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REVIEW

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Adipocytes, mast cells and angiogenesis

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Abstract

Healthy adipose tissue contains a wide variety of innate and adaptive immune cells, including macrophages, dendritic cells, mast cells, eosinophils, neutrophils, and lymphocytes. Numerous signaling molecules in the adipose microenvironment can positively or negatively modulate angiogenic processes, regulate the interaction between the vascular system and adipocytes, and participate in tumor progression. Mast cells are involved in the new formation or metabolism of fat, are present in abundant quantities in fatty tissue, among fat cells, and a number of mediators released from mast cells play a role in adipogenesis. Moreover, mast cells produce several pro-angiogenic factors and are involved in tumor angiogenesis. In this context, the angiogenic effect might be amplified when the adipocytes and mast cells act in concert, and treatment of adipose tissue- and mast cell-associated cancers with anti-angiogenic drugs may represent an alternative or adjuvant strategy for the treatment of these tumors.

Keywords: adipocytes, angiogenesis, anti-angiogenesis, mast cells, tumor growth.

Introduction

Adipose tissue can be divided into two different types, white adipose tissue (WAT) acting as a lipid deposit and brown adipose tissue (BAT). WAT is composed of pre-adipocytes and adipocytes, fibroblasts, and macrophages. White adipocytes are large cells containing a unilocular lipid droplet that occupies 90% of the total cell area. Brown adipocytes are smaller than white adipocytes, their lipid droplets are dispersed in the cytoplasm, and hold numerous and large mitochondria, responsible for the darkened appearance of the tissue. They are also present in some deposits of WAT, thus giving them a beige color, which justifies the name "beige" adipose tissue.

Moreover, BAT is more vascularized than WAT [1]. Another adipocyte cell type, called "pink adipocyte", has been described, present during lactation and gestation, due to a process wherein white adipocytes progressively transdifferentiate to acquire secretory, epithelial-like features [2].

Adipose tissue has been further categorized based on physiologic localization and function, as subcutaneous, visceral, marrow, breast, and intramuscular fat [3]. In humans, subcutaneous adipose tissue comprises ~80% of total body fat and is contained primarily in the abdominal, gluteal, and femoral depots [4]. The number of adipocytes in humans increases during childhood and adolescence and remains constant during adulthood, and adipocytes in adult humans have an annual renewal rate of about 10% [5].

Healthy adipose tissue contains a wide variety of innate and adaptive immune cells, including macrophages, dendritic cells, mast cells, eosinophils, neutrophils, and lymphocytes, which collectively constitute ~25% to 45% of stromal cells in humans [6].

Adipocytes and the vascular system

Endothelial cells and adipocytes have common progenitor cells that differentiate into adipocytes or endothelial cells, depending on exposure to different environments [7]. Immature adipocytes can be found near capillary showing the close association between adipose progenitors and vascularization of adipose tissue [8]. Numerous signaling molecules in the adipose micro-environment can positively or negatively modulate angiogenic processes and regulate the interaction between the vascular system and adipocytes.

Adipocytes and angiogenesis

Angiogenesis is essential for BAT hyperplasia [9], and the transition of WAT into BAT is accompanied by switching on an angiogenic phenotype [10]. Studies conducted in the mouse cornea and the chick embryo chorioallantoic membrane (CAM) have demonstrated that conditioned media obtained from pre-adipocytes and tissue homogenates from omentum or subcutaneous fat induces angiogenesis [11–13].

Expansion of adipose tissue during progression to obesity requires concomitant expansion of the adipose vascular bed through angiogenesis. In fact, the administration of anti-angiogenic agents in models of both genetic and diet-induced obesity either prevented weight gain [14] or induced dose-dependent, reversible weight reduction and adipose tissue loss [15].

Differentiation from pre-adipocytes to mature adipocytes is linked to high expression levels of angiogenic factors [11]. Adipose tissue produces a plethora of cytokines and growth factors involved in angiogenesis, including leptin, adiponectin, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like

growth factor 1 (IGF-1), placental growth factor (PlGF), interleukin-6 (IL-6), angiogenin, tumor necrosis factor-alpha (TNF-α), and angiopoietins (Angs) [16]. Leptin induces angiogenesis, vascular fenestration, and vascular remodeling [17, 18]. Adiponectin negatively affects angiogenesis [19]. VEGF-A overexpression in adipocytes hinders the expansion of adipose tissue [20], increases the number of beige adipocytes, and induces neovascularization of subcutaneous fat [21]. The blockade of the vascular endothelial growth factor receptor-2 (VEGFR-2) signaling pathway by a neutralizing antibody inhibits both angiogenesis and pre-adipocytes differentiation [22]. Adipose tissue produces matrix metalloproteinase-2 (MMP-2) and MMP-9, both involved in the regulation of angiogenesis [23]. Recruitment of inflammatory cells also significantly contributes to adipose neovascularization.

Several of the pro-angiogenic factors listed above, including multiple VEGF isoforms, leptin, HGF, and Ang-2, are also elevated in the serum of obese subjects and are implicated in the systemic effects of obesity on cancer progression [24–26]. Both WAT and BAT contain dense microvascular networks, but microvascular density is higher in BAT as compared to WAT [27]. Obesity impairs the vasodilator response of the muscle microvasculature to insulin VEGF and reduces microvascular density [28].

