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ABSTRACT

Obesity is a well-established risk factor for atherosclerosis. However, the mechanistic link between accumulation of adipose tissue and development of atherosclerosis is not clear. Adipose tissue comprises various depots including white adipose tissue (WAT), brown adipose tissue (BAT) and thoracic and abdominal perivascular adipose tissue (PVAT). The phenotype of thoracic PVAT resembles BAT, whereas abdominal PVAT is more like WAT. Here, we review the distinct roles of the adipose tissue depots in the development of atherosclerosis with the ultimate aim to understand how these can be targeted to reduce atherosclerosis. In obesity, increased fatty acid release by WAT and decreased lipid combustion by BAT and thoracic PVAT lead to hyperlipidaemia, which contributes to atherosclerosis development. Besides, obese WAT and abdominal PVAT release pro-inflammatory factors that further promote atherosclerosis. To discourage atherosclerosis development, strategies that reduce the release of pro-inflammatory factors and fatty acids from WAT and abdominal PVAT, or increase combustion of fatty acids by activation of BAT and thoracic PVAT and beiging of WAT are probably most efficient. Possible therapies could include anti-inflammatory compounds such as adiponectin and salicylates to lower inflammation, and β3-adrenergic receptor activators to increase fatty acid combustion. Additional and more specific strategies to promote fatty acid combustion are currently subject of investigation. In conclusion, different adipose depots differentially affect atherosclerosis development, in which atherosclerosis is promoted by energy-storing adipose depots and attenuated by energy-combusting adipose tissue. In obesity, combining therapies that reduce inflammation and increase combustion of lipids are most conceivable to restrain atherogenesis.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide (Finegold et al., 2013), and atherosclerosis is the pathology underlying most cardiovascular events. Obesity is a major risk factor for CVD (Fox et al., 2008). However, the underlying biological mechanism between accumulation of adipose tissue and atherosclerosis is not fully understood. Obesity is associated with hyperlipidaemia (Klop et al., 2013; Nordestgaard, 2016) and systemic inflammation (Hotamisligil, 2006; Shoelson et al., 2006), both of which are risk factors for atherosclerosis. Nevertheless, distinct adipose tissue types have specific functions that differentially influence atherosclerosis development. More insight into the relation between adipose tissue types and atherosclerosis will provide novel targets to treat (obese) individuals with high risk of CVD. We therefore aim to review recent advances in research on the role of different adipose tissue types, *i.e.* white, brown and perivascular adipose tissue, in atherosclerosis, and the ensuing therapeutic implications.

2. Atherosclerosis

2.1. Pathogenesis of atherosclerosis

The main risk factor for the development of atherosclerosis is hypercholesterolemia. Atherosclerosis development is initiated by enhanced retention of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) remnant particles in the vessel wall. In response, the vessel wall releases oxidative and inflammatory factors that modify these particles, for example by oxidation, resulting in oxidized LDL (oxLDL) (Hansson and Hermansson, 2011; Libby, 2002).

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LDL is also modified by hydrolysing enzymes that are present in the lesions (Oorni et al., 2005; Wooton-Kee et al., 2004). Immune cells, mainly monocytes, are recruited from the circulation upon the expression of chemoattractants like tumor necrosis factor (TNF) and monocyte chemoattractant protein-1 (MCP-1) in the lesions (Libby et al., 2013). The recruited monocytes maturate into macrophages and scavenge the accumulating and modified lipoproteins thereby developing into foam cells. Foam cells augment the inflammatory response, resulting in additional recruitment of immune cells into the atherosclerotic plaque (Hansson and Hermansson, 2011; Libby, 2002). While the atherosclerotic plaque grows and a necrotic core forms, the endothelial cap destabilizes. In an attempt to stabilize this cap, smooth muscle cells proliferate from the media into the intima and produce collagen and elastin. Once the balance is in favour of destabilizing factors the cap may rupture, potentially leading to a cardiovascular event (Libby et al., 2013).

In many cell types involved in build-up of the atherosclerotic plaque, intracellular inflammatory pathways control the expression of adhesion molecules and inflammatory chemokines and cytokines. Besides local inflammation in the vasculature, other peripheral sources of inflammation can augment the development of atherosclerosis, including chronic infection, autoimmune diseases (Khovidhunkit et al., 2004; van Diepen et al., 2013), hepatic inflammation (Wong et al., 2012) and obesity (Shoelson et al., 2006).

2.2. Triglyceride-rich lipoproteins and atherosclerosis

Novel insights from epidemiological and genetic studies suggest that elevated levels of triglyceride-rich lipoproteins (*i.e.* chylomicrons and VLDL), which mainly carry triglycerides in addition to some cholesterol, are a causal risk factor for atherosclerosis (Kannel and Vasan, 2009; Nordestgaard and Varbo, 2014). This notion is underscored by preclinical data showing that reduction of triglyceride-rich lipoproteins by enhancing lipoprotein lipase (LPL)-mediated lipolysis decreases atherosclerosis development. For example, enhancing LPL activity by apoA5 overexpression lowers plasma triglycerides without affecting cholesterol in wild-type mice (Pennacchio et al., 2001) and protects against atherosclerosis in *Apoe*$^{-/-}$ mice (Grosskopf et al., 2012). In contrast to cholesterol, most cells in the body can metabolize triglycerides. Also, unlike cholesterol, there is no build-up of triglycerides in the atherosclerotic plaque (Nordestgaard, 2016). However, removal of triglycerides from circulating triglyceride-rich lipoproteins by LPL in peripheral organs and exchange of triglycerides from VLDL for cholesteryl esters from high-density lipoproteins (HDL) by cholesteryl ester transfer protein (Karalis et al., 2013) results in formation of atherogenic cholesterol-enriched remnant particles (Berbée et al., 2015; Dong et al., 2013). Therefore, plasma triglycerides may merely reflect the presence of lipoprotein abnormalities such as increased cholesterol-enriched remnant particles, which are the actual inducers of atherogenic disease (Goldberg et al., 2011).

