognize lipid antigens and sustain M2 macrophages in VAT. Lack of invariant natural killer T (iNKT) cells in mice led to reduced AT levels of IL-4 and IL-13, as well as to increased number of M1 macrophages (Lynch et al., 2012). However, the role of iNKT cells might be changed in response to obesity leading to their loss in AT and promotion of IR following HFD (Subramanian et al., 2013). The mechanism via which iNKT cells inhibit AT inflammation under homeostasis, yet promote it in models of obesity is not clear (Wensveen et al., 2015). Nevertheless, the majority of findings suggest that adipose resident iNKT cells play a critical role in preventing local inflammation and protecting against metabolic disorder in obesity (Kohlgruber and Lynch, 2015). In addition, AT contains γδ T cells promoting inflammation and IR during HFD in mice (Mehta et al., 2015), as well as mucosal-associated invariant T (MAIT) cells – innate-like T cells that recognize bacterial ligands, and whose AT and blood levels were found to be elevated and reduced, respectively, in obese and T2DM patients. Circulating in obese subjects MAIT cells are found to be highly activated, associated with elevated Th1 and Th17 cytokine production (Carolan et al., 2015; Gapin, 2016; Magalhaes et al., 2015a). Reduced MAIT cell levels along with normalization of both immune and metabolic parameters after bariatric surgery (Magalhaes et al., 2015b) suggest a potential role of MAIT cells in obesity and T2DM.

B cells constitute another adaptive immune subset within the crown-like structures in the visceral AT (Winer et al., 2014). B cells were shown to have a predominantly pathogenic role in obesity-related IR, through the secretion of inflammatory cytokines and antigen-specific antibodies and via activation of IFNγ or IL-17 secreting Th1 cells (DeFuria et al., 2013; Winer et al., 2011, 2014). In addition, HFD induces a subtype of B cells, presumably in a T cell-dependent manner, capable of producing pro-inflammatory IgG2c that can promote macrophage TNFα production and induce IR, thus consistent with the Th1-skewed phenotype of obesity-linked inflammation (Winer et al., 2011). Recently, it has been found that blood B cells support Th17-mediated inflammation in obesity-associated T2DM subjects (Ip et al., 2016).

In addition, in obesity, eosinophils migrate into AT through α4- and αL-integrin-dependent mechanisms and sustain activation of M2 macrophages via an IL-4/IL-13-mediated mechanism. Moreover, it was shown that helminth-induced AT eosinophilia enhances glucose tolerance whereas eosinophil-deficient mice develop severe obesity and IR, thus underlying an important, "anti-obese" role of eosinophils in metabolic homeostasis (Wu et al., 2011; Qiu et al., 2014). Furthermore, eosinophils reduce chronic inflammation in AT by secreting Th2 cytokines and promoting M2 macrophages polarization (Zhang et al., 2015). Although mast cells are also activated in human obese AT, they, in contrast, seem to be induce accumulation of M1 macrophages (Divoux et al., 2012), and their number and inflammatory phenotype were found to be associated with 2TDM parameters both in humans and in HFD-obese mice (Huh et al., 2014b). It was also shown that neutrophils capable of secreting IL-17 and IL-22 (Zindl et al., 2013) as well as several proteases including neutrophil elastase (Pham, 2006), worsened HFD-induced inflammation and IR in AT and liver (Talukdar et al., 2012).

Recently, by using the mice lacking a rare subpopulation of DCs enriched with perforin-containing granules (perf-DCs), a unique role of DCs in obesity has been discovered. These mice revealed progressively gained weight, elevated serum cholesterol, TG, leptin and TNFα levels along with increased total body fat and reduced insulin sensitivity, associated with an altered repertoire of T cells residing in AT, all suggesting a protective role of perf-DCs in the development of obesity and metabolic syndrome (Zlotnikov-Klionsky et al., 2015). Surprisingly, mice lacking perf-DCs were substantially more prone to induction of experimental autoimmune encephlalomyelitis (EAE) exhibiting significant expansion of detrimental EAE antigen-specific autoimmune T cell clones compared to their wild-type counterparts. This phenotype was associated with an altered repertoire of T cells residing in AT and has been completely prevented by T cell depletion (Zlotnikov-Klionsky et al., 2015). These encouraging data seem to support the provocative hypothesis that obesity-related IR and T2DM might be autoimmune disorders (Tsai et al., 2015a). Although obesity is proposed to be an important risk factor for autoimmune diseases, such as rheumatoid arthritis (RA) and multiple sclerosis (Versini et al., 2014; Winer et al., 2009), the main and intriguing question whether obesity-related AT inflammation and IR/T2DM are a result of an activated adaptive immune response or whether such adaptive immune responses evolve from chronic age-associated AT inflammation (Tsai et al., 2015a), remains unanswered.

4.2. A cross talk between AT inflammation and skeletal muscle inflammation and dysfunction

4.2.1. Leptin and adiponectin as the inflammation-associated adipokine prototypes

Discovery of leptin and adiponectin more than 20 years ago (Scherer et al., 1995; Zhang et al., 1994) has established AT as an endocrine organ, secreting bioactive molecules called adipokines, through which AT regulates not only appetite, satiety and energy expenditure, but also glucose, insulin and lipid secretion and metabolism, fat distribution, and function of the immune system (Bluher and Mantzoros, 2015; Sakuma and Yamaguchi, 2013). Concerning the age- and obesity-associated conditions, it is well established that they possess mainly the opposite capacities. In particular, adiponectin levels decline with age and obesity (Gondim et al., 2015; Vilarrasa et al., 2005; Voss et al., 2016; You et al., 2013), whereas exercise-induced weight reduction elevates its levels with a strong negative correlation between plasma adiponectin concentrations and fat mass, and with opposite changes in the levels of leptin (Balsan et al., 2015; Gondim et al., 2015; Tilg and Moschen, 2006; Voss et al., 2016; You et al., 2013). Notably, it stimulates FA oxidation and glucose uptake in skeletal muscle and AT in an AMPK-activated signaling manner, the effect that is blunted in obesity (Chen et al., 2005). The activation of adiponectin is dependent on signaling through adiponectin receptors AdipoR1 and AdipoR2 abundantly expressed in human skeletal muscle and in primary myotubes (Jacobi et al., 2006). The capacity of adiponectin to activate AMPK and inhibit NFκB signaling was connected to decreased monocyte, macrophage, and DC production of TNFα and IFNγ while increased production of IL-10 and IL-1Ra (Tilg and Moschen, 2006). Recently, it was shown that TNFα directly impairs adiponectin signaling, mitochondrial biogenesis and myogenesis in primary human myotubes (Sente et al., 2016), while enhanced AdipoR1 expression on Tregs in AT was found to negatively correlated with epididymal fat (Ramos-Ramírez et al., 2016). In addition, HFD mice revealed reduced adiponectin serum levels in association with increased and decreased frequency of Th1 CD4+ T cells and T regs, respectively, along with reduced levels of IL-10 in AT of HFD mice as comparted to controls (Maioli et al., 2016).

In contrast to adiponectin, serum levels of leptin were found to reflect overall adipose mass (Farr et al., 2015; Friedman, 2015) in association with IR (Sakuma and Yamaguchi, 2013). It was also observed that leptin possesses a pro-inflammatory activity by increasing TNFα, IL-6 and IL-12 production by monocytes (Procaccini et al., 2013). Recently, the concept that leptin signaling 'licenses' various immune cells to differentiate and/or to engage in immune responses has been proposed (Naylor and Petri, 2016). Indeed, leptin was found to promote differentiation of $CD4^+$ cells to IL-17-producing cells and enhances IL-17A production,

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but suppress the formation of Tregs (Orlova and Shirshev, 2014; Reis et al., 2015). Moreover, deficiency of leptin receptor in $CD4^+$ T cells resulted in a defect in both autoimmune and protective Th17 responses attributed to reduced activation of the STAT3 and its downstream targets (Reis et al., 2015). Altogether, these data suggest a link between key adipokines, adiponectin and leptin, and age- and obesity-induced recruitment of pro-inflammatory immune cells in AT.

4.2.2. Osteopontin (OPN)

Dramatic upregulation of OPN expression in AT in HFD-induced and genetically obese mice, by 40 and 80-fold, respectively, (Kiefer et al., 2008) as well as elevated OPN expression in macrophages recruited to the AT in HFD mice (Kiefer et al., 2010; Nomiyama et al., 2007) indicate its involvement in obesity-associated AT inflammation. Acting through integrin and CD44 receptors, highly expressed in immune cells, AT and skeletal muscle (Kang et al., 2013; Liu et al., 2015b), OPN mediates monocyte adhesion, migration, differentiation and phagocytosis as well as recruitment of pro-inflammatory Th1 and Th17 cells to AT (Cantor and Shinohara, 2009). Plasma OPN and its expression in VAT are increased in obesity and obesity-associated T2DM; these findings are in line with the ability of OPN to promote macrophage recruitment and AT inflammation in these pathologies, in particular, to induce production of TNFα and TGFβ (Kahles et al., 2014), all well-known contributors to obesity-related inflammation. Moreover, OPN gene deletion in mice was accompanied by reduced AT expression and plasma levels of IL-6, TNFα and MCP1 along with improved whole-body glucose tolerance and reduced IR (Nomiyama et al., 2007), decreased of HFD-induced hyperlipidemia and reduced adipocyte hypertrophy (Chapman et al., 2010). In addition, OPN was found to directly stimulate inflammatory signaling pathways (phosphorylation of Akt, p38 MAPK, and ERK) and secretion of TNFα and MCP1 in isolated human adipocytes, and in AT macrophages (Zeyda et al., 2011), which are proposed as the main source of OPN (Kiefer et al., 2008; Nomiyama et al., 2007). In human subjects, OPN expression in AT as well as circulating OPN levels were substantially elevated in obese patients and were further increased in obese diabetic or IR patients, compared with lean subjects (Kiefer et al., 2008; Daniele et al., 2014). In contrast, exercise-induced weight loss was accompanied by reduced OPN circulating levels (You et al., 2013). Although there is some inconsistency in the role of OPN in skeletal muscle pathology (Pagel et al., 2014), majority of the findings imply its unfavorable effects. Indeed, it was found to inhibit cell migration and differentiation of cultured myoblasts (Uaesoontrachoon et al., 2008) and suppress muscle regeneration in inflamed muscle of MDX mice (a mouse model for human Duchenne muscular dystrophy, DMD) by promoting fibrosis and modulating immune cell subsets and intramuscular TGFβ (Vetrone et al., 2009). In addition, it was shown to be over-expressed in macrophages that infiltrate old injured mouse muscle (Paliwal et al., 2012) as well as in skeletal muscle of patients with various muscular dystrophies in association with elevated levels of inflammation-associated metalloproteinases (Zanotti et al., 2011). Its expression is also raised in muscle and serum of patients with idiopathic inflammatory myopathies (Xiao et al., 2015). In summary, OPN appears to play a negative and pro-inflammatory role in age- and obesity-mediated AT and muscle functionality.

4.2.3. Resistin

Resistin (from "resistance to insulin"), secreted by adipocytes (McTernan et al., 2002), was considered as a connector between IR and obesity, since its serum levels were found to be increased markedly in mouse models of genetic and diet-induced obesity (Steppan et al., 2001). Its expression was found also in macrophages (Patel et al., 2003), and the inflammatory conditions appear to be the main determinants of its circulating levels (Lehrke et al., 2004). In addition, resistin was shown to up-regulate the expression of TNFα, IL-6, IL-12, and MCP-1 in monocytes, macrophages, and hepatic stellate cells, mediated through the NFκB signaling pathway (Park and Ahima, 2013) and, probably, via adenylyl cyclase-associated protein 1 proposed to be a functional receptor for resistin-mediated inflammatory activity in human monocytes (Lee et al., 2014). In turn, several pro-inflammatory molecules and resistin itself were found to induce resistin expression in various cells and tissues (Bokarewa et al., 2005). In line with these findings, circulating resistin levels were found to correlate with TNFα and IL-6 in apparently healthy subjects (Pantsulaia et al., 2007), with CRP and plasminogen activator inhibitor (PAI)-1 in subjects with T2DM, RA, and sepsis often in association with disease activity and unfavorable outcome (Park and Ahima, 2013). Notably, exercise-induced weight loss led to reduced resistin circulating levels (Gondim et al., 2015). It was also found that resistin promotes fat accumulation in LDs of human macrophages via elevated expression of CD36, a FA scavenger receptor (Xu et al., 2006), as well as enhances ROS production by muscle cells (Gan et al., 2013). Inflammatory effects of resitin on human muscle cells were found to be associated with up-regulation of fractalkine and its receptor, CX3CR1 (Gan et al., 2013). Notably, resistin expression was detected in skeletal muscle (Carey et al., 2006; Jin et al., 2014), and after IL-6 infusion its expression was found to be significantly elevated in human skeletal muscle and AT (Carey et al., 2006). Overall, these observations suggest the existence of resistin-mediated link between age, obesity, oxidative stress, IR and inflammation potentially affecting skeletal muscle function.

4.2.4. Chemerin

A recently discovered adipokine chemerin and its receptors CMKLR1 (chemokine-like receptor 1) and ChemR23 (chemerin receptor 23) were found to be expressed in adipocytes, macrophages, DCs and skeletal muscle cells (Berg et al., 2010; Luangsay et al., 2009; Mattern et al., 2014). Chemerin regulates adipocyte differentiation and metabolism by auto/paracrine manner (Bozaoglu et al., 2010; Roh et al., 2007; Takahashi et al., 2008). Its expression was found to be closely linked to obesity, IR, metabolic syndrome risk factors and inflammation (Bozaoglu et al., 2010; Ernst and Sinal, 2010; Mariani and Roncucci, 2015), in negative and positive correlations with adiponectin and leptin levels, respectively (Coimbra et al., 2014). Moreover, chemerin inhibits myogenesis and induces adipogenesis in C2C12 myoblasts (Li et al., 2014). Additional evidence for a link between chemerin and obesity was documented after elimination of obesity through bariatric surgery as well as hypocaloric diet and exercise interventions accompanied by reduced chemerin circulating levels in concert with reduced IR tests, TAG and blood glucose levels (Chakaroun et al., 2012; Kim et al., 2014b; Sell et al., 2010; Venojärvi et al., 2013). Recent data demonstrated that chemerin-induced IR in skeletal muscle is associated with several mitochondrial dysfunction along with decreased expression of some muscle specific transcription factors in cultured C2C12 myocytes (Xie et al., 2015). Significant reduction in circulating chemerin levels was observed in obese and T2DM individuals after various training programs in association with decreased IR, CRP and leptin levels (Kim et al., 2014b; Lloyd et al., 2015; Stefanov et al., 2014). Notably, plasma chemerin levels were found to be increased in some chronic inflammatory diseases, and its levels correlated with the levels of TNFα, IL-6, CRP and FAs (Mariani and Roncucci, 2015; Rourke et al., 2013). Moreover, TNFα induced chemerin expression in adipocytes (Suzuki et al., 2012). Importantly, chemerin receptor ChemR23 was found to be expressed on M1 macrophages providing their enhanced chemoattraction (Herová et al., 2015). In skeletal muscle, chemerin induced elevation in TNFα and IL-6 expression (Sell et al., 2010). Over-

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all, these findings suggest a close connection between chemerin, inflammation, obesity, IR and muscle pathology.

4.2.5. PEDF

Another factor that potentially connects obesity, inflammation and muscle pathology is pigment epithelium-derived factor (PEDF), an adipokine that belongs to the serine protease inhibitor (serpin) family (Becerra, 1997). Its significantly elevated circulating levels were observed in prediabetic and T2DM patients in association with increased fat mass, TAG and TNFα levels, fasting insulin, BMI, and cardiometabolic risk factors in humans (Gattu et al., 2013; Jenkins et al., 2014; Hui et al., 2014; Sunderland et al., 2012; Tahara et al., 2011). In contrast, its reduced levels were detected upon weight loss and insulin sensitization (Crowe et al., 2009; Duggan et al., 2016), all implicating involvement of PEDF in obesity and IR. PEDF is widely expressed including skeletal myocytes and abundantly in AT where it was found to be secreted by adipocytes and macrophages. Treatment of primary human adipocytes and muscle cells with PEDF induced IR accompanied by induction of inflammatory NFκB, p38-MAPK and mTOR signaling pathways (Famulla et al., 2015). It was also shown that PEDF mobilizes free FAs from AT into the systemic circulation resulting in inflammation and ectopic lipid deposition. In skeletal muscle, PEDF was found to colocalize with ATGL in LDs (Chung et al., 2008), promoting lipolysis in an ATGL-dependent manner. PEDF administration induced an inflammatory phenotype in mice, resulting in the recruitment and activation of macrophages and monocytes that secrete increased levels of TNFα and IL-6 (Filleur et al., 2009), whereas anti-PEDF antibody reduced levels of these cytokines (Chavan et al., 2012). Although there are some contradictory reports regarding the role of PEDF in metabolic disorders (Carnagarin et al., 2016; Craword et al., 2013), majority of data supports the idea that PEDF can connect IR, AT and skeletal muscle inflammation.

4.2.6. Bone morphogenetic proteins (BMPs)

BMPs, the members of the TGFβ family of cytokines, possess pleiotropic effects in tissues other than bone, including skeletal muscle, where they enhance the muscle growth by competing with the TGFβ/myostatin/activin signaling pathway (Grgurevic et al., 2016; Sartori et al., 2014). In AT, BMP-2, −4, −6, −7, and −9 effectively induce adipogenic differentiation (Kang et al., 2009). Although BMP-2, −4, and −6 could not induce expression of thermogenic uncoupling protein 1 (UCP1) (brown adipocyte marker gene), BMP-7 and BMP-8b promoted brown adipogenesis with marked induction of UCP1 along with enhanced mitochondrial biogenesis and activity (Tseng et al., 2008; Whittle et al., 2012). In addition, BMP7 was shown to reverse obesity in mice through a central, leptin-independent mTOR pathway (Townsend et al., 2012). Recently, MB109, a recombinant derivative of human BMP-9, was found to enhance expression of brown adipogenic genes in AT and brown adipogenesis of human AT-derived stem cells as well as suppress weight gaining in HDF-induced obese mice by reducing sizes of white adipocytes and decreased fasting blood glucose levels (Kuo et al., 2014). In addition, it was shown that BMP-7 is able to reduce significantly levels of IL-6, TNFα and MCP-1 (Rocher and Singla, 2013), enhance the levels of IL-1RA and IL-10 (Singla et al., 2016) as well as polarize monocytes into M2 macrophages (Rocher and Singla, 2013; Singla et al., 2016). Collectively, these data implicate BMPs as potential activators of WAT browning and inhibitors of IR development and AT inflammation.

