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Mechanisms of Obesity and Related Pathologies: The Macro- and Microcirculation of Adipose Tissue

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SUMMARY

Adipose tissue is an endocrine organ made up of adipocytes, various stromal cells including many immune cells, and an endothelial network. Adipose secretory products, collectively referred to as adipokines, have been identified as contributors to the negative consequences of adipose tissue expansion including cardiovascular disease, diabetes, and cancer. Systemic circulation provides transport capabilities for adipokines and fuels for proper adipose tissue function. The adipose tissue microcirculation is heavily impacted by adipose tissue expansion. A subset of adipokines can induce endothelial dysfunction. Furthermore, angiogenesis is necessary to counter hypoxia arising as a result of tissue expansion. Tumors, such as invasive lesions in the mammary gland, co-opt the adipose tissue microvasculature for local growth and metastatic growth and lymphatic circulation provides an important route for lipid transport. Here, we review this area that has not received a lot of attention and focus on the established and potential interplay between adipose tissue and the microvascular endothelium.

Keywords

angiogenesis; hypoxia; adiponectin; endothelial cell; lymphatic

INTRODUCTION

With overconsumption and decreased physical activity combining to propagate an epidemic of obesity in Western cultures, the pathophysiological aspects of adipose tissue expansion are becoming increasingly appreciated. There has been a steady increase in research focusing on adipose tissue contributions towards diabetes, cardiovascular disease, and cancer. Several years ago, we outlined some of the key areas that we proposed would be essential in elucidating key systemic and local effects of adipose tissue [1]. Many of these topics are now areas of intense research and have further supported the concept of adipose tissue as an endocrine organ. In this review, we will focus on the importance of the vasculature in adipose tissue function and related pathologies. Rather than discussing the relationship between cardiovascular diseases and obesity – an area of significant importance in its own right – we will focus on the microcirculation of adipose tissue itself and the relevance of this circulatory microenvironment to pathologies and changes associated with adipose tissue including adipocyte differentiation and adipose tissue expansion, hypoxia-

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induced neovascularization, and the relationship of adipose tissue with lymphatic circulation.

ADIPOSE TISSUE

Adipose Tissue Depots and Obesity

Obesity is a potent risk factor for metabolic and cardiovascular disease at the population level. At the individual patient level, however, correlations between body mass index and cardiovascular disease are not always straightforward due, in part, to differences among adipose tissue depots with respect to the overall rate of adipocyte dysfunction, local degree of inflammation, and tissue vascularization [2]. Adipose tissue is a heterogeneous mix of adipocytes, stromal preadipocytes, immune cells, and endothelium [3]. Combined, adipose tissue functions as a complex endocrine organ, secreting a host of factors collectively referred to as adipokines [3]. The adipocyte “secretome” ranges from molecules of direct metabolic relevance to those with effects unrelated to metabolism. These include the highly adipocyte-specific proteins adiponectin and leptin, the inflammatory chemokines TNF-alpha and an array of interleukins, angiogenic and vascoactive molecules such as VEGF and angiotensin II [4]. The relative abundance of each adipokine potentially dictates the effects of adipose tissue as a whole.

Adipose tissue develops in several distinct anatomical depots within the body, and the differential expansion of these depots is of great importance. Expansion of visceral or abdominal white adipose tissue (WAT) has been most strongly correlated to insulin resistance and cardiovascular disease in humans and animals [5]. Conversely, expansion of subcutaneous WAT does not appear to have the same negative systemic consequences on metabolism [6]. At the other end of the spectrum is the condition of lipodystrophy wherein the dramatic loss of adipose tissue triggers a high degree of insulin resistance and signs of other metabolic dysregulation similar to visceral WAT expansion. The importance of maintaining at least remnants of WAT was demonstrated by injecting adipocyte progenitors into the residual adipose depots lipodystrophic mice: the depots expanded and the systemic metabolic profile was properly restored [7]. Brown adipose tissue (BAT) is in an entirely different metabolic category due to its primary function in generating body heat in infants and rodents [8]. BAT is rich in mitochondria, highly vascularized, and because it affords none of the ill effects of visceral WAT, serves as an ideal paradigm for “good” adipose, despite its limited presence in adult humans [8,9]. Combined, these disparities in the metabolic effects of distinct fat deposits not only dispel the generalized notion that adipose tissue exerts negative metabolic consequences under all conditions, but begs the question as to what distinguishes these individual depots with respect to their ability to expand. Recent results suggest that the balance between angiogenesis and hypoxia has a significant impact on the modulation of “good” versus “bad” tissue expansion, thereby implicating the local microvasculature as a key modulator of the systemic impact adipose depots [6,10,11].

