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Adipose tissue secretory profile and cardiometabolic risk in obesity

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ABSTRACT

Adipose tissue is not only an energy storage but also the largest endocrine organ in the body. The protein factors secreted from adipose tissue are collectively referred to as adipokines. Depending on the anatomical locations, adipose tissue depots show different metabolic and endocrine properties. Thus, the expansion and accumulation of adipose tissue exhibit regional variations that affect the cardiometabolic outcomes in distinctive manners. The present review includes subcutaneous, abdominal visceral, perivascular and epicardial adipose tissues for a brief discussion on their roles in the development of obesity-associated cardiometabolic diseases, with a special focus on the secretory profiles of adipokines.

1. Introduction

Obesity is characterized by the excess amount of fat, or adipose tissue, accumulated in the body (https://www.who.int/topics/obesity/). Obesity and associated comorbidities, such as insulin resistance, type 2 diabetes, cardiovascular and nonalcoholic fatty liver diseases, are reaching epidemic proportions worldwide (Martin-Rodriguez, Guillen-Grima et al. 2015). Adipose tissue plays a key role in the control of cardiovascular and energy homeostasis (Oikonomou and Antoniades 2019). The pathophysiology of obesity-associated diseases has been attributed to the abnormalities in adipose tissue, such as increased inflammation (Reilly and Saltiel 2017), endoplasmic reticulum (ER) and oxidative stress (Manna and Jain 2015, Yilmaz 2017), hypoxia (Trayhurn 2013), mitochondrial dysfunction (Woo, Jang et al. 2019), fibrosis (Marcelin, Silveira et al. 2019), impaired adipocyte expansion and angiogenesis (Hammarstedt, Gogg et al. 2018).

Adipose tissue is classified into energy-storing white adipose tissue (WAT) and thermogenic-controlling brown adipose tissue (BAT). Adipocytes in WAT contain unilocular lipid droplets that occupy 95% of the cell volume (Farese and Walther 2009). The size of white adipocytes ranges approximately from 20 to 200 μm (Luo and Liu 2016). Expansion of WAT depends on the formation of new adipocyte differentiated from the progenitors/preadipocytes and the hypertrophy of existing adipocytes (Vishvanath and Gupta 2019). Accordingly, excess formation of WAT contributes to the development of hyperplasic or hypertrophic obesity (Ghaben and Scherer 2019). BAT in humans is located in the interscapular and mediastinal regions (Sacks and Symonds 2013). Brown adipocytes are smaller, contain multilocular lipid droplet and express uncoupling protein 1 (UCP1) to convey the non-shivering thermogenesis (Wang and Seale 2016). The size of brown adipocytes ranges from 15 to 60 μm (Cedikova, Kripnerova et al. 2016). The ability of adipose tissue to dispose circulating free fatty acids (FFAs) by storage as triacylglycerols or by oxidation has important implications on metabolic and cardiovascular functions. Abnormal disposal of FFAs contributes to the accumulation of harmful metabolites in organs to cause cardiometabolic diseases (Yazici and Sezer 2017).

Adipose tissue is not only an energy-storage but also an endocrine organ. It releases polypeptides, collectively referred to as adipokines [adiponectin, leptin, visfatin, omentin, apelin, resistin etc] and cytokines [interleukin (IL)-6, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor (TNF)-α] to regulate body weight, appetite, blood pressure, glucose and lipid metabolism (Kahn, Wang et al. 2019). For example, leptin is an adipokine regulating energy intake and expenditure by inhibiting appetite and altering energy metabolism (Rehman, Akash et al. 2018). Adiponectin represents one of the most abundant adipokines eliciting anti-inflammatory and insulin-sensitizing activities (Straub and Scherer 2019). Adverse remodeling and expansion of WAT is associated with the alterations in the secretory profile of adipokines and cytokines. In particular, increased production of pro-inflammatory adipokines and decreased production of adiponectin contribute to the development of cardiometabolic diseases associated with obesity.