4.2.7. Myostatin, follistatin and irisin axis

A myokine myostatin, a member of TGFβ superfamily, is a well-known negative regulator of the growth of skeletal muscles (McPherron, 2016). Mechanisms of this suppressive effect include activation of activin type II receptors A and B, accelerated Smad2 and Smad3 phosphorylation, up-regulation of genes involved in the reduction of proliferation and differentiation of skeletal muscle precursor cells, and enhancement of protein degradation pathways in mature myofibers (Sartori et al., 2014). In addition, myostatin was shown to induce oxidative stress by producing ROS in skeletal muscle cells through TNFα signaling pathway (Sriram et al., 2011). It was also noted that myostatin is induced in aged skeletal muscle (Bowser et al., 2013). Noteworthy, resistance exercise was accompanied by reduced mRNA expression levels (Schwarz et al., 2016). In contrast, expression of follistatin (FST), a natural myostatin inhibitor (Lee and McPherron, 2001), is decreased in aged rat skeletal muscle along with up-regulation in ROS levels (Ziaaldini et al., 2015), but increased during exercise (Hansen et al., 2016). Of note, over-expression of myostatin causes IR, whereas its inhibition prevents obesity and IR (Dong et al., 2016; McPherron, 2016; Zhang et al., 2012). Surprisingly, these favorable effects of myostatin inhibition were found to be accompanied by upregulation in the mRNA and protein expression of irisin in the muscle via increased peroxisome proliferator-activated receptor γ (PPARγ) expression. Irisin, a new muscle tissue-secreted peptide, is defined as the extracellular cleaved product of fibronectin type III domain containing protein 5 (FNDC5) and whose elevated levels were found in mice in response to exercise (Boström et al., 2012). Some studies highlight irisin as a compensatory myokine to promote oxidative metabolism, mitochondrial biogenesis and uncoupling, and reduce metabolic risk (Huh et al., 2014a; Pardo et al., 2014; Vaughan et al., 2015). It is also secreted by adipocytes (Roca-Rivada et al., 2013), and its up-regulation was associated with reduced body weight and enhanced IS (Boström et al., 2012; Moreno-Navarrete et al., 2013; Yan et al., 2014). Decreased circulating irisin levels and reduced expression of its structural gene, FNDC5, in muscle and AT were observed in obese and T2DM subjects (Moreno-Navarrete et al., 2013; Zhang et al., 2016). A clear correlation in circulating levels as well as in the levels of mRNA expression in muscle biopsy samples was found between irisin and FST in healthy and obese individuals (Vamvini et al., 2013). Blood irisin levels positively correlated with muscle mass, strength and metabolism and negatively with fasting glycaemia in humans (Kurdiova et al., 2014). Irisin was also shown to reduce TNFα and IL-6 expression in muscle and induce M2 macrophage polarization in peritoneal macrophages (Dong et al., 2016). Moreover, irisin was found to improve glucose tolerance and uptake in mouse HFD diabetic skeletal muscle along with reduced expression of genes involved in gluconeogenesis and fat weight, serum cholesterol and TAG levels, presumably via AMPK pathway (Xin et al., 2016). Furthermore, irisin significantly increased expression of several genes including *PGC1α* leading to increased mitochondrial content and oxygen consumption in mouse myotubes (Vaughan et al., 2015). Altogether, these findings support the existence of a complex cross talk between muscle and AT via myostatin/FST/irisin axis regulating age- and obesity-associated IR, inflammation and muscle pathology (Fig. 4).

4.2.8. Fibroblast growth factor 21 (FGF-21)

FGF-21 has been recently proposed as a regulator of muscle-to-fat relationships. It has been shown, for example, that physical exercise induces FGF-21 secretion in healthy, but not in 2TDM individuals (Hansen et al., 2016). FGF-21 is a member of the FGF superfamily, acting through the interaction with specific FGF receptors and a cofactor called β-Klotho, expressed in adipose and muscle tissues (Hojman et al., 2009; Moyers et al., 2007; Ogawa et al., 2007). This expression is associated with several metabolic beneficial effects of FGF-21 including weight loss, decreased body fat, browning of white AT, anti-hyperglycemic and anti-hyperlipidemic activity, and enhancement of IS (Coskun et al., 2008; Fisher et al., 2014; Jeon et al., 2016). In addition, FGF-21 administration in HFD rats resulted in reduced circulating CRP

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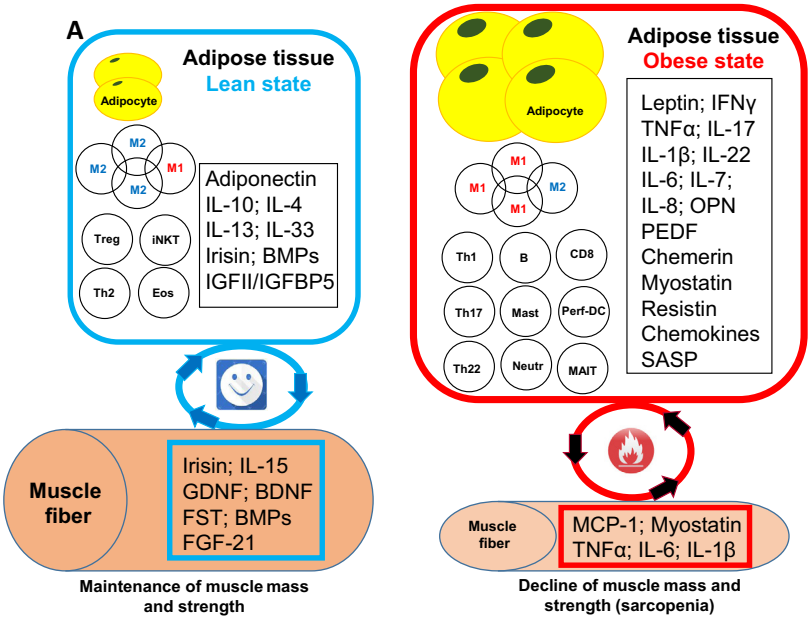

Fig. 4. Hypothesized cross talk between adipose tissue (AT) and skeletal muscle in healthy (non-inflamed) and obese (inflamed) conditions.
A. Under healthy (lean) conditions, AT is populated by macrophages in a M2-like state as well as by Th2, Tregs, iNKT and eosinophils producing anti-inflammatory cytokines such as IL-4, IL-10, IL-13, and IL-33 (Brestoff and Artis, 2015; Han et al., 2015; Odegaard and Chawla, 2015; Wensveen et al., 2015). Adipocytes secrete adipokines like adiponectin and irisin as well as several BMPs, all capable of sustaining healthy non-inflamed AT and skeletal muscle status (Grgurevic et al., 2016; Sartori and Sandri, 2015; Schering et al., 2015; Vaughan et al., 2015). Recent data suggest the ability of AT-mediated IGFII/IGFBP5 axis to stimulate myoblast proliferation and differentiation (Pellegrinelli et al., 2015). Consequently, healthy lean skeletal muscles produce several myokines such as irisin, IL-15, FST and FGF-21 as well as neurotrophic factors BDNF and GDNF, which collectively avert AT inflammation (Dong et al., 2016; Fisher and Maratos-Flier., 2016; Mwangi et al., 2014). This favorable immune-metabolic pathway is capable of maintaining healthy AT and the skeletal muscle status, thus preventing the development of sarcopenia. B. In obese state, adipocytes undego hypertrophia, hyperplasia and activation, resulting in the accumulation of M1-skewed macrophages as well as Th1, Th17 and Th22 lymphocytes and mast cells producing pro-inflammatory cytokines including IFNγ, TNFα, IL-1β, IL-6, IL-7, IL-8, IL-17 and IL-22 (Castoldi et al., 2016; Exley et al., 2014; Tateya et al., 2013; Wensveen et al., 2015). Other innate and adaptive immune cells, in particular $CD8^+$ T cells, B cells, perf-DCs and MAIT cells also play a role in obesity-induced AT inflammation (Apostolopoulos et al., 2016; Grant and Dixit, 2015; Magalhaes et al., 2015a,b; Zlotnikov-Klionsky et al., 2015). Various chemokines, such as CCL2, CCL5, CXCL12, CXCL8, and CXCL10, wich are detected in obese AT, are likely to be responsible for recruitment of macrophages and other immune cells in obese AT (Yao et al., 2014). Apparently, the pro-inflammatory milieu created (at least, partly) by these cells is the source of senescence-associated secretory phenotype (SASP), inducing and/or exacerbating skeletal muscle mass and function decline (LeBrasseur et al., 2015). In addition, several adipokines, such as leptin, CRP, OPN, chemerin, resistin, PEDF and myostatin are found abundantly in obese AT in close association with AT inflammation (Gencer et al., 2016; Mariani and Roncucci, 2015; Rodríguez et al., 2015). Obesity is also accompanied by ectopic fat accumulation in skeletal muscle in the form of IMAT and IMCLs, which separately and/or together with muscle cells, produce myostatin, CCL2, TNFα, IL-1β and IL-6. All are capable of inducing IR and lipotoxicity, thus affecting, in an auto/paracrine manner, the skeletal muscle functionality, and, in an endocrine manner, triggering and/or worsening AT inflammation (Rivas et al., 2016). This detrimental vicious circle probably maintains AT and skeletal muscle inflammation and triggers SOB development. Th – T-helper cells; Tregs – T-regulatory cells; iNKT – invariant natural killer T cells; BMPs – bone morphogenic proteins; IGFII/IGFBP5–insulin growth factor-II (IGF-II) and its binding protein-5 (IGFBP-5); FST – follistatin; FGF-21 – fibroblast growth factor-21; BDNF-brain-derived neurotrophic factor; GDNF – glial cell line-derived neurotrophic factor; perf-DCs – perforin-containing granules dendritic cells; MAIT – mucosal-associated invariant T cells; CRP – C-reactive protein; OPN – osteopontin; PEDF – pigment epithelium-derived factor; IMAT – intermuscular adipose tissue; IMCLs – intramyocellular lipids. Mast – mast cells; Eos – eosinophils; B – B-cells; Neutr – neutrophils.

levels as well as IL-6 and TNFα levels in AT, thus ameliorating obesity-related inflammation (Wang et al., 2015). Among other positive effects of FGF-21 is its capacity to protect against HFD-induced inflammation and islet hyperplasia in pancreas (Singhal et al., 2016), prevent HFD-induced obesity (Samms et al., 2016), induce expression of adiponectin (Lin et al., 2015), protect human skeletal muscle myotubes from palmitate-induced IR (Lee et al., 2014), and to defense against immune senescence by delaying age-related thymic involution (Youm et al., 2016). Although there is a contradictory observation claiming a capability of FGF-21 to suppress expression of adiponectin and up-regulate expression of leptin and IL-6 in human differentiating preadipocytes (Berti et al., 2015), the majority of published data support the notion that FGF-21 may exert anti-inflammatory and insulin sensitizing effects in AT and skeletal muscle.

4.2.9. Neurotrophic factors – BDNF and GDNF

Emerging evidence suggests deep involvement of neurotrophic factors brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) in age-associated skeletal muscle and AT pathology. BDNF exerts its effects via the tropomyosin-related kinase-B receptor (TrkBR) and the p75 neurotrophin receptor (p75NTR) to initiate several signaling cascades, including the PI3K/Akt (Numakawa et al., 2010). In skeletal muscle, BDNF is involved in the development and differentiation of myoblasts and muscle fibers as well as in the regulation of the survival of motoneuron units (MUs), the presynaptic release of neurotransmitters, and the maintenance of the postsynaptic region in skeletal myofibers (Raschke and Eckel, 2013; Sakuma et al., 2015). Moreover, local production of BDNF can be induced by exercise stimulation in skeletal muscle (Papathanassoglou et al., 2015; Tsai et al., 2015b). BDNF administration to mice led to improved IS in skeletal muscle, decreased glucose production in hepatocytes, and enhanced glucose uptake in muscle and liver (Marosi and Mattson, 2014). In obesity, impaired signaling of BDNF through TrkBR was shown to promote fat accumulation (Marosi and Mattson, 2014), suggesting that disturbed BDNF signaling in peripheral target organs such as skeletal muscle might be associated with development of obesity. This idea has been confirmed in a recent study where chronic administration of the BDNF mimetic to TrkBR knockout mice revealed ameliorated HFD-induced body weight gain and obesity (Chan et al., 2015a). The suggested mechanism was attributed to increased BDNF/TrkBR-mediated energy expenditure in skeletal muscle through activation of mitochon-

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drial uncoupling, FA oxidation, glucose uptake, and possible heat production by mitochondrial UCP1. Along with the observation of reduced expression of BDNF in AT of obese mice (Jin et al., 2015), these findings explore the therapeutic potential of the skeletal muscle TrkBR agonists in the prevention of obesity (Youn and Cai, 2015). Notably, various immune cells, including Tregs, were shown to produce BDNF (Chan et al., 2015b; Kerschensteiner et al., 1999; Papathanassoglou et al., 2015), and the preferential accumulation of BDNF-releasing activated T lymphocytes and macrophages was detected near p75NTR-positive myofibers within regeneration (Colombo et al., 2013). These observations support the notion that BDNF may serve as a local mediator for muscle regeneration via a crosstalk between immune and muscle cells (Kalinkovich and Livshits, 2015).

An additional candidate for improving neuro-muscular function impaired in sarcopenia and obesity might be another neurotrophic factor, GDNF. It is produced in target tissues of neurons, including skeletal muscle (Suzuki et al., 2012), and its receptor, Ret tyrosine kinase, is expressed in MUs (Baudet et al., 2008). GDNF overexpression or its injection causes multiple innervation and slows the processes impaired in sarcopenia, including improving presynaptic and postsynaptic plasticity of the NMJs, protecting MUs from degeneration (Keller-Peck et al., 2001; Nguyen et al., 1998) as well as supporting survival and regeneration of damaged MUs (Pajenda et al., 2012). A connection between GDNF and obesity has been also documented. Chronic hypothalamic or nigrostriatal expression of GDNF in rodents and primates can induce weight loss in animals with age-related obesity and prevent weight gain in young animals (Manfredsson et al., 2009). In addition, GDNF transgenic mice resisted the HFD-induced weight gain, IR, dyslipidemia, hyperleptinemia, and hepatic steatosis along with higher energy expenditure as compared to wild type mice despite similar food intake and activity levels (Mwangi et al., 2014). These beneficial effects were accompanied by increased expression in skeletal muscle and brown AT of *PPARγ* gene known to be associated with increased lipolysis and enhanced lipid β-oxidation. Recently, a significant increase in the expression of microglial inflammatory markers CD11b and CD68 was determined in the skeletal muscle near intramuscular axons and NMJs in a rat model of familial amyotrophic lateral sclerosis (ALS); an inflammation was accompanied by elevation in IL-1β and TNFα levels in the muscle homogenates (Van Dyke et al., 2016). It is also found that physical exercise stimulates the synthesis of BDNF and GDNF (Monteiro-Junior et al., 2015). In sum, these findings suggest the existence of a novel and beneficial role of BDNF and GDNF in the age/obesity/inflammation-associated skeletal muscle pathology.

4.2.10. IL-15

One of the most surprising observations in the field of the connection between obesity-associated inflammation and skeletal muscle pathology is the capability of IL-15, a pro-inflammatory cytokine highly expressed in skeletal muscle to increase significantly myotube FA oxidation, presumably via enhanced AMPK phosphorylation and its downstream acetyl-CoA carboxylase (Ye, 2015). In myotubes, IL-15 increased transcriptional expression of several pro-oxidative genes and induced elevation in mitochondrial density (O'Connell and Pistilli, 2015) as well as reduced mitochondrial ROS levels (Li et al., 2015). Similarly, IL-15 gene transfer was accompanied by suppressed expression of genes involved in lipogenesis and gluconeogenesis along with enhanced expression of genes responsible for lipolysis and glucose metabolism (Sun and Liu, 2015), whereas mice knockout for IL-15 receptor, IL-15Rα, were found to be hyperglycemic and IR (Loro et al., 2015). The capability of IL-15 to inhibit adipogenesis is suggested to be dependent on decrease in leptin mRNA expression in adipocytes and prevention of their differentiation (Almendro et al., 2009). In adipocytes, IL-15 reduced rate of proliferation, induced their apoptosis and blocked differentiation (Alvarez et al., 2002; Fuster et al., 2011). Moreover, IL-15 transgenic mice, as compared to wild type mice, were found to have significantly elevated mitochondrial activity and mass in AT (Barra et al., 2012). IL-15/sIL-15Rα gene transfer induced weight loss and improved glucose homeostasis in obese mice (Sun et al., 2016). In addition, endurance training enhanced skeletal muscle IL-15 expression in human subjects (Rinnov et al., 2014). Collectively, these data suggest that a reciprocal muscle-to-fat signaling pathway involves the release of IL-15 from muscle tissue providing beneficial anti-obese and insulin sensitizing effects (Quinn et al., 2013).

4.3. Chemokines

Mounting evidence implicates that the chemokine-chemokine receptor axes play a fundamental role in the triggering/facilitating of obesity-mediated AT inflammation and its link to IR and T2DM. Indeed, up-regulated expression of chemokine receptors like CCR1, CCR2, CCR3, CXCR4 and CCR5 on inflammatory cells along with increased levels of their ligands (chemokines) including CCL2 (MCP-1), CCL5 (RANTES), CXCL12 (SDF-1), CXCL8 (IL-8), and CXCL10 (IP-10) was detected in AT of obese patients. In addition, serum levels of various chemokines are found to be dramatically increased in obese versus lean individuals (Makki et al., 2013; Yao et al., 2014; Xu et al., 2015a). It was also shown that human skeletal muscle cells might actively self-promote muscular inflammation by eliciting CXCL10 secretion, which is known to amplify Th1 cell tissue infiltration (Crescioli et al., 2012) as well as to participate in inflammatory myopathies (Limongi, 2015). In addition, it has been demonstrated that intra-muscular TNFα expression is restricted to the population of intramuscular leukocytes (mainly, macrophages) and that the chemokine CCL2 is associated with skeletal muscle inflammatory markers in HFD-mice and human obese/T2DM individuals (Patsouris et al., 2014). Furthermore, in this study, an exposure of myotubes to palmitate resulted in elevated production of CCL2 and that its muscle-specific overexpression in transgenic mice induced the local recruitment of macrophages and altered local IS. Recently, it has been shown that human skeletal muscle cells might actively self-promote muscular inflammation by eliciting CXCL10 secretion, under the influence of IFNγ and TNFα, which in turn may amplify Th1 cell tissue infiltration (Limongi, 2015). Moreover, contracting myotubes are shown to release CCL2 in a NFκB manner to chemoattract monocytes/macrophages (Miyatake et al., 2016). Altogether, these observations indicate a profound involvement of chemokines not only in recruitment of inflammatory cells in AT but also in skeletal muscle where they may induce and facilitate inflammation and IR.

4.4. Senescence-associated secretory phenotype (SASP)

As discussed above, a hallmark of aging is chronic low-grade sterile inflammation, inflammaging, which is closely associated with frailty and age-related diseases, but the mechanisms are still not fully understood. Accumulating data suggest a contribution to inflammaging of senescent cells, which by secreting pro-inflammatory cytokines and chemokines establish a SASP (LeBrasseur et al., 2015; Herranz et al., 2015; Salama et al., 2014; Sikora et al., 2014), thus linking senescent cells to age-related inflammation and diseases. Senescent cells accumulate in various tissues and organs with ageing and have been hypothesized to disrupt tissue structure and function because of the components they secrete. It was found that life-long removal of senescent, p16(Ink4a)-expressing cells delayed onset and also attenuated progression of already established age-related conditions in AT and skeletal muscle (Baker et al., 2011, 2016), suggesting that

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reduction in the burden of senescent cells could ameliorate age-related disabilities and chronic diseases. Accordingly, applying the drugs selectively targeting some pro-survival networks in senescent cells, called senolytic agents, revealed that an anticancer drug dasatinib, which eliminates highly expressed in senescent cells ephrin, c-kit and several other tyrosine kinases, eradicated senescent human fat cell progenitors (Zhu et al., 2015), thus confirming a major role of senescent fat cells in AT pathology (Tchkonia et al., 2010). Moreover, it was shown that senescent fat progenitor cells – preadipocytes, also termed "adipose-derived stem cells" or "fat cell progenitors", being the most abundant progenitor cell type in humans (Tchkonia et al., 2013) and comprising 15–50% of the cells in AT, accumulate in AT with aging; they acquire SASP with dramatically (up to 46-fold) increased production of various pro-inflammatory cytokines compared with non-senescent cells (Xu et al., 2015b). Notably, exercise prevents the accumulation of senescent cells and the expression of SASP (Schafer et al., 2016). The mechanisms involved in such SASP-associated inflammaging may include mTOR (Herranz et al., 2015), NFkB (Salminen et al., 2012), p53, p15(INK4b), p21(CIP1), and JAK-STAT signaling pathways (Acosta et al., 2013; Xu et al., 2015b). Interestingly, it was shown that senescence could be transmitted in a paracrine fashion via secretion of CCL2, IL-1 and IL-8, TGFβ family members (Activin A and GDF-15), and the chemokines CCL2 and CCL20 (Acosta et al., 2013). In addition, JAK-STAT inhibition suppressed the SASP in preadipocytes and SASP-induced AT inflammation (Xu et al., 2015b). It has been suggested also that accumulation of senescent cell is a result of age-associated immune deficiency, and their removal is increased upon the use of immune stimulatory agents (Ovadya and Krizhanovsky, 2014). Collectively, these findings suggest that targeting senescent cells could be a promising way to alleviate SASP-mediated AT inflammation. Although there is no data so far regarding direct detrimental effects of SAPS on skeletal muscle function, an age- and obesity-associated ectopic lipid accumulation in skeletal muscle potentially capable of local establishing of SAPS does not exclude such possibility.