Adipose Tissue Vasculature

Adipose tissue possesses a relatively dense network of blood capillaries, ensuring adequate exposure to nutrients and oxygen. WAT varies in its vascularity both between depots and within the tissue itself. For example, the expanding tip of the epididymal WAT fat pad contains a high vessel density compared to the rest of the depot [12]. This vessel network must be considered in the diverse roles that adipose tissue performs. Metabolically, the adipose vasculature serves to transport systemic lipids to their storage depot in the adipocytes. On the other side, the vasculature also transports factors (adipokines) and nutrients (such as FFAs) from these cells in time of metabolic need. Expansion and contraction of fat mass thus relies on the adipose tissue circulation. Insufficient circulation

results in local hypoxia (whose effects will be discussed below). The microvasculature of adipose tissue is necessary for expansion of adipose mass, not only due to its ability to prevent hypoxia, but also as a potential source of the adipocyte progenitors in WAT, since these progenitor cells can derive from the microvasculature of the tissue [13]. In addition to its necessity in metabolite transport, the blood capillary network also contributes to immunity and inflammation. Adipose tissue macrophages serve multiple functions including removal of necrotic adipocytes leading to lipid-engulfed foam cells, acting as proinflammatory mediators, and serving as angiogenic precursors [14]. Often implicated in the adverse effects of adipose tissues due to their inflammatory impact, adipose-associated macrophages utilize the microcirculation to rapidly reach their targets [14]. The microcirculation is itself modulated by locally produced chemokines from macrophages, stromal cells, and adipocytes that encompass the tissue [4]. Changes in endothelial permeability or endothelial dysfunction induced by adipokines alter transendothelial transport and exclusion, and also control immune cell migration (Fig. 1). Leptin may impair nitric oxide production and sensitivity and induce angiogenesis [15]; TNF-alpha increases endothelial-immune cell adhesion molecules and immune trafficking; Adiponectin in turn downregulates each of these responses [4]. High concentrations of FFA may directly impair endothelial function, leading to further local metabolic instability [4]. HIF1-alpha induces fibrosis in response to hypoxia [10]. Overall, tissue function and homeostasis is therefore intimately tied to a properly functioning microcirculation.

Lymphatic circulation also likely contributes to adipose tissue maintenance. Despite their anatomical proximity and noted roles in lipid metabolism, storage and transport, lymphatics and adipose tissue are rarely discussed in the same context. We would like to propose that the lymphatic vasculature should be considered as an important player in adipose tissue circulation and discuss interactions between the lymphatic circulation and adipose tissue later.

ADIPOSE TISSUE ANGIOGENESIS

Studies that describe the quality of adipose tissue consistently point to the microvasculature and angiogenesis within adipose tissue as critical role players in adipose tissue health and expansion [3]. Expansion of adult adipose tissue is not unlike tumor propagation: rapid growth induces hypoxia that induces angiogenesis, which in turn fuels more growth, etc. [3]. In what has become increasingly indicative of the metabolic disease potential, the expansion of WAT results in hypoxia and increased levels of HIF1-alpha that, in turn, lead to an upregulation of the inflammatory adipokines IL–6, TNF-alpha, and MCP-1, among others [10] (Fig. 2). These pro-inflammatory secretory products have been implicated in many aspects of insulin resistance [16]. Hypoxia also induces adipose tissue fibrosis that leads to further adipose dysfunction [10,17]. Hypoxia may also block the differentiation of preadipocytes and stimulate glucose transport by adipocytes [16], though additional *in vivo* studies must validate this concept. Angiogenesis within adipose tissues is necessary to counteract hypoxia and WAT is rich in angiogenic factors as well as endothelial cells, macrophages, and circulating progenitors that contribute to this process [3]. The propensity for angiogenesis in the various adipose depots is likely reflected in their expansion potential [6]. BAT, as a model adipose depot, exhibits increased expression of VEGF, angiogenesis, and vascular density expansion in response to measured hypoxia during exposure to cold [18]. The angiogenic potential of adipose tissue may also vary from individual to individual. For example, it was recently demonstrated that with increasing age and the progression of insulin resistance in obese *db/db* mice, the tissue stroma of WAT has a decreased capacity to induce the necessary pro-angiogenic effectors for healthy adipose tissue expansion [19]; the implication for human disease are that individuals in the diabetic state are even further at risk.

