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Regulation of Stem Cell Differentiation in Adipose Tissue by Chronic Inflammation

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Abstract

1. Recent studies suggest that a local hypoxic response leads to chronic inflammation in adipose tissue of obese individuals. The adipose tissue hypoxia may reflect a compensatory failure in the local vasculature system in response to obesity.
2. Studies suggest that inflammation stimulates angiogenesis and inhibits adipocyte activities in a feedback manner within the obese adipose tissue. Adipose-derived stem cells (ASCs) are able to differentiate into multiple lineages of progenitor cells for adipocytes, endothelial cells, fibroblasts and pericytes. Differentiation of ASCs into those progenitors is regulated by the adipose tissue microenvironment.
3. As a major factor in the microenvironment, inflammation may favor ASC differentiation into the endothelial cells through induction of angiogenic factors. At the same time, inflammation inhibits ASC differentiation into adipocytes by suppressing PPAR γ activity and insulin signaling pathway. In this context, inflammation may serve as a signal mediating the competition between adipocytes and endothelial cells for the limited source of ASC.
4. It is a new concept that inflammation mediates signals in the competition between adipocytes and endothelial cells for the limited ASC in obesity. There is a lot of evidence that inflammation promotes endothelial cell differentiation. However, this activity of inflammation remains to be established in adipose tissue. Literature is explored in this review article in support of this conclusion.

Keywords

Adipose-derived stem cell; Cell differentiation; Adipose tissue; Adipocytes; Endothelial cells; Inflammation; Obesity

Adipose tissue inflammation

1. Inflammation in obesity: Inflammation occurs in adipose tissue in obesity, and exerts a broad impact on energy (glucose and fatty acids) metabolism (1-5). Obesity-associated inflammation is characterized by increased expression of pro-inflammatory cytokines in adipose tissue and elevation of inflammatory mediators in plasma (1, 6-9). Macrophage infiltration into adipose tissue provides a strong cellular basis for the inflammatory response (10-12). Inflammation inhibits adipocyte function by suppressing adipokine expression (such as adiponectin) and decreasing triglyceride storage. The molecular mechanisms are related to impairment of insulin signaling and suppression of PPAR γ function (discussed

below). In adipocytes, inflammation inhibits the insulin signaling pathway by targeting insulin receptor substrates (IRSs) (1, 13, 14). Alternatively, inflammation may impair insulin action through stimulation of lipolysis that lead to release of free fatty acids (FFA) from adipocytes. FFA induces insulin resistance through lipotoxicity (15). Recent studies from our laboratory suggest that inflammation has important beneficial activities in the body through control of energy balance and angiogenesis. Systemic inflammation in transgenic mice protects the body from obesity by induction of energy expenditure (16, 17). Local inflammation promotes angiogenesis and improves blood supply to adipose tissues through the induction of angiogenic factors (18).

2. Origin of inflammation: There are several hypotheses regarding the pathogenesis of obesity-associated inflammation (19). These include activation of toll-like receptor 4 (TLR4) by fatty acids, activation of protein kinase C (PKC) or JNK (c-JUN n-terminal kinase) by fatty acid derivatives (diacylglyceride or ceramide), endoplasmic reticulum stress (ER stress), oxidative stress, activation of macrophages by dead adipocytes, and activation of the NLRP3 inflammasome by lipids (20-23). Although these possibilities are able to explain some aspects of inflammation and provide mechanisms for metabolic disorders in obesity, their etiology remains to be identified. It is not clear why free fatty acid (FFA), ER stress, oxidative stress and adipocyte death are increased in obesity. Additionally, it is not known why adiponectin is reduced and leptin is elevated in adipose tissue. There is not yet a consensus for a single theory to account for the white adipose tissue metabolic and endocrine dysfunctions associated with obesity. However, the discovery of adipose tissue hypoxia in obese mice has provided a potential unifying mechanism.

Recent reports suggest that adipose tissue hypoxia (ATH) occurs in obese mice and obese patients (24-27). Adipose tissue hypoxia represents a novel causative risk factor for the chronic inflammation in obesity (26). Hypoxia induces inflammation through activation of two major transcription factors, HIF-1 α and NF- κ B, each of which activates transcription of a variety of angiogenic and/or pro-inflammatory cytokines (Fig. 1). The adipose tissue hypoxia not only explains the origin of inflammation in adipose tissue, also provide a mechanism for the pathological responses in adipose tissue, such as ER stress (25, 28), oxidative stress (29), adipocyte death (30), adiponectin reduction (26, 31) and leptin induction (32). Thus, the concept of ATH presents an exciting and testable hypothesis underlying the mechanisms of chronic inflammation, adipose tissue dysfunction and metabolic disorders in obesity (19).