Adipose tissues are also classified based on their anatomical locations, referred to as fat depots (Fig. 1). In general, adipose depots are divided into those having systemic effects (e.g. subcutaneous and visceral adipose tissue) or predominantly local effects (e.g. perivascular and epicardial adipose tissue). The propensity to generate new adipocytes in different adipose depots varies, thus their expansions are intrinsically different leading to diversified cellular composition, function and cardiometabolic consequences (Gruzdeva, Borodkina et al. 2018). The present mini-review provides a summary of current understanding of

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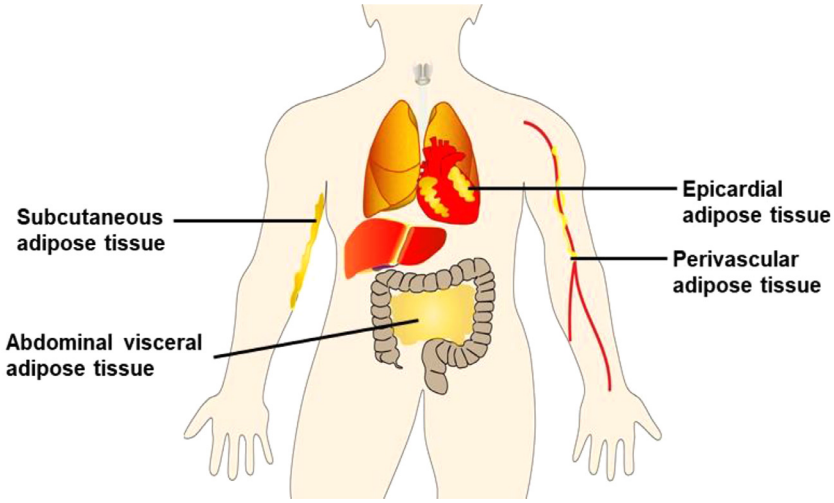

Fig. 1. Anatomical distribution of adipose tissue.

adipokines produced from different depots of adipose tissue and their role in regulating cardiometabolic functions.

1.1. Subcutaneous adipose tissue

Subcutaneous adipose tissues (SAT) is the largest fat depot composed of over 80% of total fat storage in the body. It acts as a metabolic sink to store excessive fat and protects other organs against ectopic fat deposition (Gruzdeva, Borodkina et al. 2018). During the initial stage of adipose tissue expansion, the accumulation of body fat mainly involves the expansion of subcutaneous depots , which is accompanied by increased expression of leptin (Lonnqvist, Nordfors et al. 1997). The expansion of SAT is beneficial to prevent the development of cardiometabolic syndrome. Cardiovascular risk is lower in individuals with subcutaneous obesity which is independent of the visceral obesity (Appleton, Seaborn et al. 2013, Neeland, Ayers et al. 2013). In rodents, transplantation of SAT leads to lower body weight gain with improvement in glucose metabolism (Stanford, Middelbeek et al. 2015). Compared to other fat depots, SAT is relatively resistant to metabolic dysfunction due to the decreased rate of lipolysis, protective endocrine properties and anti-inflammatory features (van Harmelen, Dicker et al. 2002, Verboven, Wouters et al. 2018).

Leptin is the product of the obese gene, which was identified in ob/ob mice by positional cloning (Zhang, Proenca et al. 1994). The majority of circulating leptin is produced from SAT. Mice lacking leptin (ob/ob mice) show abnormally increased food intake, obesity and insulin resistance, which are reversed by treatment with leptin (Friedman and Halaas 1998). Patients with congenital leptin deficiency or low level of leptin show hyperphagia, hypothalamic dysfunction, insulin resistance and lipodystrophy (Meehan, Cochran et al. 2016). Weight loss decreases the expression and release of leptin from SAT and reduces the circulating levels of this adipokine (Thong, Hudson et al. 2000). In addition to the central nervous system, leptin acts directly or indirectly to regulate adipocyte metabolism (Harris 2014). Leptin inhibits lipid accumulation and reduces the expansion of WAT (Wagoner, Hausman et al. 2006). However, leptin resistance is indicated in many obese individuals (Liu, Yang et al. 2018), and cannot be corrected by treatment with the supplementation of this adipokine (Mittendorfer, Horowitz et al. 2011).