Increasing angiogenesis in normally hypoxic adipose tissue may improve some of the negative systemic effects associate with dysfunctional WAT. Overexpression of adiponectin, which is normally reduced in expanding WAT, may potently mediate angiogenesis within hypoxic adipose tissues [6,11]. Overexpression of adiponectin in wildtype mice results in highly vascularized subcutaneous adipose tissue. More importantly, in the morbidly obese *ob/ob* mouse line, overexpression of adiponectin resulted in better overall health, despite an even further expansion of the subcutaneous WAT. The increased subcutaneous WAT in this mouse is highly vascularized [6]. VEGF secreted in both subcutaneous and visceral adipose tissues is potently angiogenic [20]. Blocking angiogenesis via the VEGF pathway in young *ob/ob* mice prevented expansion of adipose tissue, resulting in mice with normal phenotypes and a return to normal metabolic function in adulthood [21,22]. Currently prescribed anti-diabetic drug therapies also present differential effects on adipose angiogenesis despite the mutually positive effects on insulin sensitivity. The drug metformin, for example, reduces adipose tissue angiogenesis [23] while the thiazolidinedione class of drugs result in more vascularized adipose with increased adiponectin secretion [24]. The concept of healthy adipose expansion is a seeming contradiction in the context of excess caloric intake and a potential increase in other detrimental health effects arising from overnutrition. This effect can only be rationalized if either food intake is repressed and/or energy expenditure increased and has yet to be extensively studied in these circumstances. This also complicates potential anti-obesity therapies targeted at angiogenic processes as blocking vascularization of existing adipose tissue may result in increased levels of inflammation.

ADIPOSE TISSUE & TUMOR GROWTH

While adipose tissue vascularization functions in a delicate balance in tissue homeostasis, the perturbations initiated by tumor growth dysregulate all involved cell types. The most extreme example of tumor infiltration into an area rich in adipose tissue can be observed in the context of breast cancer. After filling the lumen of mammary ducts, transformed ductal epithelial cells break through the basal lamina and invade the mammary stromal compartment which is highly enriched in adipose tissue. Here, the local pro-angiogenic machinery, such as VEGF and the adipose-specific leptin and monobutyrin [25] are co-opted to function in conjunction with autonomous tumor-derived factors to meet the circulatory demands of the invading lesion. The adipokine leptin is strongly angiogenic [26] and may increase tumor angiogenesis either by directly acting on the endothelium or by increasing local VEGF secretion [27,28]. We recently reported our findings on the relative contributions adipocyte-derived adiponectin on tumor growth in the murine mammary gland [29]. Mice lacking adiponectin crossed into the MMTV-PyMT mammary tumor model initially exhibited smaller lesion size compared to tumor growth in MMTV-PyMT adiponectin-normal mice. Lesions in the adiponectin null mice had impaired vascularization and displayed increased intratumoral necrosis. However, similar to tumors grown in the presence of pharmacological angiogenesis inhibitors, these tumors adapted to the chronic hypoxic conditions and eventually assumed a much more aggressive growth phenotype [29]. Whether or not adiponectin serves as a direct angiogenic factor or tumor promoter remains to be clarified. Tumor cell entry into lymphatic capillaries en route to lymph node metastases may also be adipokine mediated. Adipose tissue expresses a milieu of lymphangiogenic growth factors [30] that, in combination with tumor, stromal, and vascular derived factors, present an environment that seemingly all but ensures metastasis [31]. There are unquestionably consequences for the local paracrine crosstalk between the tumor cells, adipocytes, and the adipose microvascualture and the marked similarities in tumor growth and hypoxia to those of adipose tissue expansion remain of great interest.

ADIPOSE TISSUE AND LYMPHATIC CIRCULATION

There has been a rapidly increasing interest in lymphatic circulation, particularly with respect to tumor progression and immunologic responses, in the past several years. As an important part of the circulatory system with roles in lipid absorption and transport, and as an emerging interest area, it is therefore necessary to examine what is known to date regarding the lymphatic vasculature and its potential interplay with adipose tissue.

The Lymphatic System

Fluid transport through the lymphatic vasculature forms an integral part of the body's circulation. Throughout nearly all tissues of the body, lymphatic capillaries drain interstitial fluid, macromolecules, and cells and transport them, through larger conducting lymphatic vessels and the lymph nodes, back to systemic blood circulation (Fig. 3A) [32]. In doing so, the lymphatic vasculature serves three critical roles. Firstly, as interstitial fluid is sourced from fluid extravasated from the blood vasculature, the lymphatics maintain tissue homeostasis and complete the body's circulatory loop [33]. Secondly, lymphatic collection of interstitial fluid permits downstream immune scavenging by sentinel lymph nodes, as well as providing the initial entry point for antigen presenting cells en route to propagating required immune responses [34]. And lastly, lymphatic capillaries serve as the entry point of all dietary lipids into circulation [35]. While all of these roles are certainly interconnected, here we focus on the role of lymphatics in lipid absorption, the consequences of lymphatic dysfunction, and the potential symbiotic relationship between the lymphatic system and adipose tissue.