Nevertheless, it remains unclear how AT affects skeletal muscle metabolism, structure and contractile function. In attempts to answer this question, Pellegrinelli et al. (2015) have examined the effects of secreted factors from AT on myocyte structure and the atrophy program within muscle by applying an elegant three-dimensional human primary cell culture experiments. The authors found that myocytes co-cultured with adipocytes obtained from VAT (but not from SAT) were smaller in accordance with gene and protein expression profile associated with muscle atrophy. Interestingly, troponin was detected among suppressed components, whose reduction has been suggested as a key element in contractile insufficiency in sarcopenia (Kalinkovich and Livshits, 2015). In addition, a reduction in pathways of oxidative metabolism and protein synthesis along with elevated production of IL-6 and IL-1β was also observed in the study. Moreover, it has been noted that harmful effect of VAT on muscle was accompanied by blockage of the expression of the myogenic growth factor IGF-II and its binding protein IGFBP-5, both known to stimulate myoblast proliferation and differentiation (Ren and Anversa, 2015). In line with these encouraging data are recent observations demonstrating that significantly elevated intramuscular storage of ceramide and DAG in HFD-obese and aged mice was closely associated with the loss of ALM and muscle strength along with the development of IR and increased expression of IL-1β and TNFα via impaired mTOR and IκBα signaling pathways as compared to young mice (Rivas et al., 2016). These findings raise a question on the potential importance of adipose-muscle proximity and the likelihood that these neighbors may be interacting in a discordant ways in obesity (Kelley and Goodpaster, 2015). Indeed, it has been observed that with aging, IMAT increases while muscle mass declines (Delmonico et al., 2009). Moreover, ceramide accumulation in skeletal muscle was found to be associated with pro-inflammatory induction of IR (Holland et al., 2011), and increased accumulation of DAG is predictive of IR in humans (Bergman et al., 2012). In addition, under palmiate-IR conditions, IGF-II/IGFBP-5 expression was found to be reduced significantly in myocytes (Deshmukh et al., 2015). Overall, these findings suggest a possibility of the age-associated and inflammation-mediated *direct* unfavorable impact of intramuscular lipids on skeletal muscle mass and function, thus being a key element in SOB pathogenesis. Hypothesized link between age- and obesity-associated AT and skeletal muscle inflammation and sarcopenia, presumably being a main mechanism of SOB, is schematically depicted in Fig. 4.

5. Concluding remarks

Obesity and sarcopenia and their comorbidity state, SOB, are the major public health problems that are anticipated to grow fast and significantly as human population ages. However, despite substantial attempts, we are still far from understanding the molecular mechanisms that govern SOB. Certainly, deciphering these mechanisms is important not only for achieving scientific progress in the field but also for creating the basis for prophylactic and therapeutic interventions. Based on the latest achievements in the study of obesity and skeletal muscle pathology, as reviewed above, we propose the existence of a cross talk between AT and skeletal muscle, two greatest tissues in the human body, via establishment of an age-associated detrimental vicious circle, in which chronic low-grade local (AT and skeletal muscle) and systemic inflammation ("inflammaging") is a major joining mechanism of SOB.

With regard to the role of sarcopenia in SOB pathogenesis, we have previously proposed that the prevalence of negative regulators of muscle growth, such as TGFβ, myostatin, activins and some others over positive regulators like BMPs, BDNF, irisin, and FST constitute a main mechanism of sarcopenia pathogenesis (Kalinkovich and Livshits, 2015). Remarkably, these molecules are found to be deeply involved in regulation of inflammation, and not only in skeletal muscle, but also in AT. For example, muscle growth inhibitors myostatin and activin A are shown to be increased in aging and capable of enhancing several key events associated with obesity as well as inducing and supporting AT and skeletal muscle inflammation (Dong et al., 2016). In contrast, muscle growth enhancers BMPs, BDNF, irisin, and FST (all produced by AT and/or skeletal muscle) were found to possess anti-inflammatory activity (Nimmo et al., 2013; Pedersen, 2013; Rashke and Eckel, 2013), confirming an idea about a close link between skeletal muscle metabolism, obesity and inflammation. A possible causal role of chronic low-grade inflammation in age- and sarcopenia-associated frailty has been recently proposed (Walston, 2015).

Moreover, MOH, proposed as "healthy" obesity phenotype, revealed a lower extent of inflammation at both the systemic and AT levels in comparison with MONW – its "non-healthy" counterpart. In particular, MOH exhibited "favorable" changes in adiponectin, leptin, TNFα, IL-6, CRP, chemerin, and resistin (Ahl et al., 2015; Badoud et al., 2015; Blüher and Schwarz, 2014; Doumatey et al., 2016; Indulekha et al., 2015; Phillips and Perry, 2013) as well as in the balance of immune cells, such as macrophages, Th22, Th17, and Tregs (Badoud et al., 2015).

Obviously, there are might be other potential mechanisms. For example, the capacity of obese- but not lean-derived adipose stem cells to induce proinflammatory environment (Th17 promotion and monocyte activation), which, in turn, inhibited adipogenesis and adipocyte insulin response (Eljaafari et al., 2015), might signify these stem cells as a new player in the development of obesity. In addition, an age-associated dysfunction of muscle stem (satellite) cells has been proposed to be involved in the fat-associated mus-

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cle pathology (Sciorati et al., 2016), thus implicating these stem cell impairments as a potential key factor in SOB. Moreover, recent proteomic and secretomic data revealed a huge amount of novel molecules and pathways that might be potentially involved in triggering and development of obesity and sarcopenia (and thus, in SOB). For instance, although the full set of human adipokines is still not entirely characterized, it has become clear that AT is a source of more than 600 potentially secretory proteins (Lehr et al., 2012). In addition, by a combined experimental and bioinformatics workflow in analyzing the secretome of lipid-induced IR skeletal muscle cells, >1000 putative secreted proteins including cytokines, chemokines and other inflammation-related molecules have been determined (Deshmukh et al., 2015). These data indicate an existence of novel factors and pathways that might be potentially involved in inflammation-mediated SOB.

Concerning the domination of AT or skeletal muscle pathology in the SOB pathogenesis accumulating data indicate that AT depots are the most vulnerable target to mediate significant immune cell infiltration and inflammation contributing to systemic inflammaging (Kwon and Pessin, 2013) and, presumably, to skeletal muscle inflammation via ectopic IMAT and IMCLs (Pellegrinelli et al., 2015; Kelley and Goodpaster, 2015). As depicted in Fig. 4, there is an intensive obesity-induced AT inflammation that appears to be self-generating finally establishing a detrimental vicious circle providing local (via paracrine/autocrine guideline) and systemic (via endocrine regulation) inflammation that targets skeletal muscle. In this setup, AT inflammation significantly dominates over skeletal muscle inflammation, and since it heads (it is the primary reason) these "hierarchical" events, it triggers skeletal muscle inflammation (a secondary event). Considering the dominating role of AT inflammation, in the etiology of this condition, we believe that the vector of events is in essence not the "sarcopenia → obesity" but rather, "obesity → sarcopenia". We therefore suggest the modified term, "obese sarcopenia", which, in view of the presented data, more accurately reflects the actual order of events in the pathological pathway leading to a combination of sarcopenia and obesity. Obviously, this idea requires further validation, and might be the subject of an emerging future study. However, regardless the terminology, deciphering the molecular mechanisms of age-associated obesity and sarcopenia might be important in distinguishing between causes and consequences of these comorbidities thus helping to improve their prevention and treatment.

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References

Acosta, J.C., Banito, A., Wuestefeld, T., Georgilis, A., Janich, P., Morton, J.P., Athineos, D., Kang, T.W., Lasitschka, F., Andrulis, M., Pascual, G., Morris, K.J., Khan, S., Jin, H., Dharmalingam, G., Snijders, A.P., Carroll, T., Capper, D., Pritchard, C., Inman, G.J., Longerich, T., Sansom, O.J., Benitah, S.A., Zender, L., Gil, J., 2013. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nat. Cell Biol. 15, 978–990.

Adams, J.M., Pratipanawatr, T., Berria, R., Wand, E., DeFronzo, R.A., Sullards, M.C., Mandarino, L.J., 2004. Ceramide content is increased in skeletal muscle from obese insulin-resistant humans. Diabetes 53, 25–31.

Addison, O., Marcus, R.L., Lastayo, P.C., Ryan, A.S., 2014. Intermuscular fat: a review of the consequences and causes. Int. J. Endocrinol. 2014, 309570.

Ahl, S., Guenther, M., Zhao, S., James, R., Marks, J., Szabo, A., Kidambi, S., 2015. Adiponectin levels differentiate metabolically healthy vs unhealthy among obese and nonobese white individuals. J. Clin. Endocrinol. Metab. 100, 4172–4180.

Akhmedov, D., Berdeaux, R., 2013. The effects of obesity on skeletal muscle regeneration. Front. Physiol. 4, 371.

Allison, D.B., Zannolli, R., Faith, M.S., Heo, M., Pietrobelli, A., VanItallie, T.B., Pi-Sunyer, F.X., Heymsfield, S.B., 1999. Weight loss increases and fat loss decreases all-cause mortality rate: results from two independent cohort studies. Int. J. Obes. Relat. Metab. Disord. 23, 603–611.

Allott, E.H., Hursting, S.D., 2015. Obesity and cancer: mechanistic insights from transdisciplinary studies. Endocr. Relat. Cancer 22, R365–386.

Almendro, V., Fuster, G., Ametller, E., Costelli, P., Pilla, F., Busquetsm, S., Figueras, M., Argilés, J.M., López-Soriano, F.J., 2009. Interleukin-15 increases calcineurin expression in 3T3-L1 cells: possible involvement on in vivo adipocyte differentiation. Int. J. Mol. Med. 24, 453–458.

Alvarez, B., Carbo, N., Lopez-Soriano, J., Drivdahl, R.H., Busquets, S., Lopez-Soriano, F.J., Argiles, J.M., Quinn, L.S., 2002. Effects of interleukin-15 (IL-15) on adipose tissue mass in rodent obesity models: evidence for direct IL-15 action on adipose tissue. Biochim. Biophys. Acta 1570, 33–37.

Andersen, C.J., Murphy, K.E., Fernandez, M.L., 2016. Impact of obesity and metabolic syndrome on immunity. Adv. Nutr. 7, 66–75.

Aon, M.A., Bhatt, N., Cortassa, S.C., 2014. Mitochondrial and cellular mechanisms for managing lipid excess. Front. Physiol. 5, 282.

Apostolopoulos, V., de Courten, M.P., Stojanovska, L., Blatch, G.L., Tangalakis, K., de Courten, B., 2016. The complex immunological and inflammatory network of adipose tissue in obesity. Mol. Nutr. Food Res. 60, 43–57.

Arner, P., Kulyté, A., 2015. MicroRNA regulatory networks in human adipose tissue and obesity. Nat. Rev. Endocrinol. 11, 276–288.

Badin, P.M., Langin, D., Moro, C., 2013. Dynamics of skeletal muscle lipid pools. Trends Endocrinol. Metab. 24, 607–615.

Badoud, F., Perreault, M., Zulyniak, M.A., Mutch, D.M., 2015. Molecular insights into the role of white adipose tissue in metabolically unhealthy normal weight and metabolically healthy obese individuals. FASEB J. 29, 748–758.

Baker, D.J., Wijshake, T., Tchkonia, T., LeBrasseur, N.K., Childs, B.G., van de Sluis, B., Kirkland, J.L., van Deursen, J.M., 2011. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479, 232–236.

Baker, D.J., Childs, B.G., Durik, M., Wijers, M.E., Sieben, C.J., Zhong, J., Saltness, R.A., Jeganathan, K.B., Verzosa, G.C., Pezeshki, A., Khazaie, K., Miller, J.D., van Deursen, J.M., 2016. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530, 184–189.

Balsan, G.A., Vieira, J.L., Oliveira, A.M., Portal, V.L., 2015. Relationship between adiponectin, obesity and insulin resistance. Rev. Assoc. Med. Bras. 61, 72–80.

Barra, N.G., Chew, M.V., Reid, S., Ashkar, A.A., 2012. Interleukin-15 treatment induces weight loss independent of lymphocytes. PLoS One 7, e39553.

Batsis, J.A., Barre, L.K., Mackenzie, T.A., Pratt, S.I., Lopez-Jimenez, F., Bartels, S.J., 2013. Variation in the prevalence of sarcopenia and sarcopenic obesity in older adults associated with different research definitions: dual-energy x-ray absorptiometry data from the National Health and Nutrition Examination Survey 1999–2004. J. Am. Geriatr. Soc. 61, 974–980.

Batsis, J.A., Mackenzie, T.A., Lopez-Jimenez, F., Bartels, S.J., 2015. Sarcopenia, sarcopenic obesity, and functional impairments in older adults: National Health and Nutrition Examination Surveys 1999–2004. Nutr. Res. 35, 1031–1039.

Baudet, C., Pozas, E., Adameyko, I., Andersson, E., Ericson, J., Ernfors, P., 2008. Retrograde signaling onto Ret during motor nerve terminal maturation. J. Neurosci. 28, 963–975.

Baumgartner, R.N., 2000. Body composition in healthy aging. Ann. N. Y. Acad. Sci. 904, 437–448.

Beaudart, C., Rizzolim, R., Bruyère, O., Reginster, J.Y., Biver, E., 2014. Sarcopenia: burden and challenges for public health. Arch. Public Health 72, 45.

Becerra, S.P., 1997. Structure-function studies on PEDF: a noninhibitory serpin with neurotrophic activity. Adv. Exp. Med. Biol. 425, 223–237.

Beenakker, K.G., Westendorp, R.G., de Craen, A.J., Slagboom, P.E., van Heemst, D., Maier, A.B., 2013. Pro-inflammatory capacity of classically activated monocytes relates positively to muscle mass and strength. Aging Cell 2, 682–689.

Bergman, B.C., Hunerdosse, D.M., Kerege, A., Playdon, M.C., Perreault, L., 2012. Localisation and composition of skeletal muscle diacylglycerol predicts insulin resistance in humans. Diabetologia 55, 1140–1150.

Berg, V., Sveinbjörnsson, B., Bendiksen, S., Brox, J., Meknas, K., Figenschau, Y., 2010. Human articular chondrocytes express ChemR23 and chemerin; ChemR23 promotes inflammatory signalling upon binding the ligand chemerin (21–157). Arthritis Res. Ther. 12, R228.

Berti, L., Irmler, M., Zdichavsky, M., Meile, T., Böhm, A., Stefan, N., Fritsche, A., Beckers, J., Königsrainer, A., Häring, H.U., de Angelis, M.H., Staiger, H., 2015. Fibroblast growth factor 21 is elevated in metabolically unhealthy obesity and affects lipid deposition adipogenesis, and adipokine secretion of human abdominal subcutaneous adipocytes. Mol. Metab. 4, 519–527.

Beyer, I., Mets, T., Bautmans, I., 2012. Chronic low- grade inflammation and age-related sarcopenia. Curr. Opin. Clin. Nutr. Metab. Care 15, 12–22.

Bing, C., 2015. Is interleukin-1β a culprit in macrophage-adipocyte crosstalk in obesity? Adipocyte 4, 149–152.

Biolo, G., Cederholm, T., Muscaritoli, M., 2014. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. Clin. Nutr. 33, 737–748.

Bischoff, S.C., 2016. Microbiota and aging. Curr. Opin. Clin. Nutr. Metab. Care. 19, 26–30.

Blüher, M., Mantzoros, C.S., 2015. From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. Metabolism 64, 131–145.

Blüher, S., Schwarz, P., 2014. Metabolically healthy obesity from childhood to adulthood – does weight status alone matter? Metabolism 63, 1084–1092.

Blau, H.M., Cosgrove, B.D., Ho, A.T., 2015. The central role of muscle stem cells in regenerative failure with aging. Nat. Med. 21, 854–862.

