Published in final edited form as:

J Mol Cell Cardiol. 2013 June ; 59: 176–178. doi:10.1016/j.yjmcc.2013.03.009.

Vascular remodeling mediated by Angptl2 produced from perivascular adipose tissue

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Levels of obesity have dramatically increased in the modern world, and this has created a major health care concern for societies to overcome [1–4]. Obesity contributes to the development of diabetes and promotes the risk of death from cardiovascular diseases [1,3,5]. It is well documented that excess adiposity will promote a state of low-grade, chronic inflammation that accelerates disease processes [6]. Adipose tissue was once thought to be purely involved in the storage of excess energy, but it is now appreciated to have endocrine functions through its ability to secrete protein factors that are referred as adipokines [6–10]. Many of these adipokines have pro-inflammatory actions. Examples include tumor necrosis factor (TNF)- α and monocyte chemoattractant protein-1 (MCP-1) [11]. In addition, adipose tissues secrete anti-inflammatory adipokines. Adiponectin is a widely studied, anti-inflammatory adipokine that has insulin-sensitizing and cardiovascular-protective properties [7,12,13]. In a lean, healthy organism, metabolic homeostasis is maintained via a balance in the expression of pro- and anti-inflammatory adipokines. However, under conditions of obesity, adipose tissue dysfunction leads to the downregulation of anti-inflammatory adipokines and the upregulation of pro-inflammatory adipokines, contributing to a chronic and systemic inflammatory state in adipose tissue and throughout the organism.

Adipokine production is influenced by the anatomical source of the adipose tissue. With regard to white adipose tissue (WAT), visceral adipose depots tend to exhibit greater dysfunction and secrete higher levels of pro-inflammatory adipokines than subcutaneous adipose tissue depots. In contrast to the WAT depots, that predominantly have a lipid storage function, brown adipose tissue (BAT) has a catabolic function that is involved in thermal regulation [14,15]. BAT is brown in appearance due to its high content of mitochondria and it expresses high levels of the uncoupling protein UCP1 to generate heat. To support this unique function, BAT is highly vascularized relative to WAT, allowing it ample access to fuel and oxygen and facilitating the dissipation of the produced heat. BAT has received much recent attention because it has been detected in human adults, where it may have a role in contributing to metabolic normalization [16,17].

Visceral fat has long been thought to be the key player in provoking detrimental vascular remodeling via the endocrine effects of inflammatory adipokines. However, recent studies have shown that perivascular adipose tissue (PVAT) depots can also have a role in inducing vessel wall remodeling in obese models [18–21]. PVAT comprises the outer layer of arteries, and has direct contact with adventitia. Besides contributing to the mechanical structure of vessels, recent findings have shown that PVAT secretes adipokines that are

involved in maintaining vessel wall homeostasis via a paracrine mechanism [22,23]. In lean organisms, PVAT is generally thought to have beneficial actions, contributing to vessel wall maintenance and the control of vascular tone [22]. Under these conditions, PVAT is reported to suppress excessive neointima formation in response to injury. Recent evidence suggests that the neointima-suppressive action of PVAT is mediated by its ability to secrete adiponectin [24,25], a factor with widely recognized vascular protective actions [26–30]. Of interest, it has recently been shown that, in some anatomical locations, PVAT is abundant in mitochondria and has many features in common with BAT [31]. Similar to BAT, the brown depots of PVAT are relatively resistant to diet-induced inflammation. While PVAT may exhibit BAT-like characteristics and protect the vascular bed from inflammatory insults in lean organisms, PVAT can also undergo qualitative changes in response to obesity leading to increased production of pro-inflammatory cytokines, including TNF- α , MCP-1 and IL6, and reduced expression of adiponectin [18,32]. Thus, PVAT may promote vascular inflammation and contribute to a hyper-proliferative responses in the major vessels.

In this issue of JMCC, Tian et al. [33] examine the role of PVAT-derived angiopoietin-like protein 2 (Angptl2) in the control of neointimal hyperplasia following endovascular injury of mouse femoral arteries. Angiopoietin-like proteins represent a multi-functional family of secreted factors with structural similarity to angiopoietin, a molecule with pro-angiogenic function. This family is characterized by a coiled-coil domain in the N-terminus and fibrinogen-like domain in the C-terminus. These factors probably do not signal through the Tie2 receptor, but it has recently been reported that the immune-inhibitory receptor human leukocyte immunoglobulin-like receptor B2 (LILRB2) and its mouse orthologue paired immunoglobulin-like receptor (PIRB) are receptors for several Angptl family members [34,35]. Angptl2 has been reported to have a myriad of functions that are involved in inflammation, metabolism, angiogenesis and cancer. Similar to Angptl1, Angptl2 is reported to promote endothelial cell sprouting in vitro and is essential for the formation of a mature vasculature [36,37]. Accordingly, Angptls are also involved in the biological processes of cancer. For example, Angptl2 expression in skin squamous cell carcinoma (SCC) correlates with cancer metastasis to lymph nodes and distant organs [38]. In a murine model of SCC, Angptl2 can induce an epithelial to mesenchymal transition and increase tumor angiogenesis and lymphangiogenesis, leading to an increase in metastatic events in mice.