Several hypotheses exist on how triglyceride-rich lipoproteins themselves induce atherogenesis (Goldberg et al., 2011). One of them states that postprandially, chylomicrons are converted to remnants which can infiltrate the vessel wall and deposit cholesterol (Zilversmit, 1973). Although proving this is complicated, data from several studies combined, as reviewed by Goldberg et al. (2011), indicate that large triglyceride-rich lipoproteins are able to deposit cholesterol in the vessel wall and thus have direct atherogenic properties, although they are not nearly as atherogenic as smaller lipoproteins are. Besides, it is postulated that triglycerides in the arterial intima are hydrolysed, *e.g.* by LPL that is expressed by macrophages, which results in release of free fatty acids and monoacylglycerols. *In vitro*, these factors promote coagulation and induce expression of adhesion molecules and inflammation, indicating that lipolysis of triglyceride-rich lipoproteins in the vessel wall leads to local and systemic low-grade inflammation (Goldberg et al., 2011; Nordestgaard, 2016). Moreover, VLDL and its remnants contain apoCI and apoCIII. In addition to inhibition of the clearance of these lipoproteins from plasma (Berbée et al., 2005; Gordts et al., 2016), they have pro-inflammatory properties. For example, apoCI enhances lipopolysaccharide-induced inflammation (Berbée et al., 2006) and lipopolysaccharide-induced atherosclerosis development (Westerterp et al., 2007). ApoCIII activates pro-inflammatory pathways in endothelial cells and macrophages, thereby promoting an atherogenic inflammatory cascade (Kawakami et al., 2006a, 2006b).

Taken together, triglyceride-rich lipoproteins contribute to atherosclerosis by being precursors for cholesterol-enriched remnant particles that deposit cholesterol in the vessel wall and by promoting inflammation by carrying apoCI and apoCIII and releasing lipolysis products, although all of these mechanisms would be hard to prove experimentally.

3. Adipose tissue types

Adipose tissue is the main site for energy storage and it is found throughout the body in distinct subcutaneous and visceral depots. It is mainly composed of adipocytes, which come in different natures, *i.e.* white, beige and brown adipocytes. The relative amount of these cell types present in a specific adipose tissue depot defines its colour. Adipose tissue is highly plastic and brown adipocytes can adopt a whiter phenotype (Shimizu et al., 2014) and beige and white adipocytes are able to transdifferentiate into one another (Rosenwald et al., 2013). Therefore, borders between distinct depots are not clear-cut and the existence of a single adipose organ existing of varying depots is often advocated (Cinti, 2005). However, as classification of the depots within the adipose organ is helpful to describe molecular findings, the main adipose tissue depots are classified as white adipose tissue (WAT), brown adipose tissue (BAT) and perivascular adipose tissue (PVAT). Although these adipose tissue depots all contribute to clearance of (postprandial) triglyceride-rich lipoproteins by hydrolysing their triglycerides through the activity of LPL, subsequent lipid handling markedly differs between the prevailing adipocyte types in the depot. This is due to the fact that the white, beige and brown adipocytes have a distinct morphology and physiology (Cinti, 2009; Puigserver and Spiegelman, 2003).

3.1. White adipose tissue

WAT is the most abundant adipose tissue type, found throughout the body in different subcutaneous and visceral depots (Cinti, 2005). WAT is a major participant in energy regulation of the body by storing excess ingested fatty acids in the form of triglycerides in the adipocytes and by releasing fatty acids (by intracellular lipolysis) to meet the energy needs of other organs. It is also an endocrine organ controlling essential metabolic processes, including lipid and glucose homeostasis (Kershaw and Flier, 2004). The spherical adipocytes characteristically contain a single large lipid droplet and a few mitochondria that are dispersed in a thin surrounding layer of cytoplasm.

3.2. Brown and beige adipose tissue

BAT is found in the neck, above the claviculae and around the spine in humans (Cypess et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). In contrast to WAT, which stores energy, BAT combusts fatty acids to generate heat and maintain body temperature, which is defined as non-shivering thermogenesis. Hence brown adipocytes, that are smaller than white adipocytes, contain many mitochondria and typically hold multiple small lipid droplets (Cinti, 2009). Catecholamines induce thermogenesis and signal *via* all types of adrenergic receptors including β1, β2, β3, α1 and α2, although not all of these have stimulatory effects on thermogenesis. Expression of the stimulatory β3-adrenergic receptor on brown adipocytes is likely

the most specific and relevant for heat production. Apart from adrenergic receptor expression, thermogenesis is dependent on intracellular lipolysis and the presence of uncoupling protein 1 (UCP1). Intracellular lipolysis yields fatty acids, which are used as substrates for heat production (Cannon and Nedergaard, 2004). UCP1 resides in the inner mitochondrial membrane and facilitates proton leak, thereby disturbing the proton gradient. This "uncouples" electron transport from synthesis of ATP and leads to production of heat (Cannon and Nedergaard, 2004; Fedorenko et al., 2012). It is known that besides classical brown adipocytes with high UCP1 expression, brown-like cells with very low basal but highly inducible UCP1 expression exist. These cells usually reside in WAT and are called beige adipocytes (Wu et al., 2012).

3.3. Perivascular adipose tissue

Mammals also have PVAT, which is distinct from WAT and BAT due to its specific location and function. PVAT surrounds systemic blood vessels with the exception of the cerebral region. PVAT's main function is to provide mechanical support to the vessels and to regulate vascular tension and torsion (Soltis and Cassis, 1991). One way by which PVAT exerts its function is by releasing biologically active molecules that have paracrine effects on the vessels (Lohn et al., 2002). Human PVAT (peritibial and popliteal artery) has a less inflammatory phenotype compared to subcutaneous WAT from the same region (Mauro et al., 2013). However, the phenotype of PVAT depends on its location in the body, as dissimilar kinds of PVAT have been found in thoracic and abdominal regions. Abdominal PVAT has been proposed to have characteristics mostly resembling WAT, whereas thoracic PVAT has more characteristics of BAT (Fitzgibbons et al., 2011; Padilla et al., 2013). Histology and electron microscopy analyses indicated structural similarities between abdominal PVAT and visceral WAT (Padilla et al., 2013). On the other hand, microarray analysis in mice revealed that BAT and thoracic PVAT have virtually identical global gene expression patterns with equally high expression of *Ucp1*, *Cidea*, and other genes known to be uniquely or very highly expressed in BAT (Fitzgibbons et al., 2011). Electron microscopy confirmed that thoracic PVAT contains multilocular lipid droplets and abundance of mitochondria, and for that reason resembles BAT (Fitzgibbons et al., 2011; Padilla et al., 2013). Abdominal PVAT thus seems to mainly store lipids whereas thoracic PVAT mainly burns lipids. One could speculate that thoracic PVAT has this lipid-burning and heat-generating function because of its proximity near the body's main vessels, which makes efficient transportation of heat throughout the body possible.