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Blundell, J.E., Dulloo, A.G., Salvador, J., Frühbeck, G., 2014. Beyond BMI-phenotyping the obesities. Obes. Facts 7, 322–328.
Boden, G., 2011. Obesity, insulin resistance and free fatty acids. Curr. Opin. Endocrinol. Diabetes Obes. 18, 139–143.
Bokarewa, M., Nagaev, I., Dahlberg, L., Smith, U., Tarkowski, A., 2005. Resistin, an adipokine with potent proinflammatory properties. J. Immunol. 174, 5789–5795.
Bosello, O., Donataccio, M.P., Cuzzolaro, M., 2016. Obesity or obesities? Controversies on the association between body mass index and premature mortality. Eat. Weight Disord. 21, 165–174.
Bosma, M., 2016. Lipid droplet dynamics in skeletal muscle. Exp. Cell Res. 340, 180–186.
Bosma, M., Kersten, S., Hesselink, M.K., Schrauwen, P., 2012. Re-evaluating lipotoxic triggers in skeletal muscle: relating intramyocellular lipid metabolism to insulin sensitivity. Prog. Lipid Res. 51, 36–49.
Bosma, M., Sparks, L.M., Hooiveld, G.J., Jorgensen, J.A., Houten, S.M., Schrauwen, P., Kersten, S., Hesselink, M.K., 2013. Overexpression of PLIN5 in skeletal muscle promotes oxidative gene expression and intramyocellular lipid content without compromising insulin sensitivity. Biochim. Biophys. Acta 1831, 844–852.
Boström, P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., Rasbach, K.A., Boström, E.A., Choi, J.H., Long, J.Z., Kajimura, S., Zingaretti, M.C., Vind, B.F., Tu, H., Cinti, S., Højlund, K., Gygi, S.P., Spiegelman, B.M., 2012. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481, 463–468.
Bouchard, D.R., Dionne, I.J., Brochu, M., 2009. Sarcopenic obesity and physical capacity in older men and women: data from the nutrition as a determinant of successful aging (Nu-Age)—the Quebec longitudinal study. Obesity 17, 2082–2088.
Boura-Halfon, S., Zick, Y., 2009. Phosphorylation of IRS proteins, insulin action, and insulin resistance. Am. J. Physiol. Endocrinol. Metab. 296, E581–E591.
Bowser, M., Herberg, S., Arounleut, P., Shi, X., Fulzele, S., Hill, W.D., Isalesm, C.M., Hamrick, M.W., 2013. Effects of the activin A-myostatin-follistatin system on aging bone and muscle progenitor cells. Exp. Gerontol. 48, 290–297.
Bozaoglu, K., Curran, J.E., Stocker, C.J., Zaibi, M.S., Segal, D., Konstantopoulos, N., Morrison, S., Carless, M., Dyer, T.D., Cole, S.A., Goring, H.H., Moses, E.K., Walder, K., Cawthorne, M.A., Blangero, J., Jowett, J.B., 2010. Chemerin, a novel adipokine in the regulation of angiogenesis. J. Clin. Endocrinol. Metab. 95, 2476–2485.
Brestoff, J.R., Artis, D., 2015. Immune regulation of metabolic homeostasis in health and disease. Cell 161, 146–160.
Bruce, C.R., Anderson, M.J., Carey, A.L., Newman, D.G., Bonen, A., Kriketos, A.D., Cooney, G.J., Hawley, J.A., 2003. Muscle oxidative capacity is a better predictor of insulin sensitivity than lipid status. J. Clin. Endocrinol. Metab. 88, 5444–5451.
Buch, A., Carmeli, E., Boker, L.K., Marcus, Y., Shefer, G., Kis, O., Berner, Y., Stern, N., 2016. Muscle function and fat content in relation to sarcopenia: obesity and frailty of old age – an overview. Exp. Gerontol. 76, 25–32.
Budui, S.L., Rossi, A.P., Zamboni, M., 2015. The pathogenetic bases of sarcopenia. Clin. Cases Miner. Bone Metab. 12, 22–26.
Calay, E.S., Hotamisligil, G.S., 2013. Turning off the inflammatory, but not the metabolic, flames. Nat. Med. 19, 265–267.
Cantor, H., Shinohara, M.L., 2009. Regulation of T-helper-cell lineage development by osteopontin: the inside story. Nat. Rev. Immunol. 9, 137–141.
Carey, A.L., Petersen, E.W., Bruce, C.R., Southgate, R.J., Pilegaard, H., Hawley, J.A., Pedersen, B.K., Febbraio, M.A., 2006. Discordant gene expression in skeletal muscle and adipose tissue of patients with type 2 diabetes: effect of interleukin-6 infusion. Diabetologia 49, 1000–1007.
Carnagarin, R., Dharmarajan, A.M., Dass, C.R., 2016. PEDF attenuates insulin-dependent molecular pathways of glucose homeostasis in skeletal myocytes. Mol. Cell. Endocrinol. 422, 115–124.
Carolan, E., Tobin, L.M., Mangan, B.A., Corrigan, M., Gaoatswe, G., Byrne, G., Geoghegan, J., Cody, D., O'Connell, J., Winter, D.C., Doherty, D.G., Lynch, L., O'Shea, D., Hogan, A.E., 2015. Altered distribution and increased IL-17 production by mucosal-associated invariant T cells in adult and childhood obesity. J. Immunol. 194, 5580–5775.
Carter, H.N., Chen, C.C., Hood, D.A., 2015. Mitochondria, muscle health, and exercise with advancing age. Physiology (Bethesda) 30, 208–223.
Casazza, K., Pate, R., Allison, D.B., 2013. Myths, presumptions, and facts about obesity. N. Engl. J. Med. 368, 2236–2237.
Castoldi, A., Naffah de Souza, C., Câmara, N.O., Moraes-Vieira, P.M., 2016. The macrophage switch in obesity development. Front. Immunol. 6, 637.
Cauley, J.A., 2015. An overview of sarcopenic obesity. J. Clin. Densitom. 18, 499–505.
Cesari, M., Landi, F., Vellas, B., Bernabei, R., Marzetti, E., 2014. Sarcopenia and physical frailty: two sides of the same coin. Front. Aging Neurosci. 6, 192.
Chakraborti, C.K., 2015. New-found link between microbiota and obesity. World J. Gastrointest. Pathophysiol. 6, 110–119.
Chakaroun, R., Raschpichler, M., Klöting, N., Oberbach, A., Flehmig, G., Kern, M., Schön, M.R., Shang, E., Lohmann, T., Dreßler, M., Fasshauer, M., Stumvoll, M., Blüher, M., 2012. Effects of weight loss and exercise on chemerin serum concentrations and adipose tissue expression in human obesity. Metabolism 61, 706–714.
Chan, A., Yan, J., Csurhes, P., Greer, J., McCombe, P., 2015a. Circulating brain derived neurotrophic factor (BDNF) and frequency of BDNF positive T cells in peripheral blood in human ischemic stroke: effect on outcome. J. Neuroimmunol. 286, 42–47.
Chan, C.B., Tse, M.C., Liu, X., Zhang, S., Schmidt, R., Otten, R., Liu, L., Ye, K., 2015b. Activation of muscular TrkB by its small molecular agonist 7,8-dihydroxyflavone sex-dependently regulates energy metabolism in diet-induced obese mice. Chem. Biol. 22, 355–368.
Chang, D.C., Piaggi, P., Hanson, R.L., Knowler, W.C., Bucci, J., Thio, G., Hohenadel, M.G., Bogardus, C., Krakoff, J., 2015. Use of a high-density protein microarray to identify autoantibodies in subjects with type 2 diabetes mellitus and an HLA background associated with reduced insulin secretion. PLoS One 10, e0143551.
Chapman, J., Miles, P.D., Ofrecio, J.M., Neels, J.G., Yu, J.G., Resnik, J.L., Wilkes, J., Talukdar, S., Thapar, D., Johnson, K., Sears, D.D., 2010. Osteopontin is required for the early onset of high fat diet-induced insulin resistance in mice. PLoS One 5, e13959.
Chavan, S.S., Hudson, L.K., Li, J.H., Ochani, M., Harris, Y., Patel, N.B., Katz, D., Scheinerman, J.A., Pavlov, V.A., Tracey, K.J., 2012. Identification of pigment epithelium-derived factor as an adipocyte-derived inflammatory factor. Mol. Med. 18, 1161–1168.
Chen, M.B., McAinch, A.J., Macaulay, S.L., Castelli, L.A., O'Brien, P.E., Dixon, J.B., Cameron-Smith, D., Kemp, B.E., Steinberg, G.R., 2005. Impaired activation of AMP-kinase and fatty acid oxidation by globular adiponectin in cultured human skeletal muscle of obese type 2 diabetics. J. Clin. Endocrinol. Metab. 90, 3665–3672.
Chen, L., Chen, R., Wang, H., Liang, F., 2015. Mechanisms linking inflammation to insulin resistance. Int. J. Endocrinol. 2015, 508409.
Chng, M.H., Alonso, M.N., Barnes, S.E., Nguyen, K.D., Engleman, E.G., 2015. Adaptive immunity and antigen-specific activation in obesity-associated insulin resistance. Mediators Inflamm. 2015, 593075.
Chung, C., Doll, J.A., Gattu, A.K., Shugrue, C., Cornwell, M., Fitchev, P., Crawford, S.E., 2008. Anti-angiogenic pigment epithelium-derived factor regulates hepatocyte triglyceride content through adipose triglyceride lipase (ATGL). J. Hepatol. 48, 471–478.
Chung, J.H., Hwang, H.J., Shin, H.Y., Han, C.H., 2016. Association between sarcopenic obesity and bone mineral density in middle-aged and elderly korean. Ann. Nutr. Metab. 68, 77–84.
Claflin, D.R., Jackson, M.J., Brooks, S.V., 2015. Age affects the contraction-induced mitochondrial redox response in skeletal muscle. Front. Physiol. 6, 21.
Cleasby, M.E., Jamieson, P., Atherton, P.J., 2016. Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. J. Endocrinol. (March (1)).
Coen, P.M., Goodpaster, B.H., 2012. Role of intramyocelluar lipids in human health. Trends. Endocrinol. Metab. 23, 391–398.
Coimbra, S., Brandão Proença, J., Santos-Silva, A., Neuparth, M.J., 2014. Adiponectin, leptin, and chemerin in elderly patients with type 2 diabetes mellitus: a close linkage with obesity and length of the disease. Biomed. Res. Int. 2014, 701915.
Colombo, E., Bedogni, F., Lorenzetti, I., Landsberger, N., Previtali, S.C., Farina, C., 2013. Autocrine and immune cell-derived BDNF in human skeletal muscle: implications for myogenesis and tissue regeneration. J. Pathol. 231, 190–198.
Conte, M., Vasuri, F., Trisolino, G., Bellavista, E., Santoro, A., Degiovanni, A., Martucci, E., D'Errico Grigioni, A., Caporossi, D., Capri, M., Maier, A.B., Seynnes, O., Barberi, L., Musaro', A., Narici, M.V., Franceschi, C., Salvioli, S., 2013. Increased Plin2 expression in human skeletal muscle is associated with sarcopenia and muscle weakness. PLoS One 8, e73709.
Conte, M., Vasuri, F., Bertaggia, E., Armani, A., Santoro, A., Bellavista, E., Degiovanni, A., D'Errico-Grigioni, A., Trisolino, G., Capri, M., Franchi, M.V., Narici, M.V., Sandri, M., Franceschi, C., Salvioli, S., 2015. Differential expression of perilipin 2and 5 in human skeletal muscle during aging and their association withatrophy-related genes. Biogerontology 16, 341.
Corcoran, M.P., Lamon-Fava, S., Fielding, R.A., 2007. Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. Am. J. Clin. Nutr. 85, 662–677.
Coskun, T., Bina, H.A., Schneider, M.A., Dunbar, J.D., Hu, C.C., Chen, Y., Moller, D.E., Kharitonenkov, A., 2008. Fibroblast growth factor 21 corrects obesity in mice. Endocrinology 149, 6018–6027.
Craword, S.E., Fitchev, P., Veliceasa, D., Volpert, O.V., 2013. The many facets of PEDF in drug discovery and disease: a diamond in the rough or split personality disorder? Expert Opin. Drug Discov. 8, 769–792.
Crescioli, C., Sottili, M., Bonini, P., Cosmi, L., Chiarugi, P., Romagnani, P., Vannelli, G.B., Colletti, M., Isidori, A.M., Serio, M., Lenzi, A., Di Luigi, L., 2012. Inflammatory response in human skeletal muscle cells: CXCL10 as a potential therapeutic target. Eur. J. Cell. Biol. 91, 139–149.
Crowe, S., Wu, L.E., Economou, C., Turpin, S.M., Matzaris, M., Hoehn, K.L., Hevener, A.L., James, D.E., Duh, E.J., Watt, M.J., 2009. Pigment epithelium-derived factor contributes to insulin resistance in obesity. Cell. Metab. 10, 40–47.
Cruz-Jentoft, A.J., Landi, F., Schneider, S.M., Zú˜niga, C., Arai, H., Boirie, Y., Chen, L.K., Fielding, R.A., Martin, F.C., Michel, J.P., Sieber, C., Stout, J.R., Studenski, S.A., Vellas, B., Woo, J., Zamboni, M., Cederholm, T., 2014. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review: report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 43, 748–759.
Dalmas, E., Venteclef, N., Caer, C., Poitou, C., Cremer, I., Aron-Wisnewsky, J., Lacroix-Desmazes, S., Bayry, J., Kaveri, S.V., Clément, K., André, S., Guerre-Millo, M., 2014. T cell-derived IL-22 amplifies IL-1β-driven inflammation in human adipose tissue: relevance to obesity and type 2 diabetes. Diabetes 63, 1966–1977.
Dam, T.T., Peters, K.W., Fragala, M., Cawthon, P.M., Harris, T.B., McLean, R., Shardell, M., Alley, D.E., Kenny, A., Ferrucci, L., Guralnik, J., Kiel, D.P., Kritchevsky, S., Vassileva, M.T., Studenski, S., 2014. An evidence-based comparison of

Please cite this article in press as: Kalinkovich, A., Livshits, G., Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.09.008

operational criteria for the presence of sarcopenia. J. Gerontol. A: Biol. Sci. Med. Sci. 69, 584–590.
Daniele, G., Guardado Mendoza, R., Winnier, D., Fiorentino, T.V., Pengou, Z., Cornell, J., Andreozzi, F., Jenkinson, C., Cersosimo, E., Federici, M., Tripathy, D., Folli, F., 2014. The inflammatory status score including IL-6, TNF-α, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. Acta Diabetol. 51, 123–131.
DeFuria, J., Belkina, A.C., Jagannathan-Bogdan, M., Snyder-Cappione, J., Carr, J.D., Nersesova, Y.R., Markham, D., Strissel, K.J., Watkins, A.A., Zhu, M., Allen, J., Bouchard, J., Toraldo, G., Jasuja, R., Obin, M.S., McDonnell, M.E., Apovian, C., Denis, G.V., Nikolajczyk, B.S., 2013. B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. Proc. Natl. Acad. Sci. U. S. A. 110, 5133–5138.
Dela, F., Helge, J.W., 2013. Insulin resistance and mitochondrial function in skeletal muscle. Int. J. Biochem. Cell Biol. 45, 11–15.
Delmonico, M.J., Harris, T.B., Visser, M., Park, S.W., Conroy, M.B., Velasquez-Mieyer, P., Boudreau, R., Manini, T.M., Nevitt, M., Newman, A.B., Goodpaster, B.H., 2009. Health, Aging, and Body. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am. J. Clin. Nutr. 90, 1579–1585.
Deshmukh, A.S., Cox, J., Jensen, L.J., Meissner, F., Mann, M., 2015. Secretome analysis of lipid-Induced insulin resistance in skeletal muscle cells by a combined experimental and bioinformatics workflow. J. Proteome Res. 14, 4885–4895.
DiSpirito, J.R., Mathis, D., 2015. Immunological contributions to adipose tissue homeostasis. Semin. Immunol. 27, 315–321.
Divoux, A., Moutel, S., Poitou, C., Lacasa, D., Veyrie, N., Aissat, A., Arock, M., Guerre-Millo, M., Clément, K., 2012. Mast cells in human adipose tissue: link with morbid obesity, inflammatory status, and diabetes. J. Clin. Endocrinol. Metab. 97, E1677–1685.
Dominguez, L.J., Barbagallo, M., 2007. The cardiometabolic syndrome and sarcopenic obesity in older persons. J. Cardiometab. Syndr. 2, 183–189.
Dong, J., Dong, Y., Dong, Y., Chen, F., Mitch, W.E., Zhang, L., 2016. Inhibition of myostatin in mice improves insulin sensitivity via irisin-mediated cross talk between muscle and adipose tissues. Int. J. Obes. (Lond.) 40, 434–442.
Doumatey, A.P., Zhou, J., Zhou, M., Prieto, D., Rotimi, C.N., Adeyemo, A., 2016. Proinflammatory and lipid biomarkers mediate metabolically healthy obesity: a proteomics study. Obesity (Silver Spring) 24, 1257–1265.
Duggan, C., Tapsoba, J.D., Wang, C.Y., McTiernan, A., 2016. Dietary weight loss and exercise effects on serum biomarkers of angiogenesis in overweight postmenopausal women: a randomized controlled trial. Cancer Res. (July (14)).
Eckel, N., Meidtner, K., Kalle-Uhlmann, T., Stefan, N., Schulze, M.B., 2016. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. Eur. J. Prev. Cardiol. 23, 956–966.
Eljaafari, A., Robert, M., Chehimi, M., Chanon, S., Durand, C., Vial, G., Bendridi, N., Madec, A.M., Disse, E., Laville, M., Rieusset, J., Lefai, E., Vidal, H., Pirola, L., 2015. Adipose tissue-derived stem cells from obese subjects contribute to inflammation and reduced insulin response in adipocytes through differential regulation of the Th1/Th17 balance and monocyte activation. Diabetes 64, 2477–2488, Endocrinology 149, 2015, 6018–6027.
Esser, N., Legrand-Poels, S., Piette, J., Scheen, A.J., Paquot, N., 2014. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res. Clin. Pract. 105, 141–150.
Evans, W.J., Paolisso, G., Abbatecola, A.M., Corsonello, A., Bustacchini, S., Strollo, F., Lattanzio, F., 2010. Frailty and muscle metabolism dysregulation in the elderly. Biogerontology 11, 527–536.
Exley, M.A., Hand, L., O'Shea, D., Lynch, L., 2014. Interplay between the immune system and adipose tissue in obesity. J. Endocrinol. 223, R41–R48.
Fabbri, E., Zoli, M., Gonzalez-Freire, M., Salive, M.E., Studenski, S.A., Ferrucci, L., 2015. Aging and multimorbidity: new tasks, priorities, and frontiers for integrated gerontological and clinical research. J. Am. Med. Dir. Assoc. 16, 640–647.
Fabbrini, E., Cella, M., McCartney, S.A., Fuchs, A., Abumrad, N.A., Pietka, T.A., Chen, Z., Finck, B.N., Han, D.H., Magkos, F., Conte, C., Bradley, D., Fraterrigo, G., Eagon, J.C., Patterson, B.W., Colonna, M., Klein, S., 2013. Association between specific adipose tissue CD4$^+$ T-cell populations and insulin resistance in obese individuals. Gastroenterology 45, 366–374.
Famulla, S., Lamers, D., Hartwig, S., Passlack, W., Horrighs, A., Cramer, A., Lehr, S., Sell, H., Eckel, J., Farr, O.M., Gavrieli, A., Mantzoros, C.S., 2015. Leptin applications in 2015: what have we learned about leptin and obesity? Curr. Opin. Endocrinol. Diabetes Obes. 22, 353–359.
Fan, J., Song, Y., Chen, Y., Hui, R., Zhang, W., 2013. Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: a meta-analysis of prospective cohort studies. Int. J. Cardiol. 12, 4761–4768.
Farr, O.M., Gavrieli, A., Mantzoros, C.S., 2015. Leptin applications in 2015: what have we learned about leptin and obesity? Curr. Opin. Endocrinol. Diabetes Obes. 22, 353–359.
Febbraio, M.A., 2014. Role of interleukins in obesity: implications for metabolic disease. Trends Endocrinol. Metab. 25, 312–319.
Ferrante Jr., A.W., 2013. The immune cells in adipose tissue. Diabetes Obes. Metab. (Suppl. 3), 34–38.
Filleur, S., Nelius, T., de Riese, W., Kennedy, R.C., 2009. Characterization of PEDF: a multi-functional serpin family protein. J. Cell. Biochem. 106, 769–775.
Fisher, F.M., Maratos-Flier, E., 2016. Understanding the physiology of FGF21. Annu. Rev. Physiol. 78, 223–241.
Fisher, F.M., Chui, P.C., Nasser, I.A., Popov, Y., Cunniff, J.C., Lundasen, T., Kharitonenkov, A., Schuppan, D., Flier, J.S., Maratos-Flier, E., 2014. Fibroblast growth factor 21 limits lipotoxicity by promoting hepatic fatty acid activation in mice on methionine and choline-deficient diets. Gastroenterology 147, 1073–1083.
Fitzgibbons, T.P., Czech, M.P., 2016. Emerging evidence for beneficial macrophage functions in atherosclerosis and obesity-induced insulin resistance. J. Mol. Med. (Berl.) 94, 267–275.
Florez, H., Troen, B.R., 2008. Fat and inflamm-aging: a dual path to unfitness in elderly people? J. Am. Geriatr. Soc. 56, 558–560.
Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., DeBenedictis, G., 2000. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908, 244–254.
Friedman, J., 2015. Leptin and the Regulation of Food Intake and Body Weight. J. Nutr. Sci. Vitaminol. (Tokyo), 61, Suppl: S202.
Fuster, G., Almendro, V., Fontes-Oliveira, C.C., Toledo, M., Costelli, P., Busquets, S., López-Soriano, F.J., Argilés, J.M., 2011. Interleukin-15 affects differentiation and apoptosis in adipocytes: implications in obesity. Lipids 46, 1033–1042.
Gaggini, M., Saponaro, C., Gastaldelli, A., 2015. Not all fats are created equal: adipose vs. ectopic fat: implication in cardiometabolic diseases. Horm. Mol. Biol. Clin. Investig. 22, 7–18.
Gan, A.M., Butoi, E.D., Manea, A., Simion, V., Stanm, D., Parvulescu, M.M., Calin, M., Manduteanu, I., Simionescu, M., 2013. Inflammatory effects of resistin on human smooth muscle cells: up-regulation of fractalkine and its receptor, CX3CR1 expression by TLR4 and Gi-protein pathways. Cell Tissue Res. 351, 161–174.
Gapin, L., 2016. Development of invariant natural killer T cells. Curr. Opin. Immunol. 39, 68–74.
Gattu, A.K., Swenson, E.S., Iwakiri, Y., Samuel, V.T., Troiano, N., Berry, R., Church, C.D., Rodeheffer, M.S., Carpenter, T.O., Chung, C., 2013. Determination of mesenchymal stem cell fate by pigment epithelium-derived factor (PEDF) results in increased adiposity and reduced bone mineral content. FASEB J. 27, 4384–4394.
Gencer, B., Auer, R., de Rekeneire, N., Butler, J., Kalogeropoulos, A., Bauer, D.C., Kritchevsky, S.B., Miljkovic, I., Vittinghoff, E., Harris, T., Rodondi, N., 2016. Association between resistin levels and cardiovascular disease events in older adults: the health, aging and body composition study. Atherosclerosis 245, 181–186.
Ghazarian, M., Luck, H., Revelo, X.S., Winer, S., Winer, D.A., 2015. Immunopathology of adipose tissue during metabolic syndrome. Turk. Patoloji. Derg. 31 (Suppl. 1), 172–180.
Goisser, S., Kemmler, W., Porzel, S., Volkert, D., Sieber, C.C., Bollheimer, L.C., Freiberger, E., 2015. Sarcopenic obesity and complex interventions with nutrition and exercise in community-dwelling older persons-a narrative review. Clin. Interv. Aging 10, 1267–1282.
Gondim, O.S., de Camargo, V.T., Gutierrez, F.A., Martins, P.F., Passos, M.E., Momesso, C.M., Santos, V.C., Gorjão, R., Pithon-Curi, T.C., Cury-Boaventura, M.F., 2015. Benefits of regular exercise on inflammatory and cardiovascular risk markers in normal weight, overweight and obese adults. PLoS One 10, e0140596.
Goodpaster, B.H., He, J., Watkins, S., Kelley, D.E., 2001. Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. J. Clin. Endocrinol. Metab. 86, 5755–5761.
Gordon, S., Taylor, P.R., 2015. Monocyte and macrophage heterogeneity. Nat. Rev. Immunol. 5, 953–964.
Grant, R.W., Dixit, V.D., 2015. Adipose tissue as an immunological organ. Obesity (Silver Spring) 23, 512–518.
Grgurevic, L., Christensen, G.L., Schulz, T.J., Vukicevic, S., 2016. Bone morphogenetic proteins in inflammation: glucose homeostasis and adipose tissue energy metabolism. Cytokine Growth Factor Rev. 27, 105–118.
Hafizi Abu Bakar, M., Kian Kai, C., Wan Hassan, W.N., Sarmidi, M.R., Yaakob, H., Zaman Hur, i., 2015. Mitochondrial dysfunction as a central event for mechanisms underlying insulin resistance: the roles of long chain fatty acids. Diabetes Metab. Res. Rev. 31, 453–475.
Han, J.M., Wu, D., Denroche, H.C., Yao, Y., Verchere, C.B., Levings, M.K., 2015. IL-33 reverses an obesity-induced deficit in visceral adipose tissue ST2$^+$ T regulatory cells and ameliorates adipose tissue inflammation and insulin resistance. J. Immunol. 194, 4777–4783.
Hansen, J.S., Pedersen, B.K., Xu, G., Lehmann, R., Weigert, C., Plomgaard, P., 2016. Exercise-induced secretion of FGF21 and follistatin are blocked by pancreatic clamp and impaired in type 2 diabetes. J. Clin. Endocrinol. Metab. 101, 2816–2825.
Harford, K.A., Reynolds, C.M., McGillicuddy, F.C., Roche, H.M., 2011. Fats, inflammation and insulin resistance: insights to the role of macrophage and T-cell accumulation in adipose tissue. Proc. Nutr. Soc. 70, 408–417.
Harris, L.A., Skinner, J.R., Shew, T.M., Pietka, T.A., Abumrad, N.A., Wolins, N.E., 2015. Perilipin 5-driven lipid droplet accumulation in skeletal muscle stimulates the expression of fibroblast growth factor 21. Diabetes 64, 2757–2768.
Hepple, R.T., 2016. Impact of aging on mitochondrial function in cardiac and skeletal muscle. Free Radic. Biol. Med. (March (23)).
Herová, M., Schmid, M., Gemperle, C., Hersberger, M., 2015. ChemR23, the receptor for chemerin and resolvin E1, is expressed and functional on M1 but not on M2 macrophages. J. Immunol. 194, 2330–2337.
Herranz, N., Gallage, S., Gil, J., 2015. TORn about SASP regulation. ABBV Cell Cycle 14, 3771–3772.
Ho-Pham, L.T., Nguyen, U.D., Nguyen, T.V., 2014. Association between lean mass, fat mass, and bone mineral density: a meta-analysis. J. Clin. Endocrinol. Metab. 99, 30–38.

