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Review

Angiogenesis and development of adipose tissue

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ABSTRACT

Obesity is a common disorder and related diseases, such as diabetes, atherosclerosis, hypertension, cardiovascular disease and cancer, are a major cause of mortality and morbidity in Western-type societies. Development of obesity is associated with substantial modulation of adipose tissue structure. The plasticity of the adipose tissue is reflected by its remarkable ability to expand or to reduce in size throughout adult lifespan. The expansion of adipose tissue is linked to the development of its vasculature. Indeed, adipogenesis is tightly associated with angiogenesis, as shown by the findings that adipose tissue explants trigger blood vessel formation, whereas in turn adipose tissue endothelial cells promote preadipocyte differentiation. Different components have been identified that play a role in adipose tissue associated angiogenesis. Modulation of angiogenesis may have the potential to impair adipose tissue development and thus may provide a novel therapeutic approach for prevention and treatment of obesity.

Contents

1. Introduction 2
2. Adipose tissue vasculature 3
3. Regulation of adipose tissue-related angiogenesis 3
   3.1. Vascular endothelial growth factors and placental growth factor 3
   3.2. VEGF and PlGF receptors 3
   3.3. Hepatocyte growth factor, fibroblast growth factor 2 and osteonectin 4
   3.4. The angiopoietins, TIE-1 and TIE-2 4
   3.5. Leptin 4
   3.6. Adiponectin 4
   3.7. Growth factors and cytokines 4
   3.8. Tissue factor 4
   3.9. Proteolytic systems 5
   3.10. Thrombospondins 5
4. Modulation of angiogenesis in adipose tissue 5
   4.1. Expression of angiogenic factors during adipose tissue development 6
   4.2. Animal models of genetic modification of angiogenic factors 6
5. Pharmacologic inhibition of angiogenesis impairs adipose tissue development 6
6. Adipose tissue as a source for therapeutic angiogenesis 7
7. Future lines of investigation 7
   References 7

1. Introduction

Over the last decades obesity and its consequences worldwide have become a major health problem. Between 1976 and 2002, the prevalence of overweight (body mass index (BMI) $\geq$25 kg/m^2) in the United States has increased from 46% to 66% of the population, and that of obesity (BMI $\geq$30 kg/m^2) from 15% to 31% (Hedley et al., 2004). Excess weight increases the risk of multiple condi-

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tions, including hypertension, cardiovascular and cerebrovascular disease, type 2 diabetes, certain types of cancer, respiratory diseases, gallstones and osteoarthritis. Obesity is frequently associated with metabolic abnormalities such as impaired glucose tolerance, hyperinsulinemia, dyslipidemia with elevated triglyceride level, decreased high-density lipoprotein cholesterol concentration and increased proportion of small dense lipoparticles. This cluster of metabolic disturbances is called the metabolic syndrome, and represents known risk factors for cardiovascular disease. In addition, obesity negatively affects physical functioning, vitality, and general quality of life (Kopelman, 2000; Roth et al., 2004).

Unlike most other tissues, adipose tissue continuously undergoes expansion and regression throughout adult life. Adipose tissue expansion requires the parallel growth of its capillary network. Therefore, adipogenesis (the formation of adipocytes) is tightly associated with angiogenesis (the formation of new blood vessels). We will review the pro- and anti-angiogenic components that have been demonstrated in adipose tissues, and discuss how modulation of angiogenesis may affect obesity.

2. Adipose tissue vasculature

A well-defined vascular system is present in adipose tissue, with every adipocyte surrounded by one or more capillaries. Fat cell development is characterized by the appearance of a number of fat cell clusters, or "primitive organs", which are vascular structures in the adipose tissue with few or no fat cells. During fetal development, arteriolar differentiation precedes adipocyte development and differentiation of blood vessel extracellular matrix (ECM) precedes differentiation of adipocyte ECM (Hausman and Richardson, 2004).

Adipose tissue consists of mature adipocytes surrounded by a stromal–vascular cell fraction containing preadipocytes, endothelial cells, pericytes, fibroblasts, macrophages, and mesenchymal stem cells. Autocrine/paracrine or developmental relationships exist between capillaries/endothelial cells and preadipocytes. *In vitro* studies revealed that adipose tissue explants in fibrin or collagen gels trigger blood vessel formation (Montesano et al., 1985), and that in turn adipose tissue endothelial cells promote preadipocyte differentiation (Varzaneh et al., 1994). Mature adipocytes in culture can de-differentiate followed by differentiation into adipocytes or endothelial cells, suggesting that these are derived from a common lineage (Planat-Benard et al., 2004).