4. White adipose tissue and atherosclerosis

Under healthy conditions, WAT acts as a lipid sink by storing lipids, which prevents lipids to accumulate in the circulation and therefore has anti-atherogenic effects (Fig. 1). In contrast, during obesity, WAT expansion leads to dysfunctional WAT that renders the circulating lipid profile pro-atherogenic, as will be explained below. WAT mass is determined by the triglyceride turnover within this tissue, *i.e.* the balance between triglyceride storage and triglyceride removal from adipocytes. This process is dynamic: Arner et al. (2011) (Spalding et al., 2008) showed that during the average ten-year lifespan of human subcutaneous white adipocytes, the triglyceride pool is renewed six times. In obesity, the triglyceride turnover in subcutaneous white adipocytes is decreased due to a combination of increased storage and decreased removal of triglycerides (Arner et al., 2011; Ryden et al., 2013).

The removal of triglycerides from white adipocytes is dependent on the process of intracellular lipolysis, in which triglycerides are broken down and fatty acids are released from the white adipocytes. These fatty acids are subsequently oxidized in other organs such as muscle, liver and BAT. Obesity is characterized by elevated plasma levels of free fatty acids, which is explained by the fact that white adipocytes have a basal intracellular lipolytic rate (*i.e.* spontaneous, unstimulated lipolysis), which increases with larger fat cell size (Ryden and Arner, 2007). Since obesity is characterized by hypertrophy of white adipocytes, obesity results in an elevated basal lipolytic rate and thus augmented release of fatty acids (Langin and Arner, 2006). Consequently, accumulation of fatty acids in plasma occurs (Fig. 1). Intracellular lipolysis within adipocytes can also be stimulated acutely *via* sympathetic innervation or hormones (*i.e.* by the catecholamines noradrenaline and adrenaline) (Bartness et al., 2010). The lipolytic responsiveness to catecholamines is dependent on the adipose tissue depot in which the white adipocytes are situated: visceral white adipocytes have higher catecholamine-induced lipolysis than subcutaneous white adipocytes (van Harmelen et al., 2002, 1997). In obesity, the responsiveness of visceral white adipocytes to catecholamines is higher due to increased β-adrenoceptor sensitivity of these cells (Hoffstedt et al., 1997), which results in more fatty acid release. In contrast, subcutaneous white adipocytes have a reduced response to catecholamines in obesity (Langin et al., 2005). Therefore, the elevated fatty acid plasma levels observed in obesity cannot be explained by the catecholamine-induced lipolysis of subcutaneous white adipocytes.

Intracellular lipolysis in white adipocytes is inhibited by insulin. The responsiveness of white adipocytes to insulin is also dependent on the adipose tissue depot in which they reside; insulin-induced inhibition of lipolysis is lower in visceral as compared to subcutaneous white adipocytes (Zierath et al., 1998). This suggests that visceral adipose tissue already releases more fatty acids than subcutaneous adipose tissue in the insulin-sensitive, non-obese state. Nevertheless, both visceral and subcutaneous white adipocytes become resistant to the anti-lipolytic effect of insulin in obesity (Jensen et al., 1989), which possibly contributes to an increased release of fatty acids by both types of white adipocytes in obesity. Taken together, white adipocytes release more fatty acids in obesity due to increased basal lipolysis and resistance to insulin. Visceral white adipocytes exhibit increased catecholamine-stimulated lipolysis during obesity, which even further elevates fatty acid release. This increased release of fatty acids by visceral white adipocytes is important, since a substantial part of WAT is situated in the visceral region, making up ~10% of total fat mass. Indeed, a strong link exists between large amounts of visceral adipose tissue and development of cardiovascular disease (Kim et al., 2015).

WAT lipolysis and the subsequent rise in circulating free fatty acid levels contribute to the development of hypertriglyceridemia and is at least in part explained by the fact that fatty acids serve as substrate for hepatic VLDL-triglyceride production (Kissebah et al., 1974). Fatty acids released by visceral adipose tissue are directly conducted to the liver *via* the portal vein (Ebbert and Jensen, 2013). Additionally, elevated circulating fatty acids induce insulin resistance in peripheral organs, which leads to decreased fatty acid oxidation and therefore reduced clearance of fatty acids from the circulation by these organs (Abate et al., 1995; Frayn, 2000). This cascade leads to a further increase of hepatic VLDL-triglyceride production and is augmented when fatty acids are deposited ectopically in muscle or liver, where they cause even more insulin resistance (Wueest et al., 2016).

