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Exploring the Crosstalk between Adipose Tissue and the Cardiovascular System

Ioannis Akoumianakis, MD, Nadia Akawi, PhD, and Charalambos Antoniades, MD, PhD

Division of Cardiovascular Medicine, University of Oxford, Oxford, United Kingdom

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Correspondence to
Charalambos Antoniades, MD, PhD
Division of Cardiovascular Medicine, University of Oxford, CVM L6 West Wing, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, United Kingdom.
Tel: +44-1865-228340
Fax: +44-1865-34615
E-mail: antoniad@well.ox.ac.uk

ORCID iDs
Ioannis Akoumianakis
https://orcid.org/0000-0002-4674-0210
Nadia Akawi
https://orcid.org/0000-0001-6311-7028
Charalambos Antoniades
https://orcid.org/0000-0002-6983-5423

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ABSTRACT

Obesity is a clinical entity critically involved in the development and progression of cardiovascular disease (CVD), which is characterised by variable expansion of adipose tissue (AT) mass across the body as well as by phenotypic alterations in AT. AT is able to secrete a diverse spectrum of biologically active substances called adipocytokines, which reach the cardiovascular system via both endocrine and paracrine routes, potentially regulating a variety of physiological and pathophysiological responses in the vasculature and heart. Such responses include regulation of inflammation and oxidative stress as well as cell proliferation, migration and hypertrophy. Furthermore, clinical observations such as the "obesity paradox," namely the fact that moderately obese patients with CVD have favourable clinical outcome, strongly indicate that the biological "quality" of AT may be far more crucial than its overall mass in the regulation of CVD pathogenesis. In this work, we describe the anatomical and biological diversity of AT in health and metabolic disease; we next explore its association with CVD and, importantly, novel evidence for its dynamic crosstalk with the cardiovascular system, which could regulate CVD pathogenesis.

Keywords: Adipose tissue; Obesity; Cardiovascular disease; Oxidative stress

INTRODUCTION

Obesity, characterised by variable expansion of adipose tissue (AT) across the body and typically defined by a body mass index (BMI) >25 kg/m^2, has long been considered a decisive risk factor for the development and progression of cardiovascular disease (CVD).[1][2] Having said that, several studies have revealed that while increased visceral AT mass has been consistently and independently associated with increased CVD risk,[3][4] lower body adiposity may have protective effects against CVD.[5] These observations suggest that the anatomical distribution of AT may be of a greater clinical importance than its overall body mass. The necessity to account for this proposed effect of anatomical variability in AT mass is reflected in the recent introduction of waist and hip circumference as clinical markers of obesity.[6] Importantly, in patients with CVD and especially patients with heart failure (HF),[7] as well as in patients with other chronic diseases (e.g., chronic kidney disease),[8] moderately obese have better cardiovascular outcomes compared to lean patients, an observation that is known as the "obesity paradox."[9] The obesity paradox may indicate that the crosstalk between AT and

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the cardiovascular system is far more complex than previously thought, and suggests that overall AT mass may be less important than AT functional quality.

MORPHOLOGICAL VARIABILITY OF AT

AT is comprised of adipocytes as well as other cell types, including fibroblasts, vascular cells and immune cells, which collectively constitute AT's stromal-vascular fraction.[10] AT can broadly be classified into white AT (WAT) and brown AT (BAT).[11]

WAT

WAT, which is expanded in obesity, is characterised by relatively large adipocytes that have energy-storing and secretory properties.[12] WAT comprises the vast majority of AT in the human body,[13] and can be further divided into anatomically distinct depots that are diversely related with CVD.[14] Both subcutaneous and visceral WAT, for example, are believed to contribute to cardiometabolic risk,[15] while femoral WAT may be protective against CVD.[5] The importance of anatomical parameters in the regulation of WAT biology is highlighted by the fact that abdominal deep subcutaneous WAT (as separated by superficial subcutaneous fat with the Scarpa's fascia) is expanded in obesity much more so than superficial subcutaneous WAT, thus resembling visceral WAT characteristics.[16] Interestingly, WAT can expand in response to metabolic stimuli as a result of adipocyte hypertrophy (increase in adipocyte size) or hyperplasia (increase in adipocyte number).[17] Crucially, adipocyte hypertrophy is associated with dysfunction of WAT, and may underline the metabolic complications of obesity such as diabetes and CVD.[18] However, small adipocyte size, rather than adipocyte hypertrophy, has also been associated with insulin resistance.[19] These findings suggest that WAT expansion is indeed critical for WAT biology, and changes in adipocyte size and/or number are associated with WAT dysfunction that may be dependent upon the underlying disease status.