Lymphatic capillaries differ from blood capillaries not only in their gene and molecular expression, but also in their strikingly different morphology [36]. Lymphatic vessels exist in the tissue as a collapsed network of overlapping lymphatic endothelial cells, are not surrounded by pericytes, possess minimal interrupted basement membrane, and are directly anchored to the extracellular matrix (ECM) by anchoring filaments where basement membrane is lacking [32]. These properties permit open fluid flow from the interstitial space through the overlapping lymphatic endothelial cells through unique cell-cell junctions [37]. These primary valves permit macromolecules and particles of up to a micron in size to freely enter lymphatic circulation [38]. It is this transport potential that allows the lymphatics to star in the role of lipid transporter.

Lymphatic function and lipid absorption

In the jejunum, dietary lipids are absorbed by enterocytes lining the luminal wall which then "package" the lipids into large lipoprotein particles called chylomicrons. These particles are exocytosed and taken up by intestinal lacteals (specialized lymphatic capillaries found within each intestinal villus) (Fig. 3B) [35]. Chylomicrons are then transported through the lymphatic network and enter venous circulation at the thoracic duct. Proper lymphatic function is clearly necessary for this process as changes in intestinal hydration, and thus lymphatic clearance rate, modulate the rate of chylomicron transport [39]. High concentrations of chylomicrons give lymph a milky white appearance and the mixture is referred to as chyle. The presence of free chyle in the peritoneum or thoracic cavity, chylous ascites and chylothorax, respectively, may indicate dysfunctional lymphatic transport. In fact, mice lacking or possessing mutations in important lymphatic genes Ang-2, Efnb2, Prox1, Sox18, VEGF-C, VEGFR-3 (among others), possess poorly developed lymphatic networks and exhibit high infant or embryonic mortality and/or notable chylous accumulation as pups [36]. Improper intestinal lymphatic function may also be present and be propagated by intestinal inflammation such as in inflammatory bowel disease and Crohn's Disease [40]. In these instances, flux of dietary lipids into lymphatics, downstream

lymphatic vessel drainage and contractility, and mesenteric lymph node immune surveillance are all significantly reduced [41]. Failures in intestinal lymphatic transport likely result in cyclic worsening of these inflammatory conditions: lymphatic immune function is compromised, leading to increased inflammation and increased inflammatory mediators which further impede the ability of lymphatics to function, and so on [41].

Lymphatic dysfunction and adipose tissue

Failures in lymphatic transport can result in marked lipid accumulation throughout the body. Lymphedema is a pathology of deficient lymphatic transport, either inherited or acquired through some inflammatory or surgical intervention, that results in significant accumulation of fluid, matrix remodeling, and adipose expansion in the affected limb [42]. Adipose expansion is also present in mouse models of secondary (induced) lymphedema [43]. VEGFR-3 heterozygote mice are used as a model for inherited lymphedema due to their lack of dermal lymphatics. These adult mice exhibit substantial thickening of the subcutaneous adipose tissue [44,45]. Most notable of the lymphatic deficient mouse models are the Prox1 heterozygous mice. Few pups of this model survive to adulthood, but those that do demonstrate adult-onset obesity with significant expansion of all fat pads [46]. When Prox1 was specifically deleted in the lymphatic vasculature and adult adipose expansion still occurred, lymphatic dysfunction was directly implicated in obesity (Fig. 3C) [46]. Collected lymph has also been demonstrated to induce adipocyte differentiation, further supporting this hypothesis [46,47]. While no treatment has been successful in providing for or restoring lymphatic function in these tissues (compression and massage can manage, but not cure the disease), liposuction has been prescribed as a potential therapeutic intervention to diminish limb volume with varying success [42]. Lymphatic dysfunction has also been noted in lipidema, a pathology of regionalized excessive lipid accumulation and adipose expansion. In these patients, malformed lymphatic vessels and improper lymphatic drainage function have been observed [48,49]. Classification of this pathology is thus difficult, as which occurs first, adipose expansion or lymphatic dysfunction is yet unknown. Adipose tissue, itself a secretory organ, can provide a source of molecules that directly affect the lymphatic endothelium by changing capillary permeability and collecting vessel tone as well as effect similar to blood endothelium as described above. Increased production of VEGF-C, for example, with adipose expansion [30] may further reduce lymphatic function by inducing hyperplasia [50]. A reduction in lymphatic drainage and degeneration of collecting lymphatic vessel smooth muscle was recently reported in a hypercholesterolemic mouse model [51]. Lymphatic dysfunction would lead to further adiposity, and so the condition worsens. Peripheral lymphatic management, uptake, and transport of adipocyte secretions and reverse transport of lipids and lipophyllic molecules from the interstitium is therefore of great importance not only to interstitial homeostasis, but potentially systemic metabolism as well.

