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REVIEW ARTICLE

Exercise effects on perivascular adipose tissue: endocrine and paracrine determinants of vascular function

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Obesity is a global epidemic, accompanied by increased risk of type 2 diabetes and cardiovascular disease. Adipose tissue hypertrophy is associated with adipose tissue inflammation, which alters the secretion of adipose tissue-derived bioactive products, known as adipokines. Adipokines determine vessel wall properties such as smooth muscle tone and vessel wall inflammation. Exercise is a mainstay of prevention of chronic, non-communicable diseases, type 2 diabetes and cardiovascular disease in particular. Aside from reducing adipose tissue mass, exercise has been shown to reduce inflammatory activity in this tissue. Mechanistically, contracting muscles release bioactive molecules known as myokines, which alter the metabolic phenotype of adipose tissue. In adipose tissue, myokines induce browning, enhance fatty acid oxidation and improve insulin sensitivity. In the past years, the perivascular adipose tissue (PVAT) which surrounds the vasculature, has been shown to control vascular tone and inflammation through local release of adipokines. In obesity, an increase in mass and inflammation of PVAT culminate in dysregulation of adipokine secretion, which contributes to vascular dysfunction. This review describes our current understanding of the mechanisms by which active muscles interact with adipose tissue and improve vascular function. Aside from the exercise-dependent regulation of canonical adipose tissue function, we will focus on the interactions between skeletal muscle and PVAT and the role of novel myokines, such as IL-15, FGF21 and irisin, in these interactions.

LINKED ARTICLES

This article is part of a themed section on Molecular Mechanisms Regulating Perivascular Adipose Tissue – Potential Pharmacological Targets? To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.20/issuetoc

Abbreviations

AMPK, AMP-activated kinase; AT, adipose tissue; atNPs, angiogenesis-targeted nanoparticles; BAT, brown adipose tissue; CLS, crown-like structures; CVD, cardiovascular diseases; HFD, high-fat diet; METRNL, meteorin-like; NPR, natriuretic peptide receptor; PGC1-α, PPARγ co-activator 1α; PRDM16, PR domain-containing 16; PVAT, perivascular adipose tissue; RT, resistance training; SKM, skeletal muscle; SNS, sympathetic nerve system; SVF, stromal vascular fraction; TLR4, toll-like receptor 4; UCP-1, uncoupling protein 1; VCAM-1, vascular cell adhesion protein 1; WAT, white adipose tissue

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Tables of Links

TARGETS	
Nuclear hormone receptors[a]	**Enzymes**[e]
PPARγ	Acetyl CoA carboxylase
Transporters[b]	Adenylate cyclase
GLUT4	Akt (PKB)
SERCA2	AMPKα1
UCP1, SLC25A7	AMPKα2
Catalytic receptors[c]	eNOS, NOS3
NPR	ERK1
IL-15Rα	ERK2
TLR4	PKA
GPCRs[d]	
β-adrenoceptors	

LIGANDS	
ACh	IL-6
Adiponectin	IL-13
ATP	IL-15
CCL2	Insulin
Hydrogen peroxide	Noradrenaline
ICAM-1	NO
IL-1β	TNF-α
IL-4	VCAM-1

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e]Alexander *et al.*, 2015a,b,c,d,e).

Introduction

Mankind has experienced profound lifestyle changes during the past decades, changes such as high consumption of foods rich in sugars, fat and salt in combination with low physical activity, leading to increased rates of obesity. Obesity increases risk of type 2 diabetes, hypertension and cardiovascular diseases (CVD) (Malnick and Knobler, 2006). Adipose tissue (AT) functions as an endocrine organ that releases bioactive molecules known as adipokines (Lago *et al.*, 2009). Despite the fact that excess of AT in obesity is generally viewed as harmful to individual's health, an adequate amount of AT and physiological levels of adipokines contribute to normal whole-body metabolic homeostasis (Lago *et al.*, 2009). In obesity, the balance between cardioprotective and pro-inflammatory adipokines shifts towards pro-inflammatory ones, most of which are risk factors for CVD (Coles, 2016).

Nearly 40% of the U.S. adult population performs less than 10 min·per week of continuous physical activity (Carlson *et al.*, 2015). These statistics contrast sharply with the American Heart Association recommendation of at least 150 min per week of moderate-intensity activity (Eckel *et al.*, 2014) to improve healthy life span and prevent chronic diseases such as CVD and type 2 diabetes (Allender *et al.*, 2007). Moreover, inactivity is related to increased central adiposity, oxidative stress, endothelial dysfunction and increased atherosclerotic lesion size in both humans (Hamburg *et al.*, 2007) and animal models (Laufs *et al.*, 2005; Pedersen, 2009). Similarly, exercise improves mood, endothelial function and arteriogenesis in the myocardium, lowers blood pressure and normalizes fat mass and inflammatory markers (Lee *et al.*, 2005; Piepoli *et al.*, 2010; McDowell *et al.*, 2016). Recent research has shown that skeletal muscle (SKM) exhibits an endocrine function similar to that of AT (Pedersen and Febbraio, 2008). A contracting muscle releases soluble molecules, called myokines, which partly explain how muscles interact with other organs. Muscle activity increases laminar shear stress in the vascular system, which is a mechanical-biological stimulus for the expression of anti-thrombotic, anti-atherogenic and vasodilator signals from the vasculature (Zhang and Friedman, 2012). Furthermore, exercise can directly modulate adipocyte physiology. Physical activity stimulates the CNS and, through noradrenalin and adrenalin, increases thermogenic activity within adipocytes by inducing mitochondrial biogenesis and uncoupling (Sutherland *et al.* 2009). In parallel, exercise ameliorates inflammation within AT by interacting with the immune cells inside AT.

Among AT depots, the perivascular adipose tissue (PVAT) displays a unique physiological role, that is, paracrine regulation of vascular function (Yudkin *et al.*, 2005). PVAT carries an anti-contractile property that influences arteriolar responses to agonists such as insulin, thereby contributing to the regulation of blood flow, nutrient uptake and tissue homeostasis (Meijer *et al.*, 2011). On the other hand, PVAT is susceptible to inflammation, and in obesity, infiltration of immune cells into the PVAT is aggravated (Greenstein *et al.*, 2009; Kranendonk *et al.*, 2015). Alterations in the properties of PVAT have been linked to insulin resistance (Rittig *et al.*, 2008), hypertension and impaired myocardial perfusion (Reifenberger *et al.*, 2007).

In this review, we will cover the effects of exercise on PVAT metabolism, structure and functional phenotype, exploring central and local influences of muscle activity, and their consequences for vascular function. Firstly, we will discuss whole-body alterations in AT and the mechanisms causing its dysfunction. Secondly, effects of exercise on PVAT and its inflammation will be highlighted. Finally, we will describe how new myokines such as FGF21, irisin and IL-15 may affect AT.

Systemic adipose tissue dysfunction in obesity

In obesity, an increased fat mass is accompanied by alterations in the cellular composition and physiology of AT. Anatomical changes (i.e. AT hypertrophy and distribution), inflammation and dysregulated adipokine secretion characterize a dysfunctional adipose organ, which contributes to cardiovascular pathology (Fuster *et al.*, 2016).

In obesity, the interplay between adipocytes and components of the immune system changes. Immune cells secrete cytokines that enhance AT inflammation, and at the same time, adipocytes express classical macrophage features (Kopp *et al.*, 2009). As AT expansion occurs, macrophages, mast cells, B cells and T-cell populations increase considerably (Huh *et al.*, 2014). Macrophages comprise the largest population of immune cells within white adipose tissues (WAT) (i.e. subcutaneous, visceral and perivascular), and a hallmark of its dysfunction is the infiltration of pro-inflammatory M1-macrophages. This phenomenon has been observed in both humans (Kranendonk *et al.*, 2015) and rodents (Kawanishi *et al.*, 2013). Canonical ATs such as visceral (i.e. omental and mesenteric) and subcutaneous AT of obese humans present similar crown-like structures (CLS), which consist of organized macrophage structures around necrotic adipocytes (Bigornia *et al.*, 2012). The macrophage number differs between these depots and visceral and PVAT display distinct abnormalities in inflammation and morphology (Kranendonk *et al.*, 2015).

In parallel, T-cell populations shift from a predominantly anti-inflammatory Treg and Th2 population to pro-inflammatory $CD4^+$ Th1, Th17 and $CD8^+$ cells (Travers *et al.*, 2015). As a consequence, there is an increased secretion of the inflammatory adipokines TNF-α and WNT5a and a reduction of anti-inflammatory adipokines such as secreted frizzled-related protein 5 (Ouchi *et al.*, 2010), adiponectin (Samaras *et al.*, 2010) and Th2 cytokines (IL-4, IL-13 and IL-10) (Feuerer *et al.*, 2009). These phenomena have been observed in gonadal and visceral fat of high-fat diet (HFD)-fed mice and in subcutaneous (Feuerer *et al.*, 2009; Zeyda *et al.*, 2011) and visceral AT of obese humans (Zeyda *et al.*, 2011). Other immune cells such as mast cells, NK-cells and B-cells also participate in this pro-inflammatory phenotype by reducing the Th2 cytokines IL-4 and IL-13, increasing release of IFN-γ and labelling necrotic adipocytes for macrophage phagocytosis (Huh *et al.*, 2014). Subsequently, the elevated inflammatory activity features activation of IKKβ/NFκB and JNK pathways, which are known to be related to insulin resistance (Zeyda *et al.*, 2011) (Figures 1 and 2).

