REVIEW

Adipokines and adipose tissue angiogenesis in obesity

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Initially described as an inert fat store, adipose tissue (AT) has been extensively studied in recent years and shown to have multifaceted roles in appetite regulation, vascular homeostasis, energy balance and systemic inflammation in chronic diseases. Composed mainly of adipocytes and stromal vascular fraction (SVCs), comprising preadipocytes, macrophages, mesenchymal stem cells (MSCs), T cells, B cells, mast cells and endothelial progenitor cells (EPCs), AT performs an endocrine role in secretion of growth factors and cytokines (termed adipocytokines). AT is extensively vascularized and, as in other tissues and organs, the growth and maintenance of AT is critically dependent on angiogenic processes. The microvasculature network surrounding the adipocytes provides efficient pathways for crosstalk with the surrounding environment. AT undergoes constant expansion and shrinkage during its entire life span. To cope with this increased metabolic demand during expansion, AT vasculature undergoes extensive remodelling, and changes to vessel density are observed. To facilitate these processes, AT secretes angiogenic/growth factors. Dysregulation in the secretion of these factors is known to play an important role in obesity and insulin-resistant states. In this article we will discuss novel therapeutic strategies to combat obesity and inflammation by inducing changes to the AT vascular network.

Keywords: Adipokines; angiogenesis; adipose tissue; obesity

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Introduction

Adipose tissue (AT) functions as an endocrine organ, and is comprised of several cell types including adipocytes, stromal cells, resident and infiltrating immune cells, and an extensive endothelial network of the vascular tree [1, 2]. The latter performs diverse roles ranging from the delivery of nutrients to the tissue and the circulation of metabolites, growth factors and adipokines from the tissue to the rest of the body. Thus the vascular tree enables interactions between different cell types facilitating autocrine/paracrine signalling.

This in turn influences AT metabolic environment [3]. The existing vascular density and function eventually fail to meet the increasing demand of the expanding AT leading to chronic inflammation [4, 5]. This state is characterized by development of local pockets of hypoxic environment leading to increased endoplasmic reticulum (ER) stress, fibrosis and inflammation accompanied by immune cell infiltration [5, 6, 7]. These processes, however, seem to be absent in 'metabolically healthy obese', since AT expansion in these cases is accompanied by adequate vascular supply [8].

Table 1. Adipocytokines and obesity-induced changes

Adipokines	Circulating levels in obesity	References
Adiponectin	↓	Asayama *et al*, 2003[14]; Hoffstedt *et al*, 2004[15]
Apelin	↑	Boucher *et al*, 2005[16]
Adipsin	↑	Napolitano *et al*, 1994 [17](human study)
Chemerin	↑	Sell *et al*, 2009[18]
FABP-4	↑	Queipo-Ortuño *et al*, 2012[19]
Leptin	↑	Harmelen *et al*, 1998[20]
Lipocalin 2	↑	Catalan *et al*, 2009[21]
Omentin	↓	De Souza Batista *et al*, 2007[22]
Perilipin	↑	Wang *et al*, 2003[23]
RBP-4	↑	Janke *et al*, 2006[24]
Resistin	↑	Way *et al*, 2001[25]
Visfatin	↑	Berndt *et al*, 2005[26]

Table 2. Effect of adipokines on endothelial angiogenesis and inflammation

Adipocykines	Effects on Angiogenesis
Adiponectin	EC proliferation, migration and angiogenesis and anti-inflammatory[29,30]
Apelin	Pro-angiogenic and anti-inflammatory[31]
Adipsin	Unknown?
Chemerin	Pro-angiogenic and pro-inflammatory[32]
IL-6	Pro-angiogenic and pro-inflammatory[33]
Leptin	Pro-angiogenic and pro-inflammatory[34]
Lipocalin 2	Pro-angiogenic and pro-inflammatory[35]
Omentin	Anti-inflammatory and anti-angiogenic[36,37]
Perilipin	Unknown?
RBP-4	Pro-angiogenic? and pro-inflammatory[38]
Resistin	Pro-angiogenic and pro-inflammatory[39]
Visfatin	Pro-angiogenic and pro-inflammatory[40, 41]

