Biochimica et Biophysica Acta 1842 (2014) 463–472

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Adipose tissue angiogenesis: Impact on obesity and type-2 diabetes ☆

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ARTICLE INFO

Article history:
Received 1 March 2013
Received in revised form 24 May 2013
Accepted 1 June 2013
Available online 12 June 2013

Keywords:
Adipocyte
Endothelial
Vascular
Fat
Capillary
Blood vessel

ABSTRACT

The growth and function of tissues are critically dependent on their vascularization. Adipose tissue is capable of expanding many-fold during adulthood, therefore requiring the formation of new vasculature to supply growing and proliferating adipocytes. The expansion of the vasculature in adipose tissue occurs through angiogenesis, where new blood vessels develop from those pre-existing within the tissue. Inappropriate angiogenesis may underlie adipose tissue dysfunction in obesity, which in turn increases type-2 diabetes risk. In addition, genetic and developmental factors involved in vascular patterning may define the size and expandability of diverse adipose tissue depots, which are also associated with type-2 diabetes risk. Moreover, the adipose tissue vasculature appears to be the niche for pre-adipocyte precursors, and factors that affect angiogenesis may directly impact the generation of new adipocytes. Here we review recent advances on the basic mechanisms of angiogenesis, and on the role of angiogenesis in adipose tissue development and obesity. A substantial amount of data points to a deficit in adipose tissue angiogenesis as a contributing factor to insulin resistance and metabolic disease in obesity. These emerging findings support the concept of the adipose tissue vasculature as a source of new targets for metabolic disease therapies. This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

1. Introduction

The growth and function of all tissues and organs are critically dependent on their appropriate vascularization. Blood flow is important for providing the correct oxygen tension in individual tissues, for the delivery and removal of nutrients and waste products, and for the transit of cells involved in tissue immune surveillance. In addition to being critical for the health of individual tissues, blood flow delivers hormones and growth factors that insure the inter-tissue and inter-organ communication necessary for whole body homeostasis. Thus, the growth of any organ or tissue must be accompanied by parallel growth of its vascular network. Most of the growth of organs and tissues occurs during development, and their final size remains relatively constant through adulthood. In contrast, adipose tissue is unique in that it can expand many-fold, to comprise more than 40% of total body composition in obese individuals, defined as a body mass index of 30 or higher. The ability of adipose tissue to expand has clear evolutionary advantages, enabling survival in times of nutrient scarcity; however, concomitant with adipose tissue expansion are metabolic alterations that enhance risk of metabolic disease. The cellular and molecular mechanisms by which adipose tissue growth is coordinated with the expansion of its capillary network are unknown. As these mechanisms may underlie the basis for adipose tissue dysfunction in metabolic disease, they comprise a fertile and exciting area of research.

While the close association between weight gain and heightened risk of type 2 diabetes (T2DM) is well established, not all individuals with obesity become diabetic, and certain individuals become diabetic after very minor weight gain [1]. This paradox is explained by the large individual variation in the size and expandability of different adipose tissue depots in humans, as expansion of some depots is associated with increase risk, while expansion of others is associated with decreased risk [2]. Strikingly, each standard deviation (SD) increase in subcutaneous adipose tissue mass decreases the odds of insulin resistance by 48%. In contrast, each SD increase in visceral adipose tissue mass increases the odds of insulin resistance by 80% [3]. The protective effect of expandable subcutaneous fat depots during weight gain is likely to be due to their capacity to properly store excess calories in the form of triglycerides, thus preventing ectopic lipid deposition into muscle, liver and visceral fat depots. Such ectopic deposition and inappropriate lipid metabolism are thought to cause insulin resistance and result in a greatly increased risk of T2DM [4,5]. Thus, understanding the specific mechanisms by which the subcutaneous adipose tissue expands is of particular interest, as these could provide new approaches for therapeutic intervention in metabolic disease. Several lines of evidence indicate that adipose tissue growth can be limited by its vascular supply [6–8], raising the possibility that the angiogenic potential of specific depots might be critical in limiting their maximal expandability. Testing this hypothesis will require a deep understanding of the basic mechanisms

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http://dx.doi.org/10.1016/j.bbadis.2013.06.003

of vascularization in expanding adult tissues, and the specific regulatory factors that operate in different adipose tissue depots.

2. Basic molecular and cellular mechanisms of angiogenesis

The de-novo formation of blood vessels during the development of the embryo occurs through the process of vasculogenesis, in which mesoderm-derived precursors, called angioblasts, organize into the first primitive blood vessels. All further vessel growth during organ and tissue development, as well as during tissue repair in adult organism, takes place through the process of angiogenesis, in which new vessels sprout from pre-existing vasculature. It is likely therefore that the vascularization of adipose tissue depots in adults proceeds through angiogenic expansion of the existing vasculature, as has been shown to occur during the formation of fat pads from implanted cells [9]. The last few years have brought great insight into the basic molecular and cellular mechanisms of angiogenesis [10–14], setting the stage for the identification of factors that regulate this process to fulfill tissue and developmental stage specific functions. Key insights into the cellular and molecular bases for angiogenesis, derived from experimental models such as the developing zebrafish embryo and the mouse retina, are very briefly summarized below.