BAT

BAT contains small mitochondria-rich adipocytes and abundant vasculature (hence its macroscopically brown appearance).[20] BAT is mainly involved in thermogenesis, but may also regulate whole body metabolism and preserve insulin sensitivity.[21] At a molecular level, BAT is distinguished from WAT by its expression of uncoupling protein 1 (UCP1), a brown adipocyte marker that is crucial to mitochondrial heat production.[20] BAT comprises a larger fraction of total AT mass in infants, when thermogenesis may have greater significance than in adults.[22] However, BAT is also present in adult humans, mainly in the neck, supraclavicular and axillary regions as well as around major vessels such as the aorta.[22] Recently, a potential endocrine role for BAT has also been proposed,[23] but what adipocytokines may be secreted by BAT in vivo and to what extent is unknown.

Beige AT

Recently, another type of AT described as “beige” has been characterised, which refers to AT depots consisting of adipocytes with intermediate phenotypical characteristics. In particular, clusters of beige AT exist within WAT (predominantly in the supraclavicular region) and can only be revealed upon potent exposure to cold under experimental conditions.[24] On the other hand, beige adipocytes express UCP1 and have the potential ability to exert thermoregulatory properties.[21] As such, it is controversial whether beige AT reflects a truly distinct AT type, a sub-type of BAT without extensive adipocyte “browning,” or even a cluster of WAT adipocytes

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that are able to upregulate UCP1 in response to severe cold expossure.[24] It has been proposed that macrophages exist in beige AT to induce adipocyte browning.[24] However, the biological consequences of this AT type are controversial.[21]

Obesity is characterised not only by WAT expansion but also by WAT dysfunction associated with qualitative changes in its biological characteristics. Indeed, nutrient overload results in WAT remodelling that, if persistent, leads to hypoxia as a result of impaired angiogenesis and unresolved inflammation; this eventually leads to an abnormal WAT expansion as observed in central obesity.[25] A variety of studies have confirmed that WAT undergoes inflammatory changes in obesity, including macrophage infiltration and pro-inflammatory cytokine secretion.[11] Interestingly, adipocytes share many functional characteristics with a variety of immune cells such as complement activation and cytokine production,[26] suggesting that they are a dynamic component of WAT inflammation rather than the passive recipient of inflammatory signals from infiltrating macrophages and lymphocytes. Additionally, the degree of WAT dysfunction in obesity is dependent upon fat distribution, with visceral WAT exhibiting higher levels of inflammation and impaired energy capacity.[27] Furthermore, dysfunctional WAT displays an altered secretory profile which is also depot-specific.[28][29]

CROSSTALK BETWEEN WAT AND THE CARDIOVASCULAR SYSTEM

Signalling from WAT to the cardiovascular system

The introductory considerations highlight the fact that obesity is characterised by regionally variable functional changes in WAT, and this biological variability affects cardiovascular biology in complex ways. Importantly, WAT has the ability to secrete various biologically active molecules that are called adipocytokines and are produced by adipocytes or WAT's stromal-vascular fraction.[10] These adipocytokines play a role in the crosstalk between WAT and the cardiovascular system.[10] Additionally, they might be responsible for the differing relationship of distinct WAT depots (such as visceral and femoral WAT) with CVD.[29]

Systemic vs. local effects of AT

Adipocytokines secreted by WAT depots remote to the cardiovascular system (such as mediastinal WAT, subcutaneous WAT, femoral WAT) are able to enter the systemic circulation, exerting direct cardiovascular effects in an endocrine way (**Figure 1**).[28][29] In fact, WAT is the major source of a variety of adipocytokines that actually determines their circulating levels. Circulating adiponectin, for example, displays a significant positive correlation with its expression in subcutaneous and mediastinal WAT depots in humans.[30]