Fatty acids are not only substrates for energy metabolism, but, dependent on the type of fatty acid, are also actively involved in modulating several signalling pathways that mediate inflammation in cells involved in atherosclerosis development. For instance, fatty acids can activate the Toll-like receptors TLR2 and TLR4, which activates NF-κB signalling in macrophages (Lee et al., 2004; Shi et al., 2006). Besides releasing fatty acids, white adipocytes secrete a wide range of pro-inflammatory factors such as adipokines, classical cytokines and chemokines (Cao, 2014). WAT is infiltrated by several types of immune cells both under lean and obese conditions as recently reviewed (Exley et al., 2014; Grant and Dixit, 2015). Adipocyte hypertrophy is associated with upregulation of JNK and NF-κB signalling pathways,

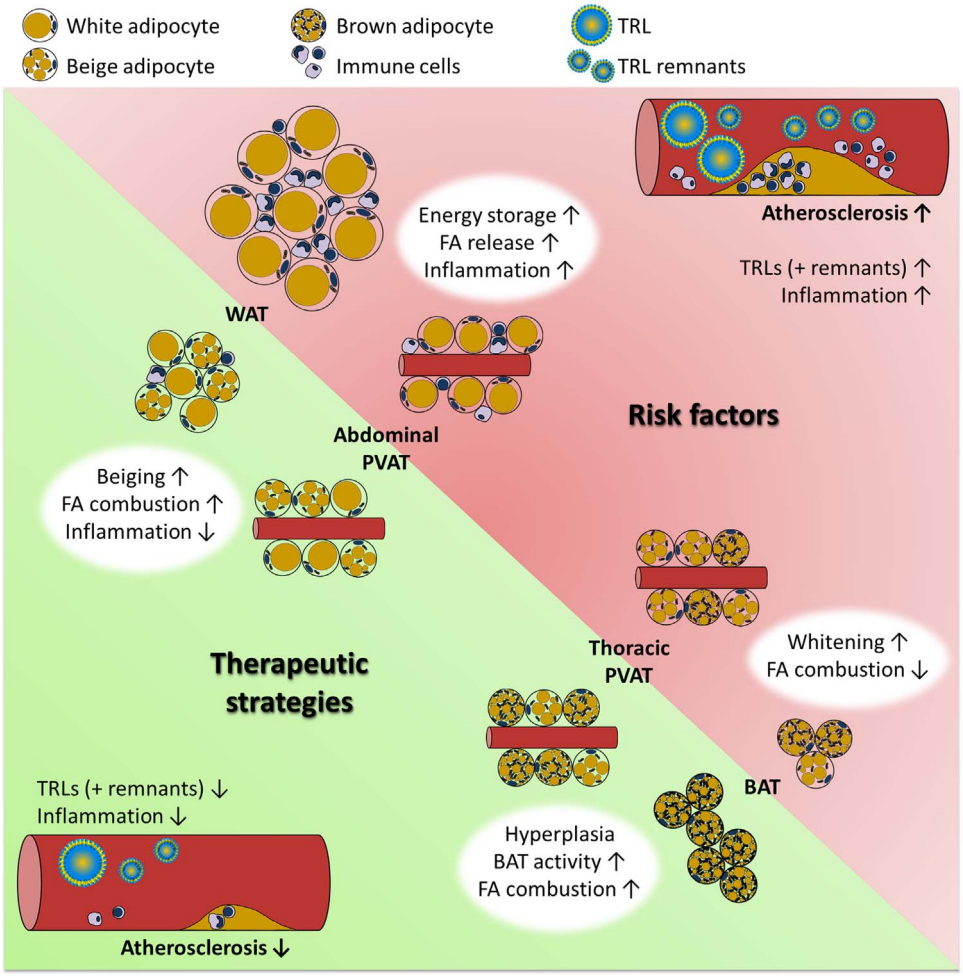

Fig. 1. The role of white, brown and perivascular adipose tissues in the development of atherosclerosis during obesity, and treatment strategies. In obesity, both energy storage and fatty acid release are enhanced in white adipose tissue (WAT). Immune cells infiltrate the WAT and abdominal perivascular adipose tissue (PVAT), causing systemic inflammation. Brown adipose tissue (BAT) and thoracic PVAT display a whitened phenotype in obesity, resulting in decreased combustion of fatty acids. Therapeutic strategies targeting the adipose tissue depots to reduce atherosclerosis development should focus on recruitment and activation of brown adipocytes to increase combustion of fatty acids in BAT and thoracic PVAT. Also, beiging of adipocytes in WAT to increase fatty acid combustion would contribute to reduced circulating triglyceride-rich lipoproteins and their remnants. This should be combined with anti-inflammatory therapies to decrease systemic inflammation and ultimately reduce atherosclerosis. WAT, white adipose tissue; PVAT, perivascular adipose tissue; BAT, brown adipose tissue; FA, fatty acid; TRL, triglyceride-rich lipoprotein.

oxidative stress, ER stress, increased release of pro-inflammatory adipokines and chemokines and apoptotic signalling in the adipocytes (Hotamisligil, 2005, 2006). As a consequence, pro-inflammatory immune cells are attracted towards WAT (Weisberg et al., 2003; Xu et al., 2003), which also secrete inflammatory factors. During WAT expansion in obesity, the number of pro-inflammatory M1 type macrophages, cytotoxic T cells, Th1 cells, B cells and mast cells increase, whereas the anti-inflammatory M2 type macrophages, regulatory T cells and eosinophils decrease (Schipper et al., 2012). Obese adipose tissue is characterized by chronic local inflammation and the presence of crown-like structures (*i.e.* macrophages that surround hypertrophic, stressed and apoptotic adipocytes) (Cinti et al., 2005; Murano et al., 2008). Obesity eventually leads to systemic inflammation, characterized by increased levels of activated circulating immune cells, elevated levels of pro-inflammatory adipokines (*e.g.* leptin), and cytokines (*i.e.* elevation of TNF, IL-1Ra and IL-6), as well as increased CRP in the circulation (Karalis et al., 2009; Visser et al., 1999).

