The relationship between inflammatory markers, angiogenesis, and obesity

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Abstract

Obesity is recognized as a chronic low grade and systemic inflammatory disease. Angiogenesis is critical for adipose tissue expansion. Several evidences have demonstrated that angiogenesis sustains inflammation by preparing oxygen and nutrients for inflammatory cells and inflammation in turn can cause insulin resistance, type 2 diabetes, and cardiovascular disease. The understanding of mechanisms of obesity especially main roles of inflammation and angiogenesis in fat mass expansion can lead to therapeutic approaches in growing field of obesity and its related disorders. In this review, we studied the relationship between obesity, angiogenesis, and inflammation.

Keywords: Obesity, Angiogenesis, Inflammation

Introduction

Inflammation is an intricate network of chemical signals, cell types and factor interactions in response to tissue damage against pathogenic, traumatic or toxic injury. The inflammatory process is the result of balance between pro- and anti-inflammatory molecules such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), leptin, resistin, monocyte chemoattractant protein-1 (MCP-1), C-reactive protein (CRP) and anti-inflammatory molecule of Adiponectin. These molecules involve in regulation of cell chemotaxis, migration and proliferation. Although inflammation participates in healing process but imbalance between pro- and anti-inflammatory molecules lead to sustained inflammation (chronic inflammation) and in turn it mediates a wide spectrum of diseases such as psoriasis, rheumatoid arthritis, osteoarthritis, metabolic syndrome-associated disorders including type 2 diabetes and atherosclerosis, ocular disorders, Crohn disease, and cancer.

Obesity is a complex metabolic disorder that is one of the most prevalent public health problems. Based on the World Health Organization (WHO) definition, obesity is considered as body mass index (BMI) of 30 kg/m² or higher. Obesity is associated with the development of most common and severe human diseases such as type 2 diabetes mellitus, coronary heart disease (CHD), hypertension, increased incidence of certain cancers, respiratory complications (obstructive sleep apnea), and osteoarthritis.

Angiogenesis is a process of growth and remodeling of an initial vascular system which is modified to create an intricate branching network and matured vasculature. It is a multistep process that consists of extracellular matrix (ECM) degradation, endothelial cell proliferation and migration, tubal formation and anastomosis. Physiological angiogenesis is essential for the wound healing, growth and action of female reproductive organs, such as ovary and endometrium during menstrual cycle and pregnancy. In addition, disturbance of the mechanisms involving in physiological angiogenesis can lead to a growing list of diseases either in the form of overproliferation of blood vessels such as cancer, psoriasis, arthritis, retinopathies, obesity, diabetes, asthma, and atherosclerosis or inadequate angiogenesis including heart and brain ischemia, neurodegeneration, hypertension, osteoporosis, respiratory distress, preeclampsia, endometriosis, postpartum cardiomyopathy, and ovarian hyper stimulation syndrome.

Chronic low grade inflammation during obesity

Obesity was identified as a chronic low grade
Inflammation especially in white adipose tissue (WAT) nearly a decade ago when increase in the cytokine (TNF-α) and progress of insulin resistance with diet-induced obesity were demonstrated in rodents. Numerous studies have demonstrated the increase in plasma levels of MCP-1 after 4 weeks high-fat diet.

In relation to the origin of the inflammatory response that leads to insulin resistance in obesity, an initial mechanism is the inhibition of signaling downstream of the insulin receptor. For example, exposure of cells with TNF-α leads to inhibitory phosphorylation of serine residues of insulin receptor substrate-1 (IRS-1). Another mechanism is that nutrient overload in adipocytes induces endoplasmic reticulum (ER) stress that leads to activation of inflammatory cascades. ER is an organelle specialized in the cell for protein folding, maturation, storage and transport of nutrients. Following nutrient surplus, misfold or unfolded proteins aggregate in the ER and create unfolded protein response. It leads to increased activity of c-Jun NH2-terminal kinase C (JNK), IκB Kinase (IKK-β), IRS-1 and nuclear factor kappa-B (NF-κB) pathways that in turn cause to increase expression of pro-inflammatory cytokines such as TNF-α, IL-6, CRP, and disruption of insulin signaling. Moreover, rapid and dynamic expansion of fat tissue in obesity leads to adipose tissue hypoxia. Finally, the ER responds to this cellular stress in the form of increased activation of inflammatory pathways.

There are at least two different states of macrophage infiltrations in obese adipose tissue. M1 or inflammatory macrophages that are induced by pro-inflammatory mediators such as lipopolysaccharide (LPS) and interferon (IFN-γ) and anti-inflammatory M2 macrophages normally exist in adipose tissue that are produced by cytokines such as IL-4, IL-13, and IL-10. Several evidences have shown that high fat diet changes phenotype of macrophages in adipose tissue from M2 to M1 that in turn accelerate adipose tissue inflammation.

Furthermore, surplus glucose metabolism also can cause to increase in mitochondrial production of reactive oxygen species (ROS). ROS production in obesity causes activation of inflammatory pathways and in turn participates in inhibition of insulin signaling including JNK, IKK (NF-κB kinase) and the activation of these kinases in obesity show the overlap of metabolic and immune pathways. The IKKB, one of the inflammatory kinases, can affect insulin signaling by at least two ways; first, direct phosphorylation of IRS-1 on serine residues and the second is the phosphorylation of inhibitor of NF-κB (IκB). Thus, activation of transcription factor can stimulate generation of several inflammatory mediators such as TNF-α and IL-6. In addition, other mechanism that participates in inflammation-induced insulin resistance is at least 3 members of the suppressor of cytokine signaling (SOCS) family with inhibition of insulin signaling through IRS-1 and IRS-2.