3. Cause of adipose tissue hypoxia: In tissues, oxygen is delivered by the circulation via hemoglobin in red blood cells. Reduction in blood supply is a common mechanism of tissue hypoxia and this is the case for ATH. Adipose tissue blood flow (ATBF, ml/min/g) is a measure of blood supply in adipose tissue. A reduction in ATBF was first described in 1966 when a decreased rate of radioisotope clearance was detected in subcutaneous fat of an obese individual (33). The reduction was confirmed in animal and human studies thereafter (34-36). The ATBF reduction has been found to be a result of obesity, but not a consequence of insulin resistance, in rat models. ATBF was compared in two rat models of type 2 diabetes with or without obesity (37). Both obese Zucker rats and non-obese Goto-Kakizaki (GK) rats suffered insulin resistance. The ATBF reduction was observed in the obese diabetic rats (obese Zucker rat), but not in the non-obese diabetic GK rats, suggesting that the ATBF reduction is a result of obesity, not insulin resistance. However, in studies of obese human subjects, the ATBF reduction has been associated with insulin resistance (38, 39), suggesting a role for ATBF reduction in the pathogenesis of insulin resistance. In addition to the ATBF reduction, the increase in adipocyte size associated with obesity may contribute to the hypoxia response in adipose tissue (for further discussion, see (26)). In vivo, oxygen can diffuse about 120 microns through tissue (40). When adipocyte diameters

increase to (or above) 120 microns, oxygen diffusion from the capillary will be compromised. Since the diameter of an adipocyte can be 150 microns, the consequences of obesity on tissue oxygenation can be substantial (41).

The capillary density was reduced in adipose tissue of obese mice and found to contribute to ATBF (18). Our initial observation has been confirmed by subsequent independent studies (27, 42, 43). Capillary density is determined by angiogenesis that requires proliferation and tube formation by endothelial cell progenitors. Capillary formation is driven by angiogenic factors including vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). A balance between these two angiogenic factors is required for the formation and function of new capillaries (44). In obese mice, PDGF expression was reduced in adipose tissue, which may contribute to the compensation failure in angiogenesis (18).

In addition to angiogenesis, a decrease in vasodilation is another possible mechanism contributing to ATBF reduction. This possibility is supported by literature on angiotensin II (Ang II), a serum peptide capable of inducing vasoconstriction. Ang II is a component in the renin-angiotensin system (RAS), and a product of Ang I after digestion by angiotensin-converting enzyme (ACE). Ang II acts on both the type 1 (AT1) and type 2 (AT2) receptors. In obesity, the Ang II activity is increased in the adipose tissue and in the circulation, thereby leading to increased vasoconstriction and reduced vasodilation. Consistent with this model, pharmacological Ang II inhibitors enhance blood perfusion in adipose tissue (45). Additionally, inflammatory cytokines (such as TNF- α) inhibit vasodilation through induction of vasoconstriction (46, 47).

Adipose tissue stem cells

1. Cell types and adipocyte turnover: Adipose tissue contains a heterogeneous population of cells including mature adipocytes, endothelial cells, fibroblast cells, lymphoid cells, macrophages, pericytes, and pre-adipocytes or adipose-derived stromal/stem cells (ASC, see below) (48-51). Adipose tissue growth and expansion is primarily determined by adipocyte hypertrophy and hyperplasia in obesity. Triglyceride accumulation is responsible for adipocyte hypertrophy while increased adipocyte differentiation contributes to hyperplasia. Studies based on carbon 14 labeling suggest that the average adipocyte's lifespan is ~10 years (52). Adipocytes undergo apoptosis and necrosis at the end of lifespan (53, 54). This type of cell death is accelerated in adipose tissue by obesity (54). Regarding the cause of adipocyte death, we reported that adipose tissue hypoxia contributes to both necrosis and apoptosis of adipocytes in obesity (30). To sustain the tissue growth, new adipocytes are generated from pre-adipocytes and/or ASC to replace the dead adipocytes and to increase total adipocyte numbers in the fat pads. When the generation of new adipocytes cannot meet the demand for triglyceride storage, adipocyte hypertrophy will take place to store triglyceride through an increase in cell size. The increased adipocyte death and enlarged cell size are associated with chronic inflammation and insulin resistance in obesity. Both inflammation and hypoxia inhibit new adipocyte generation from pre-adipocyte differentiation (30, 55). Impaired compensatory vascularization contributes to hypoxia and inflammatory response in the adipose tissue of obese individuals (56).