Many types of adipokines released by WAT have immunomodulatory properties or have direct effects on the vascular wall. For instance, leptin has been shown to promote smooth muscle cell migration (Trovati et al., 2014) and to induce the generation of reactive oxygen species (ROS) and MCP-1 expression in endothelial cells (Bouloumie et al., 1999). In addition, apoE-deficient mice treated with leptin show increased atherosclerosis development (Bodary et al., 2005). Other pro-inflammatory adipokines that may stimulate the progression of atherosclerotic plaques are resistin, visfatin and apelin (Maresca et al., 2015), all of which are increased in obesity. Some adipokines, like adiponectin and omentin, have a protective role in atherosclerosis development (Ghantous et al., 2015; Tan et al., 2015). For instance, apoE/adiponectin double-deficient mice show accelerated atherogenesis and adenoviral expression of human adiponectin in *Apoe*$^{-/-}$ mice attenuates the development of atherosclerosis (Okamoto et al., 2002). Transgenic overexpression of human omentin in adipocytes of *Apoe*$^{-/-}$ mice suppresses atherosclerosis development (Hiramatsu-Ito et al., 2016). Of note, circulating levels of both adiponectin and omentin are reduced with increased adiposity. Thus, by secreting elevated levels of pro-inflammatory adipokines or reduced levels of anti-inflammatory adipokines, WAT participates adversely in the progression of atherosclerosis development in obesity (Fig. 1). It remains to be investigated whether pro-inflammatory adipokines are able to initiate the process of atherosclerosis or whether they merely modulate atherosclerosis progression.

5. Brown adipose tissue and atherosclerosis

In contrast to WAT, which likely contributes to atherosclerosis as

mentioned above, BAT is increasingly recognized as a potential target to reduce atherosclerosis development. BAT has an important role in lipoprotein metabolism, as thermogenesis consumes large amounts of fatty acids (Fig. 1). When intracellular lipid stores are depleted, BAT takes up glucose as well as triglyceride-derived fatty acids from triglyceride-rich lipoproteins from the blood. Glucose is likely used for de novo lipogenesis and fatty acids are stored in the lipid droplets as triglycerides before they are used for oxidation in the mitochondria (Hoeke et al., 2016).

In 2011, Bartelt et al. (2011) were the first to show that activation of BAT by cold exposure significantly reduces plasma triglyceride levels of hyperlipidemic *Apoa5*$^{-/-}$ mice. Subsequently, it was demonstrated that active BAT takes up plasma triglycerides mostly after lipolysis (Khedoe et al., 2015), which is in line with the fact that LPL activity and the presence of CD36 are crucial for the clearance of triglycerides by BAT (Bartelt et al., 2011). The potential of BAT to alleviate hypertriglyceridemia was reinforced by several studies in which BAT activation reduces plasma triglyceride levels (Boon et al., 2014; Geerling et al., 2014; Sun et al., 2014; van Dam et al., 2015). Only recently, it was shown that activated BAT also protects from atherosclerosis development in mice (Berbée et al., 2015). More specifically, activation of BAT by β3-adrenergic receptor stimulation in hyperlipidemic APOE*3-Leiden. CETP mice, a well-established model for human-like lipoprotein metabolism (de Haan et al., 2008; Westerterp et al., 2006), not only lowers plasma triglycerides but also cholesterol levels. BAT itself is responsible for the uptake of triglyceride-derived fatty acids, leading to the formation of cholesterol-enriched lipoprotein remnants, which are subsequently cleared from the plasma by the liver *via* binding of apoE to the hepatic LDL receptor (LDLR). Ultimately, the lower plasma cholesterol levels result in reduced atherosclerosis (Berbée et al., 2015). An intact apoE-LDLR clearance pathway is critical for this effect, evidenced by the fact that BAT activation neither lowers cholesterol levels nor reduces atherosclerosis development in *Apoe*$^{-/-}$ or *Ldlr*$^{-/-}$ mice (Berbée et al., 2015; Dong et al., 2013). Vice versa, BAT dysfunction aggravates atherosclerosis as was shown in a model where lipoatrophic BAT was generated by knocking out the insulin receptor in BAT in *Apoe*$^{-/-}$ mice. Although these mice exhibit similar plasma cholesterol levels, they have higher plasma triglycerides and increased atherosclerosis development. Increased inflammation might underlie this phenotype as *Apoe*$^{-/-}$ mice with lipoatrophic BAT exhibited higher pro-inflammatory marker expression in adipose tissues and increased macrophage infiltration in the aortic root than *Apoe*$^{-/-}$ mice (Gomez-Hernandez et al., 2016).

While most data on the role of BAT in atherosclerosis development were obtained in rodents, some evidence exists for similar beneficial effects of BAT activation in humans. For instance, daily cold exposure for 20 min for 90 days reduces total cholesterol and LDL-cholesterol in hypercholesterolemic individuals (De Lorenzo et al., 1998). A more recent study showed that cold exposure increases lipid turnover and oxidation in overweight and obese men, possibly to fuel active brown adipocytes (Chondronikola et al., 2016). Moreover, BAT activity as measured by ^{18}F-FDG uptake is associated with reduced risk of cardiovascular events (Takx et al., 2016).

Besides merely reducing plasma lipids due to enhanced lipoprotein clearance, BAT activation also alters lipid distribution between adipose tissue depots because fatty acids are shuttled to the brown adipocytes as substrates for generation of heat while white adipocytes provide these lipids. Remarkably, LPL expression in BAT is a stronger determinant of plasma lipid levels than LPL in WAT, since deficiency of LPL in the entire adipose tissue increases plasma triglycerides particularly by reducing lipid uptake in BAT (Bartelt et al., 2013; Garcia-Arcos et al., 2013). The altered distribution of fatty acids between BAT and WAT during cold exposure is dependent on the regulation of LPL activity by Angptl4 (Dijk et al., 2015) and strengthens the idea that BAT not only lowers plasma lipid levels, but also reduces fat storage in WAT. Indeed, several studies show reduced fatty acid uptake by WAT or lower WAT mass upon activation of BAT (Boon et al., 2014; van Dam et al., 2015). Some BAT activators lead to increased fatty acid uptake in WAT even though WAT shrinks, which is likely due to beiging of this depot by these activators (Bartelt et al., 2011; Berbée et al., 2015; Kooijman et al., 2015). In humans, it has also been shown that 6 weeks of cold exposure (*i.e.* 17 °C for 2 h/day) reduces body fat mass (Yoneshiro et al., 2013). Overall, BAT activation discourages fat storage in WAT, thereby also indirectly contributing to improved cardiometabolic health.