Aging is associated with the loss of SAT. However, the levels of leptin are positively correlated with age-related adiposity and impairment in physical function (Lana, Struijk et al. 2016, Rostas, Tenk et al. 2016). Leptin resistance triggers metabolic disturbances and affects the longevity of the elderly (Carter, Caron et al. 2013, Hosoi and Maffei 2017). Mutations in the genes encoding leptin and its receptors have been suggested to be responsible for the leptin resistance (Roszkowska-Gancarz, Jonas et al. 2015). Despite the information, mechanisms underlying leptin resistance in humans remain largely unknown (Gruzdeva, Borodkina et al. 2019). Leptin resistance is more pronounced in the subcutaneous adipocytes from patients with ischemic heart disease (Dyleva, Gruzdeva et al. 2019). Leptin mediates the increase in blood pressure associated with obesity. Obese patients with a loss-of-function mutation in leptin or leptin receptor present with low blood pressure (Simonds, Pryor et al. 2014). Increased leptin levels are associated with cardiac dysfunction in obese patients (Kamimura, Suzuki et al. 2018, Imerbtham, Thitiwuthikiat et al. 2020). The obesity-associated cardiac dysfunction including heart failure with preserved ejection fraction (HFpEF), sodium retention, plasma volume expansion, microvascular inflammation, and atypical deposition of fibrotic tissues are correlated with elevated plasma leptin levels in human (Faxen, Hage et al. 2017, Obokata, Reddy et al. 2017).

Abdominal visceral adipose tissue

Visceral adipose tissue (VAT), or visceral fat, refers to those surrounding the different thoracic and abdominal organs. Abdominal VAT including the omental, mesenteric and retroperitoneal fat depots are highly metabolically active, constantly releasing FFAs into the portal circulation, and plays a more important role in the development of cardiometabolic diseases than SAT (Neeland, Ross et al. 2019). Accumulation of VAT rather than whole body adiposity is associated with an unfavorable metabolic activity and an increased risk of cardiometabolic complications including insulin resistance, impaired glucose tolerance, type 2 diabetes, hypertension, heart failure, coronary artery disease (CAD), valvular disease and arrhythmias (Mechanick, Farkouh et al. 2020).

Abdominal VAT is characterized by a high expression and secretion of pro-inflammatory cytokines, such as IL-6, IL-8, IL-1β, TNF-α and MCP-1 (Unamuno, Gomez-Ambrosi et al. 2018). Leptin expression is lower in VAT than SAT, possibly due to differences in fat cell size and/or sympathetic innervation (Fontana, Eagon et al. 2007, Samaras, Botelho et al. 2010). Both VAT and SAT produce and release adiponectin, an anti-inflammatory adipokine (Wang, Lam et al. 2008). However, visceral adipocytes show higher secretion rates of adiponectin than those of subcutaneous adipocytes (Motoshima, Wu et al. 2002, Reneau, Goldblatt et al. 2018). Weight loss increases adiponectin expression and release from abdominal VAT (Wang, You et al. 2015). Adiponectin elicits multiple beneficial functions as an insulin sensitizer, a metabolic sensor and an immune modulator (Fang and Judd 2018). It possesses potent protective properties against alcoholic and nonalcoholic fatty liver diseases (Xu, Wang et al. 2003, da Silva, Costa-Silva et al. 2018). Adiponectin levels decline with age but are positively correlated with longevity (Pareja-Galeano, Santos-Lozano et al. 2017). Centenarians have higher levels of circulating adiponectin than body mass index (BMI)-matched control subjects (Arai, Kamide et al. 2019). Omentin, another anti-inflammatory and anti-hyperglycemic adipokine is abundantly synthesized and se-