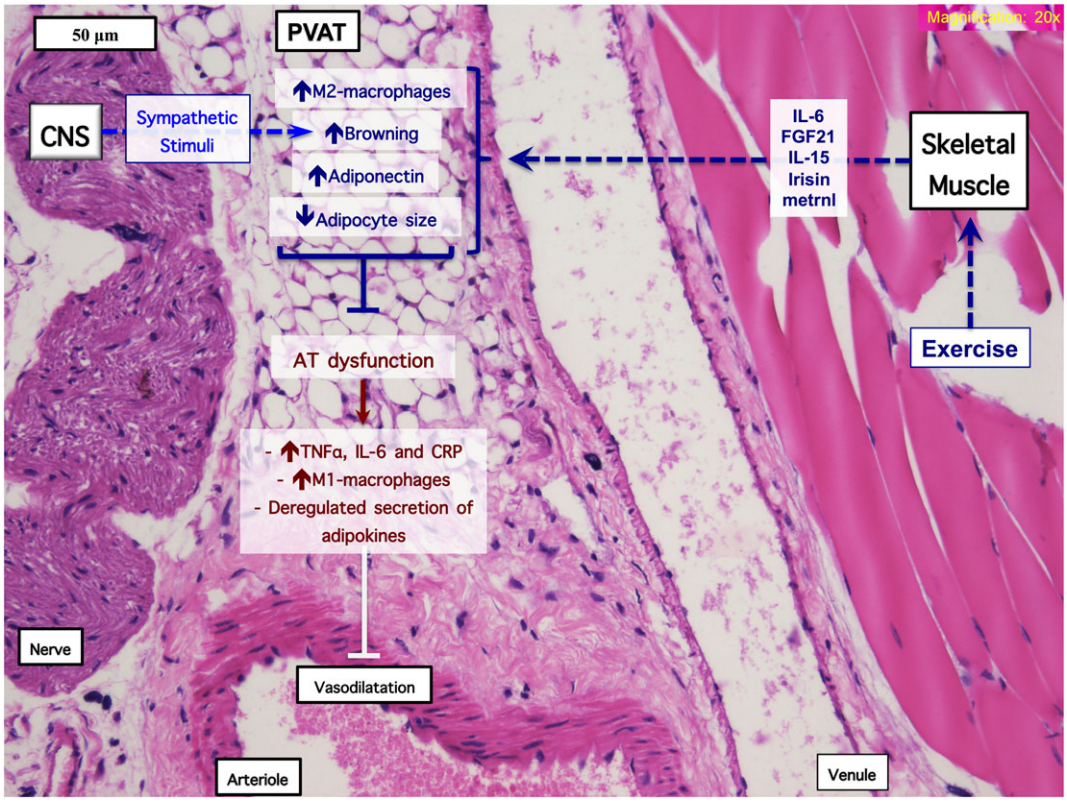

Figure 1

Central and paracrine control of the PVAT by exercise. Juxtaposition of PVAT, nerves CNS, SKM and microvessels in a transverse section of the mouse hindlimb and mechanisms of interaction with AT. First, central effects of exercise are exerted through noradrenaline from sympathetic nerve fibres, with subsequent beiging and vasodilator function of PVAT. Second, muscle activity regulates (perivascular) AT function through myokines such as FGF-21, metrnl, irisin, IL-15, IL-6, acting in a paracrine fashion to antagonize dysfunction of AT (i.e. inflammation and dysregulated secretion of adipokines).

Although it is not known whether inflamed macrophages cause AT hyperplasia, they do release cytokines responsible for altering the secretion of adipokines (Lumeng *et al.*, 2007). In addition, AT expansion requires an extensive vascular network (Sun *et al.*, 2011), and during pathological expansion, angiogenesis does not match expansion requirements (Nishimura *et al.*, 2007; Daquinag *et al.*, 2011). In monocytes of HIF-1α-deficient mice, the inflammatory marker genes *IL-6*, *F4/80*, *Cd11c*, *Il-1b* and *Nos2* and hypoxia-related genes such as *Vegfa* and *Glut 1* are markedly reduced. In epididymal fat, metabolic genes such as *adiponectin, Pparg* and *Pgcta* are increased in these mice (Takikawa *et al.*, 2016). In further studies, vascularization was also increased in eWAT of these KO-mice, with higher expression of the endothelial cell markers, *Cd31* and *VE-cad* and the pericyte marker *Cspg4*. Collectively, these data suggest that hypoxia-induced HIF-1α contributes to the pathological expansion of AT (Takikawa *et al.*, 2016).

In summary, communication between adipocytes and immune system cells increases low-grade inflammation of AT, coinciding with morphological alterations, which culminates in altered AT physiological function.

PVAT and the control of vascular tone

The PVAT resides alongside large and small vessels, exerting anti-contractile effects on conduit and resistance arteries, which are vital for maintenance of normal arterial vascular tone (Yudkin *et al.*, 2005; Meijer *et al.*, 2016). It may have a regulatory effect on metabolism (Chang *et al.*, 2012), insulin sensitivity (Meijer *et al.*, 2013) and inflammatory responses (Greenstein *et al.*, 2009) via local release of hormones, cytokines and reactive oxygen and nitrogen species. These effects are reported to be endothelium-dependent, via release of NO and alternatively through hydrogen peroxide (Gao *et al.*, 2007; Malinowski *et al.*, 2008). Although PVAT secretes adipokines, their plasma concentrations are generally insufficient to provoke systemic vascular actions. This, in combination with proven *ex vivo* effects of PVAT (Figure 1), suggests that PVAT-derived adipokines work in a paracrine fashion, through outside-to-inside intercellular crosstalk. Apparently, this crosstalk is partly mediated by adiponectin, as has been shown by a number of studies (Eringa *et al.*, 2007; Greenstein *et al.*, 2009; Meijer *et al.*, 2015). For example, globular adiponectin elicits vasodilator responses similar to the effect of PVAT incubation on mouse muscle resistance arteries (Meijer *et al.*, 2013; de Boer *et al.*, 2016). In obesity, reduced adiponectin release by PVAT is partially responsible for blunted vasodilatation in the muscle vasculature (Meijer *et al.*, 2013). Similarly, local adiponectin secretion from peri-coronary fat is relevant to myocardial perfusion in lean individuals (Date *et al.*, 2006) (Figure 1). In conclusion, these data indicate PVAT as a promising candidate for explaining how impaired AT homeostasis affects vascular function.

PVAT and exercise. PVAT has been reported to release substances responsible for affecting vascular tone, and it seems that exercise contributes to this process. First, in obesity, the microarchitecture of PVAT is altered, and therefore, the secretion of vasodilator signals to the vascular wall is altered. In obese subjects with metabolic syndrome, increased adipocyte size accompanies the loss of the anti-contractile effect of PVAT (Greenstein *et al.*, 2009). Similar findings were seen in healthy obese women, in which PVAT adipocyte size was statistically related to disturbed insulin-induced muscle microvascular perfusion but not to body mass index (Meijer *et al.*, 2015). Exercise reduced body fat (i.e. reducing PVAT depots) and, at the same time, reducing PVAT inflammation (Lee *et al.*, 2016). In obese mice, chronic exercise limits adipocyte size and reduces CLS and inflammatory cell recruitment in mesenteric fat (Haczeyni *et al.*, 2015).

Changes in PVAT morphology and inflammation occur simultaneously and may be directly related. Infiltration of T cells and macrophages has been observed in periaortic AT in both obesity and atherosclerosis (Chatterjee *et al.*, 2009). Accumulation of T lymphocytes may provoke an increase of PVAT mass, via production of 15d-PGJ_2 (15-deoxy-Δ 12,14-PGJ_2) and activation of PPARγ (Feldon *et al.*, 2006). In subsequent studies, PPARγ was confirmed as crucial for the regulation of PVAT mass (Chang *et al.*, 2012), since its deletion from PVAT precursor cells triggered a complete loss of PVAT, impaired thermoregulation and endothelial dysfunction (Chang *et al.*, 2012) (Figure 2).

Hypoxia might play a role in PVAT dysfunction (Bays, 2009). In rat mesenteric artery segments exposed to hypoxia, the anti-contractile effect of PVAT was substantially attenuated (Greenstein *et al.*, 2009). In fact, inflammation seems to precede hypoxia, and the consequent alteration of the secretory profile might be worse in PVAT compared with other depots (Chatterjee *et al.*, 2009). After a period of hypoxia, incubation of rat mesenteric arteries with anti-TNF-α or anti-IL-6 antibody restored the anti-contractile ability lost by overexpression of these inflammatory markers (Greenstein *et al.*, 2009). Although exercise has anti-inflammatory properties, its role on *hypoxia*-induced inflammation and free radical scavenging is still uncertain.

Collectively, these data provide evidence that exercise-induced improvements on PVAT might be achieved through **(1)** improvements of PVAT morphology, **(2)** reduced recruitment of inflammatory cells and **(3)** enhanced secretion of vasodilators by PVAT.

Effects of exercise on inflammation in PVAT

Inflammation of AT is an important event for the development of vascular dysfunction, destabilization of atherosclerotic plaques and increased formation of pro-thrombotic products (Deanfield *et al.*, 2007; Libby *et al.*, 2009). As mentioned above, macrophages, especially the M1 subclass, play a role in this process. A wide variety of macrophages have been characterized (Martinez and Gordon, 2014), which can be broadly divided into two subsets: M1-macrophages with predominantly inflammatory features (Hirata *et al.*, 2011) and M2-macrophages with a more immunosuppressive profile. Kranendonk and collaborators showed in patients undergoing surgery on their abdominal aorta that aortic PVAT presents a high secretion of inflammatory adipokines, such as CCL2, PAI-1 and resistin, even compared with visceral AT (Kranendonk *et al.*, 2015). This connection between vascular function and AT inflammation has also been observed in epicardial fat of coronary artery disease (Moncada and Higgs, 1993) patients. In these patients, epicardial AT showed high expression of inflammatory markers such as the M1

macrophage marker CD11c and CD68 and the cytokines IL-6, TNF-α and CCL2, compared with subcutaneous AT (Hirata *et al.*, 2011).

Exercise can be considered an anti-inflammatory treatment (Ruffino *et al.*, 2016). Firstly, exercise decreases body fat and adipocyte hypertrophy. By decreasing AT mass (Speretta *et al.*, 2012), exercise also decreases the number of inflammatory cells contained within the AT (Kawanishi *et al.*, 2013). Secondly, in moderately obese adults, chronic exercise reduces inflammatory markers (i.e. TNF-α, IL-6) and leptin in mesenteric AT (Jung *et al.*, 2008; Fritzen *et al.*, 2015). Thirdly, even after a single bout of swimming, exercise was shown to improve insulin action and inflammation in the stromal vascular fraction (SVF) of AT (Oliveira *et al.*, 2013), which are the connective tissue cells of AT. One possible mechanism by which exercise may reduce PVAT inflammation is the down-regulation of toll-like receptor 4 (TLR4) expression on monocytes and macrophages (Gleeson *et al.*, 2011). Although not demonstrated in PVAT, this down-regulation reduces mRNA for TNF-α, IL-1β and CCL2 in gonadal AT (Oliveira *et al.*, 2013).

Furthermore, exercise diminishes the number of CD4+ and CD8+ T-cells in both SVF and splenocytes (Kawanishi *et al.*, 2013). Exercise effects on T cell populations and cytokine secretion may be mediated through increased catecholamine secretion (Alvarenga-Filho *et al.*, 2016; Kruger *et al.*, 2016). High intensity interval training (Rao *et al.*, 2014) in lean subjects increases the mobilization of the anti-inflammatory regulatory T cells (Tregs) (Kruger *et al.*, 2016), as treatment of cultured human T-cells with catecholamine reduced their secretion of inflammatory cytokines (TNF-α, IL-6, IL-17, IL-21 and IL-22) (Alvarenga-Filho *et al.*, 2016). Furthermore, exercise prevents TCD4+ and TCD8+ apoptosis, by increasing telomere length and decreasing annexin V, a marker of apoptosis (Silva *et al.*, 2016). Further investigations are necessary to address how exercise modulates survival and T-cell subpopulations inside PVAT, as well as their cytokine release.