The growth of white adipose tissue (WAT) requires continuous remodeling of the vascular network, primarily of primitive capillary networks. Expansion of adipose tissue can be supported by both neovascularization (for adipocyte hyperplasia) and dilation and remodeling of existing capillaries (for adipocyte hypertrophy) (Hausman and Kauffman, 1986). Brown adipose tissue (BAT) is mainly responsible for energy metabolism, and its function requires efficient blood perfusion to supply nutrients and oxygen and to export heat. BAT hyperplasia is critically dependent on angiogenesis, as it requires rapid activation of mitosis in fat precursor cells and endothelial cells to develop capillaries (Bukowiecki et al., 1980).

Blood vessel density may not truly reflect angiogenic activity. Microvessel density is often considered a prognostic indicator for cancer. However, microvessel density does not reflect the angiogenic activity or angiogenic dependence of a tumor. The metabolic needs of cancer cells vary with the tissue of origin and change with tumor progression. Thus, the number of tumor cells that can be supported by a vessel varies, influencing in turn the vascular density (Hlatky et al., 2002). In addition, capillary endothelium has important structural features such as microvascular endothelial cells surrounded by capillary fenestrations and transendothelial channels. Several soluble growth factors are found to regulate vascular fenestrations and permeability in adipose tissue. For example leptin increases the vascular permeability in adipose tissue and consequently, influences the microvessel density (Cao et al., 2001). To take this into account, blood vessel density in adipose tissues can be normalized to the adipocyte density.

3. Regulation of adipose tissue-related angiogenesis

Both WAT and BAT produce and secrete many different types of proangiogenic factors such as vascular endothelial growth factor (VEGF)-A and hepatocyte growth factor (HGF), the two key angiogenic factors produced by adipocytes. Other adipose tissue-derived factors with proangiogenic effects include VEGF-B, VEGF-C, placental growth factor (PlGF), fibroblast growth factor (FGF)-2, SPARC/osteonectin, angiopoietin (Ang)-1, Ang-2, leptin, platelet-derived growth factor (PDGF)-β, transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, tissue factor (TF), matrix metalloproteinases (MMPs), plasminogen activators and cathepsins. Adipose tissue also produces endogenous antiangiogenic factors, such as adiponectin, thrombospondin (TSP)-1, TSP-2, ADAM and ADAMTS family members. Thus, the regulation of angiogenesis in adipose tissue may depend on the local balance between proangiogenic and antiangiogenic factors. The angiogenic potential of the main pro- or anti-angiogenic components is sometimes context-dependent and different in different fat pads.

3.1. Vascular endothelial growth factors and placental growth factor

VEGF-A (17–23 kDa) is a major angiogenic factor that stimulates proliferation and migration of endothelial cells. Three forms of VEGF-A are produced in the mouse as a result of alternative splicing (VEGF-A121, VEGF-A165 and VEGF-A189). Several studies indicate that VEGF-A stimulates both physiological and pathological angiogenesis by signaling through vascular endothelial growth factor receptor (VEGFR)-2 in a strict dose-dependent manner. Loss of a single VEGF-A allele causes embryonic vascular defects, while reduction of VEGF-A levels by only 25% impairs spinal cord perfusion, resulting in motor neuron degeneration reminiscent of amyotrophic lateral sclerosis (Carmeliet et al., 1996; Ferrara et al., 1996; Oosthuyse et al., 2001). VEGF-A is believed to be responsible for most of adipose tissue's angiogenic capacity (Zhang et al., 1997). VEGF-B (21 kDa) is 43% identical to VEGF-A165; it also promotes angiogenesis and is implicated in ECM degradation via regulation of plasminogen activation (Olofsson et al., 1998). VEGF-C (23 kDa) displays 30% homology with VEGF-A165 and plays an important role both in angiogenesis and lymphangiogenesis (Joukov et al., 1996; Karkkainen et al., 2004). VEGF-D (22 kDa) is 48% identical to VEGF-C and also promotes the growth of lymphatic vessels (Stacker et al., 2001). VEGF is expressed by both stromavascular fraction cells and mature adipocytes, as described in both animals and humans (Ledoux et al., 2008).

PlGF, a 25 kDa homologue of VEGF-A (53% sequence identity with VEGF-A165), enhances angiogenesis, but only in pathological conditions. Loss of PlGF impairs angiogenesis in the ischemic retina, limb, and heart, in wounded skin and in tumors, without affecting physiological angiogenesis (Carmeliet et al., 2001). PlGF is expressed in murine adipose tissue, both in adipocytes and in the stromal–vascular cell fraction (Voros et al., 2005).

3.2. VEGF and PlGF receptors

The members of the VEGF family bind to transmembrane tyrosine kinase receptors (VEGFR-1 (206 kDa), VEGFR-2 (218 kDa) and VEGFR-3 (150 kDa)). VEGF-A interacts with both VEGFR-1 and VEGFR-2, whereas VEGF-B and PlGF bind to VEGFR-1. VEGF-C and