Whether BAT affects the immunological aspect of atherosclerosis is a field scantily studied. Recent research mostly focused on immunological pathways that mediate brown and beige adipocyte development and function and this has been reviewed by van den Berg et al. (2016). BAT does contain immune cells (macrophages) (Nguyen et al., 2011) and also secretes cytokines (*e.g.* IL-6). Although the transcript levels of pro-inflammatory cytokines in BAT are lower compared to WAT, augmented expression of pro-inflammatory cytokines has been found in obese BAT. These pro-inflammatory factors are thought to diminish BAT function (Villarroya et al., 2016), which could result in reduced combustion of plasma lipids by BAT and thereby promote atherosclerosis development. Besides, release of pro-inflammatory factors contributes to systemic inflammation, which also stimulates atherogenesis. Interestingly, housing of obese mice at thermoneutrality, which renders BAT inactive, results in increased inflammation in gonadal WAT, BAT and in the vasculature, and enhanced development of atherosclerosis (Tian et al., 2016). Whether BAT activation also protects from atherosclerosis by decreasing inflammation remains to be investigated. Of note, in humans, ^{18}F-FDG uptake within BAT negatively correlates with arterial inflammation, suggesting that BAT activity negatively relates to arterial inflammation (Takx et al., 2016).

Obesity is associated with a reduced BAT function, evidenced by lipid accumulation and mitochondrial dysfunction and loss, *i.e.* "whitening" (Hung et al., 2014; Sanchez-Gurmaches et al., 2016; Shimizu et al., 2014) (Fig. 1). Therefore, it is possible that in an obese and/or unhealthy state, dysfunctional BAT further contributes to hyperlipidaemia and atherosclerosis instead of counteracting plaque development. Given the fact that obesity is a prominent risk factor for CVD (Fox et al., 2008), future research should focus on the potential to activate BAT in obese individuals, despite its whitened phenotype.

6. Perivascular adipose tissue and atherosclerosis

PVAT is in direct contact with the adventitia of the vessels without any organized barrier to separate the two, suggesting that PVAT has a direct local role in atherosclerosis development. Due to its direct contact, the paracrine effects of PVAT on vessel walls are probably stronger than potential effects of factors released by WAT. PVAT adipocytes, immune cells and fibroblasts all release vasoactive molecules such as NO, angiotensin, leptin and adiponectin, which have a net anti-contractile effect under healthy conditions. PVAT also releases adipocyte derived relaxing factor (ADRF), which counteracts vasoconstriction and thereby regulates vascular tone (Lohn et al., 2002).

Like the other adipose tissues, PVAT expands in obesity. As a result, PVAT becomes dysfunctional, which is characterized by hypoxia, infiltration of immune cells (monocytes, lymphocytes and granulocytes) and production of pro-inflammatory adipokines, cytokines and chemokines (Greenstein et al., 2009; Henrichot et al., 2005; Police et al., 2009). High-fat diet-feeding (Chatterjee et al., 2009) and hypercholesterolemia without obesity (Lohmann et al., 2009) increase inflammation in PVAT. This inflammation may propagate to the underlying vessel wall, causing local smooth muscle cell and endothelial dysfunction, ultimately contributing to atherosclerosis development (Lee et al., 2014; Wang et al., 2009). Moreover, the protective anti-contractile properties of PVAT which are present in a healthy state are abolished in obese patients (Greenstein et al., 2009). Recently, Zou et al. (2016) provided direct evidence that dysfunctional PVAT is linked

to vascular dysfunction and hypertension by using perilipin-deficient mice. Even though *Perilipin*$^{-/-}$ mice resemble the obese state as they have increased PVAT basal lipolysis, angiotensin II secretion, macrophage infiltration and oxidative stress, they have reduced PVAT mass. Their dysfunctional PVAT is accompanied by undesirable contraction and vasoconstriction of aortic/mesenteric arteries and structural damage of endothelial and smooth muscle cells, indicating that dysfunctional PVAT may promote atherosclerosis development.

The phenotypic differences between the PVAT depots (*i.e.* the WAT-like abdominal PVAT and the BAT-like thoracic PVAT) may contribute to differences in atherosclerosis susceptibility among the vessels that these specific PVAT depots surround. Both abdominal PVAT and thoracic PVAT act as a buffer against toxic levels of fatty acids in the arterial circulation, but abdominal PVAT clears fatty acids by storing fatty acids in triglycerides whereas thoracic PVAT does this *via* inducing thermogenesis (Fig. 1). Expression of inflammatory genes and markers of immune cell infiltration (*i.e.* macrophages and T cells) are higher in abdominal PVAT than in thoracic PVAT (Padilla et al., 2013). Abdominal WAT-like PVAT may thus contribute to atherosclerosis development whereas thoracic BAT-like PVAT may protect against atherosclerosis development. Indeed, it has recently been shown that impaired thermogenesis in PVAT leads to atherosclerosis development (Chang et al., 2012). In this study, smooth muscle cell-specific peroxisome proliferator-activated receptor (PPAR) γ-deficiency led to loss of PVAT and resulted in impaired intra-vascular thermogenic capacity and increased atherosclerosis. Cold exposure inhibited atherosclerosis development and improved endothelial function in mice with intact PVAT but not in the smooth muscle cell-specific PPARγ-deficient mice as a result of impaired lipid clearance (Chang et al., 2012). Thus, functional adaptive thermogenesis in PVAT could protect against atherosclerosis development. However, it is likely that obesity leads to whitening and reduced thermogenesis in BAT-like PVAT, which promotes atherosclerosis development.

Overall, PVAT has beneficial effects on vessel function under healthy conditions because it has vaso- relaxing effects and a fatty acid-buffering capacity. In obesity, this adipose tissue depot becomes dysfunctional and has net vasoconstrictive effects. Dysfunctional PVAT releases elevated levels of disadvantageous pro-inflammatory adipokines that contribute to atherosclerosis development by acting directly on the vascular wall. The thermogenic capacity of PVAT is reduced, as obesity likely induces whitening of BAT-like PVAT.