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Hojman, P., Pedersen, M., Nielsen, A.R., Krogh-Madsen, R., Yfanti, C., Akerstrom, T., Nielsen, S., Pedersen, B.K., 2009. Fibroblast growth factor-21 is induced in human skeletal muscles by hyperinsulinemia. Diabetes 58, 2797–2801.
Holland, W.L., Bikman, B.T., Wang, L.P., Yuguang, G., Sargent, K.M., Bulchand, S., Knotts, T.A., Shui, G., Clegg, D.J., Wenk, M.R., Pagliassotti, M.J., Scherer, P.E., Summers, S.A., 2011. Lipid-induced insulin resistance mediated by the proinflammatory receptor TLR4 requires saturated fatty acid-induced ceramide biosynthesis in mice. J. Clin. Invest. 121, 1858–1870.
Hotamisligil, G.S., 1999. The role of TNF alpha and TNF receptors in obesity and insulin resistance. J. Intern. Med. 245, 621–625.
Hruschka, D.J., Hadley, C., 2016. How much do universal anthropometric standards bias the global monitoring of obesity and undernutrition? Obes. Rev. (July (7)).
Huh, J.Y., Dincer, F., Mesfum, E., Mantzoros, C.S., 2014a. Irisin stimulates muscle growth-related genes and regulates adipocyte differentiation and metabolism in humans. Int. J. Obes. (Lond.) 38, 1538–1544.
Huh, J.Y., Park, Y.J., Ham, M., Kim, J.B., 2014b. Crosstalk between adipocytes and immune cells in adipose tissue inflammation and metabolic dysregulation in obesity. Mol. Cells 37, 365–371.
Hui, E., Yeung, C.Y., Lee, P.C., Woo, Y.C., Fong, C.H., Chow, W.S., Xu, A., Lam, K.S., 2014. Elevated circulating pigment epithelium-derived factor predicts the progression of diabetic nephropathy in patients with type 2 diabetes. J. Clin. Endocrinol. Metab. 99, E2169–2177.
Ilich, J.Z., Kelly, O.J., Inglis, J.E., Panton, L.B., Duque, G., Ormsbee, M.J., 2014. Interrelationship among muscle, fat, and bone: connecting the dots on cellular hormonal, and whole body levels. Ageing Res. Rev. 15, 51–60.
Ilich, J.Z., Inglis, J.E., Kelly, O.J., McGee, D.L., 2015. Osteosarcopenic obesity is associated with reduced handgrip strength, walking abilities, and balance in postmenopausal women. Osteoporos. Int. 26, 2587–2595.
Indulekha, K., Surendar, J., Anjana, R.M., Geetha, L., Gokulakrishnan, K., Pradeepa, R., Mohan, V., 2015. Metabolic obesity, adipocytokines, and inflammatory markers in Asian Indians-CURES-124. Diabetes Technol. Ther. 17, 134–141.
Ip, B., Cilfone, N.A., Belkina, A.C., DeFuria, J., Jagannathan-Bogdan, M., Zhu, M., Kuchibhatla, R., McDonnell, M.E., Xiao, Q., Kepler, T.B., Apovian, C.M., Lauffenburger, D.A., Nikolajczyk, B.S., 2016. Th17 cytokines differentiate obesity from obesity-associated type 2 diabetes and promote TNFα production. Obesity (Silver Spring) 24, 102–112.
Jacobi, S.K., Gabler, N.K., Ajuwon, K.M., Davis, J.E., Spurlock, M.E., 2006. Adipocytes, myofibers, and cytokine biology: new horizons in the regulation of growth and body composition. J. Anim. Sci. 84 (Suppl), E140–E149.
Javadov, S., Jang, S., Rodriguez-Reyes, N., Rodriguez-Zayas, A.E., Soto Hernandez, J., Krainz, T., Wipf, P., Frontera, W., 2015. Mitochondria-targeted antioxidant preserves contractile properties and mitochondrial function of skeletal muscle in aged rats. Oncotarget 6, 39469–39481.
Jenkins, A.J., Fu, D., Azar, M., Stoner, J.A., Kaufman, D.G., Zhang, S., Klein, R.L., Lopes-Virella, M.F., Ma, J.X., Lyons, T.J., 2014. Clinical correlates of serum pigment epithelium-derived factor in type 2 diabetes patients. J. Diabetes Complications 28, 353–359.
Jeon, J.Y., Choi, S.E., Ha, E.S., Kim, T.H., Jung, J.G., Han, S.J., Kim, H.J., Kim, D.J., Kang, Y., Lee, K.W., 2016. Association between insulin resistance and impairment of FGF21 signal transduction in skeletal muscles. Endocrine (January (12)).
Jiang, H., Westerterp, M., Wang, C., Zhu, Y., Ai, D., 2014. Macrophage mTORC1 disruption reduces inflammation and insulin resistance in obese mice. Diabetologia 57, 2393–2404.
Jin, P., Zhu, L., Zhang, J., Xie, S., Pan, D., Wen, H., Meng, W., Lin, L., Chen, D., 2014. A correlation study of the expression of resistin and glycometabolism in muscle tissue after traumatic brain injury in rats. Chin. J. Traumatol. 17, 125–129.
Jin, Y.J., Cao, P.J., Bian, W.H., Li, M.E., Zhou, R., Zhang, L.Y., Yang, M.Z., 2015. BDNF levels in adipose tissue and hypothalamus were reduced in mice with MSG-induced obesity. Nutr. Neurosci. 18, 376–382.
Johannsen, D.L., Conley, K.E., Bajpeyi, S., Punyanitya, M., Gallagher, D., Zhang, Z., Covington, J., Smith, S.R., Ravussin, E., 2012. Ectopic lipid accumulation and reduced glucose tolerance in elderly adults are accompanied by altered skeletal muscle mitochondrial activity. J. Clin. Endocrinol. Metab. 97, 242–250.
Johnson, A.M., Olefsky, J.M., 2013. The origins and drivers of insulin resistance. Cell 152, 673–684.
Kaeberlein, M., Rabinovitch, P.S., Martin, G.M., 2015. Healthy aging: the ultimate preventative medicine. Science 350, 1191–1193.
Kahles, F., Findeisen, H.M., Bruemmer, D., 2014. Osteopontin A novel regulator at the cross roads of inflammation, obesity and diabetes. Mol. Metab. 3, 384–393.
Kalinkovich, A., Livshits, G., 2015. Sarcopenia – the search for emerging biomarkers. Ageing Res. Rev. 22, 58–71.
Kang, Q., Song, W.X., Luo, Q., Tang, N., Luo, J., Luo, X., Chen, J., Bi, Y., He, B.C., Park, J.K., Jiang, W., Tang, Y., Huang, J., Su, Y., Zhu, G.H., He, Y., Yin, H., Hu, Z., Wang, Y., Chen, L., Zuo, G.W., Pan, X., Shen, J., Vokes, T., Reid, R.R., Haydon, R.C., Luu, H.H., He, T.C., 2009. A comprehensive analysis of the dual roles of BMPs in regulating adipogenic and osteogenic differentiation of mesenchymal progenitor cells. Stem Cells Dev. 18, 545–559.
Kang, H.S., Liao, G., DeGraff, L.M., Gerrish, K., Bortner, C.D., Garantziotis, S., Jetten, A.M., 2013. CD44 plays a critical role in regulating diet-induced adipose inflammation, hepatic steatosis, and insulin resistance. PLoS One 8, e58417.
Kase, E.T., Feng, Y.Z., Badin, P.M., Bakke, S.S., Lauren s, C., Coue, M., Langin, D., Gaster, M., Thoresen, G.H., Rustan, A.C., Moro, C., 2015. Primary defects in lipolysis and insulin action in skeletal muscle cells from type 2 diabetic individuals. Biochim. Biophys. Acta 1851, 1194–1201.
Keller-Peck, C.R., Feng, G., Sanes, J.R., Yan, Q., Lichtman, J.W., Snider, W.D., 2001. Glial cell line-derived neurotrophic factor administration in postnatal life results in motor unit enlargement and continuous synaptic remodeling at the neuromuscular junction. J. Neurosci. 21, 6136–6146.
Kelley, D.E., Goodpaster, B.H., 2015. Stewing in not-so-good juices: interactions of skeletal muscle with adipose secretions. Diabetes 64, 3055–3057.
Kerschensteiner, M., Gallmeier, E., Behrens, L., Leal, V.V., Misgeld, T., Klinkert, W.E., Kolbeck, R., Hoppe, E., Oropeza-Wekerle, R.L., Bartke, I., Stadelmann, C., Lassmann, H., Wekerle, H., Hohlfeld, R., 1999. Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: a neuroprotective role of inflammation? J. Exp. Med. 189, 865–870.
Kiefer, F.W., Zeyda, M., Todoric, J., Huber, J., Geyeregger, R., Weichhart, T., Aszmann, O., Ludvik, B., Silberhumer, G.R., Prager, G., Stulnig, T.M., 2008. Osteopontin expression in human and murine obesity: extensive local up-regulation in adipose tissue but minimal systemic alterations. Endocrinology 149, 1350–1357.
Kiefer, F.W., Zeyda, M., Gollinger, K., Pfau, B., Neuhofer, A., Weichhart, T., Säemann, M.D., Geyeregger, R., Schlederer, M., Kenner, L., Stulnig, T.M., 2010. Neutralization of osteopontin inhibits obesity-induced inflammation and insulin resistance. Diabetes 59, 935–946.
Kiens, B., Alsted, T.J., Jeppesen, J., 2011. Factors regulating fat oxidation in human skeletal muscle. Obes. Rev. 12, 852–858.
Kim, T.N., Park, M.S., Ryu, J.Y., Choi, H.Y., Hong, H.C., Yoo, H.J., Kang, H.J., Song, W., Park, S.W., Baik, S.H., Newman, A.B., Choi, K.M., 2014a. Impact of visceral fat on skeletal muscle mass and vice versa in a prospective cohort study: the Korean Sarcopenic Obesity Study (KSOS). PLoS One 9, e115407.
Kim, Y.S., Jeon, J.Y., Nam, M., 2014b. Effect of lifestyle modification on serum chemerin concentration and its association with insulin sensitivity in overweight and obese adults with type 2 diabetes. Clin. Endocrinol. (Oxf.) 80, 825–833.
Kintscher, U., Hartge, M., Hess, K., Foryst-Ludwig, A., Clemenz, M., Wabitsch, M., Fischer-Posovszky, P., Barth, T.F., Dragun, D., Skurk, T., Hauner, H., Blüher, M., Unger, T., Wolf, A.M., Knippschild, U., Hombach, V., arx, M., 2008. T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. Arterioscler. Thromb. Vasc. Biol. 28, 1304–1310.
Kob, R., Bollheimer, L.C., Bertsch, T., Fellner, C., Djukic, M., Sieber, C.C., Fischer, B.E., 2015. Sarcopenic obesity: molecular clues to a better understanding of its pathogenesis? Biogerontology 16, 15–29.
Kohara, K., 2014. Sarcopenic obesity in aging population: current status and future directions for research. Endocrine 45, 15–25.
Kohlgruber, A., Lynch, L., 2015. Adipose tissue inflammation in the pathogenesis of type 2 diabetes. Curr. Diab. Rep. 15, 92.
Konopka, A.R., Sreekumaran, N.K., 2013. Mitochondrial and skeletal muscle health with advancing age. Mol. Cell Endocrinol. 379, 19–29.
Kopelman, P.G., 2000. Obesity as a medical problem. Nature 404, 635–643.
Korostishevsky, M., Steves, C.J., Malkin, I., Spector, T., Williams, F.M., Livshits, G., 2016. Genomics and metabolomics of muscular mass in community-based sample of UK females. Eur. J. Hum. Genet. 24, 277–283.
Kraakman, M.J., Murphy, A.J., Jandeleit-Dahm, K., Kammoun, H.L., 2014. Macrophage polarization in obesity and type 2 diabetes: weighing down our understanding of macrophage function? Front. Immunol. 5, 470.
Kramer, C.K., Zinman, B., Retnakaran, R., 2013. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. Ann. Intern. Med. 159, 758–769.
Kratz, M., Coats, B.R., Hisert, K.B., Hagman, D., Mutskov, V., Peris, E., Schoenfelt, K.Q., Kuzma, J.N., Larson, I., Billing, P.S., Landerholm, R.W., Crouthamel, M., Gozal, D., Hwang, S., Singh, P.K., Becker, L., 2014. Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages. Cell. Metab. 20, 614–625.
Krssak, M., Falk Petersen, K., Dresner, A., DiPietro, L., Vogel, S.M., Rothman, D.L., Roden, M., Shulman, G.I., 1999. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a ^{1}H NMR spectroscopy study. Diabetologia 42, 113–116.
Kuo, M.M., Kim, S., Tseng, C.Y., Jeon, Y.H., Choe, S., Lee, D.K., 2014. BMP-9 as a potent brown adipogenic inducer with anti-obesity capacity. Biomaterials 35, 3172–3179.
Kurdiova, T., Balaz, M., Vician, M., Maderova, D., Vlcek, M., Valkovic, L., Srbecky, M., Imrich, R., Kyselovicova, O., Belan, V., Jelok, I., Wolfrum, C., Klimes, I., Krssak, M., Zemkova, E., Gasperikova, D., Ukropec, J., Ukropcova, B., 2014. Effects of obesity, diabetes and exercise on Fndc5 gene expression and irisin release in human skeletal muscle and adipose tissue: in vivo and in vitro studies. J. Physiol. 592, 1091–1107.
Kwon, H., Pessin, J.E., 2013. Adipokines mediate inflammation and insulin resistance. Front. Endocrinol. (Lausanne) 4, 71.
Lackey, D.E., Olefsky, J.M., 2016. Regulation of metabolism by the innate immune system. Nat. Rev. Endocrinol. 12, 15–28.
Lavie, C.J., Milani, R.V., Artham, S.M., Patel, D.A., Ventura, H.O., 2009. The obesity paradox, weight loss, and coronary disease. Am. J. Med. 122, 1106–1114.
LeBrasseur, N.K., Tchkonia, T., Kirkland, J.L., 2015. Cellular senescence and the biology of aging disease, and frailty. Nestle Nutr. Inst. Workshop Ser. 83, 11–18.
Leduc-Gaudet, J.P., Picard, M., St-Jean Pelletier, F., Sgarioto, N., Auger, M.J., Vallée, J., Robitaille, R., St-Pierre, D.H., Gouspillou, G.m, 2015. Mitochondrial morphology is altered in atrophied skeletal muscle of aged mice. Oncotarget 6, 17923–17937.
Lee, S.J., McPherron, A.C., 2001. Regulation of myostatin activity and muscle growth. Proc. Natl. Acad. Sci. U. S. A. 98, 9306–9311.