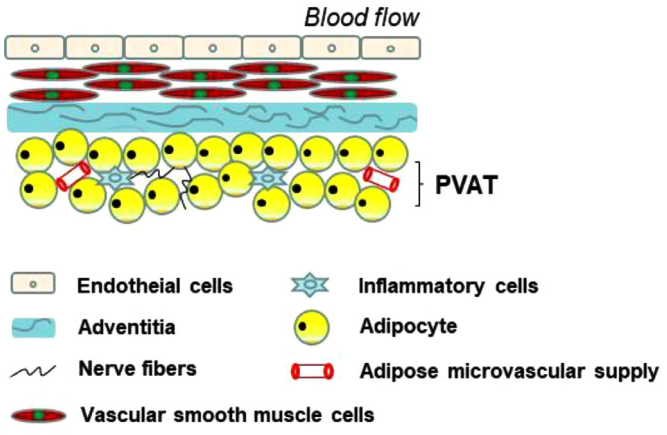

Fig. 2. Perivascular adipose tissue (PVAT) refers to the fat depots surrounding the vascular wall.

creted from abdominal VAT (Pan, Kaminga et al. 2019). Serum omentin levels are decreased in obese subjects with insulin resistance and type 2 diabetes (Pan, Guo et al. 2010, Elsaid, Sadik et al. 2018), but increased in response to weight loss (Antonio de Luis, Izaola et al. 2018).

In obese human and animals, the expression of lipocalin-2, a pro-inflammatory adipokine, is significantly upregulated in abdominal VAT (Wang, Lam et al. 2007, Catalan, Gomez-Ambrosi et al. 2009). There is a strong positive correlation between lipocalin-2 expression and the mean diameter of adipocytes in abdominal VAT (Auguet, Quintero et al. 2011). Lipocalin-2 production in adipocytes is highly sensitive to metabolic stress, cytokine stimulation and nutrient signals, suggesting an important role of this molecule in adipocyte metabolism and inflammation (Zhang, Foncea et al. 2014, Li, Sun et al. 2020). The serum concentrations of lipocalin-2 are positively associated with adiposity, hyperglycaemia and insulin resistance (Wang, Lam et al. 2007, Cakal, Ozkaya et al. 2011, Luo, Ma et al. 2016, Rashad, El-Shal et al. 2017). Animal studies suggest that lipocalin-2 plays a causative role in insulin resistance, endothelial dysfunction, non-alcoholic steatohepatitis as well as cardio-renal injuries (Law, Xu et al. 2010, Liu, Song et al. 2012, Ye, Yang et al. 2016, Sun, Bai et al. 2018), thus supporting this molecule as a potential therapeutic target for cardiometabolic diseases.

2. Perivascular adipose tissue

Most blood vessels are surrounded by perivascular adipose tissue (PVAT) (Fig. 2), which releases adipokines and cytokines to maintain vascular homeostasis (Soltis and Cassis 1991, Lohn, Dubrovska et al. 2002). While the subcutaneous and visceral adipose tissues represent 82-97% and 10-15%, respectively, PVAT only contributes ~0.3% of total adiposity (Grigoras, Amalinei et al. 2019). PVAT develops from mesenchymal precursors characterized by SM22α+, Myf5+, PAX3+, PDGFRα+ or CD31-CD34+ (Chang, Villacorta et al. 2012, Tran, Fitzgibbons et al. 2018, Ye, Ruan et al. 2019). Each type of the precursors differentiate within a specific environment or at different times during embryogenesis (Chang, Villacorta et al. 2012, Sanchez-Gurmaches and Guertin 2014, Vishvanath, MacPherson et al. 2016). However, depending on the anatomical positions, the cellular compositions and the properties of PVAT are different. For example, PVAT associated with the thoracic aorta resembles BAT, whereas PVAT surrounding the abdominal aorta exhibits similarities with WAT (van Dam, Boon et al. 2017, Restini, Ismail et al. 2018, Tran, Fitzgibbons et al. 2018). PVAT associated with coronary arteries is composed of small adipocytes with a reduced state of differentiation and a lower expression of adiponectin and leptin than those of perirenal and subcutaneous depots (Fernandez-Alfonso, Somoza et al. 2017). The origins of PVAT may be different from the classical adipocyte lineages of other WAT depots. The differences in PVAT may facilitate the use of specific treatment for a particular type of blood vessel diseases (Randrianarisoa, Stefan et al. 2018, Grigoras, Amalinei et al. 2019).