7. Therapeutic implications

Obese individuals exhibit elevated plasma triglyceride levels and increased systemic inflammation, both of which contribute to atherosclerosis development. Hence, approaches to attenuate atherosclerosis in obesity should aim at reducing plasma triglyceride levels and lowering inflammation. To achieve this, the distinct properties of different adipose tissue depots could be specifically targeted. Although we will mainly exploit the possibilities to target certain properties of WAT and BAT, the strategies also hold true for PVAT, depending on whether it has a more WAT- or more BAT-like phenotype.

7.1. Triglyceride-lowering strategies

7.1.1. Lipid storage in WAT

One therapeutic approach to reduce plasma triglyceride levels by targeting WAT could be to stimulate lipid storage instead of lipid release into the circulation (Okuno et al., 1998). As energy overload in white adipocytes leads to hypertrophy, insulin resistance and inflammation in WAT, healthy expansion of white adipocytes should be achieved while maintaining insulin sensitivity. A well-known class of compounds that promotes healthy lipid storage are the insulin-sensitizing agents to which the thiazolidinediones (TZDs) and metformin belong. TZDs are PPARγ agonists that stimulate insulin sensitivity, adipocyte differentiation and fat storage (Yamauchi et al., 2001). Indeed, the TZD rivoglitazone lowers plasma triglycerides, total cholesterol and fatty acids and reduces atherosclerosis in mice (Hiuge-Shimizu et al., 2011). In humans, the TZD pioglitazone decreases triglycerides, carotid intima–media thickness (Mazzone et al., 2006) and atheroma volume in a coronary artery (Hanefeld, 2009; Nissen et al., 2008; Park et al., 2011). Metformin increases insulin sensitivity and is widely used as a glucose-lowering agent in the treatment of type 2 diabetes (Goodarzi and Bryer-Ash, 2005). It is thought to act by activating 5' adenosine monophosphate-activated protein kinase (AMPK), of which activation and phosphorylation are elevated in WAT upon metformin treatment (Boyle et al., 2011). Interestingly, metformin also lowers plasma triglycerides and VLDL-cholesterol (Salpeter et al., 2008), probably *via* BAT activation (Geerling et al., 2014), which might account for its cardioprotective effect in obese patients (UKPDS, 1998). Conclusive evidence for an effect of metformin on atherosclerosis development is currently studied in clinical trials.

Promoting lipid storage in WAT also has disadvantages. Although circulating lipid levels drop, the lipids residing in WAT can lead to lipotoxicity. Besides, insulin-sensitizing agents not only affect adipose tissue but also other tissues such as the heart by overloading them with fatty acids, which has detrimental effects. TZDs have adverse side effects that limit their use in the clinic (Cariou et al., 2012; Wang et al., 2016). For instance, rosiglitazone is associated with increased risk of myocardial infarction (Nissen and Wolski, 2007), but the reason for these differential effects on cardiovascular outcomes remains undefined (Cariou et al., 2012; Goldberg et al., 2005; Khan et al., 2002). Together, these drawbacks hold back the use of TZDs to combat atherosclerosis.

7.1.2. Lipid combustion by BAT

Apart from targeting WAT, a therapeutic approach to reduce plasma triglyceride levels could be to increase combustion of fatty acids by BAT and thereby decrease plasma lipid levels. Activation of the β3-adrenergic receptors is the most well-known and potent way to induce thermogenesis and lipid combustion (Cannon and Nedergaard, 2004; Cypess et al., 2015) and β3-adrenergic receptor agonists such as CL-316243 potently induce lipid uptake by BAT (Berbée et al., 2015).

In humans, cold (van der Lans et al., 2013; Yoneshiro et al., 2013), activation of transient receptor potential channels by capsinoids (Yoneshiro et al., 2012) and thyroid hormones (Broeders et al., 2016; Doniach, 1975) have been demonstrated to activate BAT. To date, it has not been established that BAT activation lowers plasma triglyceride levels in humans, likely because most studies have applied cold exposure that increases hepatic VLDL-triglyceride production in addition to enhancing triglyceride clearance (Hoeke & Nahon et al., unpublished). In preclinical studies, many compounds have been identified to activate BAT. Among these, rimonabant (Boon et al., 2014), metformin (Geerling et al., 2014), GLP1 receptor activation (Kooijman et al., 2015) and salsalate (van Dam et al., 2015) also reduce plasma triglycerides. Since all of these pharmacological strategies also lower triglycerides in humans, BAT activation may therefore be a promising treatment option to reduce atherosclerosis.

7.1.3. Beiging of WAT

An alternative therapeutic approach is to induce the formation of beige adipocytes in WAT. Although it has not been demonstrated to date (Bartelt and Heeren, 2014), beige adipocytes probably also use triglycerides for nonshivering thermogenesis like classic brown adipocytes do. The fact that fatty acid uptake in beige WAT upon β3-adrenergic stimulation increases while the WAT depots shrink (Berbée et al., 2015) indicates that beige adipocytes do combust triglycerides. Thus, beiging of WAT likely contributes to the lowering of plasma triglyceride levels, ultimately resulting in reduced atherosclerotic development.

Beiging of WAT is typically induced by cold and catecholamine stimulation (Berbée et al., 2015; Kuji et al., 2008; Yamaga et al., 2008), but many other stimuli that promote a beige phenotype are rapidly being discovered and include pharmacological activation of β3-adrenergic receptors (Berbée et al., 2015; Cypess et al., 2015), lactate (Carriere et al., 2014), gut microbiota (Chevalier et al., 2015; Suarez-Zamorano et al., 2015), thyroid hormone (Lin et al., 2015), glucagon-like peptide 1 receptor (GLP1R) activation (Kooijman et al., 2015), fibroblast growth factor (FGF) 21 (Fisher et al., 2012), bone morphogenetic protein (BMP) 4 (Qian et al., 2013) and BMP7 (Boon et al., 2013). Furthermore, various components of the immune system have been implicated to promote beiging, such as macrophages (Fabbiano et al., 2016; Nguyen et al., 2011), eosinophils (Qiu et al., 2014) and ILC2s (Brestoff et al., 2015; Lee et al., 2015) (reviewed in van den Berg et al., 2016). Several cytokines were identified to be involved in the underlying mechanisms and recent evidence also points towards a prominent role for interferon regulatory factors in the regulation of beiging (Kong et al., 2014; Kumari et al., 2016). Non-endogenous compounds that induce beiging include AMPK activation (Wang et al., 2015), inhibitors of Notch signalling (Bi et al., 2014) as well as PPARγ and PPARα agonists. It must be noted however, that many studies identifying beiging agents have not reported the effects of the compound on possible loss of insulation, for example upon alterations in skin or fur. Therefore, the possibility exists that the beiging observed is (partly) a consequence of increased heat loss rather than a direct effect of the agent. Moreover, the metabolic effects observed upon treatment with a beiging compound may not necessarily be caused by beiging and to verify this, future experiments into beiging agents should include *Ucp1*$^{-/-}$ mice and/or thermoneutrality (Nedergaard and Cannon, 2014).