Perivascular and perinodal adipose tissue

While lymphatic capillaries have not been identified within the bulk of adipose tissues, adipose tissue does surround all collecting lymphatic vessels and lymph nodes. These larger lymphoid vessels and structures are morphologically different than the lymphatic capillaries discussed thus far, but their anatomical proximity demands attention and suggests synergistic potential. Indeed, the work of the Pond laboratory has defined this perilymphatic adipose tissue as metabolically essential for proper immune responses and as a source of energy for immune activation and proliferation [52]. Expansion of these adipose deposits appears to occur with localized chronic inflammation [52], supporting the energy source hypothesis. Additionally, antigen presenting cells may migrate between the contiguous tissues. Appreciation for the relevance of perinodal adipose tissue is increasing within the immunology community. It should be noted that it is the intimacy of the lymphatic and

perinodal adipose that provides these benefits, and that dyslipidemia and obesity as a whole result in decreased immune trafficking [53]. A hypothesis has also been put forward in which the immune system and leukocytes may directly buffer the increase in circulating glucose following a meal [54]. By adding this additional metabolic function, this interesting concept would further strengthen the importance of the lymphatic network. Combined, these observations highlight the important roles of the lymphatic system: fluid and macromolecular transport, immune modulation, and lipid uptake. All of these processes are tightly interconnected. As adipose tissue is an organ that requires macromolecular transport, impacts inflammation and immunity, and provides a metabolic depot, the symbiosis of the lymphatic circulation with adipose tissue is certainly worthy of further study.

CONCLUSIONS

The role of adipose tissue as an endocrine organ critically depends on its microcirculation for metabolic function and transport. Variations in the vascularization of different types of adipose tissue and between WAT depots likely contribute to the metabolic dysfunction, or lack thereof, associated with adipose expansion and obesity. Rich in vasculogenic and proinflammatory adipokines, adipose tissue serves as an intriguing model system in understanding contributory molecules in angiogenesis and tumor progression. Increased study in modulating adipose tissue expansion and in the emerging interplay between adipose tissue pathophysiology and lymphatic microcirculation provides a strong basis for future research into this complex tissue.

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Abreviations used

TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
VEGF-C	vascular endothelial growth factor-C
WAT	white adipose tissue
BAT	brown adipose tissue
FFA	free fatty acid
HIF1alpha	hypoxia inducible factor 1 alpha
MCP-1	monocyte chemotactic protein-1

References

1. Rajala MW, Scherer PE. Minireview: The adipocyte--at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology. 2003; 144:3765–3773. [PubMed: 12933646]
2. Despres JP, Arsenault BJ, Cote M, Cartier A, Lemieux I. Abdominal obesity: the cholesterol of the 21st century? Can J Cardiol. 2008; 24(Suppl D):7D–12D.
3. Halberg N, Wernstedt-Asterholm I, Scherer PE. The adipocyte as an endocrine cell. Endocrinol Metab Clin North Am. 2008; 37:753–768. x–xi. [PubMed: 18775362]
4. Chudek J, Wiecek A. Adipose tissue, inflammation and endothelial dysfunction. Pharmacol Rep. 2006; 58(Suppl):81–88. [PubMed: 17332676]