Exercise has been shown to induce a phenotype switch from M1- to M2-macrophages. In HFD-fed mice, regardless of effects on body fat, exercise decreases TNF-α, IL-6, the adhesion molecules ICAM1 and VCAM1, CD11c and TLR4 expression and increases expression of the M2 marker CD163 (Kawanishi *et al.*, 2010) in gonadal AT. In another study, exercise prevented infiltration of M1-macrophages and reduced the total macrophage number in the stromal vascular fraction of 16 weeks HFD-fed mice (Kawanishi *et al.*, 2013). Nevertheless, similar questions need testing in PVAT as well.

Generally, resistance training (RT) changes body composition without alterations in body weight of both lean and obese subjects (Dias *et al.*, 2015). RT changes the vascular system in concert with alterations in body fat in obese/overweight patients. In both obese adolescents and in older men, RT improved endothelium-dependent vasodilatation after ACh (Dias *et al.*, 2015) and increased femoral artery blood flow, microvascular blood flow and volume of the vastus lateralis muscle (Phillips *et al.*, 2015). However, data on the influence of different exercise characteristics (i.e. intensity and volume) on AT properties such as inflammation are scarce, and this relationship needs to be further elucidated.

Collectively, these data suggest that exercise prevents or attenuates infiltration of immune cells into PVAT, improving insulin sensitivity and vascular function.

Mechanisms of exercise-dependent control of adiponectin secretion by PVAT. Circulating adiponectin exerts pleiotropic control over genes that regulate plasma HDL and triglyceride levels (Cnop *et al.*, 2003; Tschritter *et al.*, 2003), as plasma adiponectin is positively related to plasma levels of HDL and negatively correlated to those of triglyceride.

Exercise, alone (Bluher *et al.*, 2006) or combined with a dietary intervention, (Esposito *et al.*, 2003) increases adiponectin in obese subjects. Although exercise incorporated in weight loss programs showed the most favourable changes in adiponectin (Hara *et al.*, 2005), there are conflicting data concerning the effects of acute versus chronic exercise protocols (Simpson and Singh, 2008; Pop *et al.*, 2010; Saunders *et al.*, 2012).

Exercise influences on PVAT physiology may be concomitantly mediated by three different tissues: PVAT, SKM and the blood vessels. Adiponectin released by PVAT acts on the vessel wall through up-regulation of AMP-activated kinase (AMPK) activity (depending on its α subunit) (Fentz *et al.*, 2015). Resistance arteries obtained from AMPKα2$^{-/-}$ mice presented a blunted effect of PVAT on insulin-induced vasodilatation (Meijer *et al.*, 2013). Therefore, it is likely that exercise locally improves vascular function by increasing adiponectin secretion by PVAT, which acts directly on the vascular wall. By increasing expression of the intracellular mediators of adiponectin signalling (α1 and α2), exercise also increases NO bioavailability, ROS scavenging, reduces adhesion molecules and attenuates endothelial activation (Cao *et al.*, 2012; Kroller-Schon *et al.*, 2012). Adiponectin also acts indirectly on the vascular endothelium, protecting it against inflammation by inhibiting lipid accumulation in macrophages (Ouchi *et al.*, 2001), promoting macrophage M2-polarization and attenuating TLR4-mediated activation of endothelial cells (Ohashi *et al.*, 2010). Due to the heterogeneity of exercise regarding frequency, intensity and effects on body composition, a conclusion on how adiponectin is affected by exercise requires further investigation.

Exercise effects on metabolism of AT

In general, there are three types of AT: WAT (Huang *et al.*, 2007), which stores fat and produces adipokines; brown adipose tissue (BAT) (Abate and Garg, 1995) that dissipates energy through heat, a function mediated by the uncoupling protein 1 (UCP-1); and 'beige' AT which, like BAT, has thermogenic functions and expresses UCP-1, albeit to a lesser extent. In humans, a higher number of brown/beige adipocytes are related to a metabolically healthy phenotype (Min *et al.*, 2016).

In obesity, infiltration of macrophages into visceral AT is related to a reduction of the thermogenic capability of BAT (i.e. lower UCP-1 expression in BAT) (Xu *et al.*, 2011). Within the PVAT, loss of thermogenic activity decreased its anti-atherogenic properties and endothelial effects (Chang *et al.*, 2012). Notably, implantation of beige adipocytes in HFD-fed mice improved glucose tolerance, reduced liver steatosis and normalized adiponectin levels (Min *et al.*, 2016). Furthermore, angiogenesis-targeted nanoparticles (atNP) prevented

obesity in mice by promoting the transformation from white to beige adipocytes (Xue *et al.*, 2016), suggesting that previous angiogenesis is required for the 'beigeing' processes (De Matteis *et al.*, 2013; Frontini *et al.*, 2013; Disanzo and You, 2014). Based on this information, atNPs could be used to target dysfunctional PVAT.

Nevertheless the process of browning or beigeing must be accompanied by vascularization, which is required to fulfil the increased oxygen demand of beige AT (Tran *et al.*, 2012). These events will involve the up-regulation of browning-associated genes (i.e. *Ucp-1*) and organelles (i.e. mitochondrial biogenesis). However, it is not fully clear whether exercise interacts with adipocytes through the vasculature, with the vasculature through PVAT, or with both.

Subsequently and concomitantly to the vascularization and perfusion of AT, there is the contribution of the CNS. BAT is more densely innervated than WAT (Lee and Tontonoz, 2014). Therefore, sympathetic activity and perfusion will be two contributors of thermogenesis in BAT (Morrison and Nakamura, 2011). In WAT, myokines and activation of natriuretic peptide receptors (NPR) mediate AT beigeing (Morrison and Nakamura, 2011). Interestingly, it has been shown that PVAT is not only autonomically innervated but also expresses β_1, β_2 and β_3 adrenoceptors (Bulloch and Daly, 2014). Recently, electrical stimulation of murine mesenteric arteries showed functional effects of the sympathetic nervous system (SNS) activity on anti-contractile properties of PVAT. SNS determines anti-contractile properties of PVAT by triggering the release of vasodilators upon adrenergic stimulation (Saxton *et al.*, 2016). Moreover, exercise increases the production of NO, which synergistically interacts with adrenaline to trigger the expression of NPR and β-adrenoceptors. Thermogenesis will be stimulated with increased expression of BAT-related genes such as *Ucp-1*. By increasing BAT-sites inside WAT, and enhancing intrinsic thermogenesis of BAT, obesity development is prevented, as lipid and carbohydrate metabolism is modulated in HFD-mice (Zed and James, 1986; Wijers *et al.*, 2011).

In addition to direct SNS effects, exercise-induced AT browning may occur through autonomic stimulation of the release of browning-related myokines, such as irisin and FGF-21, which will be discussed below. Both chronic voluntary wheel exercise (Jenkins *et al.*, 2013) and swimming (Sutherland *et al.*, 2009), in rats, increase expression of NPRs, β_2 and β_3 adrenoceptors and mitochondrial genes, such as those for PPARγ co-activator 1 α (PGC1-α) and citrate synthase (mRNA and protein) in WAT. Nevertheless, conflicting data have been obtained in gonadal and retroperitoneal fat, suggesting different responses to exercise stimuli in different fat depots (Sutherland *et al.*, 2009; Jenkins *et al.*, 2013). For instance, chronic exercise increased *Ucp-1* gene expression in abdominal subcutaneous AT, but not in retroperitoneal and gonadal fat pads (Wu *et al.*, 2014). In a study on the full genome DNA of thoracic aortic PVAT and BAT, the first had a brown-like phenotype, as expression of uniquely BAT genes was identical in BAT (Fitzgibbons *et al.*, 2011). This phenotype provided protection against inflammation, which was lower after HFD.

Aerobic exercise (1 or 6 weeks) in Sprague Dawley rats increased sympathetic noradrenergic tone, a more uniform distribution of lipid droplets and a more intense labelling of UCP-1 in brown adipocytes, regardless of the duration of exercise (De Matteis *et al.*, 2013). Interestingly, exercise increased sympathetic tone in BAT in a time-dependent fashion, as 6 week exercised rats showed more tyrosine hydroxylase-positive fibres and capillaries per adipocyte and a lower average size of lipid droplets compared with 1 week exercised rats.

Another exercise-related stimulus of adipocyte browning is the protein, PR domain-containing 16 (PRDM16). PRDM16 acts as a transcriptional cofactor, which is present in SKM and in both white and BATs (Seale *et al.*, 2011). It controls a bidirectional cell fate switch between skeletal myoblasts and brown adipocytes (Seale *et al.*, 2008) and participates in brown adipogenesis by binding and activating PPARγ. This feature was proven in PRDM16 knockout mice, which displayed not only an abnormal brown fat tissue morphology but also completely ablated gene expression of several BAT-specific genes (i.e. *Ucp-1*, *Cidea* and *Cig30*) (Seale *et al.*, 2008). PRDM16 is up-regulated by exercise and becomes more expressed during the transformation from white to brown-like adipocytes in the mesentery (Xu *et al.*, 2011). Nonetheless, further investigations that elucidate the role of PRDM16 in exercise-induced browning are important.

Local control of exercise on AT: myokines

As mentioned in the previous section, exercise alters AT physiology centrally through the CNS and locally through myokine secretion by muscles. Myokines are bioactive molecules released by contracting muscles, which mediate exercise-induced metabolic alterations in organs such as the AT (Pedersen *et al.*, 2007). Here, we will discuss some important myokines, such as irisin, meteorin-like (metrnl), FGF21, IL-15 and the classical myokine IL-6 to discuss their effects on AT physiology. The summarized findings of myokines studies on AT physiology discussed here, are shown in Table 1.

Browning myokines

Irisin and meteorin-like (metrnl). *Irisin* is a hormone secreted by SKM that has been proposed as a novel preventive and therapeutic target for obesity and type 2 diabetes. It has been linked to browning and increased thermogenesis of AT (Bostrom *et al.*, 2012), being induced by PGC1-α (Kim *et al.*, 2016). However, inconsistent data concerning serum concentrations of irisin in human studies and incompatibility with rodent data are required to elucidate its physiological role (Albrecht *et al.*, 2015). First, the starting codon from the human gene encoding irisin, FNDC5 (ATG to ATA), is different between humans and rodents. As there may be transcription of a different protein, there are doubts concerning the translational value of rodent evidence to human physiology (Bostrom *et al.*, 2012). Both *in vitro* and *in vivo* data from mice have shown that irisin increases UCP-1. Secondly, effects of exercise on irisin levels are quite variable. Acute exercise interventions normally increase the levels of irisin, whereas the effects of chronic exercise vary between neutral and increased irisin (Albrecht *et al.*, 2015; Kim *et al.*, 2016). Interestingly, irisin levels are negatively related to key muscle metabolites (i.e. ATP) after a chronic exercise, suggesting that altered muscle metabolism triggers irisin secretion (Huh *et al.*, 2012).