Table 3. Studies relating to adipose tissue angiogenesis in obesity

Pro-angiogenesis	Anti-angiogenesis
Sung *et al*, 2013-VEGF↑ in VEGF^AdΔ mice[44]	Rupnick *et al*, 2002-downregulating AT angiogenesis in genetically obese mice by TNP-470[27]
Sun *et al*, AT specific VEGF-A ↑, -Early stimulation of WAT angiogenesis in obese mice[12]	Brakenhielm *et al*, 2004, down regulating AT angiogenesis in DIO mice by TNP-470[46]
Elias *et al*, 2012, VEGF-A overexpression in diet-induced obese (DIO) model[47]	Kolonin *et al*, 2004, Targeted induction of apoptosis in AT vasculature by prohibitin[48]
Aprahamian *et al*, 2014, Stimulation of angiogenesis by inducing adiponectin expression in Adipo-/- mice[49]	Lu *et al*, 2012, ↓VEGF-A leads to VEGF-B↑ in HFD genetically modified mice – not linked to vascularization[50]

Adipose tissue expansion is characterized by substantial structural remodelling involving adipocyte hyperplasia and/or hypertrophy, recruitment of inflammatory cells achieved primarily through vascular remodelling and neovascularization, thus making angiogenesis a pivotal process in influencing the rate of AT expansion [2, 9].

AT angiogenesis is dependent on both locally secreted and perfused angiogenic factors. The differential regulation of these angiogenic adipokines in obesity could contribute to changes in AT angiogenic profiles [10]. These factors are further regulated by the presence of tissue hypoxia, vascular perfusion and local inflammatory cells, suggesting the involvement of autocrine-paracrine related events.

Recent advances in AT angiogenesis have established that in advanced stages of metabolically challenged AT, disruption of AT vascularity results in substantial decreases in AT size and body weight [11]. However, other reports have demonstrated a contrasting evidence of beneficial effects of improving AT angiogenesis in reducing AT inflammation and decreasing body weight; albeit in different phases of AT expansion. In this context, a doxycycline (Dox)-inducible adipocyte-specific VEGF-A overexpression mice model exhibited enhanced AT angiogenesis and improved insulin sensitivity and weight loss [12]. Similar results were found in metabolic disease-resistant 11β-hydroxysteroid dehydrogenase Type 1 (HSD1)-deficient mice, which have an increased AT angiogenesis compared to their wild types. This increased induction of AT angiogenesis was accounted for by an HIF-1α independent up regulation of VEGF-A and angiopoeitin-4 [13].

Adipokines and angiogenic mediators

As noted, AT produces and secretes several hormones and

cytokines (adipokines/adipocytokines) which have multiple functions in inflammation, vascular homeostasis, carbohydrate-lipid metabolism and, more specifically for this review, in angiogenesis. As summarized in **Table 1**, the secretion levels of these adipokines vary with changes in AT mass (i.e. lean and obese states). It is interesting to note that adipokines with anti-inflammatory properties are decreased in obesity despite increased adipocyte/AT mass, thus demonstrating changes to the secretory profile of adipocytes/stromal-vascular fraction following hypertrophic/hyperplastic changes.

Adipokines and angiogenesis

As mentioned earlier, AT expansion is critically dependent on angiogenesis, and both locally secreted and circulating growth factors have been implicated in the dysregulation of AT angiogenesis in obesity [27,28]. In addition to well-known angiogenic/growth factors such as VEGF, FGF and HGF produced both locally (AT-derived) and systemically; some of the adipokines (leptin, visfatin, adiponectin, TNF-α, chemerin, vaspin, IL-6, angiogenesin, omentin and PAI-1) have recently been shown to exert their influence in AT angiogenesis. As shown in **Table 2,** pro- and anti-angiogenic adipokines may perhaps play an important role in maintaining AT vascular homeostasis.