5. Haffner SM. Abdominal adiposity and cardiometabolic risk: do we have all the answers? Am J Med. 2007; 120:S10–16. discussion S16–17. [PubMed: 17720354]
6. Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, et al. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest. 2007; 117:2621–2637. [PubMed: 17717599]
7. Rodeheffer MS, Birsoy K, Friedman JM. Identification of white adipocyte progenitor cells in vivo. Cell. 2008; 135:240–249. [PubMed: 18835024]
8. Seale P, Kajimura S, Spiegelman BM. Transcriptional control of brown adipocyte development and physiological function--of mice and men. Genes Dev. 2009; 23:788–797. [PubMed: 19339685]
9. Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. Am J Physiol Endocrinol Metab. 2007; 293:E444–452. [PubMed: 17473055]
10. Halberg N, Khan T, Trujillo ME, Wernstedt-Asterholm I, Attie AD, Sherwani S, Wang ZV, Landskroner-Eiger S, Dineen S, Magalang UJ, et al. HIF 1 alpha Induces Fibrosis and Insulin Resistance in White Adipose Tissue. Mol Cell Biol. 2009
11. Landskroner-Eiger S, Qian B, Muise ES, Nawrocki AR, Berger JP, Fine EJ, Koba W, Deng Y, Pollard JW, Scherer PE. Proangiogenic contribution of adiponectin toward mammary tumor growth in vivo. Clin Cancer Res. 2009; 15:3265–3276. [PubMed: 19447867]
12. Cho CH, Koh YJ, Han J, Sung HK, Jong Lee H, Morisada T, Schwendener RA, Brekken RA, Kang G, Oike Y, et al. Angiogenic role of LYVE-1-positive macrophages in adipose tissue. Circ Res. 2007; 100:e47–57. [PubMed: 17272806]
13. Tang W, Zeve D, Suh JM, Bosnakovski D, Kyba M, Hammer RE, Tallquist MD, Graff JM. White fat progenitor cells reside in the adipose vasculature. Science. 2008; 322:583–586. [PubMed: 18801968]
14. Heilbronn LK, Campbell LV. Adipose tissue macrophages, low grade inflammation and insulin resistance in human obesity. Curr Pharm Des. 2008; 14:1225–1230. [PubMed: 18473870]
15. Talavera-Adame D, Xiong Y, Zhao T, Arias AE, Sierra-Honigmann MR, Farkas DL. Quantitative and morphometric evaluation of the angiogenic effects of leptin. J Biomed Opt. 2008; 13:064017. [PubMed: 19123663]
16. Trayhurn P, Wang B, Wood IS. Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? Br J Nutr. 2008; 100:227–235. [PubMed: 18397542]
17. Khan T, Muise ES, Iyengar P, Wang ZV, Chandalia M, Abate N, Zhang BB, Bonaldo P, Chua S, Scherer PE. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI. Mol Cell Biol. 2009; 29:1575–1591. [PubMed: 19114551]
18. Xue Y, Petrovic N, Cao R, Larsson O, Lim S, Chen S, Feldmann HM, Liang Z, Zhu Z, Nedergaard J, et al. Hypoxia-independent angiogenesis in adipose tissues during cold acclimation. Cell Metab. 2009; 9:99–109. [PubMed: 19117550]
19. El-Ftesi S, Chang EI, Longaker MT, Gurtner GC. Aging and diabetes impair the neovascular potential of adipose-derived stromal cells. Plast Reconstr Surg. 2009; 123:475–485. [PubMed: 19182604]
20. Ledoux S, Queguiner I, Msika S, Calderari S, Rufat P, Gasc JM, Corvol P, Larger E. Angiogenesis associated with visceral and subcutaneous adipose tissue in severe human obesity. Diabetes. 2008; 57:3247–3257. [PubMed: 18835936]
21. Brakenhielm E, Cao R, Gao B, Angelin B, Cannon B, Parini P, Cao Y. Angiogenesis inhibitor, TNP-470, prevents diet-induced and genetic obesity in mice. Circ Res. 2004; 94:1579–1588. [PubMed: 15155527]
22. Rupnick MA, Panigrahy D, Zhang CY, Dallabrida SM, Lowell BB, Langer R, Folkman MJ. Adipose tissue mass can be regulated through the vasculature. Proc Natl Acad Sci U S A. 2002; 99:10730–10735. [PubMed: 12149466]
23. Tan BK, Adya R, Chen J, Farhatullah S, Heutling D, Mitchell D, Lehnert H, Randeva HS. Metformin decreases angiogenesis via NF-{kappa}B and Erk1/2/Erk5 pathways by increasing the antiangiogenic thrombospondin-1. Cardiovasc Res. 2009
24. Gealekman O, Burkart A, Chouinard M, Nicoloro SM, Straubhaar J, Corvera S. Enhanced angiogenesis in obesity and in response to PPARgamma activators through adipocyte VEGF and

ANGPTL4 production. Am J Physiol Endocrinol Metab. 2008; 295:E1056–1064. [PubMed: 18728224]