Initially irisin was proposed to enhance metabolism. However, serum levels of irisin were negatively associated with adiponectin in subjects with metabolic syndrome, while being positively related to body mass index, blood pressure and fasting glucose (Park *et al.*, 2013). These results reinforce the inconsistency between human and rodent data.

Collectively, the data show that irisin increases after exercise, is linked to browning of AT, increases energy expenditure (Bostrom *et al.*, 2012) and is associated with improvements of vascular function and insulin sensitivity in mice (Jiang *et al.*, 2015; Lu *et al.*, 2015). Nonetheless, clarification of the regulatory mechanisms of irisin levels and its physiological consequences in obese and lean human subjects are questions to future interventional studies.

Metrnl is a novel myokine, with features similar to those of irisin. Although studies on effects of exercise on metrnl are scarce, resistance exercise and cold stimuli are likely to up-regulate metrnl (Lee and Tontonoz, 2014). Metrnl can incite the browning process in adipocytes but it may act indirectly through enhancing the number of eosinophils in AT. Recent reports showed that overexpression of metrnl is associated with eosinophil accumulation in the AT (Lee and Tontonoz, 2014), and observations in mice suggest that these cells are required for metrnl-mediated browning (Rao *et al.*, 2014). Metrnl induces the overexpression and secretion of type II cytokines IL-4 and IL-13 by eosinophils (Qiu *et al.*, 2014), which in turn activate the cascade of alternative-activated macrophages (M2-), responsible for the secretion of catecholamine that promotes browning (Rao *et al.*, 2014). Nevertheless, further studies in humans and mice are required to establish metrnl as an AT 'browning' myokine.

Other myokines

FGF21. Fibroblast growth factor 21 (FGF21) is mainly produced by the liver (Nishimura *et al.*, 2000) and acts as a nutrient stress sensor (Zhang *et al.*, 2015) that regulates the metabolism of carbohydrates and lipids. Changes in the level of FGF21 are related to insulin resistance, glucose intolerance and dyslipidemia (Coskun *et al.*, 2008). Muscle production of FGF21 is regulated by insulin via the PI3kinase-Akt pathway (Izumiya *et al.*, 2008). In young subjects, hyperinsulinaemia increases both plasma FGF21 and its mRNA in SKM (Hojman *et al.*, 2009). FGF21 acts through the *β*Klotho co-receptor (*β*KR), which is strongly expressed in AT, but not in SKM (Ogawa *et al.*, 2007). Overexpression of *β*KR in the AT protected mice against diet-induced obesity and preserved insulin sensitivity (Samms *et al.*, 2016). Consistent with a role in exercise effects, FGF21 treatment prevented weight gain, enhanced fat excretion and energy expenditure, thus decreasing insulin levels and fat mass, all in a dose-dependent fashion in *db/db* and obese mice (Coskun *et al.*, 2008).

On the other hand, AT-derived FGF21 might be implicated in CVD, as it was positively associated with cardiometabolic risk factors, increased intima-media thickness on both carotid and iliac arteries, high levels of C-reactive protein, dysglycaemia, dyslipidaemia and decreased adiponectin levels (Chow *et al.*, 2013; Xiao *et al.*, 2015). These apparently conflicting findings on different tissue sources of FGF-21 indicate the existence of tissue-specific physiological functions of FGF21, which require further investigation.

Acute exercise is the most used intervention for raising FGF21 and indeed increases serum FGF21 in both healthy humans and mice (Cuevas-Ramos *et al.*, 2012), in addition to increased expression in SKM and liver (Kim *et al.*, 2013b; Tanimura *et al.*, 2016). Nevertheless, acute exercise does not increase FGF21 levels in either obese subjects (Slusher *et al.*, 2015) or patients with type 2 diabetic (Hansen *et al.*, 2016). Therefore, chronic studies are necessary to elucidate whether FGF21 expression and circulatory levels might be up-regulated in obese and diabetic subjects.

Similar to the myokines mentioned above, FGF21 enhances the thermogenic capacity of the AT by switching on a brown-fat gene programme in WAT (Lee *et al.*, 2013). In BAT-positive men, incubation of primary adipocytes from the neck with FGF21, increased BAT markers (i.e. UCP1 protein), oxygen consumption and infrared thermogenic images in a dose-dependent manner (Lee *et al.*, 2014). Moreover, BAT was an important source of FGF21 in men. Intriguingly, these effects were more robust during co-incubation with irisin, suggesting a synergetic action of FGF21 and irisin on WAT browning. Additionally, the correlation between serum FGF21 and sympathetic nervous system activity supports a role of this protein as an exercise-activated enhancer of whole-body thermogenesis (Cuevas-Ramos *et al.*, 2012; Lee *et al.*, 2013).

Together, these findings demonstrate FGF21 is a potential druggable target for obesity and diabetes. However, incomplete knowledge of its intracellular signalling pathways and tissue-specific effects require studies to discriminate FGF21 actions on AT, muscle and liver.

IL-15. IL-15 is a cytokine that supports survival and proliferation of T lymphocytes (Grabstein *et al.*, 1994). The plasma membrane receptor for IL-15 is a trimer and this receptor is distributed throughout the body. It is composed of IL-2 receptor β (IL-2Rβ), a common γ chain (γc), and a specific IL-15Rα chain (Giri *et al.*, 1995). Interestingly, IL-15 is found in abundance in SKM, but at very low levels in the AT (Pistilli *et al.*, 2011). Additionally, it has been suggested that the α subunit of IL-15 receptor (IL-15Rα) regulates IL-15 release from SKM (O'Connell and Pistilli, 2015). Paradoxically, lack of the α-receptor (IL-15R$\alpha^{-/-}$ mice) increased IL-15 serum levels and at the same time driving a change in SKM to an oxidative phenotype (Pistilli *et al.*, 2011; Quinn *et al.*, 2014). These mice show increased activity and exercise endurance, accompanied by molecular (i.e. increased mRNA from *Pgc-1α* and *citrate synthase*) and morphological signs (i.e. increased fibre number and single-fibre area) of a beneficial change in muscle phenotype.

Although IL-15 is considered a pro-inflammatory cytokine, the fact that its circulating levels are negatively related to obesity, WAT mass and type 2 diabetes is also consistent with a role as a myokine (Quinn *et al.*, 2009). Moreover, both endurance training in Zucker rats (Kim *et al.*, 2013a) and RT in controls and athletes increased circulating IL-15 levels (Bazgir *et al.*, 2015). In both cases, exercise was negatively related to body fat and inflammatory markers.

Nevertheless, data from knockout models show the necessity of further studies concerning the differential action of IL-15 on AT. For instance, IL-15R$\alpha^{-/-}$ mice display an obesity-resistant phenotype, with less body and liver fat

Table 1

Summary of myokine studies: effects of exercise training

Study	Subjects/ animals	Intervention	Tissue examined	Main findings
Irisin				
Bostrom *et al.*, 1995	Muscle creatine kinase promoter (MCK)-PGC1-α transgenic and wild type BALB/c mice	3 weeks of swimming	–	Increase of brown-like genes on the WAT
			Epididymal fat	Twofold increase in *Ucp1* mRNA
			Subcutaneous inguinal	65-fold increase in *Ucp1* mRNA
		3 weeks of wheel running	Visceral, epididymal	Twofold increase in *Ucp1* mRNA
			Subcutaneous inguinal	25-fold increase in *Ucp1* mRNA
			Brown adipose tissue	Increase whole-body energy expenditure
	Non-diabetic men	10 weeks of endurance training at ~65% of VO_{2max}	Muscle biopsies	↑ *FNDC5, VEGFB* and *TIMP4, LRG1* and *m*RNAs
			Blood	↑ Circulating Irisin
	BALB/c mice, primary adipocytes	Incubation with FNDC5	Cell culture	7 to 500-fold increase of *Ucp1;* threefold in *PPARγ* mRNA
Kim *et al.*, 2013	Lean and overweight/obese adults	8 weeks of resistance training at 65–80% of 1RM	Blood	↑ ~17.5% irisin plasma levels
		8 weeks of endurance training at 65–80% of HR_{max}		↓ body fat and BMI
Huh *et al.*, 2005	Young males(± 20 years)	8 weeks or 30 min of endurance training	Blood	↑ ~18% circulating irisin
Metrnl				
Rao *et al.*, 2010	Young men	RT at 80% 1RM + 30 min of cycling at 70% VO_{2peak}	Vastus lateralis muscle biopsies	↑*metrnl* up to 4 h post exercise. mRNA peak expression was at 1 h
	Wild-type C57/ BL6J, BALB/cJ Myo-PGC-1α4, ΔdbGATA mice, metrnl KO mice		Subcutaneous fat; epididymal fat;	↑M2-macrophages gene markers; ↓inflammation genes in the AT (*TNF-α, IFN-γ and IL-1β*)
		60 min of downhill running exercise at 15 $m \cdot min^{-1}$		↑ Thermogenesis; mitochondrial gene programme; *UCP-1* (↑~3.5), *DIO2*, *PGC-1α*, *ERR-α* mRNA
			Brown adipose tissue	↑*metrnl* mRNA and thermogenic gene programme; ↑*UCP-1 mRNA* in BAT
			Quadriceps and triceps muscle	~fourfold increase of *metrnl* mRNA
			Blood	~twofold increase in circulating metrnl
		Adenovirus injection to deliver full-length metrnl to the liver	Liver and blood	~20-fold increase in liver mRNA and ~five to sixfold in plasma
			Culture of myotubes ↑PGC-1α4 expression	~eightfold increase of *metrnl* mRNA

continues

Table 1 (Continued)