The cardinal features of angiogenesis comprise the proliferation of endothelial cells, their directed migration through the extracellular matrix, the establishment of intercellular junctions, the formation of a lumen, the organization of perivascular supporting cells, the anastomosis with existing vessels, and the establishment of circulation. The cardinal initiating event is the stimulation of endothelial cell proliferation, which is mediated by the VEGF family of growth factors. These growth factors and their receptors have been established as master regulators of endothelial cell growth. In particular, VEGF-A, acting through the VEGFR2 (VEGF receptor 2, also known as KDR in humans or Flk1 in mice) represents the most potent mitogenic and chemo attractant signal for endothelial cells. In response to VEGF-A gradients, endothelial cells divide, and acquire a specific phenotype (tip cell phenotype) characterized by the formation of branches and numerous filopodia, which extend towards the direction in which the endothelial cell migrates. The action of VEGFs and their receptors are critically controlled by the Notch signaling pathway, which modulates the responsiveness of endothelial cells to VEGF, and their subsequent specialization. Thus, tip cells are characterized by high levels of expression of Delta-like 4 (Dll4), which is a ligand for Notch. The stimulation of Notch signaling by Dll4 in the tip cell suppresses VEGF signaling in adjacent cell, resulting in the acquisition of a stalk-cell phenotype. The continuous dynamic interaction between VEGF, Notch and Dll4 results in the development of angiogenic sprouts. Newly formed sprouts are then stabilized by interactions with smooth muscle cells and pericytes, and become lumenized, through processes that appear to involve junctional trans-membrane proteins such as VE-cadherin, as well as matrix proteins which are broken down and reorganized dynamically during vessel growth [14]. Newly formed sprouts anastomose with existing vessels, thus extending tissue microcirculation.

While the basic steps of angiogenesis outlined above are expected to operate, it is likely that the vascular network of each organ and tissue will be established through key tissue-specific mechanisms. A prominent example is the regulation of angiogenesis in the central nervous system, where specific G-protein coupled receptors are uniquely expressed and play dominant roles in angiogenic vascularization of the developing brain [15,16]. What mechanisms operate in adipose tissue, and how they modulate the basic steps of angiogenesis described above, are outstanding questions in adipose tissue biology.

3. Adipose tissue angiogenesis; what are the triggers?

One of the guiding questions for understanding angiogenic growth in adipose tissue is whether the mechanisms involved during embryonic and early postnatal development are similar to those involved in response to excess calorie consumption in adults. In both cases, two broad possibilities can be considered: First, angiogenic expansion may be triggered in response to signals emanating from proliferating and enlarging adipocytes. The second possibility is that angiogenic growth is triggered by developmental and/or metabolic signals, and parallels or precedes adipocyte proliferation and enlargement (Fig. 1). These two possibilities are not mutually exclusive, and in all likelihood tissue expansion involves both local cues arising from expanding adipocytes, as well as distant cues reflecting the developmental and metabolic states of the whole organism.

The first option, in which vascular growth ensues secondarily to parenchymal growth is the canonical model for oncogenic vascularization [17–19]. In this model, the rapid growth of tumor cells and the formation of a tumor mass elicit regions of hypoxia. Hypoxia is sensed through multiple mechanisms, prominent amongst which is the inactivation of oxygen-dependent prolyl-hydroxylases. Inactivation of these enzymes results in the protection of HIF-1α from proteolytic degradation, allowing its dimerization with constitutively expressed HIF-1β to form the functional transcription factor HIF1. This transcription factor potently activates a program of hypoxia adaptation, which includes decreased transcription and translation and increased VEGF-A expression. The angiogenic expansion of the vasculature in response to VEGF-A enhances blood flow and relieves hypoxia, allowing further tumor growth. This model, in which tumor growth is absolutely dependent on stimulation of angiogenesis, forms the basis for the development and use of anti-angiogenic therapies in cancer [11].

4. Role of hypoxia in adipose tissue angiogenesis

The most relevant evidence consistent with a possible role for hypoxia in adipose tissue angiogenesis are the findings that adipose tissue in rodents becomes hypoxic in response to obesity that is rapidly induced by high fat diet (HFD). This finding has been documented repeatedly, using both chemical indicators of hypoxia, as well as direct monitoring of tissue oxygen tension using microelectrodes [20–22]. Using directly placed microelectrodes, adipose tissue in obese humans has been found to be hypoxic [23]. Other findings consistent with a role for hypoxia are that the expression and secretion of pro-angiogenic factors by cultured adipocytes are strongly stimulated under low oxygen culture conditions [24]. These results suggest that, in a manner analogous to that occurring during tumor growth, adipose tissue hypoxia might be a driver for angiogenesis. However, the reported levels of hypoxia in human adipose tissue are relatively small, and one study actually finds increased oxygen tension in adipose tissue of obese subjects [25]. Moreover, it has been previously noted that expansion of adipose tissue in response to HFD is not accompanied by a corresponding increased blood flow [26]. Collectively, these results suggest that the response to hypoxia in adipose tissue may be insufficient to elicit sufficient compensatory angiogenic expansion.

A powerful, direct approach to defining the role of hypoxia in adipose tissue growth has been the tissue-specific overexpression and ablation of both HIF-1α and HIF-1β. Overexpression of a constitutively active form of HIF-1α in adipose tissue failed to induce a pro-angiogenic response; rather, it resulted in a fibrotic response and an increase in local inflammation [27]. Conversely, ablation of HIF-1α or HIF-1β (ARNT) in adipose tissue reduced fat formation, and protected from HFD-induced obesity and insulin resistance [28,29]. Furthermore, anti-sense mediated depletion of HIF-1α in obese mice resulted in amelioration of HFD-induced insulin resistance [30], as did pharmaceutical inhibition of HIF-1α, as well as inducible expression of a dominant negative form [31]. Overall, these results are consistent with a model where adipose tissue hypoxia induces HIF-1α, which induces a fibrotic and inflammatory response rather than a compensatory pro-angiogenic response. Nevertheless, HIF-1α may be relevant for the growth and maintenance of brown