Certain WAT depots are able to exert direct, paracrine effects on the cardiovascular system. Perivascular AT (PVAT), namely the fat surrounding the vessels, is able to secrete adipocytokines that diffuse into the underlying vascular wall, exerting local effects (**Figure 1**). Consistently, vascular disease has been associated with increased neighbouring PVAT mass as well as increased local inflammation of PVAT.[10][31] Similarly, epicardial AT (EpAT) surrounds both the myocardium and the large coronary artery branches and as such, it can also be considered as a unique type of PVAT. Adipocytokines secreted by the EpAT are proven to influence both myocardial and coronary artery biology;[32-34] moreover, EpAT has been recognized as a source of proinflammatory adipocytokines in the context of CVD.[35][36]

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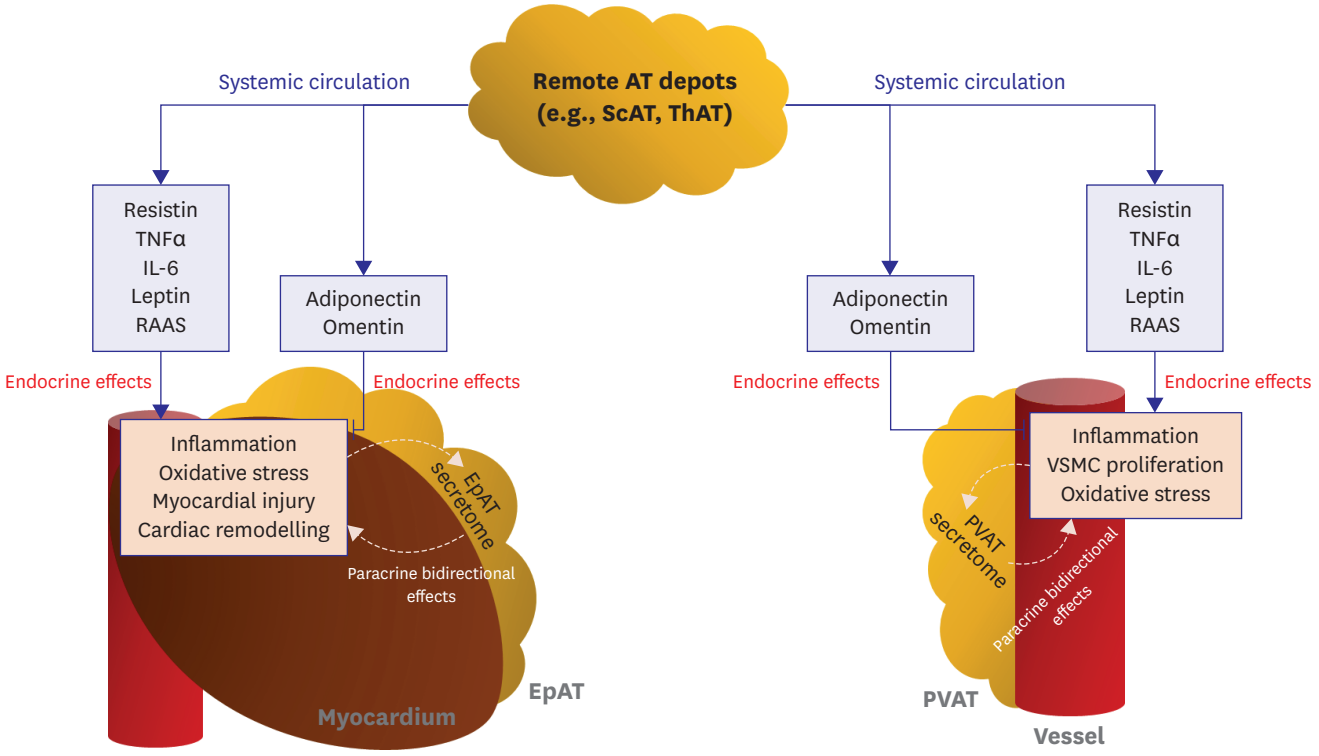