25. Halvorsen YD, Bursell SE, Wilkison WO, Clermont AC, Brittis M, McGovern TJ, Spiegelman BM. Vasodilation of rat retinal microvessels induced by monobutyrin. Dysregulation in diabetes. J Clin Invest. 1993; 92:2872–2876. [PubMed: 8254042]
26. Cao Y. Angiogenesis modulates adipogenesis and obesity. J Clin Invest. 2007; 117:2362–2368. [PubMed: 17786229]
27. Birmingham JM, Busik JV, Hansen-Smith FM, Fenton JI. Novel mechanism for obesity-induced colon cancer progression. Carcinogenesis. 2009; 30:690–697. [PubMed: 19221001]
28. Cirillo D, Rachiglio AM, la Montagna R, Giordano A, Normanno N. Leptin signaling in breast cancer: an overview. J Cell Biochem. 2008; 105:956–964. [PubMed: 18821585]
29. Landskroner-Eiger S, Qian B, Muise E, Nawrocki AR, Berger JP, Fine EJ, Koba W, Deng Y, Pollard JW, Scherer PE. Proangiogenic Contribution of Adiponectin Towards Mammary Tumor Growth in vivo. Clinical Cancer Research. 2009 in press.
30. Silha JV, Krsek M, Sucharda P, Murphy LJ. Angiogenic factors are elevated in overweight and obese individuals. Int J Obes (Lond). 2005; 29:1308–1314. [PubMed: 15953938]
31. Issa A, Le TX, Shoushtari AN, Shields JD, Swartz MA. Vascular endothelial growth factor-C and C-C chemokine receptor 7 in tumor cell-lymphatic cross-talk promote invasive phenotype. Cancer Res. 2009; 69:349–357. [PubMed: 19118020]
32. Swartz MA. The physiology of the lymphatic system. Adv Drug Deliv Rev. 2001; 50:3–20. [PubMed: 11489331]
33. Rutkowski JM, Swartz MA. A driving force for change: interstitial flow as a morphoregulator. Trends Cell Biol. 2007; 17:44–50. [PubMed: 17141502]
34. Randolph GJ, Angeli V, Swartz MA. Dendritic-cell trafficking to lymph nodes through lymphatic vessels. Nat Rev Immunol. 2005; 5:617–628. [PubMed: 16056255]
35. Phan CT, Tso P. Intestinal lipid absorption and transport. Front Biosci. 2001; 6:D299–319. [PubMed: 11229876]
36. Tammela T, Petrova TV, Alitalo K. Molecular lymphangiogenesis: new players. Trends Cell Biol. 2005; 15:434–441. [PubMed: 16005628]
37. Baluk P, Fuxe J, Hashizume H, Romano T, Lashnits E, Butz S, Vestweber D, Corada M, Molendini C, Dejana E, et al. Functionally specialized junctions between endothelial cells of lymphatic vessels. J Exp Med. 2007; 204:2349–2362. [PubMed: 17846148]
38. Lynch PM, Delano FA, Schmid-Schonbein GW. The primary valves in the initial lymphatics during inflammation. Lymphat Res Biol. 2007; 5:3–10. [PubMed: 17508898]
39. Tso P, Pitts V, Granger DN. Role of lymph flow in intestinal chylomicron transport. Am J Physiol. 1985; 249:G21–28. [PubMed: 4014464]
40. Van Kruiningen HJ, Colombel JF. The forgotten role of lymphangitis in Crohn's disease. Gut. 2008; 57:1–4. [PubMed: 18094195]
41. Wu TF, MacNaughton WK, von der Weid PY. Lymphatic vessel contractile activity and intestinal inflammation. Mem Inst Oswaldo Cruz. 2005; 100(Suppl 1):107–110. [PubMed: 15962107]
42. Warren AG, Brorson H, Borud LJ, Slavin SA. Lymphedema: a comprehensive review. Ann Plast Surg. 2007; 59:464–472. [PubMed: 17901744]
43. Rutkowski JM, Moya M, Johannes J, Goldman J, Swartz MA. Secondary lymphedema in the mouse tail: Lymphatic hyperplasia, VEGF-C upregulation, and the protective role of MMP-9. Microvasc Res. 2006; 72:161–171. [PubMed: 16876204]
44. Karkkainen MJ, Saaristo A, Jussila L, Karila KA, Lawrence EC, Pajusola K, Bueler H, Eichmann A, Kauppinen R, Kettunen MI, et al. A model for gene therapy of human hereditary lymphedema. Proc Natl Acad Sci U S A. 2001; 98:12677–12682. [PubMed: 11592985]
45. Makinen T, Jussila L, Veikkola T, Karpanen T, Kettunen MI, Pulkkanen KJ, Kauppinen R, Jackson DG, Kubo H, Nishikawa S, et al. Inhibition of lymphangiogenesis with resulting lymphedema in transgenic mice expressing soluble VEGF receptor-3. Nat Med. 2001; 7:199–205. [PubMed: 11175851]