PVAT attenuates the vasoconstriction of both resistance and conduit arteries (Soltis and Cassis 1991). The vasorelaxant effects are mediated by substances released from PVAT, including adipokines, such as adiponectin and angiotensin 1-7 (Greenstein, Khavandi et al. 2009, Lee, Bader et al. 2011), and other bioactive molecules such as hydrogen sulfide (H_2S), nitric oxide (NO), prostacylin and methyl palmitate (Lee, Chang et al. 2011, Chang, Villacorta et al. 2012, Cacanyiova, Majzunova et al. 2019, Nobrega, Araujo et al. 2019). Adiponectin stimulates the phosphorylation of endothelial nitric oxide synthase that induces vasodilatation via the release and action of NO (Cheng, Lam et al. 2007). Adiponectin also promotes the release of H_2S and palmitic acid methyl ester from PVAT, which induce vasodilatation via activation of ATP-dependent and voltage-gated potassium channels respectively (Adriana Grigoras 2019). In obese patients, the loss of the anti-contractile activity of PVAT is correlated with the development of hypertension (Greenstein, Khavandi et al. 2009). Obese condition is associated with a decreased release of adiponectin, and an increased production of pro-inflammatory cytokines and adipokines from PVAT, including TNF-α, MCP-1, IL-6, angiotensin-II, chemerin, resistin and visfatin (Aghamohammadzadeh, Unwin et al. 2015, Huang Cao, Stoffel et al. 2017). TNF-α stimulates reactive oxygen species (ROS) generation and reduces NO bioavailability (Virdis, Santini et al. 2011). Decreased adiponectin production and an increase in TNF-α level attenuate the anti-contractile function of PVAT (Greenstein, Khavandi et al. 2009, Al-Jarallah and Oriowo 2016, Almabrouk, White et al. 2018). Chemerin released from PVAT causes contraction in arteries (Watts, Dorrance et al. 2013). Increased chemerin levels are correlated with inflammatory markers TNFα, IL-6, and C-reactive protein (Weigert, Neumeier et al. 2010, Sawicka, Michalska-Jakubus et al. 2019). It downreguates endothelial nitric oxide synthase (eNOS) and NO production (Neves, Nguyen Dinh Cat et al. 2015). Chemerin also amplifies electric field-stimulated contraction in mesenteric artery through the ChemR23 receptor (Darios, Winner et al. 2016, Flood and Watts 2020). As a result of increased adiponectin and decreased chemerin production, weight loss restores the anti-contractile activity of PVAT (Aghamohammadzadeh, Greenstein et al. 2013).