Figure 1. Overview of the interactions between AT and the cardiovascular system. AT is able to secrete a variety of biologically active molecules called adipocytokines which influence cardiovascular biology. Some of these adipocytokines (e.g., adiponectin, omentin) have overall protective effects on the heart and vasculature. In contrast, other adipocytokines (such as resistin, leptin, TNFα, and IL-6) promote inflammation and oxidative stress in the cardiovascular system, while facilitating myocardial injury and remodelling in the heart as well as endothelial dysfunction and VSMC proliferation in the vessels. The overall effect of AT on cardiovascular biology is determined by the balance between protective and detrimental adipocytokines, while anatomically different AT depots often have distinct secretomes. The cardiovascular system may be influenced by the endocrine effect of adipocytokines secreted in the systemic circulation by "remote" AT depots; in addition, the heart and vessels are in bidirectional interaction with AT depots directly surrounding them (i.e., EpAT and PVAT, respectively). This mutual paracrine crosstalk allows for EpAT and PVAT to directly influence cardiovascular biology while also acting as recipients of biological signals originating from the cardiovascular system. Further elucidation of the complex interactions between AT and the cardiovascular system may reveal new diagnostic, prognostic or therapeutic strategies against CVD. Arrows denote a positive (stimulatory) effect; lines with a straight horizontal end symbolize a negative (inhibitory) effect.
AT = adipose tissue; CVD = cardiovascular disease; EpAT = epicardial AT; IL-6 = interleukin 6; PVAT = perivascular adipose tissue; RAAS = renin-angiotensin-aldosterone system; ScAT = subcutaneous adipose tissue; ThAT = thoracic adipose tisse; TNFα = tumour necrosis factor alpha; VSMC = vascular smooth muscle cell.

Adipocytokines secreted by PVAT may diffuse through the underlying vascular wall deep enough to enter the vascular lumen, subsequently being able to propagate signals along the downstream circulation.[37)38)] This hypothetical type of signalling is different to the global effects of adipocytokines via the systemic circulation as well as to the local paracrine effects of limited range; therefore, it has distinctly called "vasocrine."[37)] The potential ability of PVAT to regulate the biology of entire vascular beds might plausibly influence the ability of organs such as skeletal muscle and the liver to handle glucose, eventually regulating systemic insulin sensitivity.[37)]

Effects of WAT's secretome on cardiovascular biology

1) Adiponectin

Adiponectin is an adipokine produced almost exclusively by the adipocytes, and it has well-established anti-inflammatory and anti-oxidant properties in both the heart and the vasculature.[39)40)] In particular, adiponectin reverses the detrimental effects of tumour necrosis factor alpha (TNFα) on endothelial cells,[41)] reduces endothelial cell adhesion molecule expression[42)] and inhibits endothelial cell apoptosis;[43)] furthermore, adiponectin increases

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vascular nitric oxide (NO) bioavailability[30] while decreasing nicotinamide adenine dinucleotide phosphate (NADPH)-oxidases activity in humans.[44] Adiponectin also has beneficial roles in the myocardium, where it inhibits NADPH-oxidases activity,[45] reduces ischaemic infarct size,[46] inhibits cardiomyocyte autophagy[47] and reverses abnormal cardiac remodelling.[48]

Despite adiponectin's beneficial cardiovascular effects as described in vitro and ex vivo, its clinical applications as a biomarker are not clear. Adiponectin release from WAT is under the combined regulation of systemic inflammatory status and brain natriuretic peptide (BNP), which is dependent upon the underlying CVD status.[49] In particular, systemic inflammation reduces adiponectin expression in WAT, hence reduced circulating adiponectin may predict early-onset CVD associated with systemic inflammation such as coronary artery disease (CAD). On the contrary, BNP is a potent stimulus for adiponectin production in WAT, and therefore severe CVD status characterised by elevated plasma BNP is also associated with elevated plasma adiponectin,[45] therefore in conditions with increased BNP levels (e.g., severe HF), plasma adiponectin is actually predictive of adverse cardiovascular outcomes. Finally, apart from the challenges associated with its use as a prognostic biomarker, adiponectin is also difficult to manipulate for therapeutic purposes due to its extremely short half-life.[40]