46. Harvey NL. The link between lymphatic function and adipose biology. Ann N Y Acad Sci. 2008; 1131:82–88. [PubMed: 18519961]

47. Nougues J, Reyne Y, Dulor JP. Differentiation of rabbit adipocyte precursors in primary culture. Int J Obes. 1988; 12:321–333. [PubMed: 3198310]

48. Amann-Vesti BR, Franzeck UK, Bollinger A. Microlymphatic aneurysms in patients with lipedema. Lymphology. 2001; 34:170–175. [PubMed: 11783595]

49. Bilancini S, Lucchi M, Tucci S, Eleuteri P. Functional lymphatic alterations in patients suffering from lipedema. Angiology. 1995; 46:333–339. [PubMed: 7726454]

50. Jeltsch M, Kaipainen A, Joukov V, Meng X, Lakso M, Rauvala H, Swartz M, Fukumura D, Jain RK, Alitalo K. Hyperplasia of lymphatic vessels in VEGF-C transgenic mice. Science. 1997; 276:1423–1425. [PubMed: 9162011]

51. Lim HY, Rutkowski JM, Helft J, Reddy ST, Swartz MA, Randolph GJ, Angeli V. Hypercholesterolemic mice exhibit lymphatic vessel dysfunction and degeneration. Am J Physiol Heart Circ Physiol. 2009 in press.

52. Pond CM. Adipose tissue and the immune system. Prostaglandins Leukot Essent Fatty Acids. 2005; 73:17–30. [PubMed: 15946832]

53. Angeli V, Llodra J, Rong JX, Satoh K, Ishii S, Shimizu T, Fisher EA, Randolph GJ. Dyslipidemia associated with atherosclerotic disease systemically alters dendritic cell mobilization. Immunity. 2004; 21:561–574. [PubMed: 15485633]

54. Newsholme EA, Dimitriadis G. The role of the lymphoid system in the regulation of the blood glucose level. Horm Metab Res. 2007; 39:730–733. [PubMed: 17952835]

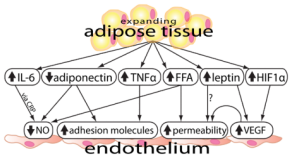

Figure 1.

Interactions between expanding adipose tissue and the endothelium via adipokine secretions. Adipokines induce a reduction in nitric oxide (NO), hindering vasodilation, upregulated adhesion molecules promoting immune infiltration, and increase vessel permeability. Adiponectin, which decreases in expanded adipose, can thus be suggested to have positive effects. (This figure is an adaptation of that appearing in the excellent Chudek and Wiecek review [4].)

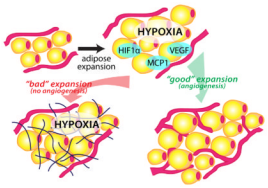

Figure 2.

Adipose expansion results in tissue hypoxia that necessitates angiogenesis for healthy tissue function. Hypoxia in expanding adipose depots induces the upregulation of an array of adipokines, among them HIF1alpha, MCP1, and VEGF. In early expansion, or in depots in which angiogenesis progresses slowly, the adipose matrix becomes fibrotic and induces further metabolic dysfunction. Angiogenic adipose tissues, however, expand with limited systemic consequence. Paradoxically, a complete inhibition of angiogenesis may completely stop adipose tissue expansion.

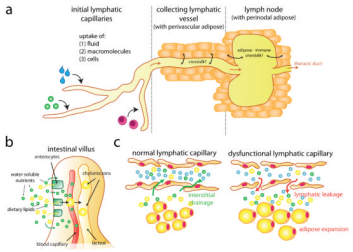

Fig 3.

Lymphatic circulation is an important transporter of lipids and plays a role in metabolic functions. A) Fluid, macromolecules, and cells enter lymphatic circulation in the periphery through initial lymphatic capillaries and form lymph. Lymph is transported through collecting lymphatic vessels, passes through the lymph nodes, and enters venous circulation at the venous duct. Both collecting lymphatic vessels and lymph nodes are surrounded by adipose tissue such that crosstalk between the two tissues' functions may occur. B) In the villi of the small intestine, enterocytes package dietary lipids into chylomicrons that are exclusively taken up by lacteals, the lymphatic capillaries of the intestine. Water soluble nutrients are absorbed through the blood. C) Normal lymphatic capillaries drain the interstitium through initial lymphatic "valves". Dysfunctional lymphatics result in lymph leakage, which stimulates adipogenesis. Adipogenesis may, in turn, further decrease lymphatic capillary quality.