Study	Subjects/ animals	Intervention	Tissue examined	Main findings
Fibroblast growth factor 21				
Cuevas-Ramos *et al.*, 2009	Sedentary young women	2 weeks of endurance exercise at 85% of HR	Blood	↑~66% circulating levels of FGF-21; ↓~25% triglycerides; ↑Epinephrine; ↑FFA (~50%)
Tanimura *et al.*, 2015	Male ICR mice	60 min of endurance exercise at 10–30 m·min^{-1}	Liver	↑mRNA and protein levels of FGF-21
			Blood	↑Serum FGF-21
			Gastrocnemius muscle	↑mRNA and protein of FGF-21; ↑p-Akt/Akt protein
	Young sedentary men	Single bout for 60 min at 75% of VO2max	Blood	↑Serum FGF-21, NEFA, 3-hydroxybutyric acid
Kim *et al.*, 2015	Male C57/BL6 mice	30 min of endurance exercise at 25 m·min^{-1}	Blood	↑FGF-21 serum levels
	Male adults	30 min of endurance exercise at 50 or 80% of VO_{2max}	Liver	↑*FGF-21, PPARα, ATF4* mRNA
			Blood	↑FGF-21 serum levels only 1 h after end of bout
Slusher *et al.*, 2016	Obese and lean adults	30 min of endurance training at 75% of VO_{2max}	Blood	↑FGF-21 in lean subjects regardles the time and in the obese only after 1 h post bout Increased circulatory FGF-21 correlates to total relative energy expenditure
Hansen *et al.*, 2016	Young lean and type 2 diabetic men	2 h of endurance exercise at 60% of VO_{2max} + Patients that underwent through pancreatic clamp	Blood	↑Glucagon/Insulin ratio; ↑Plasma FGF-21 in controls; In type 2 diabetic patients and Pancreatic clamp FGF-21 is abolished in plasma
IL-15				
Kim *et al.*, 2015	Male Zucker diabetic fatty rats	12 weeks – 60 min of endurance training at 15–20 m·min^{-1}	Soleus and gastrocnemius muscles	↑IL-15 protein levels in S. muscle
Bazgir *et al.*, 2015e	Young male non- and athletes	Two bouts of RT, one focusing on CON at 70–80% 1RM and the second on ECC at 90–100% 1RM -with 8 to 10 repetitions	Blood	↑IL-15 serum levels ↓hs-CRP levels in athletes ↓hs-CRP and TNF-α levels in non-athletes
Quinn *et al.*, 2015	IL-15-KO and IL-15Rα KO mice	Endurance training at 15-17 m·min^{-1} until exhaustion	Gastrocnemius muscle	↓Endurance capacity in KO mice;↓ MHC mRNA ↓ *IL-15* mRNA in G. muscle; ↑Serum IL-15 in KO mice ↑*PPARδ and SIRT1* mRNA and protein after IL-15 injection and 3 h post bout
		Acute injection of IL-15	Blood	↓ IL-15Rα in Control and KO-mice ↑IL-15 circulating levels in IL-15Rα-KO mice ↑PGC-1α and 1β in SKM of IL-15KO ↓IL15Rα after an acute bout of exercise

continues

Table 1 (Continued)

Study	Subjects/ animals	Intervention	Tissue examined	Main findings
Pistilli *et al.*, 2008	IL-15Rα KO mice	14 h data from Voluntary wheel exercise	EDL, gastrocnemius and quadriceps muscle	↑Ambulatory activity, fatigue resistance and wheel revolutions ↑*IL-15* mRNA in muscles of IL-15Rα-KO mice ↑*IL-15, Ppard, Pgc-1α, citrate synthase, SERCAII* and ↓*calsequestrin* mRNA in EDL and gastrocnemius of IL-15Rα-KO mice
IL-6				
McGinnis *et al.*, 2015	C57/Bl6 or IL-6$^{-/-}$ mice	3 days of 60 min of treadmill exercise at 18 m·min^{-1} prior I/R surgery procedure	Serum	↑~4.5-fold in IL-6 and sIL-6R serum concentration after 30 min exercise in controls; ↑ IL-6R in G. muscle and heart after exercise in C57/Bl6 mice
			Gastrocnemius muscle	↑*COX-2* mRNA and protein post exercise; iNOS and p-STAT protein before and after exercise in IL-6$^{-/-}$ in G. muscle ↓ of ~65% of necrotic area, ECG score protection against arrhythmias in C57/Bl6
			Heart	↑p-p44/42 MAPK and p-p38 MAPK proteins in the myocardium after the exercise in C57/Bl6 mice

accumulation (Loro *et al.*, 2015). It seems that these effects of IL-15 result from increased whole-body energy metabolism, as IL-15Rα$^{-/-}$ mice display increased oxygen consumption and utilization of muscle fatty acids (He *et al.*, 2010). These data were corroborated by findings that IL-15$^{-/-}$ mice presented decreased lipid accumulation in both white and BAT depots (Lacraz *et al.*, 2016).

The effects of IL-15 on vascular health are not known at present, but *in vitro* data showed that IL-15 treatment of 3T3-L1 pre-adipocytes increased adiponectin production (Quinn *et al.*, 2005), an important contributor to the anti-contractile properties of PVAT (as already discussed). On the other hand, intravenous injections of IL-15 provoked vasoconstriction in larger order arterioles (A1 and A2) in the microvascular bed of the cremaster muscle (Baker and Abel, 1995).

In conclusion, IL-15 seems promising as a therapeutic approach not only to chronic diseases, such as obesity and type 2 diabetes, but also to improvements of muscle function. However, further investigations on metabolic and molecular changes linked to the expression of the IL15 receptor α are necessary.

IL-6. In most physiological circumstances, IL-6 is a pro-inflammatory adipokine, which is abundantly secreted by PVAT, compared with retroperitoneal and subcutaneous fat (Gonzalez *et al.*, 2016). IL-6 is a mediator of inflammation and therefore related to AT dysfunction (Bays *et al.*, 2009). Circulating IL-6 levels are related to vascular dysfunction in men (Esposito *et al.*, 2003), and IL-6 is primarily viewed as an indirect mediator of vascular inflammation (Yudkin *et al.*, 2000). IL-6 levels are positively related to other inflammatory factors such as C-reactive protein (Yudkin *et al.*, 2000) and TNF-α, which in turn are involved in endothelial dysfunction. IL-6 derived from aortic PVAT is related to arterial stiffness in mice (Du *et al.*, 2015). Nevertheless, there is no solid evidence at present pointing to IL-6 itself as a major cause of vascular injury.

On the other hand, Pedersen and collaborators have shown an endocrine role of IL-6 in active muscles, as part of the group of myokines (Pedersen *et al.*, 2007). Circulating levels of IL-6 are among the most markedly increased myokines during exercise (Pedersen and Febbraio, 2008), and muscle-derived IL-6 increased insulin sensitivity, metabolism and triggered muscle hypertrophy (Pedersen and Febbraio, 2008). In muscle-specific IL-6 knockout mice, there was decreased GLUT4 protein content in WAT and more inguinal WAT after HFD (Knudsen *et al.*, 2015). These data strongly indicate that SKM IL-6 exerts positive effects on WAT metabolism (Knudsen *et al.*, 2015). Further investigations are crucial to differentiate between physiological effects of IL-6 derived from AT and that derived from muscle.

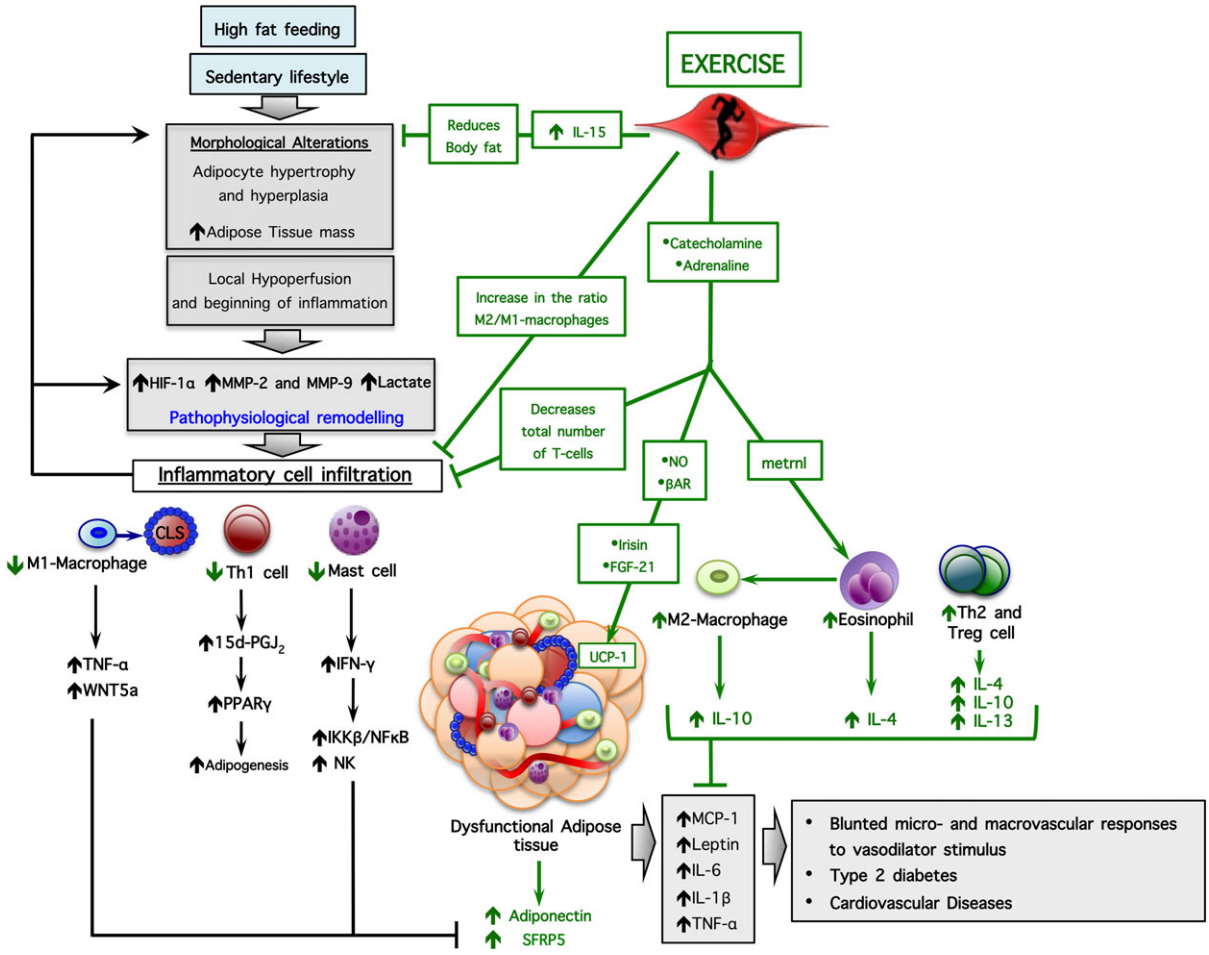

Figure 2

Signalling pathways involved in dysfunction of AT and effects of exercise. HFD feeding and a sedentary lifestyle change AT morphology, such as adipocyte hypertrophy and hyperplasia. Subsequently, AT shows hypoperfusion, inflammation and remodelling, with consequent inflammatory cell infiltration and abnormal secretion of inflammatory adipokines. Exercise exerts an anti-inflammatory effect on dysfunctional AT. It activates the CNS and stimulates release of myokines, resulting in a reduced AT mass and an improved functional and metabolic phenotype. βAR, β-adrenoceptors.