2) Leptin

Leptin is secreted by WAT and, via its actions in the central nervous system (CNS), it modulates appetite and consequently energy consumption and whole body metabolism.[50] Obesity is associated with hyperleptinaemia as well as leptin resistance at the cellular level.[51] Apart from its use as a marker of obesity, most clinical studies have associated increased circulating leptin levels with higher risk for atherosclerosis, myocardial infarction, and HF.[52]

Although hyperleptinaemia in most clinically relevant settings appears to be detrimental in terms of CVD risk, experimental studies have introduced controversy to the overall cardiovascular roles of leptin. Indeed, leptin induces hypertension and atherogenesis in animal models, although these effects are not widely accepted.[53] In addition, leptin may participate in cardiomyocyte apoptosis and cardiac hypertrophy,[54-56] although in some other studies it has been suggested to have cardioprotective effects.[57] The effects of leptin on endothelial function are also controversial; although leptin reportedly impairs endothelium-dependent ex vivo vasorelaxations,[51] other mouse studies suggest that leptin potentiates insulin's NO-mediated vasodilatory action.[52] These controversial results are further complicated by the difficulty to separate leptin's actions in the CNS from its direct cardiovascular actions. Furthermore, it is unclear whether leptin resistance accompanying obesity is globally observed or reserved only in the CNS. Taken all together the integrated role of leptin in CVD is unclear.

3) Resistin

Resistin is a novel adipocytokine expressed in adipocytes as well as in monocytes/macrophages who are considered its main source in humans. Therefore, the vascular-stromal fraction of WAT is likely to be a major component of resistin secretion.[58] Although resistin's detailed mechanism of action is unknown, adenylyl cyclase-associated protein 1 (CAP1) is believed to be a functional receptor for resistin, being potentially responsible for many of its biological actions.[58]

Resistin is believed to have pro-inflammatory, pro-oxidant and pro-atherogenic roles in the vasculature. Indeed, resistin acting via CAP1 has been found to induce a chronic, low-grade

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inflammatory response in macrophages and has been adversely associated with a variety of inflammatory diseases.[58] Resistin has been found to be abundantly secreted in EpAT of patients with acute coronary syndromes in the context of CAD.[59] Furthermore, resistin is secreted by macrophages of atheromatous plaques in humans, implying that it may directly promote atherogenesis.[60] In addition, elevated plasma resistin levels have been revealed as a marker of subclinical atherosclerosis as well as a predictor of worsened cardiovascular outcomes in a variety of observational studies.[61-63] Collectively, these findings further support the clinically relevant association of resistin with vascular disease progression.

Resistin has also been reported to negatively influence cardiac biology. In particular, resistin was observed to promote cardiac hypertrophy[64] and potentiate ischaemia-reperfusion injury.[65] Long-term overexpression of resistin in rats results in impaired myocardial function and abnormal cardiac remodelling.[66] Studies in humans have revealed that increased circulating resistin correlates with myocardial oxidative stress in patients undergoing cardiac surgery,[67] while also conveying high risk for clinical outcome in patients with HF.[68] This highlights resistin as a promising therapeutic target in cardiac disease.

4) Omentin

Omentin is expressed in a variety of tissues in humans, including WAT. The stromal-vascular fraction of visceral WAT, in particular, is a major source of omentin.[69] Although studies have linked omentin with cardiovascular biology, its clinical significance and interpretation as a biomarker are not well understood.

Omentin has displayed a variety of potentially protective cardiovascular effects in experimental studies. Indeed, omentin has presented revealed antioxidant,[70] anti-inflammatory[71][72] and anti-atherogenic properties[69][73] in cell culture and animal models. Omentin decreases vascular smooth muscle cell (VSMC) migration[70] and also has cardioprotective effects via reduction of myocardial oxidative stress, ischaemic injury and apoptosis.[74][75] Therefore, it can be presumed that the direct effects of omentin on the cardiovascular system may result in improved CVD status.