Angiogenesis inhibitors reduce fat mass expansion in mice [15, 29, 30]. Angiogenesis inhibitor TNP-470 prevents diet-induced obesity in mice, decreases appetite, fat mass, and expansion of adipose tissue by inhibiting aminopeptidase-2 [29]. Angiostatin and endostatin reduce fat mass [31]. A significant higher vessel density is present in the adipose tissue of tissue inhibitor of metalloproteinase-1 (TIMP-1) knockout mice compared with control mice [32, 33].

Mast cells and adipocytes

The first reports on the measurement of mast cell numbers in different body sites date to 1950 [34]. Skin biopsy specimens of normal subjects contained 38.4±4 mast cells per square millimeter, while in the adipose tissue their number is 10.4±2 per square millimeter.

Studies on the effect of the thyrotrophic hormone on connective tissue showed that at the same time, as fat is mobilized from the normal depots, there is an accumulation of mast cells [35].

Mast cells are involved in the new formation or metabolism of fat. They are present in abundant quantities in fatty tissue, among fat cells (Figure 1). Visceral WAT of obese mice shows a higher number of mast cells compared with those of lean mice, while there is no significant difference in their number in subcutaneous WAT between obese and lean mice [36].

Mast cells release several mediators, such as cytokines, chemokines, proteases, and prostaglandins, that play a role in adipogenesis [36]. As concerns the different role of tryptase and chymase stored in mast cell secretory granules, mast cells stimulate angiogenesis in adipose tissue by releasing chymase and inducing preadipocyte differentiation and also the proliferation of adipocytes [37]. Increased number of mast cells stained with tryptase has been reported in WAT of obese patients [38].

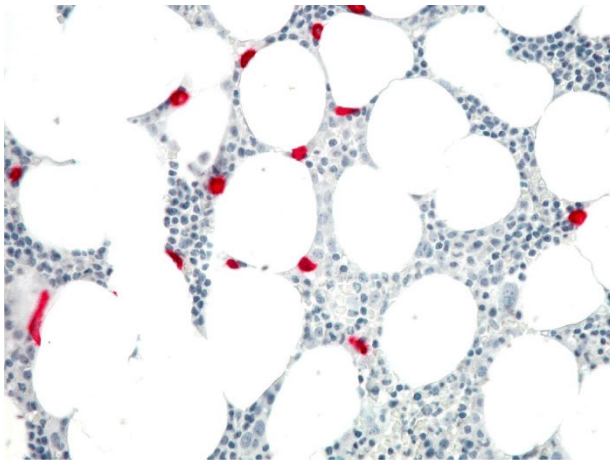

Figure 1 – ***Close spatial relationship between tryptase-positive mast cells (in red) and adipocytes in a human bone marrow sample. A murine monoclonal antibody against tryptase (mAb AA1, Dako) was used. The immunodetection was performed with alkaline phosphatase anti-alkaline phosphatase (APAAP, Dako) and Fast Red as chromogen. Original magnification, ×200.***

Mast cells from the rat peritoneal cavity express the receptors for both leptin and adiponectin, whose activation induces cytokines and reactive oxygen species production. Both adipokines induce migration of mast cells, leptin induces histamine and cysteinyl leukotriene secretion, and expression of C–C motif chemokine ligand 3 (CCL3) [39, 40], while adiponectin induces the production of anti-inflammatory IL-10 [41].

Altintas *et al.* [42] found significantly more mast cells in visceral fat of obese mice compared with lean ones and found that subcutaneous fat behaved very differently as in the latter, obesity is accompanied only by a modest increase in mast cells density. Moreover, they found that a significant number of mast cells in the epididymal fat of obese mice were in the process of degranulation and secreted TNF-α, which contributes to local and systemic insulin resistance.

Ishijima *et al.* [43] demonstrated a key role for mast cells in the preadipocyte to adipocyte transition under both obese and non-obese conditions. By the mean of reverse transcription polymerase chain reaction (RT-PCR) and *in vitro* studies, they have shown that in the epididymal WAT and stromal vascular fraction (SVF) of mast cell-deficient ($Kit^{W\text{-}sh/W\text{-}sh}$) mice, the messenger ribonucleic acid (mRNA) amount of preadipocyte markers, such as preadipocyte factor-1 (Pref-1), adipocyte enhancer-binding protein 1 (AEBP1), and GATA binding protein 2 (GATA2), but not mature adipocyte ones, such as adipocyte protein 2 (aP2), peroxisome proliferator-activated receptor gamma (PPARγ), acyl-coenzyme A synthetase 1 (Acsl1), and adipsin, increase compared to wild-type mice under both physiological and pathological conditions. Mast cells accumulate in the adipose tissue of obese individuals [44, 45].