Future perspectives and conclusions

In the context of worldwide obesity, there is strong evidence that the properties of AT determine vascular health. Specifically, PVAT produces vasoactive substances that can either impair or improve vascular function. In obesity, AT homeostasis is greatly changed, and exercise has been shown to normalize this process. Despite a number of unanswered questions, muscle-derived hormones might be one group of substances holding great promise for future therapy. Therefore, goals for future research are first to perform careful analysis to separate effects mediated by muscle- and AT-derived hormones, secondly, to further characterize specific myokine effects on human physiology and, finally, to clarify the effects of exercise on different AT depots.

Conflict of interest

The authors declare no conflicts of interest.

References

Abate N, Garg A (1995). Heterogeneity in adipose tissue metabolism: causes, implications and management of regional adiposity. Prog Lipid Res 34: 53–70.

Albrecht E, Norheim F, Thiede B, Holen T, Ohashi T, Schering L *et al.* (2015). Irisin – a myth rather than an exercise-inducible myokine. Sci Rep 5: 8889.

Alexander SPH, Cidlowski JA, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015a). The Concise Guide to PHARMACOLOGY 2015/16: Nuclear hormone receptors. Br J Pharmacol 172: 5956–5978.

Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E *et al.* (2015b). The Concise Guide to PHARMACOLOGY 2015/16: Transporters. Br J Pharmacol 172: 6110–6202.

Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015c). The Concise Guide to PHARMACOLOGY 2015/16: Catalytic receptors. Br J Pharmacol 172: 5979–6023.

Alexander SPH, Davenport AP, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015d). The Concise Guide to PHARMACOLOGY 2015/16: G protein-coupled receptors. Br J Pharmacol 172: 5744–5869.

Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015e). The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 172: 6024–6109.

Allender S, Foster C, Scarborough P, Rayner M (2007). The burden of physical activity-related ill health in the UK. J Epidemiol Community Health 61: 344–348.

Alvarenga-Filho H, Sacramento PM, Ferreira TB, Hygino J, Abreu JE, Carvalho SR *et al.* (2016). Combined exercise training reduces fatigue and modulates the cytokine profile of T-cells from multiple sclerosis patients in response to neuromediators. J Neuroimmunol 293: 91–99.

Baker CH, Abel FL (1995). Macro- and microcirculatory effects of IL-15. Shock 4: 307–310.

Bays HE (2009). 'Sick fat', metabolic disease, and atherosclerosis. Am J Med 122: S26–S37.

Bazgir B, Salesi M, Koushki M, Amirghofran Z (2015). Effects of eccentric and concentric emphasized resistance exercise on IL-15 serum levels and its relation to inflammatory markers in athletes and non-athletes. Asian J Sports Med 6: e27980.

Bigornia SJ, Farb MG, Mott MM, Hess DT, Carmine B, Fiscale A *et al.* (2012). Relation of depot-specific adipose inflammation to insulin resistance in human obesity. Nutr Diabetes 2: e30.

Bluher M, Bullen JW Jr, Lee JH, Kralisch S, Fasshauer M, Kloting N *et al.* (2006). Circulating adiponectin and expression of adiponectin receptors in human skeletal muscle: associations with metabolic parameters and insulin resistance and regulation by physical training. J Clin Endocrinol Metab 91: 2310–2316.

Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC *et al.* (2012). A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481: 463–468.

Bulloch JM, Daly CJ (2014). Autonomic nerves and perivascular fat: interactive mechanisms. Pharmacol Ther 143: 61–73.

Cao S, Li B, Yi X, Chang B, Zhu B, Lian Z *et al.* (2012). Effects of exercise on AMPK signaling and downstream components to PI3K in rat with type 2 diabetes. PLoS One 7: e51709.

Carlson SA, Fulton JE, Pratt M, Yang Z, Adams EK (2015). Inadequate physical activity and health care expenditures in the United States. Prog Cardiovasc Dis 57: 315–323.

Chang L, Villacorta L, Li R, Hamblin M, Xu W, Dou C *et al.* (2012). Loss of perivascular adipose tissue on peroxisome proliferator-activated receptor-gamma deletion in smooth muscle cells impairs intravascular thermoregulation and enhances atherosclerosis. Circulation 126: 1067–1078.

Chatterjee TK, Stoll LL, Denning GM, Harrelson A, Blomkalns AL, Idelman G *et al.* (2009). Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding. Circ Res 104: 541–549.

Chow WS, Xu A, Woo YC, Tso AW, Cheung SC, Fong CH *et al.* (2013). Serum fibroblast growth factor-21 levels are associated with carotid atherosclerosis independent of established cardiovascular risk factors. Arterioscler Thromb Vasc Biol 33: 2454–2459.

Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ *et al.* (2003). Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 46: 459–469.

Coles CA (2016). Adipokines in healthy skeletal muscle and metabolic disease. Adv Exp Med Biol 900: 133–160.

Coskun T, Bina HA, Schneider MA, Dunbar JD, Hu CC, Chen Y *et al.* (2008). Fibroblast growth factor 21 corrects obesity in mice. Endocrinology 149: 6018–6027.

Cuevas-Ramos D, Almeda-Valdes P, Meza-Arana C, Brito-Cordova G, Gomez-Perez F, Mehta R *et al.* (2012). Exercise increases serum fibroblast growth factor 21 (FGF21) levels. PLoS One 7: e38022.

Daquinag AC, Zhang Y, Kolonin MG (2011). Vascular targeting of adipose tissue as an anti-obesity approach. Trends Pharmacol Sci 32: 300–307.

Date H, Imamura T, Ideguchi T, Kawagoe J, Sumi T, Masuyama H *et al.* (2006). Adiponectin produced in coronary circulation regulates coronary flow reserve in nondiabetic patients with angiographically normal coronary arteries. Clin Cardiol 29: 211–214.

De Boer MP, Meijer RI, Richter EA, Van Nieuw Amerongen GP, Sipkema P, Van Poelgeest EM *et al.* (2016). Globular adiponectin controls insulin-mediated vasoreactivity in muscle through AMPKalpha2. Vascul Pharmacol 78: 24–35.

De Matteis R, Lucertini F, Guescini M, Polidori E, Zeppa S, Stocchi V *et al.* (2013). Exercise as a new physiological stimulus for brown adipose tissue activity. Nutr Metab Cardiovasc Dis 23: 582–590.

Deanfield JE, Halcox JP, Rabelink TJ (2007). Endothelial function and dysfunction: testing and clinical relevance. Circulation 115: 1285–1295.

Dias I, Farinatti P, De Souza MG, Manhanini DP, Balthazar E, Dantas DL *et al.* (2015). Effects of resistance training on obese adolescents. Med Sci Sports Exerc 47: 2636–2644.

Disanzo BL, You T (2014). Effects of exercise training on indicators of adipose tissue angiogenesis and hypoxia in obese rats. Metabolism 63: 452–455.

Du B, Ouyang A, Eng JS, Fleenor BS (2015). Aortic perivascular adipose-derived interleukin-6 contributes to arterial stiffness in low-density lipoprotein receptor deficient mice. Am J Physiol Heart Circ Physiol 308: H1382–H1390.

Eckel RH, Jakicic JM, Ard JD, De Jesus JM, Houston Miller N, Hubbard VS *et al.* (2014). 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 63: 2960–2984.

Eringa EC, Bakker W, Smulders YM, Serne EH, Yudkin JS, Stehouwer CD (2007). Regulation of vascular function and insulin sensitivity by adipose tissue: focus on perivascular adipose tissue. Microcirculation 14: 389–402.

Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R *et al.* (2003). Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA 289: 1799–1804.

Feldon SE, O'loughlin CW, Ray DM, Landskroner-Eiger S, Seweryniak KE, Phipps RP (2006). Activated human T lymphocytes express cyclooxygenase-2 and produce proadipogenic prostaglandins that drive human orbital fibroblast differentiation to adipocytes. Am J Pathol 169: 1183–1193.

Fentz J, Kjobsted R, Kristensen CM, Hingst JR, Birk JB, Gudiksen A *et al.* (2015). AMPKalpha is essential for acute exercise-induced gene responses but not for exercise training-induced adaptations in mouse skeletal muscle. Am J Physiol Endocrinol Metab 309: E900–E914.

Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A *et al.* (2009). Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 15: 930–939.

Fitzgibbons TP, Kogan S, Aouadi M, Hendricks GM, Straubhaar J, Czech MP (2011). Similarity of mouse perivascular and brown adipose tissues and their resistance to diet-induced inflammation. Am J Physiol Heart Circ Physiol 301: H1425–H1437.

Fritzen AM, Lundsgaard AM, Jordy AB, Poulsen SK, Stender S, Pilegaard H *et al.* (2015). New nordic diet-induced weight loss is accompanied by changes in metabolism and AMPK signaling in adipose tissue. J Clin Endocrinol Metab 100: 3509–3519.

Frontini A, Vitali A, Perugini J, Murano I, Romiti C, Ricquier D *et al.* (2013). White-to-brown transdifferentiation of omental adipocytes in patients affected by pheochromocytoma. Biochim Biophys Acta 1831: 950–959.

Fuster JJ, Ouchi N, Gokce N, Walsh K (2016). Obesity-induced changes in adipose tissue microenvironment and their impact on cardiovascular disease. Circ Res 118: 1786–1807.

Gao YJ, Lu C, Su LY, Sharma AM, Lee RM (2007). Modulation of vascular function by perivascular adipose tissue: the role of endothelium and hydrogen peroxide. Br J Pharmacol 151: 323–331.

Giri JG, Kumaki S, Ahdieh M, Friend DJ, Loomis A, Shanebeck K *et al.* (1995). Identification and cloning of a novel IL-15 binding protein that is structurally related to the alpha chain of the IL-2 receptor. EMBO J 14: 3654–3663.

Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA (2011). The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 11: 607–615.

Gonzalez AM, Hoffman JR, Townsend JR, Jajtner AR, Boone CH, Beyer KS *et al.* (2016). Intramuscular MAPK signaling following high volume and high intensity resistance exercise protocols in trained men. Eur J Appl Physiol 116: 1663–1670.

Grabstein KH, Eisenman J, Shanebeck K, Rauch C, Srinivasan S, Fung V *et al.* (1994). Cloning of a T cell growth factor that interacts with the beta chain of the interleukin-2 receptor. Science 264: 965–968.

Greenstein AS, Khavandi K, Withers SB, Sonoyama K, Clancy O, Jeziorska M *et al.* (2009). Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. Circulation 119: 1661–1670.