PVAT dysfunction not only contributes to obesity-related hypertension but also involved in the pathogenesis of atherosclerotic plaque formation and contributes to the development of ischemic coronary disease (Okamoto, Couse et al. 2001, Aghamohammadzadeh and Heagerty 2012). Under physiological conditions, the thermogenic and FFAs storage effects of PVAT contribute to the reduction of lipid accumulation in the vasculature (Qi, Qu et al. 2018). Moreover, adiponectin released from PVAT enhances the anti-atherogenic action of NO by stimulating the activity of eNOS (Withers, Bussey et al. 2014). In obesity, dysfunctional PVAT leads to increased production of pro-inflammatory substances in turn causing vascular inflammation and atheromatous plaque formation (Ohman, Luo et al. 2011). Pro-inflammatory adipokines and cytokines such as leptin, resistin, lipocalin-2, TNF-α and IL-6 counterbalance the anti-atheromatous factors by stimulating angiogenesis, ROS production, endothelial activation, macrophage infiltration and smooth muscle cell proliferation (Huang Cao, Stoffel et al. 2017, Numaguchi, Furuhashi et al. 2019). Under obese condition, TNF-α excess causes the endothelin-1/NO imbalance and abolishes the vascular protective properties of PVAT (Virdis, Duranti et al. 2015). TNF-α neutralization by infliximab ameliorates vascular inflammation (Schinzari, Armuzzi et al. 2008, Tesauro, Schinzari et al. 2008, Esser, Paquot et al. 2015). In skeletal muscle, PVAT associated with intramuscular vessels secretes adipokines and cytokines for the regulation of nutrient perfusion, glucose uptake and insulin sensitivity (Natali Baltieri et al. 2018). In patients with type 2 diabetes, PVAT dysfunction is correlated with decreased glucose transport due to diminished muscle perfusion (Natali Baltieri et al. 2018). Skeletal muscle fibers release a newly discovered

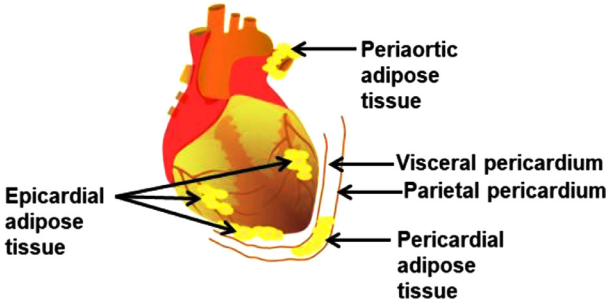

Fig. 3. Anatomical localization of epicardial, pericardial and periaortic adipose tissues surrounding the heart.

adipokine called irisin after intense exercise. This adipokine induces browning of WAT, but may contribute to endothelial dysfunction and atheromatous lesions in obesity and diabetes. Circulating irisin levels were found to be higher in insulin resistance patients, and it has been positively correlated with increased cardiovascular risk (Paul Lee, Linderman Joyce D. et al. 2014, Lidia I. Arhire 2019).

Taken together, the involvement of PVAT in the vascular tone maintenance, endothelial and smooth muscle homeostasis, nutrient metabolism and insulin sensitivity may lead to a new therapeutic approach in obesity, diabetes mellitus, and cardiovascular diseases.

3. Epicardial adipose tissue

WAT surrounding the heart comprises the epicardial adipose tissue (ECAT) and pericardial adipose tissue (PCAT), with the visceral pericardium being the boundary between the two depots (Iacobellis 2015). ECAT is located on top of the myocardium and underneath the visceral pericardium, in the atrioventricular and interventricular grooves as well as alongside the coronary arteries of human heart. PCAT splits to form the parietal pericardium and the outer thoratic wall (Fig. 3). ECAT is originated from splanchnopleuric mesoderm and anatomically contiguous with the myocardium (referred to as myocardial ECAT) or the coronary arteries (referred to as pericoronary ECAT). PCAT originates from the primitive thoracic mesenchyme (Eszter Nagy 2017). The mesenchymal cells in the epicardium are the source of progenitor cardiomyocytes during fetal development but give rise to adipocytes in adulthood (von Gise and Pu 2012). While the blood supply to ECAT is from coronary circulation, PCAT rely on non-coronary sources (Chhabra and Gurukripa Kowlgi 2015). PCAT and ECAT possess different metabolic and endocrine properties. However, the role of PCAT in cardio-protection is less clear. Another term, paracardial fat, refers to those located on the external surface of the parietal pericardium (Yukiko Yamaguchi 2015) .