Changes to regional AT concentrations of adipokines in obesity

Clinical studies measuring circulating adipokine levels and their AT concentrations have found significant changes in lean and obese human subjects.

Studies by You *et al* have demonstrated significant differences in regional AT concentrations of adipokines (adiponectin and leptin) before and after weight loss. Following a 20-week weight loss programme there was significant decrease in leptin production in gluteal and abdominal AT and increased expression and secretion of adiponectin from abdominal AT. Also, the changes to circulating levels of adipokines in pre- and post-intervention seemed to follow tissue expression patterns [42].

Adipose tissue angiogenesis in early and late stages of obesity

With the progression of obesity, adipocytes undergo either hypertrophic or hyperplastic changes, resulting in local tissue hypoxia and inflammation [43]. Studies have shown that anti-angiogenic interventions in stages of early obesity result in increased AT hypoxia, inflammation and apoptosis [12, 44]. By contrast, reduced adiposity and improved glucose

tolerance are observed in late-stage suppression of AT angiogenesis, plausibly through increased clearance of apoptotic adipocytes, reduced inflammation and hypoxia leading to regression of AT [44].

Therapeutic pro-/anti-angiogenic approaches to combat obesity

Studies have shown that by limiting the vascular supply, growth of AT can be controlled [27, 45]. This suggests the 'hypoxic' hypothesis, where the rapidly expanding AT in HFD mice models, not accompanied by an adequately parallel growth of capillary network, results in tissue hypoxia, inflammation and insulin resistance. In this context AT-VEGF-ablated animals display a net decrease in depot size, accompanied by increased inflammation and marked deterioration of glucose tolerance and insulin sensitivity, most evident in response to HFD [27]. Conversely, overexpression of VEGF in AT results in increased vascularization, decreased inflammation, and amelioration of HFD-induced insulin resistance [44]. Other studies have shown that overexpression of ANGPTL4 (thus inducing AT angiogenesis) in obese mice ameliorates insulin resistance and glucose intolerance [46]. In accordance with this, 11β-hydroxysteroid dehydrogenase type 1 KO mice with high fat feeding show AT expansion accompanied by increased AT vascularity and expression of pro-angiogenic factors [13].

As listed in **Table 3**, numerous studies have shown both pro- and anti-angiogenic approaches have resulted in weight loss, albeit in varied rodent models and at differing stages of obesity.

To add to the complexity of these approaches in treating obesity, studies have shown diametrically opposing actions of two splice variants of a well-known angiogenic factor, VEGF-A (VEGF$_{165}$ and VEGF$_{165}$b). In a report by Ngo *et al* 2014, the anti-angiogenic effect of VEGF$_{165}$b (in AT) is demonstrated in human obesity [51].