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Lee, S., Lee, H.C., Kwon, Y.W., Lee, S.E., Cho, Y., Kim, J., Lee, S., Kim, J.Y., Lee, J., Yang, H.M., Mook-Jung, I., Nam, K.Y., Chung, J., Lazar, M.A., Kim, H.S., 2014. Adenylyl cyclase-associated protein 1 is a receptor for human resistin and mediates inflammatory actions of human monocytes. Cell Metab. 19, 484–497.
Lee, J., Hong, Y.P., Shin, H.J., Lee, W., 2016. Associations of sarcopenia and sarcopenic obesity with metabolic syndrome considering both muscle mass and muscle strength. J. Prev. Med. Public Health 49, 35–44.
Lehr, S., Hartwig, S., Sell, H., 2012. Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. Proteomics Clin. Appl. 6, 91–101.
Lehrke, M., Reilly, M.P., Millington, S.C., Iqbal, N., Rader, D.J., Lazar, M.A., 2004. An inflammatory cascade leading to hyperresistinemia in humans. PLoS Med. 1, e45.
Lenk, K., Schuler, G., Adams, V., 2010. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. J. Cachexia Sarcopenia Muscle 1, 9–21.
Li, F., Li, Y., Tang, Y., Lin, B., Kong, X., Oladele, O.A., Yin, Y., 2014. Protective effect of myokine IL-15 against H2O2-mediated oxidative stress in skeletal muscle cells. Mol. Biol. Rep. 41, 7715–7722.
Li, H.X., Chen, K.L., Wang, H.Y., Tang, C.B., Xu, X.L., Zhou, G.H., 2015. Chemerin inhibition of myogenesis and induction of adipogenesis in C2C12 myoblasts. Mol. Cell. Endocrinol. 414, 216–223.
Limongi, F., 2015. The CXCR3 chemokines in inflammatory myopathies. Clin. Ther. 166, e56–61.
Lin, Z., Pan, X., Wu, F., Ye, D., Zhang, Y., Wang, Y., Jin, L., Lian, Q., Huang, Y., Ding, H., Triggle, C., Wang, K., Li, X., Xu, A., 2015. Fibroblast growth factor 21 prevents atherosclerosis by suppression of hepatic sterol regulatory element-binding protein-2 and induction of adiponectin in mice. Circulation 131, 1861–1871.
Liu, H.H., Lim, J.J., 2015. Aging and dyslipidemia: a review of potential mechanisms. Ageing Res. Rev. 19, 43–52.
Liu, K., Zhao, E., Ilyas, G., Lalazar, G., Lin, Y., Haseeb, M., Tanaka, K.E., Czaja, M.J., 2015a. Impaired macrophage autophagy increases the immune response in obese mice by promoting proinflammatory macrophage polarization. Autophagy 11, 271–284.
Liu, L.F., Kodama, K., Wei, K., Tolentino, L.L., Choi, O., Engleman, E.G., Butte, A.J., McLaughlin, T., 2015b. The receptor CD44 is associated with systemic insulin resistance and proinflammatory macrophages in human adipose tissue. Diabetologia 58, 1579–1586.
Livshits, G., Kato, B.S., Wilson, S.G., Spector, T.D., 2007. Linkage of genes to total lean body mass in normal women. J. Clin. Endocrinol. Metab. 92, 3171–3176.
Lloyd, J.W., Zerfass, K.M., Heckstall, E.M., Evans, K.A., 2015. Diet-induced increases in chemerin are attenuated by exercise and mediate the effect of diet on insulin and HOMA-IR. Ther. Adv. Endocrinol. Metab. 6, 189–198.
Loftus, R.M., Finlay, D.K., 2016. Immunometabolism: cellular metabolism turns immune regulator. J. Biol. Chem. 291, 1–10.
Lopez-Miranda, J., Perez-Martinez, P., 2013. It is time to define metabolically obese but normal-weight (MONW) individuals. Clin. Endocrinol. (Oxf.) 79, 314–315.
Loro, E., Seifert, E.L., Moffat, C., Romero, F., Mishra, M.K., Sun, Z., Krajacic, P., Anokye-Danso, F., Summer, R.S., Ahima, R.S., Khurana, T.S., 2015. IL-15Rα is a determinant of muscle fuel utilization, and its loss protects against obesity. Am. J. Physiol. Regul. Integr. Comp. Physiol. 309, R835–844.
Louche, K., Badin, P.M., Montastier, E., Laurens, C., Bourlier, V., de Glisezinski, I., Thalamas, C., Viguerie, N., Langin, D., Moro, C., 2013. Endurance exercise training up-regulates lipolytic proteins and reduces triglyceride content in skeletal muscle of obese subjects. J. Clin. Endocrinol. Metab. 98, 4863–4871.
Luangsay, S., Wittamer, V., Bondue, B., De Henau, O., Rouger, L., Brait, M., Franssen, J.D., de Nadai, P., Huaux, F., Parmentier, M., 2009. Mouse ChemR23 is expressed in dendritic cell subsets and macrophages, and mediates an anti-inflammatory activity of chemerin in a lung disease model. J. Immunol. 183, 6489–6499.
Lumeng, C.N., Deyoung, S.M., Saltiel, A.R., 2007. Macrophages block insulin action in adipocytes by altering expression of signaling and glucose transport proteins. Am. J. Physiol. Endocrinol. Metab. 292, E166–174.
Lynch, L., Nowak, M., Varghese, B., Clark, J., Hogan, A.E., Toxavidis, V., Balk, S.P., O'Shea, D., O'Farrelly, C., Exley, M.A., 2012. Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine production. Immunity 37, 574–587.
Müller, M.J., Bosy-Westphal, A., Heller, M., 2009. 'Functional' body composition: differentiating between benign and non-benign obesity. F1000 Biol. Rep. 1, 75.
Müller, M.J., Braun, W., Enderle, J., Bosy-Westphal, A., 2016. Beyond BMI: conceptual issues related to overweight and obese patients. Obes. Facts 9, 193–205.
MacPherson, R.E., Peters, S.J., 2015. Piecing together the puzzle of perilipin proteins and skeletal muscle lipolysis. Appl. Physiol. Nutr. Metab. 40, 641–651.
MacPherson, R.E., Ramos, S.V., Wandenboom, R., Roy, B.D., Peters, S.J., 2013. Skeletal muscle PLIN proteins, ATGL and CGI-58: interactions at rest and following stimulated contraction. Am. J. Physiol. Regul. Integr. Comp. Physiol. 304, R644–R650.
Macaulay, R., Akbar, A.N., Henson, S.M., 2013. The role of the T cell in age-related inflammation. Age (Dordr) 35, 563–572.
Magalhaes, I., Kiaf, B., Lehuen, A., 2015a. iNKT and MAIT cell alterations in diabetes. Front. Immunol. 6, 341.
Magalhaes, I., Pingris, K., Poitou, C., Bessoles, S., Venteclef, N., Kiaf, B., Beaudoin, L., Da Silva, J., Allatif, O., Rossjohn, J., Kjer-Nielsen, L., McCluskey, J., Ledoux, S., Genser, L., Torcivia, A., Soudais, C., Lantz, O., Boitard, C., Aron-Wisnewsky, J., Larger, E., Clément, K., Lehuen, A., 2015b. Mucosal-associated invariant T cell alterations in obese and type 2 diabetic patients. J. Clin. Invest. 125, 1752–1762.
Maioli, T.U., Gonçalves, J.L., Miranda, M.C., Martins, V.D., Horta, L.S., Moreira, T.G., Godard, A.L., Santiago, A.F., Faria, A.M., 2016. High sugar and butter (HSB) diet induces obesity and metabolic syndrome with decrease in regulatory T cells in adipose tissue of mice. Inflamm. Res. 65, 169–178.
Makki, K., Froguel, P., Wolowczuk, I., 2013. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm. 22, 139239.
Manfredsson, F.P., Tumer, N., Erdos, B., Landa, T., Broxson, C.S., Sullivan, L.F., Rising, A.C., Foust, K.D., Zhang, Y., Muzyczka, N., Gorbatyuk, O.S., Scarpace, P.J., Mandel, R.J., 2009. Nigrostriatal rAAV-mediated GDNF overexpression induces robust weight loss in a rat model of age-related obesity. Mol. Ther. 17, 980–991.
Mariani, F., Roncucci, L., 2015. Chemerin/chemR23 axis in inflammation onset and resolution. Inflamm. Res. 64, 85–95.
Marosi, K., Mattson, M.P., 2014. BDNF mediates adaptive brain and body responses to energetic challenges. Trends Endocrinol. Metab. 25, 89–98.
Martin, C.J., Peters, K.N., Behar, S.M., 2014. Macrophages clean up: efferocytosis and microbial control. Curr. Opin. Microbiol. 17, 17–23.
Marzetti, E., Calvani, R., Cesari, M., Buford, T.W., Lorenzi, M., Behnke, B.J., Leeuwenburgh, C., 2013. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. Int. J. Biochem. Cell Biol. 45, 2288–22301.
Mason, R.R., Mokhtar, R., Matzaris, M., Selathurai, A., Kowalski, G.M., Mokbel, N., Meikle, P.J., Bruce, C.R., Watt, M.J., 2014. PLIN5 deletion remodels intracellular lipid composition and causes insulin resistance in muscle. Mol. Metab. 3, 652–663.
Mathis, D., Shoelson, S.E., 2011. Immunometabolism: an emerging frontier. Nat. Rev. Immunol. 11, 81.
Mattern, A., Zellmann, T., Beck-Sickinger, A.G., 2014. Processing, signaling, and physiological function of chemerin. IUBMB Life 66, 19–26.
Maynard, S., Fang, E.F., Scheibye-Knudsen, M., Croteau, D.L., Bohr, V.A., 2015. DNA damage, DNA, repair, aging, and neurodegeneration. Cold Spring Harb. Perspect. Med. 5, 10.
McGregor, R.A., Cameron-Smith, D., Poppitt, S.D., 2014. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. Longev. Healthspan 3, 9.
McLaughlin, T., Liu, L.F., Lamendola, C., Shen, L., Morton, J., Rivas, H., Winer, D., Tolentino, L., Choi, O., Zhang, H., Hui Yen Chng, M., Engleman, E., 2014. T-cell profile in adipose tissue is associated with insulin resistance and systemic inflammation in humans. Arterioscler. Thromb. Vasc. Biol. 34, 2637–2643.
McPherron, A.C., 2016. The ups and downs of exercise and insulin sensitivity: a role for the myokine myostatin in glucose metabolism? Acta Physiol. (Oxf.) 217, 6–10.
McTernan, C.L., McTernan, P.G., Harte, A.L., Levick, P.L., Barnett, A.H., Kumar, S., 2002. Resistin, central obesity, and type 2 diabetes. Lancet 359, 46–47.
Mehta, P., Nuotio-Antar, A.M., Smith, C.W., 2015. γδ T cells promote inflammation and insulin resistance during high fat diet-induced obesity in mice. J. Leukoc. Biol. 97, 121–134.
Meijer, K., de Vries, M., Al-Lahham, S., Bruinenberg, M., Weening, D., Dijkstra, M., Kloosterhuis, N., van der Leij, R.J., van der Want, H., Kroesen, B.J., Vonk, R., Rezaee, F., 2011. Human primary adipocytes exhibit immune cell function: adipocytes prime inflammation independent of macrophages. PLoS One 6, e17154.
Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., Cesari, M., Nourhashemi, F., Minihane, A.M., Vinoy, S., Russell, W.R., Baka, A., Roche, H.M., Tuohy, K.M., Teeling, J.L., Blaak, E.E., Fenech, M., Vauzour, D., McArdle, H.J., Kremer, B.H., Sterkman, L., Vafeiadou, K., Benedetti, M.M., Williams, C.M., Calder, P.C., 2015. Low-grade inflammation, diet composition and health: current research evidence and its translation. Br. J. Nutr. 114, 999–1012.
Minihane, A.M., Vinoy, S., Russell, W.R., Baka, A., Roche, H.M., Tuohy, K.M., Teeling, J.L., Blaak, E.E., Fenech, M., Vauzour, D., McArdle, H.J., Kremer, B.H., Sterkman, L., Vafeiadou, K., Benedetti, M.M., Williams, C.M., Calder, P.C., 2015. Low-grade inflammation, diet composition and health: current research evidence and its translation. Br. J. Nutr. 114, 999–1012.
Mitchell, W.K., Williams, J., Atherton, P., Larvin, M., Lund, J., Narici, M., 2012. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Front. Physiol. 3, 260.
Miyatake, S., Bilan, P.J., Pillon, N.J., Klip, A., 2016. Contracting C2C12 myotubes release CCL2 in an NF-κB-dependent manner to induce monocyte chemoattraction. Am. J. Physiol. Endocrinol. Metab. 310, E160–170.
Molino, S., Dossena, M., Buonocore, D., Verri, M., 2016. Sarcopenic obesity: an appraisal of the current status of knowledge and management in elderly people. J. Nutr. Health Aging 20, 780–788.
Monteiro-Junior, R.S., Cevada, T., Oliveira, B.R., Lattari, E., Portugal, E.M., Carvalho, A., Deslandes, A.C., 2015. We need to move more: neurobiological hypotheses of physical exercise as a treatment for Parkinson's disease. Med. Hypotheses 85, 537–541.
Moreno-Navarrete, J.M., Ortega, F., Serrano, M., Guerra, E., Pardo, G., Tinahones, F., Ricart, W., Fernández-Real, J.M., 2013. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. J. Clin. Endocrinol. Metab. 98, E769–778.
Morris, D.L., Cho, K.W., Delproposto, J.L., Oatmen, K.E., Geletka, L.M., Martinez-Santibanez, G., Singer, K., Lumeng, C.N., 2013. Adipose tissue macrophages function as antigen-presenting cells and regulate adipose tissue CD4+ T cells in mice. Diabetes 62, 2762–2772.