Under physiological conditions, ECAT makes up 20% of the heart mass (Villasante Fricke and Iacobellis 2019). Epicardial adipocytes are smaller than those of the SAT and other VAT depots (Aitken-Buck, Babakr et al. 2019). The thickness of ECAT increases along with body weight and represents a risk factor for cardiovascular and metabolic diseases (Villasante Fricke and Iacobellis 2019). ECAT thickness is positively correlated with systolic and diastolic blood pressure, fasting insulin, low-density lipoprotein (LDL) cholesterol and glucose levels, but negatively correlated with plasma adiponectin and high-density lipoprotein (HDL) (Rosalinda Madonna 2019) . ECAT expansion is associated with atherosclerotic cardiovascular diseases, including CAD (Mancio, Azevedo et al. 2018, Berg, Miksztowicz et al. 2019). Increased or decreased ECAT with bi-ventricular hypertrophy and impaired diastolic relaxation and filling are found in patients with HFpEF (Haykowsky, Nicklas et al. 2018, Le Jemtel, Samson et al. 2019). A loss of BAT-like features of ECAT contributes to the development of heart failure with reduced ejection fraction (HFrEF) (Perez-Belmonte, Moreno-Santos et al. 2017). ECAT elicits cardioprotective roles by providing mechanical protection and energy source to the heart, as well as secreting anti-inflammatory adipokines such as adiponectin (Alexios S. Antonopoulos 2017). In response to cold exposure, ECAT functions like BAT to generate heat (Aldiss, Davies et al. 2017). The proximity of ECAT to the myocardium allows the two to communicate by paracrine and vasocrine signaling (Rosalinda Madonna 2019). Compared to other visceral adipose depots, ECAT exhibits low glucose utilization but high capacity for the synthesis, release and uptake of FFAs. ECAT contains higher saturated (e.g. stearate, palmitate, tetradecanoate) and lower unsaturated (e.g. oleate, linoleate, linolenate) fatty acids than SAT (Pezeshkian, Noori et al. 2009). ECAT expresses fatty-acid-binding protein 4 (FABP-4), which plays a role in the transport of FFAs between ECAT and the myocardium for oxidation and energy supply (Furuhashi, Fuseya et al. 2016, Furuhashi 2019).

Under obese conditions, ECAT expands and causes cardiac pathology via vasocrine and paracrine secretion of proinflammatory adipokines and FFAs (Rosalinda Madonna 2019). Increased aldosterone production and mineralocorticoid signaling promote the accumulation of ECAT and are critically involved in the transition of ECAT into a pro-inflammatory and pro-fibrotic state, in turn causing atherosclerosis in coronary vessels, atrial tachyarrhythmias and heart failure (Iacobellis, Petramala et al. 2016). The inflammation caused by adiposity further promotes the accumulation of ECAT, which synthesizes a number of adipokines and cytokines, including leptin, TNF-α, resistin, IL-1β and IL-6, in turn triggering endothelial dysfunction, reactive tissue injuries and fibrosis (Packer 2018). The expression of FABP-4 significantly increases in ECAT of patients with metabolic syndrome or heart failure (Vural, Atalar et al. 2008, Elie, Jensen et al. 2016, Yang, Deng et al. 2017). Serum levels of FABP-4 are associated with left ventricular diastolic dysfunction (Baessler, Lamounier-Zepter et al. 2014, Fuseya, Furuhashi et al. 2014), and are an independent predictor of cardiovascular risk (Chow, Tso et al. 2013). The locally produced FABP4 is involved in coronary atherosclerosis (Masato Furuhashi 2016). ECAT-derived FABP4 reduces the contractility of the cardiomyocytes (Ricardo Rodríguez-Calvo 2017). Deficiency of FABP4 improves left ventricular function, attenuates ischaemia/reperfusion-induced myocardial injuries and protects against the development of atherosclerosis (Zhou, Bao et al. 2015).