More insight into the formation of beige adipocytes would also help to develop beiging strategies. It was long thought that in contrast to white adipocytes, beige adipocytes are derived from precursor cells that have a gene expression profile similar to muscle, including the expression of the muscle differentiation factor *Myf5* (Timmons et al., 2007). However, the current model of the differentiation process seems more complex as Myf5^{+} cells can also differentiate into white adipocytes (Sanchez-Gurmaches et al., 2012). More specific factors that mark brown/beige adipogenesis (*i.e.* the transcription factor Ebf2) (Wang et al., 2014) are presently being discovered. But then again, how exactly beige adipocytes develop remains elusive as investigating this requires cutting-edge labelling strategies and has yielded dissimilar conclusions so far (Sanchez-Gurmaches et al., 2016). Gaining a better understanding of adipocyte development is a prerequisite for the development of compounds that promote beige adipocyte differentiation and is under investigation.

7.1.4. Lipolysis in WAT and BAT: a double-edged sword

Intracellular lipolysis plays a crucial role in both WAT and BAT, however the effects on plasma triglyceride levels are opposite. Lipolysis in WAT increases fatty acid release which can lead to hypertriglyceridemia, while lipolysis in BAT promotes combustion of fatty acids to generate heat, which can lower plasma triglyceride levels. To decrease triglyceride levels and thereby atherosclerosis, a method to induce or increase lipolysis specifically in BAT is desirable. Alternatively, intracellular lipolysis in WAT and BAT should be balanced in such a way that fatty acids released by WAT are burned by BAT instead of being used for hepatic VLDL-triglyceride production. Increased release of fatty acids by WAT upon treatment with a β3-adrenergic receptor agonist can indeed be balanced by increased fatty acid combustion in BAT and beiging of WAT, evidenced by decreased plasma triglycerides and increased fatty acid uptake in WAT and BAT (Berbée et al., 2015). Nevertheless, the presence of the β3-adrenergic receptor in the cardiovascular system (Dessy and Balligand, 2010) is a drawback for the clinical use of these agonists. Therefore, novel ways to specifically target brown and beige adipocytes are warranted.

7.2. Anti-inflammatory strategies

Although studies on immune cells in BAT and PVAT are scarce, immune cells and cytokines are abundant in all WAT depots and may be causally related to the negative effects of obesity, including atherosclerosis. The inflammatory cytokines released by adipose tissue in obesity contribute to obesity-associated systemic inflammation, but their exact mechanisms of action in inflammation-induced atherosclerosis during obesity remain unknown (Berg and Scherer, 2005) and contradictory results from clinical studies also impede the development of cytokine inhibitors. For example, anti-TNF therapy did not improve the clinical condition of patients with heart failure (Chung et al., 2003; Mann et al., 2004), but reduced the incidence of cardiovascular events in rheumatoid arthritis patients (Jacobsson et al., 2005).

Increasing levels of the anti-inflammatory adipokine, adiponectin, is a promising approach to reduce obesity-induced inflammation and strategies to boost adiponectin levels or receptor activity are under investigation (Yamauchi and Kadowaki, 2008). Although targeting adiponectin and its receptors has been beneficial in metabolic experimental studies, adiponectin-based drug development has not yielded any clinical applications yet.

Taking into account the wide spectrum of inflammatory cytokines that are elevated in obesity, targeting a single cytokine might not be efficient to reduce systemic inflammation and ways to manage the overall metabolic inflammation should be considered. In this light, salicylates, such as salsalate, are favourable as they inhibit NF-κB and thereby transcription of many inflammatory cytokines (Shoelson et al., 2003). Indeed, salicylates were shown to lower overall inflammation in WAT (van Dam et al., 2015) and to stabilize pre-existing atherosclerosis (de Vries-van der Weij et al., 2010).

8. Conclusion

Taken together, WAT, BAT and PVAT play important albeit tissue-specific roles in the development of atherosclerosis. In healthy lean individuals, WAT functions as a lipid sink to keep the vessels clean. Active BAT combusts lipids to generate heat and therefore takes up triglyceride-derived fatty acids from the blood, resulting in cholesterol-rich remnants that are cleared by the liver. PVAT has properties of both BAT and WAT, since it is capable of storing and combusting lipids and thus has fatty acid-buffering properties. In obesity, increased lipolysis from WAT leads to hypertriglyceridemia, BAT is inactivated and PVAT becomes dysfunctional, all of which contributes to atherosclerosis development. On top of that, the balance of inflammatory cytokines and adipokines released by WAT and PVAT shifts towards a more pro-inflammatory equilibrium as a consequence of lipid overflow in obesity. The immunomodulatory properties of this array of pro-inflammatory factors further promotes atherosclerosis development.

To reduce atherosclerosis risk in obese individuals, treatment should focus on the distinct properties of WAT, BAT and PVAT to reduce plasma triglyceride levels and systemic inflammation. The most favourable approach to eliminate triglycerides is by increasing combustion of fatty acids in BAT, thoracic PVAT and beige adipocytes in WAT. Combining this with anti-inflammatory therapies to restrain systemic and adipose tissue inflammation currently seems the most promising strategy to constrain atherosclerosis (Fig. 1).

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