Haczeyni F, Barn V, Mridha AR, Yeh MM, Estevez E, Febbraio MA *et al.* (2015). Exercise improves adipose function and inflammation and ameliorates fatty liver disease in obese diabetic mice. Obesity (Silver Spring) 23: 1845–1855.

Hamburg NM, Mcmackin CJ, Huang AL, Shenouda SM, Widlansky ME, Schulz E *et al.* (2007). Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. Arterioscler Thromb Vasc Biol 27: 2650–2656.

Hansen JS, Pedersen BK, 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.

Hara T, Fujiwara H, Nakao H, Mimura T, Yoshikawa T, Fujimoto S (2005). Body composition is related to increase in plasma adiponectin levels rather than training in young obese men. Eur J Appl Physiol 94: 520–526.

He Y, Wu X, Khan RS, Kastin AJ, Cornelissen-Guillaume GG, Hsuchou H *et al.* (2010). IL-15 receptor deletion results in circadian changes of locomotor and metabolic activity. J Mol Neurosci 41: 315–321.

Hirata Y, Tabata M, Kurobe H, Motoki T, Akaike M, Nishio C *et al.* (2011). Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue. J Am Coll Cardiol 58: 248–255.

Hojman P, Pedersen M, Nielsen AR, Krogh-Madsen R, Yfanti C, Åkerstrom T *et al.* (2009). Fibroblast growth factor-21 is induced in human skeletal muscles by hyperinsulinemia. Diabetes 58: 2797–2801.

Huang AL, Silver AE, Shvenke E, Schopfer DW, Jahangir E, Titas MA *et al.* (2007). Predictive value of reactive hyperemia for cardiovascular events in patients with peripheral arterial disease undergoing vascular surgery. Arterioscler Thromb Vasc Biol 27: 2113–2119.

Huh JY, Panagiotou G, Mougios V, Brinkoetter M, Vamvini MT, Schneider BE *et al.* (2012). FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism 61: 1725–1738.

Huh JY, Park YJ, Ham M, Kim JB (2014). Crosstalk between adipocytes and immune cells in adipose tissue inflammation and metabolic dysregulation in obesity. Mol Cells 37: 365–371.

Izumiya Y, Bina HA, Ouchi N, Akasaki Y, Kharitonenkov A, Walsh K (2008). FGF21 is an Akt-regulated myokine. FEBS Lett 582: 3805–3810.

Jenkins NT, Padilla J, Rector RS, Laughlin MH (2013). Influence of regular physical activity and caloric restriction on beta-adrenergic and natriuretic peptide receptor expression in retroperitoneal adipose tissue of OLETF rats. Exp Physiol 98: 1576–1584.

Jiang M, Wan F, Wang F, Wu Q (2015). Irisin relaxes mouse mesenteric arteries through endothelium-dependent and endothelium-independent mechanisms. Biochem Biophys Res Commun 468: 832–836.

Jung SH, Park HS, Kim KS, Choi WH, Ahn CW, Kim BT *et al.* (2008). Effect of weight loss on some serum cytokines in human obesity: increase in IL-10 after weight loss. J Nutr Biochem 19: 371–375.

Kawanishi N, Mizokami T, Yano H, Suzuki K (2013). Exercise attenuates M1 macrophages and CD8+ T cells in the adipose tissue of obese mice. Med Sci Sports Exerc 45: 1684–1693.

Kawanishi N, Yano H, Yokogawa Y, Suzuki K (2010). Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophages in high-fat-diet-induced obese mice. Exerc Immunol Rev 16: 105–118.

Kim HJ, Lee HJ, So B, Son JS, Yoon D, Song W (2016). Effect of aerobic training and resistance training on circulating irisin level and their association with change of body composition in overweight/obese adults: a pilot study. Physiol Res 65: 271–279.

Kim HJ, Park JY, Oh SL, Kim YA, So B, Seong JK *et al.* (2013a). Effect of treadmill exercise on interleukin-15 expression and glucose tolerance in zucker diabetic Fatty rats. Diabetes Metab J 37: 358–364.

Kim KH, Kim SH, Min YK, Yang HM, Lee JB, Lee MS (2013b). Acute exercise induces FGF21 expression in mice and in healthy humans. PLoS One 8: e63517.

Knudsen JG, Bertholdt L, Joensen E, Lassen SB, Hidalgo J, Pilegaard H (2015). Skeletal muscle interleukin-6 regulates metabolic factors in iWAT during HFD and exercise training. Obesity (Silver Spring) 23: 1616–1624.

Kopp A, Buechler C, Neumeier M, Weigert J, Aslanidis C, Scholmerich J *et al.* (2009). Innate immunity and adipocyte function: ligand-specific activation of multiple toll-like receptors modulates cytokine, adipokine, and chemokine secretion in adipocytes. Obesity (Silver Spring) 17: 648–656.

Kranendonk ME, Van Herwaarden JA, Stupkova T, De Jager W, Vink A, Moll FL *et al.* (2015). Inflammatory characteristics of distinct abdominal adipose tissue depots relate differently to metabolic risk factors for cardiovascular disease: distinct fat depots and vascular risk factors. Atherosclerosis 239: 419–427.

Kroller-Schon S, Jansen T, Hauptmann F, Schuler A, Heeren T, Hausding M *et al.* (2012). alpha1AMP-activated protein kinase mediates vascular protective effects of exercise. Arterioscler Thromb Vasc Biol 32: 1632–1641.

Kruger K, Alack K, Ringseis R, Mink L, Pfeifer E, Schinle M *et al.* (2016). Apoptosis of T-cell subsets after acute high-intensity interval exercise. Med Sci Sports Exerc 48: 2021–2029.

Lacraz G, Rakotoarivelo V, Labbe SM, Vernier M, Noll C, Mayhue M *et al.* (2016). Deficiency of interleukin-15 confers resistance to obesity by diminishing inflammation and enhancing the thermogenic function of adipose tissues. PLoS One 11 e0162995.

Lago F, Gomez R, Gomez-Reino JJ, Dieguez C, Gualillo O (2009). Adipokines as novel modulators of lipid metabolism. Trends Biochem Sci 34: 500–510.

Laufs U, Wassmann S, Czech T, Munzel T, Eisenhauer M, Bohm M *et al.* (2005). Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis. Arterioscler Thromb Vasc Biol 25: 809–814.

Lee P, Brychta RJ, Linderman J, Smith S, Chen KY, Celi FS (2013). Mild cold exposure modulates fibroblast growth factor 21 (FGF21) diurnal rhythm in humans: relationship between FGF21 levels, lipolysis, and cold-induced thermogenesis. J Clin Endocrinol Metab 98: E98–102.

Lee P, Linderman JD, Smith S, Brychta RJ, Wang J, Idelson C *et al.* (2014). Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. Cell Metab 19: 302–309.

Lee SD, Tontonoz P (2014). Eosinophils in fat: pink is the new brown. Cell 157: 1249–1250.

Lee S, Kuk JL, Davidson L, Hudson R, Kilpatrick K, Graham TE *et al.* (2005). Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without type 2 diabetes. J Appl Physiol (1985) 99: 1220–1225.

Lee S, Norheim F, Langleite TM, Noreng HJ, Storas TH, Afman LA *et al.* (2016). Effect of energy restriction and physical exercise intervention on phenotypic flexibility as examined by transcriptomics analyses of mRNA from adipose tissue and whole body magnetic resonance imaging. Physiol Rep 4: e13019.

Libby P, Ridker PM, Hansson GK (2009). Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol 54: 2129–2138.

Loro E, Seifert EL, Moffat C, Romero F, Mishra MK, Sun Z *et al.* (2015). IL-15R alpha is a determinant of muscle fuel utilization, and its loss protects against obesity. Am J Physiol Regul Integr Comp Physiol 309: R835–R844.

Lu J, Xiang G, Liu M, Mei W, Xiang L, Dong J (2015). Irisin protects against endothelial injury and ameliorates atherosclerosis in apolipoprotein E-Null diabetic mice. Atherosclerosis 243: 438–448.

Lumeng CN, Bodzin JL, Saltiel AR (2007). Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 117: 175–184.

Malinowski M, Deja MA, Golba KS, Roleder T, Biernat J, Wos S (2008). Perivascular tissue of internal thoracic artery releases potent nitric oxide and prostacyclin-independent anticontractile factor. Eur J Cardiothorac Surg 33: 225–231.

Malnick S, Knobler H (2006). The medical complications of obesity. Qjm 99: 565–579.

Martinez FO, Gordon S (2014). The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000Prime Rep 6: 13.

Mcdowell CP, Campbell MJ, Herring MP (2016). Sex-related differences in mood responses to acute aerobic exercise. Med Sci Sports Exerc 48: 1798–1802.

McGinnis GR, Ballmann C, Peters B, Nanayakkara G, Roberts M, Amin R *et al.* (2015). Interleukin-6 mediates exercise preconditioning against myocardial ischemia reperfusion injury. Am J Physiol Heart Circ Physiol 308: H1423–H1433.

Meijer RI, Bakker W, Alta CL, Sipkema P, Yudkin JS, Viollet BC *et al.* (2013). Perivascular adipose tissue control of insulin-induced vasoreactivity in muscle is impaired in db/db mice. Diabetes 62: 590–598.

Meijer RI, Serne EH, Korkmaz HI, Van Der Peet DL, De Boer MP, Niessen HW *et al.* (2015). Insulin-induced changes in skeletal muscle microvascular perfusion are dependent upon perivascular adipose tissue in women. Diabetologia 58: 1907–1915.

Meijer RI, Serne EH, Smulders YM, van Baak Hinsbergh VW, Yudkin JS, Eringa EC (2011). Perivascular adipose tissue and its role in type 2 diabetes and cardiovascular disease. Curr Diab Rep 11: 211–217.

Meijer RI, Serne EH, Yudkin JS, van Baak Hinsbergh VW, Smulders YM, Eringa EC (2016). Perivascular fat in human muscle. Lancet Diabetes Endocrinol 4: 958.

Min SY, Kady J, Nam M, Rojas-Rodriguez R, Berkenwald A, Kim JH *et al.* (2016). Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. Nat Med 22: 312–318.

Moncada S, Higgs A (1993). The L-arginine-nitric oxide pathway. N Engl J Med 329: 2002–2012.

Morrison SF, Nakamura K (2011). Central neural pathways for thermoregulation. Front Biosci (Landmark Ed) 16: 74–104.

Nishimura S, Manabe I, Nagasaki M, Hosoya Y, Yamashita H, Fujita H *et al.* (2007). Adipogenesis in obesity requires close interplay between differentiating adipocytes, stromal cells, and blood vessels. Diabetes 56: 1517–1526.