Adipose tissue expansion and angiogenesis

Adipose tissue has a large vascularity and each adipocyte is enclosed by one or more capillaries. Reciprocal interplay between endothelial cells and adipocytes is nicely shown, as dysfunction of each compartment can has a substantial effect on the other system. Functional vascular system is critical for adipose tissue expansion by several mechanisms including, supplying oxygen and nutrients, waste products removal, and trigger of growth and survival signals for physiological function of adipocytes by growth factors and cytokines available in plasma. During expansion of adipose tissue, hypoxia is an important factor for vascular growth and remodeling. Likewise, increased adipocyte size leads to over longer distance for diffusion of oxygen and nutrients to adipocytes and results in a decrease of partial oxygen pressure to 20 mmHg against 40 mmHg in obese versus lean mice, respectively. Adipose tissue in response to hypoxia generates hypoxia inducible factor 1-α (HIF1-α) a heterodimer consisting of the oxygen regulated HIF1-α subunit and the constitutively expressed HIF1-β. In normoxic condition, HIF1-α is degraded by an oxygen-dependent hydroxylation of two proline residues. In contrast, in hypoxic conditions the level of prolyl hydroxylation decreases and protein translocates into the nucleus, and binds to hypoxia response elements (HRE) of target genes such as VEGF-A and angiopoietin-2 and thus, induces an angiogenic response that can participate in better oxygenated and nutritionally-enriched microenvironment of tumors.

Adipose tissue generates several angiogenic and angiostatic factors including placental growth factor (PLGF), FGF2, angiopoietin-2, angioptatin, endostatin, leptin, thrombospondin (TSP-1), resistin, IGF (insulin growth factor), HGF, etc., but most of the angiogenic activity is attributed to vascular endothelial growth factor.
Angiogenesis maintains inflammation by supplying oxygen and nutrients for the cells of inflammatory region. In chronic inflammatory condition such as obesity, nitric oxide (NO), an inflammatory cytokine, is produced by inducible NO synthase (iNOS). NO dilates vessels and stimulates its permeability that leads to immune cell extravasation. Adhesion of immune cells to the endothelium is one of the most important steps in inflammatory process.53 Adhesion molecules such as E-selectin play a communication role in inflammatory process and can have a role in immune cell extravasation.56 There are similar roles for adhesion molecules, intracellular adhesion molecule (ICAM-1), vascular cellular adhesion molecule (VCAM-1), and integrins.57

Inflammatory cells also release angiogenic factors including: VEGF, Angiopoietins, fibroblast growth factor (bFGF), Hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), etc that have mitogenic and migratory effects on endothelium.58-60 A common stimulus for both chronic inflammation and angiogenesis is hypoxia that induces HIF’s expression; it in turn increases transcription of angiogenic genes such as, VEGF and Ang-2.3

Activation of transcription factor NF-κB is considered as the primary event in inflammation.63,64 Several studies have demonstrated interplay between NF-κB and Ang-Tie2 signaling pathway.65 Ang-2 is an angiogenic factor that upregulates several pro-inflammatory pathways that can be led to leukocyte recruitment and infiltration through NF-κB signaling interaction.66

Adipose tissue remodeling is the changes in turnover of the adipocytes, angiogenesis and rebuild of the extra cellular matrix in response to factors such as growth factors and expansion of adipose tissue, variations of hormonal concentrations, aging and diseases such as cancer and cachexia.67 Some studies have shown that high fat diet (60% calories of fat) approximately stimulates complete remodeling of epididymal fat tissue of male mice.68

During adipose tissue expansion, blood flow per unit adipocyte surface and delivery rate of oxygen and nutrients to the adipocyte becomes suboptimal.69 On the other hand, PO2 is inversely correlated with pro-inflammatory markers. Therefore, hypoxic condition of adipose tissue during obesity leads to inflammation, fibrosis and adipocyte dysfunction.70,71 Adipocyte dysfunction may participate in the cycle of adipose tissue remodeling.72 Hypoxia in adipose tissue leads to increase of transcription factor of HIF that in turn causes angiogenic response by binding to the HRE of target genes such as VEGFA, angiopoietin-273,74 and lysyl oxidase (LOX), one enzyme with cross-link between elastins and collagens in the extracellular matrix that increases extracellular tensile strength and leads to HIF-1α mediated fibrosis.75 Furthermore, adipose tissue macrophages in obesity shift to an M1 inflammatory phenotype and the increase in the number of M1 macrophages and the M1/M2 ratio can lead to systemic inflammation and induction of insulin resistance that have been shown in figure 1.76,77

In conclusion, obesity is identified as a chronic low grade inflammation state and macrophages possibly play a critical role in inflammation. Hypoxia is considered as a common stimulus for inflammation and angiogenesis. Thus, there is a reciprocal interplay between inflammation and angiogenesis and both are involved in pathophysiology of obesity. Close relationship between inflammatory cells, angiogenesis and adipose tissue expansion should be considered in prevention and/or treatment of obesity.

Conflict of Interests
Authors have no conflict of interests.
Inflammation, obesity and angiogenesis

**Figure 1. Relationship between adipose tissue expansion, angiogenesis and inflammation**

- **Adipose tissue expansion**
  - Macrophage infiltration
  - M1 Macrophage
  - M1/M2 Macrophage

- **Hypoxia**
  - HIF1

- **Adipocyte dysfunction**
  - Adipocyte remodeling

- **Adipose tissue fibrosis**
  - VEGF
  - FGF2
  - Ang-2 PLGF
  - Leptin
  - HGF
  - TSP-1

- **Inflammation**
  - IL-6
  - TNF-α
  - IL-8
  - CRP

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