Recent findings have shown that Angptl2 has a role as an adipokine in inducing adipose inflammation and systemic insulin resistance in obesity [39]. Angptl2 is abundantly expressed in visceral fat, and this expression increases with obesity. Mechanistically, Angptl2 induces adipose tissue inflammation by promoting contact between endothelial cells and monocytes/macrophages via an upregulation of integrin signaling [39]. It is reported that hypoxia and endoplasmic reticulum stress, features of dysfunctional adipose tissue, promote the expression of Angptl2 via an HIF1- α -independent pathway [40]. Other reports are also consistent with the notion that Angptl2 has a pro-inflammatory function. For example, Tazume et al. have reported that Angptl2 is secreted from macrophages in the blood vessel wall, leading to inflammation and degradation of extracellular matrix that contributes to abdominal aortic aneurysm formation [41]. Other reports have shown that Angptl2 has a role in regulating inflammatory responses in rheumatoid arthritis [42] and endotoxin-induced acute inflammation in the eye [43].

In the accompanying manuscript [33], Tian et al. demonstrate that Angptl2 is secreted by PVAT and that it contributes to pathological vascular remodeling. They showed that Angptl2 protein levels were very similar between visceral WAT and PVAT, and that Angptl1 expression by PVAT is upregulated upon aging, hypercholesterolemia and endovascular injury of the femoral artery. To test the hypothesis that Angptl2 secreted from PVAT has a role for vessel remodeling, they performed an endovascular wire injury model

in mice lacking Angptl2 (Angptl2^{-/-}). This procedure was also performed in wild-type mice with visceral fat extracted from Angptl2^{-/-} mice and transplanted around the site of femoral artery injury (after endogenous perivascular fat removal). In both of these experimental conditions, the periadventitial fat pad displayed diminished inflammatory markers, including decreases in TNF- α , MCP1, F4/80 and CD68 expressions. Furthermore, injury-induced neointimal lesion formation was ameliorated in both models. Conversely, vessel injury in mice overexpressing Angptl2 in fat (ap2-Angptl2 mice) and wild-type mice transplanted with the visceral fat of ap2-Angptl2 mice showed significantly aggravated vascular inflammation and remodeling. Collectively, these data suggest that Angptl2 secreted from perivascular fat has a pathological role in vascular remodeling. This work extends the observations of Takaoka et al. who provided evidence that PVAT plays a critical role in injury-induced vascular remodeling showing that adiponectin protects whereas TNF α promotes lesion formation in these types of murine models of endovascular injury [44,45].

Finally, in a small subset of patients, Tian et al. report that levels of Angptl2 in epicardial adipose tissue did not differ between individuals with or without coronary heart disease (CHD) [33]. However, they found the positive correlation of Angptl2 and adiponectin in non-CHD patients, and a positive correlation between Angptl2 and TNF α in CHD patients. Thus, they speculate that Angptl2 may have a clinical role in contributing to the balance between pro- and anti-inflammatory responses in cardiovascular tissues.

Further studies are required to clarify the molecular mechanisms by which Angptls act on target cells. In this regard, there is a growing awareness that cardiovascular pathology is influenced by the status of the organism's adipose tissue. Studies by Tian et al. [33] and others [18,22,24,25,44,45] provide initial evidence that PVAT can influence neointimal lesion formation in response to acute injury. However, one must acknowledge the limitations of these studies because they rely on evidence derived from the transplantation of visceral or subcutaneous adipose tissue to macrovessels that are denuded of PVAT. Far more definitive studies could be performed by development of molecular tools that allow the genetic ablation or overexpression of genes within specific adipose tissue depots. In this regard, it would be ideal to identify PVAT-specific promoters to allow the targeting of genes within this tissue. If developed, such reagents would also allow one to more rigorously dissect the roles of PVAT-encoded genes on chronic vascular lesions, such as atherosclerosis. Currently, the tools allowing depot-specific adipose tissue specific gene expression are lacking, impeding progress in our understanding of adipose tissue biology. However, a glimmer of hope that such reagents can be developed for PVAT comes from the realization that PVAT exhibits phenotypic characteristics that distinguish it from visceral and subcutaneous adipose tissues [31]. In-depth studies of PVAT biology, possibly enabled by the development of new molecular tools, could lead to a better understanding of how vascular diseases are influenced by obesity and metabolic dysfunction.

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