Differential role of VEGF$_{165A}$ and VEGF$_{165B}$ in AT angiogenesis

A well-studied angiogenic growth factor VEGF (vascular endothelial growth factor) exists as 5 distinct ligands (VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor). Furthermore, there are two splice variants of VEGF-A; VEGF-A$_{165}$ (pro-angiogenic) and VEGF-A$_{165}$b (anti-angiogenic) [52]. The differential regulations of these splice variants resulting in either pro- or anti-angiogenic processes have been studied in cancers [53, 54]. This process has been recently reported in visceral AT where it is
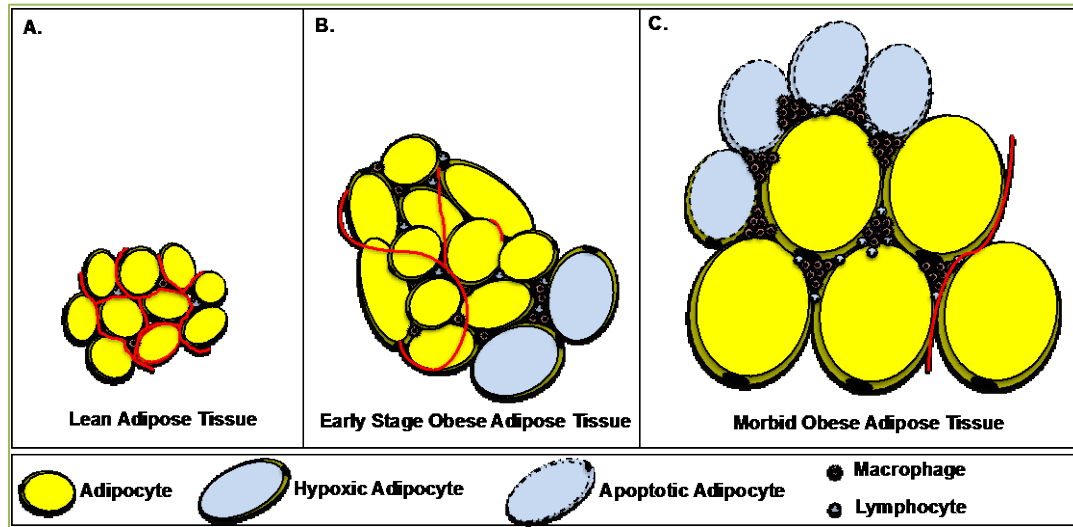
Figure 1. Changes in vascularity and resident inflammatory cell population in AT through stages of obesity. A. Lean AT is highly vascularized with smaller adipocytes and sparse inflammatory cells (macrophages and lymphocytes). B. With the onset of obesity, rapidly expanding adipocytes (hypertrophic) with a lag in vascular density leads to local hypoxia and increase in populations of inflammatory cells. C. In morbid obesity, there is decreased vascularity, evident tissue hypoxia with apoptotic adipocytes and increased influx of inflammatory cells.

responsible for regulating AT angiogenesis in obesity (Ngo *et al*) [51]. More importantly, in obesity a 'VEGF paradox' occurs, resulting in decreased AT angiogenesis in spite of increased circulating levels of VEGF. This can be explained by apparent overexpression of anti-angiogenic VEGF$_{165b}$ in obese visceral AT and subsequently decreased angiogenesis [55]. Thus a detailed understanding of angiogenic modulators in AT is vital in developing therapeutic strategies in combating obesity.

This may also be true for other adipokines which are secreted from AT to have a differential effect on AT angiogenesis. We have previously reported the differential angiogenic effects of two forms of adiponectin (globular and full length), which may play a role in AT angiogenesis in states of obesity [30].

Obesity, adiponectin and adipose tissue angiogenesis

Circulating adiponectin levels have been shown to be decreased in states of obesity and insulin resistance [14, 15]. In post-bariatric surgical and exercise-induced weight-loss subjects, circulating adiponectin levels have been demonstrated to increase significantly [56]. Research by Kern *et al*, 2003 has demonstrated that AT expression levels of adiponectin are decreased in obese AT and this correlated with circulating levels as well [57].

Adiponectin has been shown by various groups to have contrasting effects in promoting endothelial angiogenesis.

Studies by Ouchi *et al* reported adiponectin (full length fraction of adiponectin-fAd) induced angiogenesis [28]. However, other groups have demonstrated potent anti-angiogenic effects of adiponectin [58]. We have previously performed experiments with both fractions of adiponectin [full length (fAd) and globular (gAd) adiponectin] on human endothelial cells. We found that fAd was pro-proliferative with no effects on migration and capillary tube formation. The gAd fraction showed proliferative, migratory and angiogenic effects in HMECs (human microvascular endothelial cells) [30]. Our findings are different from those described above, possibly because of differences in experimental material and methods.