Nishimura T, Nakatake Y, Konishi M, Itoh N (2000). Identification of a novel FGF, FGF-21, preferentially expressed in the liver. Biochim Biophys Acta 1492: 203–206.

O'Connell GC, Pistilli EE (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.

Ogawa Y, Kurosu H, Yamamoto M, Nandi A, Rosenblatt KP, Goetz R *et al.* (2007). BetaKlotho is required for metabolic activity of fibroblast growth factor 21. Proc Natl Acad Sci U S A 104: 7432–7437.

Ohashi K, Parker JL, Ouchi N, Higuchi A, Vita JA, Gokce N *et al.* (2010). Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. J Biol Chem 285: 6153–6160.

Oliveira AG, Araujo TG, Carvalho BM, Guadagnini D, Rocha GZ, Bagarolli RA *et al.* (2013). Acute exercise induces a phenotypic switch in adipose tissue macrophage polarization in diet-induced obese rats. Obesity (Silver Spring) 21: 2545–2556.

Ouchi N, Higuchi A, Ohashi K, Oshima Y, Gokce N, Shibata R *et al.* (2010). Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. Science 329: 454–457.

Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y *et al.* (2001). Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation 103: 1057–1063.

Park KH, Zaichenko L, Brinkoetter M, Thakkar B, Sahin-Efe A, Joung KE *et al.* (2013). Circulating irisin in relation to insulin resistance and the metabolic syndrome. J Clin Endocrinol Metab 98: 4899–4907.

Pedersen BK, Febbraio MA (2008). Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev 88: 1379–1406.

Pedersen BK (2009). The diseasome of physical inactivity – and the role of myokines in muscle – fat cross talk. J Physiol 587: 5559–5568.

Pedersen BK, Akerstrom TC, Nielsen AR, Fischer CP (2007). Role of myokines in exercise and metabolism. J Appl Physiol (1985) 103: 1093–1098.

Phillips BE, Atherton PJ, Varadhan K, Limb MC, Wilkinson DJ, Sjoberg KA *et al.* (2015). The effects of resistance exercise training on macro- and micro-circulatory responses to feeding and skeletal muscle protein anabolism in older men. J Physiol 593: 2721–2734.

Piepoli MF, Corra U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D *et al.* (2010). Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil 17: 1–17.

Pistilli EE, Bogdanovich S, Garton F, Yang N, Gulbin JP, Conner JD *et al.* (2011). Loss of IL-15 receptor alpha alters the endurance, fatigability, and metabolic characteristics of mouse fast skeletal muscles. J Clin Invest 121: 3120–3132.

Pop D, Bodisz G, Petrovai D, Borz B, Zdrenghea V, Zdrenghea D (2010). The effect of very short duration acute physical exercise upon adiponectin and leptin in overweight subjects. Rom J Intern Med 48: 39–45.

Qiu Y, Nguyen KD, Odegaard JI, Cui X, Tian X, Locksley RM *et al.* (2014). Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat. Cell 157: 1292–1308.

Quinn LS, Anderson BG, Conner JD, Wolden-Hanson T, Marcell TJ (2014). IL-15 is required for postexercise induction of the pro-oxidative mediators PPARdelta and SIRT1 in male mice. Endocrinology 155: 143–155.

Quinn LS, Anderson BG, Strait-Bodey L, Stroud AM, Argiles JM (2009). Oversecretion of interleukin-15 from skeletal muscle reduces adiposity. Am J Physiol Endocrinol Metab 296: E191–E202.

Quinn LS, Strait-Bodey L, Anderson BG, Argiles JM, Havel PJ (2005). Interleukin-15 stimulates adiponectin secretion by 3T3-L1 adipocytes: evidence for a skeletal muscle-to-fat signaling pathway. Cell Biol Int 29: 449–457.

Rao RR, Long JZ, White JP, Svensson KJ, Lou J, Lokurkar I *et al.* (2014). Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. Cell 157: 1279–1291.

Reifenberger MS, Turk JR, Newcomer SC, Booth FW, Laughlin MH (2007). Perivascular fat alters reactivity of coronary artery: effects of diet and exercise. Med Sci Sports Exerc 39: 2125–2134.

Rittig K, Staib K, Machann J, Bottcher M, Peter A, Schick F *et al.* (2008). Perivascular fatty tissue at the brachial artery is linked to insulin resistance but not to local endothelial dysfunction. Diabetologia 51: 2093–2099.

Ruffino JS, Davies NA, Morris K, Ludgate M, Zhang L, Webb R *et al.* (2016). Moderate-intensity exercise alters markers of alternative activation in circulating monocytes in females: a putative role for PPARgamma. Eur J Appl Physiol 116: 1671–1682.

Samaras K, Botelho NK, Chisholm DJ, Lord RV (2010). Subcutaneous and visceral adipose tissue gene expression of serum adipokines that predict type 2 diabetes. Obesity (Silver Spring) 18: 884–889.

Samms RJ, Cheng CC, Kharitonenkov A, Gimeno RE, Adams AC (2016). Overexpression of beta-Klotho in adipose tissue sensitizes male mice to endogenous FGF21 and provides protection from diet-induced obesity. Endocrinology 157: 1467–1480.

Saunders TJ, Palombella A, Mcguire KA, Janiszewski PM, Despres J, Ross R (2012). Acute exercise increases adiponectin levels in abdominally obese men. J Nutr Metab 2012: 148729.

Saxton S, Withers S, Ohanian J, Heagerty AM (2016). [OP.5A.07] The role of sympathetic nerves and noradrenertic transmission in perivascular adipose tissue function. J Hypertens 34 (Suppl 2): e55–e56.

Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S *et al.* (2008). PRDM16 controls a brown fat/skeletal muscle switch. Nature 454: 961–967.

Seale P, Conroe HM, Estall J, Kajimura S, Frontini A, Ishibashi J *et al.* (2011). Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. J Clin Invest 121: 96–105.

Silva LC, De Araujo AL, Fernandes JR, Matias Mde S, Silva PR, Duarte AJ *et al.* (2016). Moderate and intense exercise lifestyles attenuate the effects of aging on telomere length and the survival and composition of T cell subpopulations. Age (Dordr) 38: 24.

Simpson KA, Singh MA (2008). Effects of exercise on adiponectin: a systematic review. Obesity (Silver Spring) 16: 241–256.

Slusher AL, Whitehurst M, Zoeller RF, Mock JT, Maharaj M, Huang CJ (2015). Attenuated fibroblast growth factor 21 response to acute aerobic exercise in obese individuals. Nutr Metab Cardiovasc Dis 25: 839–845.

Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SPH *et al.* (2016). The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 44 (Database Issue): D1054–D1068.

Speretta GF, Rosante MC, Duarte FO, Leite RD, Lino AD, Andre RA *et al.* (2012). The effects of exercise modalities on adiposity in obese rats. Clinics (Sao Paulo) 67: 1469–1477.

Sun K, Kusminski CM, Scherer PE (2011). Adipose tissue remodeling and obesity. J Clin Invest 121: 2094–2101.

Sutherland LN, Bomhof MR, Capozzi LC, Basaraba SA, Wright DC (2009). Exercise and adrenaline increase PGC-1α mRNA expression in rat adipose tissue. J Physiol 587: 1607–1617.

Takikawa A, Mahmood A, Nawaz A, Kado T, Okabe K, Yamamoto S *et al.* (2016). HIF-1alpha in myeloid cells promotes adipose tissue remodeling toward insulin resistance. Diabetes 65: 3649–3659.

Tanimura Y, Aoi W, Takanami Y, Kawai Y, Mizushima K, Naito Y *et al.* (2016). Acute exercise increases fibroblast growth factor 21 in metabolic organs and circulation. Physiol Rep 4: 12 pii; e12828.

Tran KV, Gealekman O, Frontini A, Zingaretti MC, Morroni M, Giordano A *et al.* (2012). The vascular endothelium of the adipose tissue gives rise to both white and brown fat cells. Cell Metab 15: 222–229.

Travers RL, Motta AC, Betts JA, Bouloumie A, Thompson D (2015). The impact of adiposity on adipose tissue-resident lymphocyte activation in humans. Int J Obes (Lond) 39: 762–769.

Tschritter O, Fritsche A, Thamer C, Haap M, Shirkavand F, Rahe S *et al*. (2003). Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. Diabetes 52: 239–243.

Wijers SL, Schrauwen P, van Baak MA, Saris WH, van Markenl Lichtenbelt WD (2011). Beta-adrenergic receptor blockade does not inhibit cold-induced thermogenesis in humans: possible involvement of brown adipose tissue. J Clin Endocrinol Metab 96: E598–E605.

Wu MV, Bikopoulos G, Hung S, Ceddia RB (2014). Thermogenic capacity is antagonistically regulated in classical brown and white subcutaneous fat depots by high fat diet and endurance training in rats: impact on whole-body energy expenditure. J Biol Chem 289: 34129–34140.

Xiao Y, Liu L, Xu A, Zhou P, Long Z, Tu Y*et al*. (2015). Serum fibroblast growth factor 21 levels are related to subclinical atherosclerosis in patients with type 2 diabetes. Cardiovasc Diabetol 14: 72.

Xu X, Ying Z, Cai M, Xu Z, Li Y, Jiang SY *et al*. (2011). Exercise ameliorates high-fat diet-induced metabolic and vascular dysfunction, and increases adipocyte progenitor cell population in brown adipose tissue. Am J Physiol Regul Integr Comp Physiol 300: R1115–R1125.

Xue Y, Xu X, Zhang XQ, Farokhzad OC, Langer R (2016). Preventing diet-induced obesity in mice by adipose tissue transformation and angiogenesis using targeted nanoparticles. Proc Natl Acad Sci U S A 113: 5552–5557.

Yudkin JS, Eringa E, Stehouwer CD (2005). 'Vasocrine' signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. Lancet 365: 1817–1820.

Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V (2000). Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis 148: 209–214.

Zed C, James WP (1986). Dietary thermogenesis in obesity. Response to carbohydrate and protein meals: the effect of beta-adrenergic blockade and semistarvation. Int J Obes (Lond) 10: 391–405.

Zeyda M, Huber J, Prager G, Stulnig TM (2011). Inflammation correlates with markers of T-cell subsets including regulatory T cells in adipose tissue from obese patients. Obesity (Silver Spring) 19: 743–748.

Zhang F, Yu L, Lin X, Cheng P, He L, Li X *et al*. (2015). Minireview: roles of fibroblast growth factors 19 and 21 in metabolic regulation and chronic diseases. Mol Endocrinol 29: 1400–1413.

Zhang J, Friedman MH (2012). Adaptive response of vascular endothelial cells to an acute increase in shear stress magnitude. Am J Physiol Heart Circ Physiol 302: H983–H991.