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Targeting white, brown and perivascular adipose tissue in atherosclerosis development

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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