However, there is very limited understanding regarding the ular aspects of adiponectin and AT angiogenesis. Studies manipulating AT adiponectin levels in DIO (diet-induced obesity) models have demonstrated the role of adipokine-mediated AT angiogenesis in obesity. As demonstrated by studies of Aprahamian *et al*, AT levels of adiponectin were critical in the maintenance of adequate vascularity and tissue perfusion in AT [49]. Overexpression of AT adiponectin levels in DIO mice led to increased vascularity, decreased tissue hypoxia, increased VEGF-A expression levels and decreased AT infiltration of macrophages. Similarly the expressions of AT angiogenic factors (VEGF, Arnt2, erythropoietin, and notch1) were consistently upregulated in apn-TG mice in comparison with wild type and apn-KO mice [49].

The dual pro/anti-angiogenic profiles demonstrated by

VEGF and adiponectin could be true for other adipokines and growth factors. Thus detailed *in vivo* analyses of angiogenic profiles of growth factors in various stages of obesity are required to understand the mechanisms in obesity.

Changes to adipokine expression profile in obesity

As shown in **Table 1**, pathological AT expansion in obesity leads to increased production of AT-derived adipokines including VEGF-A, leptin, resistin, IL-6, TNF-α, MCP-1, PAI-1, chemerin, visfatin and vaspin in contrast to reduction in secretory levels of adiponectin, omentin, and angiopoietin-4 [14, 18, 20, 22, 25, 26, 60]. More importantly, the physiological depot-specific differences in adipokine expression profiles are altered in obesity. There is a marked increase in both AT and circulating levels of pro-inflammatory adipokines *vs* anti-inflammatory ones. These changes could be attributed to hypertrophic/hyperplastic adipocytes and increased macrophage content of obese AT [60, 61].

Angiogenic responses in stages of obesity

In the initial phases of AT expansion, due to increased production of local angiogenic factors, there is a switch to pro-angiogenic phenotype, thus facilitating further AT expansion. Obese AT, in addition to angiogenic factors, produces more pro-inflammatory molecules, eventually causing endothelial dysfunction of the AT vascular tree. This results in 'angiogenic refractoriness' of AT despite increased production of pro-angiogenic growth factors. In accordance with this theory, studies have described reduced capillary density and angiogenic ability of AT in morbid obesity [5,63]. Decreased vascularity (relative) in obese AT and accompanying inflammation further promotes local tissue hypoxia and leads to dysregulation of AT secretory factors [13,64]. This further affects the systemic circulatory levels leading to pathologies in distant organs. This phenomenon forms the foundation hypotheses for suggesting therapeutic induction of angiogenesis in obesity, increasing vascularity and decreasing local inflammation [47]. The AT microenvironment has been shown to be dynamically altered through stages of obesity, finally reaching a hypoxic, proinflammatory stage.

Conclusion

The loss of the delicate balance of angiogenic and inflammatory factors responsible for maintaining AT homeostasis is implicated as the main causative factor for inflammation in obesity. Very similar to tumour angiogenesis, AT angiogenesis is controlled by multiple pathways and constantly varies with AT expansion. Furthermore the concept of enhancing AT angiogenesis by targeted (site-specific) manipulation of adipokines/angiogenic factors provides a therapeutic target to counter obesity.

Insufficient angiogenic tissue responses seem to be at the heart of the pathological phenotype of the adipose tissues observed in obesity and may constitute the link between excessive adipose tissue growth and adipokine dysregulation.

A detailed understanding of AT microenvironment through the stages of obesity is vital in developing novel strategies to control obesity. This will also include the introduction of therapeutic drugs to revert the deranged adipokine/growth factor expression profiles in obese AT, restoring sufficient AT vascularisation.

It is also important that we accept the limitations and drawbacks of obtaining conclusions from *in vitro* and animal models of obesity if we are to better understand the pathophysiological events in human obesity.

Acknowledgements

Conflict of interest

There are no conflicts of interest

Abbreviations

AT: Adipose tissue; SVC: stromal vascular fraction; MSCs: mesenchymal stem cells; EPCs: endothelial progenitor cells; VEGF: vascular endothelial growth factor.

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