Conversely, human observational studies have linked elevated omentin expression and circulating levels with a variety of clinical endpoints associated with poor CVD prognosis. Omentin expression in EpAT was noticed to be increased in CAD,[76] while elevated serum omentin independently predicts cardiovascular outcomes in patients with atherosclerosis and HF.[77][78] Obviously, such associations do not imply causality. On the contrary, the systemic upregulation of omentin may reflect a potential endogenous defence mechanism against CVD, as discussed in the subsequent sections, which warrants further investigation.

5) Visfatin

Visfatin is an adipocytokine expressed in adipocytes and immune cells of various WAT depots.[79] Visfatin has intrinsic nicotinamide phosphoribosyltransferase (Nampt) activity and participates to the biosynthesis of nicotinamide adenine dinucleotide (NAD^+), a substance involved in a number of biological redox reactions.[80] Several studies have explored visfatin's effects on cardiovascular biology, but its role in CVD progression is not fully understood.

In vitro and ex vivo studies indicate that visfatin may have detrimental effects on cardiovascular biology, although other evidence suggests otherwise. For instance, visfatin was proposed to induce oxidative stress via stimulation of NADPH-oxidases activity,[81] while also promoting

inflammation in the vasculature and myocardium.[79] These pro-inflammatory effects include adhesion molecule expression, monocyte infiltration and local pro-inflammatory cytokine secretion.[79] Importantly, visfatin has been associated with atherosclerotic plaque destabilisation in mice.[82] In contrast, on the other hand, visfatin may also upregulate endothelial nitric oxide synthase (eNOS) expression, potentially increasing NO synthesis,[83] while certain studies suggest that visfatin may induce endothelium-dependent vasorelaxation, albeit at supra-physiological concentrations.[84] Visfatin has also been proposed as being cardioprotective, inhibiting myocardial apoptosis.[85][86] To conclude, although the majority of experimental studies point towards a detrimental role for visfatin, this needs to be further addressed.

Clinical studies have associated circulating visfatin levels with major clinical outcomes. For instance, circulating visfatin is elevated in obesity and type 2 diabetes mellitus (T2DM),[87] and may be a marker of atherosclerosis.[88] Other studies demonstrated that visfatin expression is upregulated in monocytes of atherosclerotic plaques in humans,[89] while plasma visfatin is able to predict cardiovascular outcome following ST-segment elevating myocardial infarction.[90] In essence, although such associations may not be causal, they suggest a clinically relevant role for visfatin in CVD progression.

6) TNFα and interleukin 6 (IL-6)

TNFα and IL-6 are established enhancers of inflammation and, as such, important regulators of CVD.[91] These cytokines are secreted by the infiltrating immune cells but also by the adipocytes of WAT, especially in the context of pathological WAT expansion and obesity.[26] Interestingly, monoclonal antibody-based biological treatments targeting TNFα and IL-6 have been developed. Conversely, the global involvement of these adipocytokines in most inflammatory diseases and the lack of specificity of the respective treatments challenge the targeted diagnostic, prognostic and therapeutic manipulation of TNFα and IL-6 in CVD.

TNFα and IL-6 have established pre-atherogenic roles, ranging from local monocyte recruitment, NADPH-oxidases activation, VSMC proliferation and migration, low-density lipoprotein (LDL) oxidation and uptake by macrophages and increased coagulation of platelets.[91][92] Furthermore, both adipocytokines reportedly impair endothelial dysfunction.[93] Furthermore, they have been implicated in the induction of cardiomyocyte apoptosis and adverse cardiac remodelling following myocardial infarction as well as chronic pressure overload, via the activation of multiple cell death pathways and nuclear factor kappa B (NF-κB) signalling respectively.[94-96]

As mentioned previously, TNFα and IL-6 are involved in a multitude of inflammatory diseases, and consequently the use of their circulating levels as specific biomarkers of CVD is limited. On the contrary, therapeutic targeting of these adipocytokines would be exceptionally reasonable compared to other adipocytokines with less clear roles. In fact, administration of anti-TNFα and anti-interleukin 6 receptor (IL-6R) monoclonal antibodies (e.g., infliximab, tocilizumab, respectively) has been associated with improved endothelial function[97] and vascular stiffness.[98][99] The high cost and the non-specific side-effects of such therapies, however, compromise their potential implications, considering that their long-term effect on CVD risk is controversial.[100]

7) Renin-angiotensin-aldosterone system (RAAS)

RAAS is responsible for the regulation of fluid and sodium balance in the human body, and contributes to the pathogenesis of CVD. Notably, all components of RAAS are expressed in

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various levels in WAT.[101] This suggests that WAT may play a part in the systemic actions of RAAS and perhaps propagate local, RAAS-mediated effects via paracrine interactions with the cardiovascular system.