Mast cell-deficient mice present improved glucose tolerance and insulin sensitivity compared with wild-type mice [38]. Obesity and type 2 diabetes are inflammatory diseases, characterized by an excess of adipose tissue and chronic insulin exposition induces the formation of lipid bodies in mast cells [46]. Moreover, several animal

models have demonstrated a pathogenetic role of mast cells also in human type 1 diabetes mellitus [36]. Intraperitoneal injection of Disodium Cromoglycate, an inhibitor of mast cell activation and degranulation, reduces diet-induced obesity and diabetes in mice [38].

Mast cells and angiogenesis

Mast cells produce several pro-angiogenic factors, including fibroblast growth factor-2 (FGF-2), VEGF, IL-8, TNF-α, transforming growth factor-beta (TGF-β), and nerve growth factor (NGF) [47-56]. As shown by *in vivo* and *in vitro* experiments, mast cells migrate in response to VEGF and PlGF-1 [57–59]. Granulated murine mast cells and their granules are able to stimulate an intense angiogenic reaction in the CAM assay, inhibited by anti-FGF-2 and -VEGF antibodies [60]. Intraperitoneal injection of the degranulating compound 48/80 stimulates angiogenesis in the rat and mouse mesentery window angiogenic assay [61, 62]. Histamine and heparin induce the proliferation of endothelial cells *in vitro* and *in vivo* [63, 64]. Tryptase, stored in mast cell secretory granules [65], stimulates the proliferation of endothelial cells, promotes vascular tube formation *in vitro*, degrades connective tissue matrix, and activates MMPs and plasminogen activator (PA), which in turn degrade the extracellular matrix with consequent release of VEGF or FGF-2 [66]. Mast cell-deficient W/Wv mice exhibit a decreased rate of tumor angiogenesis [67]. In human papillomavirus 16 (HPV16)-infected transgenic mouse model of epithelial carcinogenesis, mast cells infiltrated hyperplasia, dysplasias, and the invasive front of carcinomas, but not the core of tumors. Accumulation occurred proximal to developing capillaries and the stroma surrounding the advancing tumor mass [68]. Mast cells infiltrate and MMP-9 activation coincided with the angiogenic switch in premalignant lesions, and premalignant angiogenesis was abrogated in a mast cell-deficient HPV16 transgenic mouse [68, 69]. In prostate tumors derived from both transgenic adenocarcinoma of the mouse prostate (TRAMP) mice and human patients, mast cells promote well-differentiated adenocarcinoma growth [70]. Mast cell infiltration around gastric cancer cells correlated with tumor angiogenesis and metastasis [71].

A high number of mast cells have been demonstrated in tumor angiogenesis, like hemangioma and hemangioblastoma [72], as well as several hematological and solid tumors, including lymphomas [73, 74], multiple myeloma [75], myelodysplastic syndrome [76], B-cell chronic lymphocytic leukemia [77, 78], breast cancer [79, 80], squamous cell carcinoma of the esophagus [81], colon-rectal cancer [82], uterine cervix cancer [83–85], melanoma [86, 87], pulmonary adenocarcinoma [88–91].

Cross-talk between adipocytes and mast cells in angiogenesis

Both adipocytes and mast cells are closely related to capillaries and secrete cytokines and growth factors involved in angiogenesis. Among them, VEGF and TNF-α are expressed by both cells, while other ones are expressed or by adipocytes or by mast cells. In this context, the angiogenic effect might be amplified when the adipocytes and mast cells act in concert. In fact, a close relationship exists between adipocytes and mast cells. Different mediators released from mast cells, such as cytokines, chemokines, proteases, and prostaglandins, are involved in adipogenesis [36]. Mast cells express the receptors for both leptin and adiponectin, both released by adipocytes and acting on angiogenesis. Leptin induces angiogenesis, vascular fenestration, and vascular remodeling [17, 18], while adiponectin negatively affects angiogenesis [19].

The microenvironment during the accumulation of adipose tissue resembles the tumor microenvironment during tumor vascularization. Human cancers, including breast cancer, prostate cancer, colorectal cancer, and pancreatic cancer are all originating from the adipose environment, and adipose vasculature predetermines the tumor microenvironment that supports tumor growth. Implantation of tumor cells in highly vascularized WAT and BAT tissues accelerates tumor growth, as it has been demonstrated in breast cancer, melanoma, and fibrosarcoma. Inoculation of tumor cells in the subcutaneous tissue, WAT and BAT resulted in markedly differential tumor growth rates and angiogenesis, which correlated with the degree of pre-existing vascularization in these tissues [92]. Metastatic cancers grow in a highly vascularized mesentery environment where the adipose tissue is a major component at an accelerated rate [93]. Peritoneal adipose tissue is a metastatic site for ovarian cancer [94, 95].

In this context, the treatment of adipose tissue- and mast cell-associated cancers with anti-angiogenic drugs may represent an alternative or adjuvant strategy for the treatment of these tumors. Finally, mast cells thus appear to be new cellular actors of adipose tissue, inflammation, contributing to the complex paracrine interplay between the various immune cells that accumulate in adipose tissue in different pathological conditions, deserving further mechanistic evaluation to determine the potential causal role of mast cells in the physiopathology of these diseases.

Conflict of interests

The authors declare that they have no conflict of interests.

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