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Moyers, J.S., Shiyanova, T.L., Mehrbod, F., Dunbar, J.D., Noblitt, T.W., Otto, K.A., Reifel-Miller, A., Kharitonenkov, A., 2007. Molecular determinants of FGF-21 activity-synergy and cross-talk with PPARgamma signaling. J. Cell. Physiol. 210, 1–6.
Muoio, D.M., 2012. Revisiting the connection between intramyocellular lipids and insulin resistance: a long and winding road. Diabetologia 55, 2551–2554.
Mwangi, S.M., Nezami, B.G., Obukwelu, B., Anitha, M., Marri, S., Fu, P., Epperson, M.F., Le, N.A., Shanmugam, M., Sitaraman, S.V., Tseng, Y.H., Anania, F.A., Srinivasan, S., 2014. Glial, cell line-derived neurotrophic factor protects against high-fat diet-induced obesity. Am. J. Physiol. Gastrointest. Liver Physiol. 306, G515–525.
Naylor, C., Petri Jr., W.A., 2016. Leptin regulation of immune responses. Trends Mol. Med. 22, 88–98.
Nguyen, Q.T., Parsadanian, A.S., Snider, W.D., Lichtman, J.W., 1998. Hyperinnervation of neuromuscular junctions caused by GDNF overexpression in muscle. Science 279, 1725–1729.
Nimmo, M.A., Leggate, M., Viana, J.L., King, J.A., 2013. The effect of physical activity on mediators of inflammation. Diabetes Obes. Metab. (Suppl. 3), 51–60.
Nishimura, S., Manabe, I., Nagasaki, M., Eto, K., Yamashita, H., Ohsugi, M., Otsu, M., Hara, K., Ueki, K., Sugiura, S., Yoshimura, K., Kadowaki, T., Nagai, R., 2009. CD8 effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat. Med. 15, 914–920.
Nomiyama, T., Perez-Tilve, D., Ogawa, D., Gizard, F., Zhao, Y., Heywood, E.B., Jones, K.L., Kawamori, R., Cassis, L.A., Tschöp, M.H., Bruemmer, D., 2007. Osteopontin mediates obesity-induced adipose tissue macrophage infiltration and insulin resistance in mice. J. Clin. Invest. 117, 2877–2888.
Numakawa, T., Suzuki, S., Kumamaru, E., Adachi, N., Richards, M., Kunugi, H., 2010. BDNF function and intracellular signaling in neurons. Histol. Histopathol. 25, 237–258.
O'Connell, G.C., Pistilli, E.E., 2015. Interleukin-15 directly stimulates pro-oxidative gene expression in skeletal muscle in-vitro via a mechanism that requires interleukin-15 receptor alpha. Biochem. Biophys. Res. Commun. 458, 614–619.
O'Neill, S., O'Driscoll, L., 2015. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes. Rev. 16, 1–12.
Odegaard, J.I., Chawla, A., 2015. Type 2 responses at the interface between immunity and fat metabolism. Curr. Opin. Immunol. 36, 67–72.
Odegaard, J.I., Ricardo-Gonzalez, R.R., Goforth, M.H., Morel, C.R., Subramanian, V., Mukundan, L., Red Eagle, A., Vats, D., Brombacher, F., Ferrante, A.W., Chawla, A., 2007. Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance. Nature 447, 1116–1120.
Ogawa, Y., Kurosu, H., Yamamoto, M., Nandi, A., Rosenblatt, K.P., Goetz, R., Eliseenkova, A.V., Mohammadi, M., Kuro-o, M., 2007. BetaKlotho is required for metabolic activity of fibroblast growth factor 21. Proc. Natl. Acad. Sci. U. S. A. 104, 7432–7437.
Olefsky, J.M., Glassm, C.K., 2010. Macrophages, inflammation, and insulin resistance. Annu. Rev. Physiol. 72, 219–246.
Oreopoulos, A., Kalantar-Zadeh, K., Sharma, A.M., Fonarow, G.C., 2009. The obesity paradox in the elderly: potential mechanisms and clinical implications. Clin. Geriatr. Med. 25, 643–659.
Orlova, E.G., Shirshev, S.V., 2014. Role of leptin and ghrelin in induction of differentiation of IL-17-producing and T-regulatory cells. Bull. Exp. Biol. Med. 156, 819–822.
Ormsbee, M.J., Prado, C.M., Ilich, J.Z., Purcell, S., Siervo, M., Folsom, A., Panton, L., 2014. Osteosarcopenic obesity: the role of bone, muscle, and fat on health. J. Cachexia Sarcopenia Muscle 5, 183–192.
Osborn, O., Olefsky, J.M., 2012. The cellular and signaling networks linking the immune system and metabolism in disease. Nat. Med. 18, 363–374.
Ovadya, Y., Krizhanovsky, V., 2014. Senescent cells: sASPected drivers of age-related pathologies. Biogerontology 15, 627–642.
Pagel, C.N., Wasgewatte Wijesinghe, D.K., Taghavi Esfandouni, N., Mackie, E.J., 2014. Osteopontin, inflammation and myogenesis: influencing regeneration, fibrosis and size of skeletal muscle. J. Cell. Commun. Signal. 8, 95–103.
Pajenda, G., Hercher, D., Márton, G., Pajer, K., Feichtinger, G.A., Maléth, J., Redl, H., Nógrádi, A., Paliwal, P., Pishesha, N., Wijaya, D., Conboy, I.M., 2012. Age dependent increase in the levels of osteopontin inhibits skeletal muscle regeneration. Aging (Albany NY) 4, 553–566.
Pantsulaia, I., Livshits, G., Trofimov, S., Kobyliansky, E., 2007. Genetic and environmental determinants of circulating resistin level in a community-based sample. Eur. J. Endocrinol. 156, 129–135.
Papathanassoglou, E.D., Miltiadous, P., Karanikola, M.N., 2015. May BDNF Be implicated in the exercise-Mediated regulation of inflammation?: critical review and synthesis of evidence. Biol. Res. Nurs. 17, 521–539.
Pardo, M., Crujeiras, A.B., Amil, M., Aguera, Z., Jiménez-Murcia, S., Baños, R., Botella, C., de la Torre, R., Estivill, X., Fagundo, A.B., Fernández-Real, J.M., Fernández-García, J.C., Fruhbeck, G., Gómez-Ambrosi, J., Rodríguez, R., Tinahones, F.J., Fernández-Aranda, F., Casanueva, F.F., 2014. Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. Int. J. Endocrinol. 2014, 857270.
Park, H.K., Ahima, R.S., 2013. Resistin in rodents and humans. Diabetes Metab. J. 37, 404–414.
Patel, L., Buckels, A.C., Kinghorn, I.J., Murdock, P.R., Holbrook, J.D., Plumpton, C., Macphee, C.H., Smith, S.A., 2003. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem. Biophys. Res. Commun. 300, 472–476.
Patsouris, D., Cao, J.J., Vial, G., Bravard, A., Lefai, E., Durand, A., Durand, C., Chauvin, M.A., Laugerette, F., Debard, C., Michalski, M.C., Laville, M., Vidal, H., Rieusset, J., 2014. Insulin resistance is associated with MCP1-mediated macrophage accumulation in skeletal muscle in mice and humans. PLoS One 9, e110653.
Pedersen, B.K., 2013. Muscle as a secretory organ. Compr. Physiol. 3, 1337–1362.
Pellegrinelli, V., Rouault, C., Rodriguez-Cuenca, S., Albert, V., Edom-Vovard, F., Vidal-Puig, A., Clément, K., Butler-Browne, G.S., Lacasa, D., 2015. Human adipocytes induce inflammation and atrophy in muscle cells during obesity. Diabetes 64, 3121–3134.
Pereira, S.S., Alvarez-Leite, J.I., 2014. Low-grade inflammation, obesity, and diabetes. Curr. Obes. Rep. 3, 422–431.
Peters, S.J., Samjoo, I.A., Devries, M.C., Stevic, I., Robertshaw, H.A., Tarnopolsky, M.A., 2012. Perilipin family (PLIN) proteins in human skeletal muscle: the effect of sex, obesity, and endurance training. Appl. Physiol. Nutr. Metab. 37, 724–735.
Pham, C.T., 2006. Neutrophil serine proteases: specific regulators of inflammation. Nat. Rev. Immunol. 6, 541–550.
Phillips, C.M., Perry, I.J., 2013. Does inflammation determine metabolic health status in obese and nonobese adults? J. Clin. Endocrinol. Metab. 98, E1610–E1619.
Pol, A., Gross, S.P., Parton, R.G., 2014. Review: biogenesis of the multifunctional lipid droplet: lipids, proteins, and sites. J. Cell. Biol. 204, 635–646.
Prado, C.M., Cushen, S.J., Orsso, C.E., Ryan, A.M., 2016. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. Proc. Nutr. Soc. 75, 188–198.
Procaccini, C., Jirillo, E., Matarese, G., 2013. Leptin as an immunomodulator. Mol. Aspects Med. 33, 35–45.
Qiu, Y., Nguyen, K.D., Odegaard, J.I., Cui, X., Tian, X., Locksley, R.M., Palmiter, R.D., Chawla, A., 2014. Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat. Cell 157, 1292–1308.
Quinn, L.S., Anderson, B.G., Conner, J.D., Wolden-Hanson, T., 2013. IL-15 overexpression promotes endurance, oxidative energy metabolism, and muscle PPARδ, SIRT1, PGC-1α, and PGC-1β expression in male mice. Endocrinology 154, 232–245.
Ramos, S.V., MacPherson, R.E., Turnbull, P.C., Bott, K.N., LeBlanc, P., Ward, W.E., Peters, S.J., Higher, M., 2014. PLIN5 but not PLIN3 content in isolated skeletal muscle mitochondria following acute in vivo contraction in rat hindlimb. Physiol. Rep. 2, e12154.
Ramos-Ramírez, P., Malmhäll, C., Johansson, K., Lötvall, J., Bossios, A., 2016. Weight gain alters adiponectin receptor 1 expression on adipose tissue-resident helios+regulatory T cells. Scand. J. Immunol. 83, 244–254.
Raschke, S., Eckel, J., 2013. Adipo-myokines: two sides of the same coin–mediators of inflammation and mediators of exercise. Mediators Inflamm. 2013, 320724.
Ren, J., Anversa, P., 2015. The insulin-like growth factor I system: physiological and pathophysiological implication in cardiovascular diseases associated with metabolic syndrome. Biochem. Pharmacol. 93, 409–417.
Reis, B.S., Lee, K., Fanok, M.H., Mascaraque, C., Amoury, M., Cohn, L.B., Rogoz, A., Dallner, O.S., Moraes-Vieira, P.M., Domingos, A.I., Mucida, D., 2015. Leptin receptor signaling in T cells is required for Th17 differentiation. J. Immunol. 194, 5253–5260.
Rey-López, J.P., de Rezende, L.F., Pastor-Valero, M., Tess, B.H., 2014. The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used. Obes. Rev. 15, 781–790.
Rinnov, A., Yfanti, C., Nielsen, S., Akerstrom, T.C., Peijs, L., Zankari, A., Fischer, C.P., Pedersen, B.K., 2014. Endurance training enhances skeletal muscle interleukin-15 in human male subjects. Endocrine 45, 271–278.
Ritter, O., Jelenik, T., Roden, M., 2015. Lipid-mediated muscle insulin resistance: different fat, different pathways? J. Mol. Med. (Berl.) 93, 831–843.
Rivas, D.A., Mcdonald, D.J., Rice, N.P., Haran, P.H., Dolnikowski, G.G., Fielding, R.A., 2016. Diminished anabolic signaling response to insulin induced by intramuscular lipid accumulation is associated with inflammation in aging but not obesity. Am. J. Physiol. Regul. Integr. Comp. Physiol. (January (13)).
Robenek, H., Robenek, M.J., Buers, I., Lorkowski, S., Hofnagel, O., Troyer, D., Severs, N.J., 2005. Lipid droplets gain PAT family proteins by interaction with specialized plasma membrane domains. J. Biol. Chem. 280, 26330–26338.
Roberson, L.L., Aneni, E.C., Maziak, W., Agatston, A., Feldman, T., Rouseff, M., Tran, T., Blaha, M.J., Santos, R.D., Sposito, A., Al-Mallah, M.H., Blankstein, R., Budoff, M.J., Nasir, K., 2014. Beyond BMI: The Metabolically healthy obese phenotype and its association with clinical/subclinical cardiovascular disease and all-cause mortality – a systematic review. BMC Public Health 14, 14.
Roca-Rivada, A., Castelao, C., Senin, L.L., Landrove, M.O., Baltar, J., Belén Crujeiras, A., Seoane, L.M., Casanueva, F.F., Pardo, M., 2013. FNDC5/irisin is not only a myokine but also an adipokine. PLoS One 8, e60563.
Rocher, C., Singla, D.K., 2013. SMAD-PI3K-Akt-mTOR pathway mediates BMP-7 polarization of monocytes into M2 macrophages. PLoS One 8, e84009.
Rodríguez, A., Ezquerro, S., Méndez-Giménez, L., Becerril, S., Frühbeck, G., 2015. Revisiting the adipocyte: a model for integration of cytokine signaling in the regulation of energy metabolism. Am. J. Physiol. Endocrinol. Metab. 309, E691–E714.
Roh, S.G., Song, S.H., Choi, K.C., Katoh, K., Wittamer, V., Parmentier, M., Sasaki, S., 2007. Chemerin-a new adipokine that modulates adipogenesis via its own receptor. Biochem. Biophys. Res. Commun. 362, 1013–1018.
Rolland, Y., Lauwers-Cances, V., Cristini, C., van Kan, G.A., Janssen, I., Morley, J.E., Vellas, B., 2009. Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: the EPIDOS (EPIDemiologie de l'OSteoporose) Study. Am. J. Clin. Nutr. 89, 1895–1900.

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Romacho, T., Glosse, P., Richter, I., Elsen, M., Schoemaker, M.H., van Tol, E.A., Eckel, J., 2015. Nutritional ingredients modulate adipokine secretion and inflammation in human primary adipocytes. Nutrients 7, 865–886.
Romanello, V., Sandri, M., 2016. Mitochondrial quality control and muscle mass maintenance. Front. Physiol. 6, 422.
Rosenberg, I.H., 1989. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. Am. J. Clin. Nutr. 50, 1231–1233.
Roubenoff, R., 2000. Sarcopenic obesity: does muscle loss cause fat gain?: Lessons from rheumatoid arthritis and osteoarthritis. Ann. N.Y. Acad. Sci. 904, 553–557.
Rourke, J.L., Dransem, H.J., Sinal, C.J., 2013. Towards an integrative approach to understanding the role of chemerin in human health and disease. Obes. Rev. 14, 245–262.
Ruderman, N.B., Schneider, S.H., Berchtold, P., 1981. The "metabolically-obese," normal-weight individual. Am. J. Clin. Nutr. 34, 1617–1621.
Rutkowski, J.M., Stern, J.H., Scherer, P.E., 2015. The cell biology of fat expansion. J. Cell. Biol. 208, 501–512.
Sakuma, K., Yamaguchi, A., 2013. Sarcopenic obesity and endocrinal adaptation with age. Int. J. Endocrinol., 204164.
Sakuma, K., Aoi, W., Yamaguchi, A., 2015. Current understanding of sarcopenia: possible candidates modulating muscle mass. Pflugers Arch. 467, 213–229.
Salama, R., Sadaie, M., Hoare, M., Narita, M., 2014. Cellular senescence and its effector programs. Genes Dev. 28, 99–114.
Salminen, A., Kauppinen, A., Kaarniranta, K., 2012. Emerging role of NF-κB signaling in the induction of senescence-associated secretory phenotype (SASP). Cell. Signal. 24, 835–845.
Samms, R.J., Cheng, C.C., Kharitonenkov, A., Gimeno, R.E., Adams, A.C., 2016. Overexpression of β-Klotho in adipose tissue sensitizes male mice to endogenous FGF21 and provides protection from diet-Induced obesity. Endocrinology 157, 1467–1480.
Samuel, V.T., Shulman, G.I., 2016. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J. Clin. Invest. 126, 12–22.
Santilli, V., Bernetti, A., Mangone, M., Paoloni, M., 2014. Clinical definition of sarcopenia. Clin. Cases Miner. Bone Metab. 11, 177–180.
Sartori, R., Sandri, M., 2015. BMPs and the muscle-bone connection. Bone 80, 37–42.
Sartori, R., Gregorevic, P., Sandri, M., 2014. TGFβ and BMP signaling in skeletal muscle: potential significance for muscle-related disease. Trends Endocrinol. Metab. 25, 464–471.
Schafer, M.J., White, T.A., Evans, G., Tonne, J.M., Verzosa, G.C., Stout, M.B., Mazula, D.L., Palmer, A.K., Baker, D.J., Jensen, M.D., Torbenson, M.S., Miller, J.D., Ikeda, Y., Tchkonia, T., van Deursen, J.M., Kirkland, J.L., LeBrasseur, N.K., 2016. Exercise prevents diet-Induced cellular senescence in adipose tissue. Diabetes 65, 1606–1615.
Schelbert, K.B., 2009. Comorbidities of obesity. Prim. Care 2, 271–285.
Scherer, P.E., Williams, S., Fogliano, M., Baldini, G., Lodish, H.F., 1995. A novel serum protein similar to C1q, produced exclusively in adipocytes. J. Biol. Chem. 270, 26746–26749.
Schering, L., Hoene, M., Kanzleiter, T., Jähnert, M., Wimmers, K., Klaus, S., Eckel, J., Weigert, C., Schürmann, A., Maak, S., Jonas, W., Sell, H., 2015. Identification of novel putative adipomyokines by a cross-species annotation of secretomes and expression profiles. Arch. Physiol. Biochem. 121, 194–205.
Schipper, H.S., Prakken, B., Kalkhoven, E., Boes, M., 2012. Adipose tissue-resident immune cells: key players in immunometabolism. Trends Endocrinol. Metab. 23, 407–415.
Schrager, M.A., Metter, E.J., Simonsick, E., Ble, A., Bandinelli, S., Lauretani, F., Ferrucci, L., 2007. Sarcopenic obesity and inflammation in the InCHIANTI study. J. Appl. Physiol. 102, 919–925.
Schwarz, N.A., McKinley-Barnard, S.K., Spillane, M.B., Andre, T.L., Gann, J.J., Willoughby, D.S., 2016. Effect of resistance exercise intensity on the expression of PGC-1α isoforms and the anabolic and catabolic signaling mediators IGF-1 and myostatin, in human skeletal muscle. Appl. Physiol. Nutr. Metab. 41, 856–863.
Sciorati, C., Rigamonti, E., Manfredi, A.A., Rovere-Querini, P., 2016. Cell death, clearance and immunity in the skeletal muscle. Cell Death Differ. (February (12)).
Seijkens, T., Kusters, P., Chatzigeorgiou, A., Chavakis, T., Lutgens, E., 2014. Immune cell crosstalk in obesity: a key role for costimulation? Diabetes 63, 3982–3991.
Sell, H., Divoux, A., Poitou, C., Basdevant, A., Bouillot, J.L., Bedossa, P., Tordjman, J., Eckel, J., Clément, K., 2010. Chemerin correlates with markers for fatty liver in morbidly obese patients and strongly decreases after weight loss induced by bariatric surgery. J. Clin. Endocrinol. Metabol. 95, 2892–2896.
Sell, H., Habich, C., Eckel, J., 2012. Adaptive immunity in obesity and insulin resistance. Nat. Rev. Endocrinol. 8, 709–716.
Sente, T., Van Berendoncks, A.M., Fransen, E., Vrints, C.J., Hoymans, V.Y., 2016. Tumor necrosis factor-α impairs adiponectin signalling, mitochondrial biogenesis and myogenesis in primary human myotubes cultures. Am. J. Physiol. Heart Circ. Physiol. (February (26)).
Shepherd, S.O., Cocks, M., Tipton, K.D., Ranasinghe, A.M., Barker, T.A., Burniston, J.G., Wagenmakers, A.J.M., Shaw, C.S., 2013. Sprint interval and traditional endurance training increase net intramuscular triglyceride breakdown and expression of perilipin 2 and 5. J. Physiol. 591, 657–675.
Sikora, E., Bielak-Zmijewska, A., Mosieniak, G., 2014. Cellular senescence in ageing, age-related disease and longevity. Curr. Vasc. Pharmacol. 12, 698–706.
Singhal, G., Fisher, F.M., Chee, M.J., Tan, T.G., El Ouaamari, A., Adams, A.C., Najarian, R., Kulkarni, R.N., Benoist, C., Flier, J.S., Maratos-Flier, E., 2016. Fibroblast growth factor 21 (FGF21) protects against high fat diet induced inflammation and islet hyperplasia in pancreas. PLoS One 11, e0148252.
Singla, D.K., Singla, R., Wang, J., 2016. BMP-7 treatment increases M2 macrophage differentiation and reduces inflammation and plaque formation in apo E-/- mice. PLoS One 11, e0147897.
Sjöblom, S., Suuronen, J., Rikkonen, T., Honkanen, R., Kröger, H., Sirola, J., 2013. Relationship between postmenopausal osteoporosis and the components of clinical sarcopenia. Maturitas 75, 175–180.
Smitka, K., Marešová, D., 2015. Adipose tissue as an endocrine organ: an update on pro-inflammatory and anti-inflammatory microenvironment. Prague Med. Rep. 116, 87–111.
Sousa-Victor, P., Muñoz-Cánoves, P., 2016. Regenerative decline of stem cells in sarcopenia. Mol. Aspects Med. 24.
Sriram, S., Subramanian, S., Sathiakumar, D., Venkatesh, R., Salerno, M.S., McFarlane, C.D., Kambadur, R., Sharma, M., 2011. Modulation of reactive oxygen species in skeletal muscle by myostatin is mediated through NF-κB. Aging Cell 10, 931–948.
Stefan, N., Kantartzis, K., Machann, J., Schick, F., Thamer, C., Rittig, K., Balletshofer, B., Machicao, F., Fritsche, A., Häring, H.U., 2008. Identification and characterization of metabolically benign obesity in humans. Arch. Intern. Med. 168, 1609–1616.
Stefanov, T., Blüher, M., Vekova, A., Bonova, I., Tzvetkov, S., Kurktschiev, D., Temelkova-Kurktschiev, T., 2014. Circulating chemerin decreases in response to a combined strength and endurance training. Endocrine 45, 382–391.
Stenholm, S., Harris, T.B., Rantanen, T., Visser, M., Kritchevsky, S.B., Ferrucci, L., 2008. Sarcopenic obesity: definition, cause and consequences. Curr. Opin. Clin. Nutr. Metab. Care 11, 693–700.
Stephenson, E.J., Smiles, W., Hawley, J.A., 2014. The relationship between exercise, nutrition and type 2 diabetes. Med. Sport Sci. 60, 1–10.
Steppan, C.M., Bailey, S.T., Bhat, S., Brown, E.J., Banerjee, R.R., Wright, C.M., Patel, H.R., Ahima, R.S., Lazar, M.A., 2001. The hormone resistin links obesity to diabetes. Nature 409, 212–307.
Stinkens, R., Goossens, G.H., Jocken, J.W., Blaak, E.E., 2015. Targeting fatty acid metabolism to improve glucose metabolism. Obes. Rev. 16, 715–757.
Subramanian, S., Turner, M.S., Ding, Y., Goodspeed, L., Wang, S., Buckner, J.H., O'Brien, K., Getz, G.S., Reardon, C.A., Chait, A., 2013. Increased levels of invariant natural killer T lymphocytes worsen metabolic abnormalities and atherosclerosis in obese mice. J. Lipid Res. 54, 2341–2813.
Sun, H., Liu, D., 2015. Hydrodynamic delivery of interleukin 15 gene promotes resistance to high fat diet-induced obesity, fatty liver and improves glucose homeostasis. Gene Ther. 22, 341–347.
Sun, H., Ma, Y., Gao, M., Liu, D., 2016. IL-15/sIL-15Rα gene transfer induces weight loss and improves glucose homeostasis in obese mice. Gene Ther. (January (16)).
Sunderland, K.L., Tryggestad, J.B., Wang, J.J., Teague, A.M., Pratt, L.V., Zhang, S.X., Thompson, D.M., Short, K.R., 2012. Pigment epithelium-derived factor (PEDF) varies with body composition and insulin resistance in healthy young people. J. Clin. Endocrinol. Metab. 97, E2114–2118.
Suzuki, Y., Hong, Y.H., Song, S.H., Ardiyanti, A., Kato, D., So, K.H., Katoh, K., Roh, S.G., 2012. The regulation of chemerin and CMKLR1 genes expression by TNF-α adiponectin, and chemerin analog in bovine differentiated adipocytes. Asian-Australas J. Anim. Sci. 25, 1316–1321.
Sztalryd, C., Kimmel, A.R., 2014. Perilipins: lipid droplet coat proteins adapted for tissue-specific energy storage and utilization and lipid cytoprotection. Biochimie 96, 96–101.
Tahara, N., Yamagishi, S., Tahara, A., Nitta, Y., Kodama, N., Mizoguchi, M., Mohar, D., Ishibashi, M., Hayabuchi, N., Imaizumi, T., 2011. Serum level of pigment epithelium-derived factor is a marker of atherosclerosis in humans. Atherosclerosis 219, 311–315.
Takahashi, M., Takahashi, Y., Takahashi, K., Zolotaryov, F.N., Hong, K.S., Kitazawa, R., Iida, K., Okimura, Y., Kaji, H., Kitazawa, S., Kasuga, M., Chihara, K., 2008. Chemerin enhances insulin signaling and potentiates insulin-stimulated glucose uptake in 3T3-L1 adipocytes. FEBS Lett. 582, 573–578.
Talukdar, S., Ohda, Y., Bandyopadhyay, G., Li, D., Xu, J., McNelis, J., Lu, M., Li, P., Yan, Q., Zhu, Y., Ofrecio, J., Lin, M., Brenner, M.B., Olefsky, J.M., 2012. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. Nat. Med. 18, 1407–1412.
Tard, C., Rouxel, O., Lehuen, A., 2015. Regulatory role of natural killer T cells in diabetes. Biomed. J. 38, 484–495.
Tateya, S., Kim, F., Tamori, Y., 2013. Recent advances in obesity-induced inflammation and insulin resistance. Front. Endocrinol. (Lausanne) 4, 93.
Tchkonia, T., Morbeck, D.E., Von Zglinicki, T., Van Deursen, J., Lustgarten, J., Scrable, H., Khosla, S., Jensen, M.D., Kirkland, J.L., 2010. Fat tissue, aging, and cellular senescence. Aging Cell 9, 667–684.
Tchkonia, T., Thomou, T., Zhu, Y., Karagiannides, I., Pothoulakis, C., Jensen, M.D., Kirkland, J.L., 2013. Mechanisms and metabolic implications of regional differences among fat depots. Cell Metab. 17, 644–656.
Tilg, H., Moschen, A.R., 2006. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat. Rev. Immunol. 6, 772–783.
Torres, A., Makowski, L., Wellen, K.E., 2016. Metabolism fine-tunes macrophage activation. Elife 5, e14354.
Townsend, K.L., Suzuki, R., Huang, T.L., Jing, E., Schulz, T.J., Lee, K., Taniguchi, C.M., Espinoza, D.O., McDougall, L.E., Zhang, H., He, T.C., Kokkotou, E., Tseng, Y.H., 2012. Bone morphogenetic protein 7 (BMP7) reverses obesity and regulates appetite through a central mTOR pathway. FASEB J. 26, 2187–2196.