RAAS may be involved in a variety of pathogenic processes including induction of inflammation and adverse vascular remodelling,[102] stimulation of vascular oxidative stress,[103] establishment of peripheral insulin resistance[101][103] and involvement in cardiac remodelling.[104] Recent evidence suggests that WAT-specific mineralocorticoid receptor (MR) activation is associated with direct detrimental effects on WAT in terms of insulin sensitivity and expansion, and it impairs endothelial function via a presumed paracrine effect of PVAT on the vascular wall.[105] Interestingly, MR inhibition reversed these effects.[105] This work suggests that RAAS and aldosterone in particular are at the crossroads between obesity and CVD. Consistently, a variety of clinical studies have documented the benefit of RAAS blockade on cardiovascular outcomes.[106]

8) Adipo-fibrokines

Recently, it has been discovered that EpAT is able to secrete certain adipocytokines such as activin A and metalloproteinases, including MMP8, which are able to induce marked fibrosis in the human myocardium.[107][108] Activin A belongs to the transforming growth factor beta (TGF-β) superfamily, and is secreted by pre-adipocytes, fibroblasts and macrophages of EpAT, especially in the presence of an inflammatory micro-environment.[107] The marked fibrotic effect of activin A on the myocardium might facilitate an anatomical re-entry substrate for the establishment of atrial fibrillation (AF).[108] AF risk has been associated with EpAT expansion and inflammation in the past,[35][109] thus adipo-fibrokines may provide a novel mechanistic explanation for the association between the two. This implies that fibrokines such as activin A may prove to be promising therapeutic targets against AF.

Signalling from the cardiovascular system to WAT

As explained previously, WAT can propagate signals to the cardiovascular system, thus influencing cardiovascular biology. Novel evidence suggests that WAT can additionally act as a recipient of biological signals originating from the cardiovascular system, consequently modifying its biology (**Figure 1**).[10][40] Further elucidation of WAT's ability to dynamically sense cardiovascular biology may prove to be extremely useful as a diagnostic, risk stratification or even therapeutic tool in CVD.

Crosstalk between PVAT and the vascular wall

Signalling from the vascular wall to PVAT has been proposed as a critical regulator of local adiponectin expression in humans.[30] Indeed, in a cohort of patients undergoing coronary artery bypass graft surgery (CABG), elevated circulating adiponectin was found to correlate with reduced oxidative stress in internal mammary artery (IMA) segments and with increased adiponectin expression in WAT depots distal to the vascular wall, suggesting that these WAT depots contribute to the circulating pool of adiponectin.[30] In contrast, adiponectin expression in peri-IMA AT was positively correlated with increased oxidative stress in the neighbouring vessel,[30] suggesting that local, potentially redox-sensitive, parameters influence the expression of adiponectin in PVAT rather than systemic factors. In the same work, it was shown that vascular oxidative stress can increase the production and diffusion of lipid peroxidation products such as 4-hydroxynonenal (4-HNE) to PVAT, where they were able to upregulate adiponectin expression via a peroxisome proliferator-activated receptor gamma (PPAR-γ)-mediated mechanism.[30] This may comprise a local bidirectional defence

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loop against vascular oxidative stress, allowing for adiponectin exert its anti-oxidant effects in a paracrine way.

It is likely that similar crosstalk is involved in the local regulation of the expression of other adipocytokines in PVAT, although this possibility has not been explored so far. The notion that the phenotype of PVAT can dynamically change in response to alterations in vascular biology may prove to be an exciting diagnostic, prognostic or even therapeutic tool against CVD.