2. Adipose-derived stem cells (ASCs): After digestion by collagenase, adipose tissue can be divided into two fractions, adipocyte fraction and "stromal vascular fraction" (SVF) (57, 58). Among SVF, there is a plastic adherent subpopulation known as adipose-derived stromal/stem cells (ASCs) (58). ASCs are multipotent cells that can differentiate along the adipocyte, chondrocyte, epithelial cell, hepatocyte, myocyte, neuronal-like, and osteoblast lineage pathways (57-61). In vitro, ASCs have the capacity of self-renewal and maintain their capacity for multilineage differentiation at the clonal level, consistent with the

definition of a “stem cell” (61-63). In part, the ASC’s differentiation and proliferation are determined by the microenvironment where the stem cells are maintained, i.e., its “stem cell niche”. The ASC’s microenvironment is changed during the chronic inflammation and ATH associated with obesity. This implies that the metabolic conditions associated with obesity have consequences potentially extending to the stem cell level.

3. ASC differentiation in adipose tissue: Inhibition of ASC differentiation into preadipocytes represents one mechanism by which adipocyte hyperplasia can be suppressed in adipose tissue. It is reported that pre-adipocyte numbers are reduced in adipose tissue in obesity and this reduction is associated with impaired glucose metabolism (64). Pre-adipocytes derive from ASCs in adipose tissue and their generation may be inhibited by obesity-associated responses. Endothelial cells are the source of paracrine factors that influence pre-adipocyte generation. Endothelial cells are required for formation of new blood vessels that control blood supply to adipose tissue. Endothelial progenitor cells are derived from ASC (65) or circulating bone marrow-derived cells (66). Differentiation of endothelial progenitor cells into endothelial cells is required for formation of new blood vessels in adipose tissue (67-71). Inhibition of endothelial progenitor cell recruitment may lead to suppression of adipose tissue growth and remodeling in obesity (reviewed in (72)). When obese murine models such as the leptin deficient ob/ob were treated with the anti-angiogenic compounds TNP-40 or angiostatin, they displayed a time and dose dependent weight loss similar to that observed with leptin administration alone (73). Likewise, weight loss was achieved in mice treated with a peptide targeting a vascular-associated protein, prohibitin, in adipose tissue (74). When this peptide was coupled to a pro-apoptotic molecule, it prevented and reversed weight gain in wild type mice on a high fat diet (74).

Regulation of Adipose Tissue Stem Cells by Inflammation

1. Inhibition of adipogenesis: Inflammation may inhibit ASC differentiation into pre-adipocytes through suppression of the transcription factor PPAR γ and the insulin signaling pathway (Fig. 2). The nuclear receptor PPAR γ is a lipid sensor that promotes lipid accumulation through gene transcription. Inhibition of PPAR γ activity by TNF- α leads to the suppression of adipocyte differentiation, and involves in the pathogenesis of several conditions including insulin resistance. PPAR γ activity is regulated by TNF- α at pre-translational and post-translational levels (75). Activation of serine kinases including IKK, ERK, JNK and p38 underlies the TNF- α inhibition of PPAR γ activity. Of the four kinases, IKK is a dominant signaling molecule in the regulation of PPAR γ by TNF- α . IKK activates the transcription factor NF- κ B, which in turn suppresses PPAR γ activity (75).

Insulin is required for adipocyte differentiation. Insulin activates its receptor to induce uptake of glucose and free fatty acids by adipocytes. Glucose and free fatty acids are building materials in the biosynthesis of triglycerides, which is stored in the cytoplasm of adipocytes and often used as a marker of adipocyte differentiation. Additionally, insulin inhibits hydrolysis of triglyceride in adipocytes by suppressing lipases (76). When the insulin signaling pathway is impaired due to insulin resistance, triglyceride synthesis will be reduced and hydrolysis of triglyceride will be enhanced. Under these conditions, adipocyte differentiation will be inhibited due to a lack of triglyceride. Inflammation inhibits insulin signaling by targeting insulin receptor substrate 1 (IRS-1) (Fig. 2).