Please cite this article in press as: Kalinkovich, A., Livshits, G., Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.09.008

Travers, R.L., Motta, A.C., Betts, J.A., Bouloumié, A., Thompson, D., 2015. The impact of adiposity on adipose tissue-resident lymphocyte activation in humans. Int. J. Obes. (Lond.) 39, 762–769.
Tsai, S., Clemente-Casares, X., Revelo, X.S., Winer, S., Winer, D.A., 2015a. Are obesity-related insulin resistance and type 2 diabetes autoimmune diseases? Diabetes 64, 1886–1897.
Tsai, S.W., Chan, Y.C., Liang, F., Hsu, C.Y., Lee, I.T., 2015b. Brain-derived neurotrophic factor correlated with muscle strength in subjects undergoing stationary bicycle exercise training. J. Diabetes Complications 29, 367–371.
Tseng, Y.H., Kokkotou, E., Schulz, T.J., Huang, T.L., Winnay, J.N., Taniguchi, C.M., Tran, T.T., Suzuki, R., Espinoza, D.O., Yamamoto, Y., Ahrens, M.J., Dudley, A.T., Norris, A.W., Kulkarni, R.N., Kahn, C.R., 2008. New role of bone morphogenetic protein 7 in brown adipogenesis and energy expenditure. Nature 454, 1000–1004.
Tumova, J., Andel, M., Trnka, J., 2015. Excess of free fatty acids as a cause of metabolic dysfunction in skeletal muscle. Physiol. Res. (October (8)).
Tuomi, T., Santoro, N., Caprio, S., Cai, M., Weng, J., Groop, L., 2014. The many faces of diabetes: a disease with increasing heterogeneity. Lancet 383, 1084–1094.
Tyrovolas, S., Koyanagi, A., Olaya, B., Ayuso-Mateos, J.L., Miret, M., Chatterji, S., Tobiasz-Adamczyk, B., Koskinen, S., Leonardi, M., Haro, J.M., 2015. The role of muscle mass and body fat on disability among older adults: a cross-national analysis. Exp. Gerontol. 69, 27–35.
Uaesoontrachoon, K., Yoo, H.J., Tudor, E.M., Pike, R.N., Mackie, E.J., Pagel, C.N., 2008. Osteopontin and skeletal muscle myoblasts: association with muscle regeneration and regulation of myoblast function in vitro. Int. J. Biochem. Cell. Biol. 40, 2303–2314.
Unger, R.H., Clark, G.O., Scherer, P.E., Orci, L., 2010. Lipid homeostasis, Lipotoxicity and the metabolic syndrome. Biochim. Biophys. Acta 1801, 209–214.
Vamvini, M.T., Aronis, K.N., Panagiotou, G., Huh, J.Y., Chamberland, J.P., Brinkoetter, M.T., Petrou, M., Christophi, C.A., Kales, S.N., Christiani, D.C., Mantzoros, C.S., 2013. Irisin mRNA and circulating levels in relation to other myokines in healthy and morbidly obese humans. Eur. J. Endocrinol. 169, 829–834.
Van Dyke, J.M., Smit-Oistad, I.M., Macrander, C., Krakora, D., Meyer, M.G., Suzuki, M., 2016. Macrophage-mediated inflammation and glial response in the skeletal muscle of a rat model of familial amyotrophic lateral sclerosis (ALS). Exp. Neurol. 277, 275–282.
Vaughan, R.A., Gannon, N.P., Mermier, C.M., Conn, C.A., 2015. Irisin, a unique non-inflammatory myokine in stimulating skeletal muscle metabolism. J. Physiol. Biochem. 71, 679–689.
Venojärvi, M., Wasenius, N., Manderoos, S., Heinonen, O.J., Hernelahti, M., Lindholm, H., Surakka, J., Lindström, J., Aunola, S., Atalay, M., Eriksson, J.G., 2013. Nordic walking decreased circulating chemerin and leptin concentrations in middle-aged men with impaired glucose regulation. Ann. Med. 45, 162–170.
Versini, M., Jeandel, P.Y., Rosenthal, E., Shoenfeld, Y., 2014. Obesity in autoimmune diseases: not a passive bystander. Autoimmun. Rev. 13, 981–1000.
Vetrone, S.A., Montecino-Rodriguez, E., Kudryashova, E., Kramerova, I., Hoffman, E.P., Liu, S.D., Miceli, M.C., Spencer, M.J., 2009. Osteopontin promotes fibrosis in dystrophic mouse muscle by modulating immune cell subsets and intramuscular TGF-beta. J. Clin. Invest. 119, 1583–1594.
Vigelso, A., Prats, C., Ploug, T., Dela, F., Helge, J.W., 2015. Higher muscle content of perilipin 5 and endothelial lipase protein in trained than untrained middle-aged men. Physiol. Res. (October (8)).
Vilarrasa, N., Vendrell, J., Maravall, J., Broch, M., Estepa, A., Begia, A., Soler, J., Simon, I., Richart, C., Gomez, J.M., 2005. Distribution and determinants of adiponectin: resistin and ghrelin in a randomly selected healthy population. Clin. Endocrinol. 63, 329–335.
Voss, S.C., Nikolovski, Z., Bourdon, P.C., Alsayrafi, M., Schumacher, Y.O., 2016. The effect of cumulative endurance exercise on leptin and adiponectin and their role as markers to monitor training load. Biol. Sport 33, 23–28.
Walston, J.D., 2015. Connecting age-Related biological decline to frailty and late-Life vulnerability. Nestle Nutr. Inst. Workshop Ser. 83, 1–10.
Wang, Y., Liu, X., Hou, L., Wu, W., Zhao, S., Xiong, Y., 2015. Fibroblast growth factor 21 suppresses adipogenesis in pig intramuscular fat cells. Int. J. Mol. Sci. 17, E11.
Wannamethee, S.G., Atkins, J.L., 2015. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. Proc. Nutr. Soc. 74, 405–412.
Weisberg, S.P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R.L., Ferrante Jr., A.W., 2003. Obesity is associated with macrophage accumulation in adipose tissue. J. Clin. Invest. 112, 1796–1808.
Wensveen, F.M., Valentić, S., Šestan, M., Turk Wensveen, T., Polić, B., 2015. The Big Bang in obese fat: events initiating obesity-induced adipose tissue inflammation. Eur. J. Immunol. 45, 2446–2456.
Whittle, A.J., Carobbio, S., Martins, L., Slawik, M., Hondares, E., Vázquez, M.J., Morgan, D., Csikasz, R.I., Gallego, R., Rodriguez-Cuenca, S., Dale, M., Virtue, S., Villarroya, F., Cannon, B., Rahmouni, K., López, M., Vidal-Puig, A., 2012. BMP8B increases brown adipose tissue thermogenesis through both central and peripheral actions. Cell 149, 871–885.
Winer, S., Paltser, G., Chan, Y., Tsui, H., Engleman, E., Winer, D., Dosch, H.M., 2009. Obesity predisposes to Th17 bias. Eur. J. Immunol. 39, 2629–2635.
Winer, D.A., Winer, S., Shen, L., Wadia, P.P., Yantha, J., Paltser, G., Tsui, H., Wu, P., Davidson, M.G., Alonso, M.N., Leong, H.X., Glassford, A., Caimol, M., Kenkel, J.A., Tedder, T.F., McLaughlin, T., Miklos, D.B., Dosch, H.M., Engleman, E.G., 2011. B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. Nat. Med. 17, 610–617.
Winer, D.A., Winer, S., Chng, M.H., Shen, L., Engleman, E.G., 2014. B Lymphocytes in obesity-related adipose tissue inflammation and insulin resistance. Cell. Mol. Life Sci. 71, 1033–1043.
Wronska, A., Kmiec, Z., 2012. Structural and biochemical characteristics of various white adipose tissue depots. Acta Physiol. (Oxf.) 205, 194–208.
Wu, D., Molofsky, A.B., Liang, H.E., Ricardo-Gonzalez, R.R., Jouihan, H.A., Bando, J.K., Chawla, A., Locksley, R.M., 2011. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science 332, 243–247.
Xiao, F., Tan, J.Z., Xu, X., Zhu, B.L., Fang, S., Wang, X.F., 2015. Increased osteopontin in muscle and serum from patients with idiopathic inflammatory myopathies. Clin. Exp. Rheumatol. 33, 399–404.
Xie, Q., Deng, Y., Huang, C., Liu, P., Yang, Y., Shen, W., Gao, P., 2015. Chemerin-induced mitochondrial dysfunction in skeletal muscle. J. Cell. Mol. Med. 19, 986–995.
Xin, C., Liu, J., Zhang, J., Zhu, D., Wang, H., Xiong, L., Lee, Y., Ye, J., Lian, K., Xu, C., Zhang, L., Wang, Q., Liu, Y., Tao, L., 2016. Irisin improves fatty acid oxidation and glucose utilization in type 2 diabetes by regulating the AMPK signaling pathway. Int. J. Obes. (Lond.) 40, 443–451.
Xu, H., Barnes, G.T., Yang, Q., Tan, G., Yang, D., Chou, C.J., Sole, J., Nichols, A., Ross, J.S., Tartaglia, L.A., Chen, H., 2003. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J. Clin. Invest. 112, 1821–1830.
Xu, W., Yu, L., Zhou, W., Luo, M., 2006. Resistin increases lipid accumulation and CD36 expression in human macrophages. Biochem. Biophys. Res. Commun. 351, 376–382.
Xu, X., Grijalva, A., Skowronski, A., van Eijk, M., Serlie, M.J., Ferrante Jr., A.W., 2013. Obesity activates a program of lysosomal-dependent lipid metabolism in adipose tissue macrophages independently of classic activation. Cell. Metab. 18, 816–830.
Xu, L., Kitade, H., Ni, Y., Ota, T., 2015a. Roles of chemokines and chemokine receptors in obesity-associated insulin resistance and nonalcoholic fatty liver disease. Biomolecules 5, 1563–1579.
Xu, M., Tchkonia, T., Ding, H., Ogrodnik, M., Lubbers, E.R., Pirtskhalava, T., White, T.A., Johnson, K.O., Stout, M.B., Mezera, V., Giorgadze, N., Jensen, M.D., LeBrasseur, N.K., Kirkland, J.L., 2015b. JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age. Proc. Natl. Acad. Sci. U. S. A. 112, E6301–6310.
Yan, B., Shi, X., Zhang, H., Pan, L., Ma, Z., Liu, S., Liu, Y., Li, X., Yang, S., Li, Z., 2014. Association of serum irisin with metabolic syndrome in obese Chinese adults. PLoS One 9, e94235.
Yao, L., Herlea-Pana, O., Heuser-Baker, J., Chen, Y., Barlic-Dicen, J., 2014. Roles of the chemokine system in development of obesity, insulin resistance, and cardiovascular disease. J. Immunol. Res. 2014, 181450.
Yao-Borengasser, A., Varma, V., Coker, R.H., Ranganathan, G., Phanavanh, B., Rasouli, N., Kern, P.A., 2011. Adipose triglyceride lipase expression in human adipose tissue and muscle Role in insulin resistance and response to training and pioglitazone. Metabolism 60, 1012–1020.
Ye, J., 2015. Beneficial metabolic activities of inflammatory cytokine interleukin 15 in obesity and type 2 diabetes. Front. Med. 9, 139–145.
You, J.S., Ji, H.I., Chang, K.J., Yoo, M.C., Yang, H.I., Jeong, I.K., Kim, K.S., 2013. Serum osteopontin concentration is decreased by exercise-induced fat loss but is not correlated with body fat percentage in obese humans. Mol. Med. Rep. 8, 579–584.
Youm, Y.H., Horvath, T.L., Mangelsdorf, D.J., Kliewer, S.A., Dixit, V.D., 2016. Prolongevity hormone FGF21 protects against immune senescence by delaying age-related thymic involution. Proc. Natl. Acad. Sci. U. S. A. 113, 1026–1031.
Youn, J.Y., Cai, H., 2015. Fueling up skeletal muscle to reduce obesity A TrkB story. Chem. Biol. 22, 311–312.
Zamboni, M., Mazzali, G., Zoico, E., Harris, T.B., Meigs, J.B., DiFrancesco, V., Fantin, F., Bissoli, L., Bosello, O., 2005. Health consequences of obesity in the elderly: a review of four unresolved questions. Int. J. Obes. (Lond.) 29, 1011–1029.
Zamboni, M., Mazzali, G., Fantin, F., Rossi, A., Di Francesco, V., 2008. Sarcopenic obesity: a new category of obesity in the elderly. Nutr. Metab. Cardiovasc. Dis. 18, 388–395.
Zanotti, S., Gibertini, S., Di Blasi, C., Cappelletti, C., Bernasconi, P., Mantegazza, R., Morandi, L., Mora, M., 2011. Osteopontin is highly expressed in severely dystrophic muscle and seems to play a role in muscle regeneration and fibrosis. Histopathology 59, 1215–1228.
Zeyda, M., Gollinger, K., Todoric, J., Kiefer, F.W., Keck, M., Aszmann, O., Prager, G., Zlabinger, G.J., Petzelbauer, P., Stulnig, T.M., 2011. Osteopontin is an activator of human adipose tissue macrophages and directly affects adipocyte function. Endocrinology 152, 2219–2227.
Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., Friedman, J.M., 1994. Positional cloning of the mouse obese gene and its human homologue. Nature 372, 425–432.
Zhang, C., McFarlane, C., Lokireddy, S., Masuda, S., Ge, X., Gluckman, P.D., Sharma, M., Kambadur, R., 2012. Inhibition of myostatin protects against diet-induced obesity by enhancing fatty acid oxidation and promoting a brown adipose phenotype in mice. Diabetologia 55, 183–193.
Zhang, Y., Yang, P., Cui, R., Zhang, M., Li, H., Qian, C., Sheng, C., Qu, S., Bu, L., 2015. Eosinophils reduce chronic inflammation in adipose tissue by secreting Th2 cytokines and promoting M2 macrophages polarization. Int. J. Endocrinol. 2015, 565760.

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Zhang, C., Ding, Z., Lv, G., Li, J., Zhou, P., Zhang, J., 2016. Lower irisin level in patients with type 2 diabetes mellitus: a case-control study and meta-analysis. J. Diabetes. 8, 56–62.

Zhu, Y., Tchkonia, T., Pirtskhalava, T., Gower, A.C., Ding, H., Giorgadze, N., Palmer, A.K., Ikeno, Y., Hubbard, G.B., Lenburg, M., O'Hara, S.P., LaRusso, N.F., Miller, J.D., Roos, C.M., Verzosa, G.C., LeBrasseur, N.K., Wren, J.D., Farr, J.N., Khosla, S., Stout, M.B., McGowan, S.J., Fuhrmann-Stroissnigg, H., Gurkar, A.U., Zhao, J., Colangelo, D., Dorronsoro, A., Ling, Y.Y., Barghouthy, A.S., Navarro, D.C., Sano, T., Robbins, P.D., Niedernhofer, L.J., Kirkland, J.L., 2015. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell 14, 644–658.

Ziaaldini, M.M., Koltai, E., Csende, Z., Goto, S., Boldogh, I., Taylor, A.W., Radak, Z., 2015. Exercise training increases anabolic and attenuates catabolic and apoptotic processes in aged skeletal muscle of male rats. Exp. Gerontol. 67, 9–14.

Zindl, C.L., Lai, J.F., Lee, Y.K., Maynard, C.L., Harbour, S.N., Ouyang, W., Chaplin, D.D., Weaver, C.T., 2013. IL-22-producing neutrophils contribute to antimicrobial defense and restitution of colonic epithelial integrity during colitis. Proc. Natl. Acad. Sci. U. S. A. 110, 12761–12768.

Zlotnikov-Klionsky, Y., Nathansohn-Levi, B., Shezen, E., Rosen, C., Kagan, S., Bar-On, L., Jung, S., Shifrut, E., Reich-Zeliger, S., Friedman, N., Aharoni, R., Arnon, R., Yifa, O., Aronovich, A., Reisner, Y., 2015. Perforin-positive dendritic cells exhibit an immuno-regulatory role in metabolic syndrome and autoimmunity. Immunity 43, 776–787.

Please cite this article in press as: Kalinkovich, A., Livshits, G., Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.09.008