Crosstalk between EpAT and the myocardium

By being attached on to the myocardium, EpAT can not only regulate myocardial biology in paracrine ways but it also receives signals from the myocardium. Consistently, we have recently shown that the expression of adiponectin in EpAT is independent of systemic factors and mainly regulated by myocardial oxidative stress in humans undergoing cardiac surgery.[45] In fact, increased myocardial oxidative stress results in the formation of stable lipid peroxidation products such as 4-HNE, which are able to reach the EpAT and trigger the PPAR-γ-mediated upregulation of adiponectin, which has direct anti-oxidant effects on the myocardium.[45] This bidirectional crosstalk may, constitute a local defence mechanism that, similarly to the vascular wall-PVAT crosstalk, attempts to counterbalance excessive local oxidative stress.

Considering that myocardial oxidative stress is a critical regulator of cardiac disease that correlates with clinically relevant endpoints such as post-operative AF,[110] the ability of EpAT to track changes in myocardial redox state and modify its secretome accordingly could in theory comprise a novel target for therapeutic or diagnostic applications in cardiac disease. It also highlights the importance of endogenous mechanisms in the dynamic regulation of WAT secretome and its clinical implications. Conversely, it is not yet known to what extent similar bidirectional crosstalk loops between the EpAT and the myocardium contribute to the regulation of adipocytokines other than adiponectin.

Systemic crosstalk between WAT and the cardiovascular system

WAT is apparently influenced by signals originating from the cardiovascular system at a systemic level, thus influencing the circulating levels of various adipocytokines.[30][45] This concept has not been addressed adequately, but it may be extremely helpful in the clinical interpretation of biomarkers that are secreted (exclusively or partially) by WAT.

The aforementioned crosstalk has been shown as clinically relevant in the case of adiponectin. In particular, it has already been mentioned that adiponectin expression in the various WAT depots of the body is inversely influenced by systemic stimuli, namely downregulated by systemic inflammation and upregulated by circulating BNP.[49] Therefore, the clinical association of circulating adiponectin is biphasic; low adiponectin predicts CAD onset, while high adiponectin predicts poor prognosis in advanced CVD.[49] The global upregulation of adiponectin in the context of severe CVD, which is triggered by increased BNP resulting from cardiac dysfunction, may reflect a systemic defence mechanism attempting to potentiate adiponectin's beneficial effects against advanced cardiovascular dysfunction. Although elucidation of such systemic interactions between WAT and the cardiovascular system is challenging, these findings reveal a new level of WAT-cardiovascular system crosstalk that may help explain paradoxical associations between various adipocytokines and clinical outcome.

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CONCLUSION

AT is a dynamic organ with the ability to secrete a wide range of hormones and cytokines collectively described as adipocytokines. Obesity is associated with a number of phenotypic changes in AT, including inflammatory cell recruitment and dysregulation of AT's secretome; abnormal AT expansion associated with inflammation predisposes, in turn, to CVD. Interestingly, the secretome of AT involves adipocytokines with both beneficial (e.g., adiponectin) and detrimental (e.g., resistin) effects on the cardiovascular system. Consequently, it is the dynamic balance between the protective and the detrimental adipocytokines that determines AT's net role in CVD. Importantly, little is known about the regulation of this balance in the context of CVD, while elucidation of the relevant mechanisms may reveal novel diagnostic and therapeutic targets.

Although the majority of AT in adults in regarded as WAT, certain anatomical regions also contain BAT as well as what is described by many as beige AT, thus potentially displaying thermoregulatory properties. Adipocyte browning is a largely unexplored biological process that is now increasingly postulated to be a promising, biologically important player in the regulation of whole body metabolism and maintenance of insulin sensitivity.

Adipocytokines secreted by WAT may reach the cardiovascular system via the systemic circulation, thus acting in endocrine ways; certain depots such as PVAT and EpAT, in particular, may also interact with the cardiovascular system in paracrine ways due to their anatomical proximity. Recently, it has been revealed that WAT may also receive a variety of biological signals originating from the (healthy or diseased) cardiovascular system, modifying its secretome appropriately. The ability of AT to track cardiovascular biology may change the way in which we view AT biology in the context of CVD, and could provide promising diagnostic or therapeutic options for better management of CVD.

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