2. Molecular mechanism: There are three models for TNF- α inhibition of PPAR γ (75). Firstly, PPAR γ expression is reduced at the mRNA level by TNF- α through the inhibition of the C/EBP family. This is observed in 3T3-L1 adipocytes treated with TNF- α for 24 hours or longer. The mechanism is related to inhibition of C/EBP δ expression by TNF- α . C/EBP δ has been shown to activate the PPAR γ gene promoter through a direct protein-DNA

interaction. When C/EBP δ expression is reduced by TNF- α , PPAR γ gene transcription will be suppressed. Secondly, PPAR γ mRNA expression is not changed, but its activity remains decreased. This mechanism was demonstrated in cells transfected with a PPAR γ expression vector. In the second model, the ligand-dependent transcriptional activity of PPAR γ is reduced as a result of loss of PPAR γ DNA-binding activity. It was shown that the inhibition of DNA binding activity was dependent on a direct association of NF- κ B and PPAR γ (77). Thirdly, the transcriptional activity of PPAR γ is inhibited by TNF- α through the activation of a nuclear co-repressor (78). In this mechanism, the DNA-binding activity of PPAR γ was not reduced by TNF- α itself. Instead, the DNA-bound PPAR γ was inactivated by histone deacetylase 3 (HDAC3). Nevertheless, all three mechanisms are dependent on activation of the IKK/NF- κ B pathway as the TNF- α activity was abolished by the super repressor I κ B α (Inhibitor kappa B α) (78, 79). Furthermore, the inhibitory activities of TNF- α impact both PPAR γ 1 and PPAR γ 2 (77, 78, 80).

TNF- α activates the intracellular signaling pathways through cell membrane receptors. TNF- α activates many signaling pathways, such as IKK/NF- κ B, MAPK (JNK, ERK, and p38) and apoptosis pathway through its receptors (81, 82). The NF- κ B transcription factor stays in the cytoplasm in the absence of its activators. This inhibition is mediated by I κ B α that prevents NF- κ B shuttling between the cytoplasm and nucleus (reviewed in (83)). I κ B α degradation is controlled by a phosphorylation-mediated and proteasome-dependent mechanism that is initiated by activation of IKK2 (IKK β) (84). In the TNF- α signaling pathways, activation of IKK, ERK and JNK (c-JUN NH2 terminal kinase) were reported to inhibit the transcriptional activity of PPAR γ (75), but p38 was reported to enhance the function of PPAR γ (85-88).

Summary

The current literature suggests that multiple cell types within adipose tissue share a common progenitor, the adipose-derived stromal/stem cell (ASC). Differentiation of each lineage of progenitor cells from ASC is modulated by the physical microenvironment within adipose tissue. In obesity, there may be a competition between these differentiation pathways for the limited number of ASCs (Fig. 3). This competition has metabolic consequences when the tissue is undergoing a rapid expansion leading to obesity. Inflammation and angiogenesis are two important microenvironmental factors that determine the outcome in the competition for lineage commitment of progenitor cells. Inflammation may suppress the generation of pre-adipocytes from ASC by inhibition of adipocyte differentiation. In contrast, inflammation may promote differentiation of ASC into endothelial precursors. As a result, the dynamics of adipocyte turnover in adipose tissue will be interrupted. This disbalance can be restored by drugs such as TZDs, which induces pre-adipocytes differentiation to adipocytes. Lack of endothelial cells impairs angiogenesis and leads to ATH, which triggers the compensatory inflammatory response. This engages a feedback response, whereby inflammation promotes ASC differentiation into endothelial cells to improve blood supply in adipose tissue through angiogenesis. Although these possibilities are supported by much evidence, direct proof of the possibilities remains to be done in the adipose tissue in obesity.

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Fig. 1. Induction of inflammatory response by hypoxia in adipose tissue

Hypoxia activates transcription factors HIF-1 α (hypoxia inducible factor 1 alpha) and NF- κ B (nuclear factor kappa B). Those transcription factors activates transcription of inflammatory genes, such as inducible nitric oxide synthase (iNOS), macrophage migration inhibitory factor (MIF), transforming growth factor beta (TGF- β), tumor necrosis factor alpha (TNF- α), interleukin 6 (IL-6), monocyte chemotactic protein 1 (MCP-1), et al. Expression of these genes will lead to macrophage infiltration and activation in adipose tissue.

Fig. 2. Regulation of adipocyte differentiation by inflammation

Insulin receptor substrate 1 (IRS-1) mediates insulin receptor signal in adipocytes for glucose and fatty acid uptake. Inhibition of IRS-1 function by inflammation leads to suppression of triglyceride synthesis in adipocytes. Inflammation inhibits PPAR γ activity to block the transcriptional program for adipocyte differentiation. IRS-1 and PPAR γ are two representative targets of inflammation in the inhibition of adipocyte differentiation.

Fig. 3. Regulation of ASC differentiation by inflammation

Adipose-derived stem cells (ASCs) are the common progenitors of adipocytes and endothelial cells. Inflammation inhibits ASC differentiation into adipocytes, but promotes ASC differentiation into endothelial cells. In this way, inflammation mediates competition between adipocytes and endothelial cells for the limited source of stem cells in adipose tissue in obesity. This possibility represents a new activity of chronic inflammation in adipose tissue.