Adiponectin maintains cardiac architecture by regulating glucose and lipid metabolism. Plasma adiponectin has been used as a biomarker for cardiac structure and function (Maiolino, Cesari et al. 2008, Luo, Chen et al. 2020). The expression of adiponectin decreases by 40% in ECAT of patients with CAD when compared to normal controls (Iacobellis, Pistilli et al. 2005). The low expression levels of adiponectin in ECAT are a strong predictor for prognosis in patients with cardiovascular diseases (Teijeira-Fernandez, Eiras et al. 2012). Treatment with adiponectin attenuates contractile dysfunction and restores the architecture in hearts of obese animals (Dong and Ren 2009). Adiponectin improves coronary no-reflow injury by protecting the endothelial function (Han, Wu et al. 2017). ECAT-derived omentin is decreased in patients with coronary atherosclerosis. Omentin expression in ECAT adjacent to coronary stenotic segments is lower than that in non-stenotic segments of patients with coronary atherosclerosis (Du, Ji et al. 2016). Its expression increases in the ECAT of non-obese patients with coronary atherosclerosis, despite a decrease in plasma levels (Harada, Shibata et al. 2016). Myocardial injury leads to a decrease in omentin expression in the heart but an increase in plasma (Saddic, Nicoloro et al. 2017). Omentin attenuates the cardiac hypertrophic responses (Matsuo, Shibata et al. 2015). Omentin treatment improves the anti-inflammatory activity and the paracrine benefit of human epicardial fat (Fernandez-Trasancos, Agra et al. 2017).

The expression of lipocalin-2 significantly increases in ECAT of patients with heart failure (Yang, Deng et al. 2017). Lipocalin-2 expression in heart is highly induced by stimuli including interleukin-1β, H_2O_2 and agonists activating the innate immune system (Yndestad, Landro et al. 2009),. Lipocalin-2 induces cardiomyocyte apoptosis by increasing intracellular iron accumulation and attenuating the autophagy (Xu, Ahn et al. 2012, Sung, Chan et al. 2017). In cultured cardiomyocytes, lipocalin-

2 activates molecular hypertrophic pathways and increases cell size. The inflammation in heart tissue of mice is enhanced by lipocalin-2 under pressure overload challenge (Song, Jahng et al. 2017). Elevated circulating lipocalin-2 levels represent an independent predictor of cardiovascular events (Wu, Li et al. 2014). In hypertrophic heart, both cardiac and circulating lipocalin-2 levels are significantly increased and associated with diastolic dysfunction (Marques, Prestes et al. 2017). Increased lipocalin-2 levels are also associated with the development of atherosclerosis (Xiao, Xu et al. 2013). Lipocalin-2 is critically involved in the pathogenesis of and played a pivotal role in the systemic adaptation to chronic heart failure (Marques, Prestes et al. 2017).

4. Summary

The traditional perception of the adipose tissue as an inert energy reservoir has suffered radical challenges during the last couple of decades. More and more evidence suggest that adipose tissue is a complex with remarkable diversity in the origin, structure and function, which are determined by intrinsic mechanisms. Our present understanding of different adipose tissue depots is limited. Nevertheless, regional variations represent a main concern when studying and analyzing the adipose tissue phenotypes. For example, PVAT is not only a vascular support but also an endocrine and a paracrine depot involved in both the homeostasis and dysfunctional state of the cardiovascular system. The identification and characterization of the secretory profile of PVAT under different pathophysiological conditions will open new regulatory pathways for targeted therapeutic development. Overall, improved knowledge of various fat depots will benefit the understanding of obesity-related cardiometabolic diseases.

Declaration of Competing Interest

All authors declared no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.endmts.2020.100061.

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