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The Role of Adipocyte Hypertrophy and Hypoxia in the Development of Obesity-Associated Adipose Tissue Inflammation and Insulin Resistance

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Abstract

Adipose tissue inflammation has been suggested to play a central role in the pathogenesis of many obesity-associated complications including insulin resistance and type 2 diabetes. Adipocyte hypertrophy and hypoxia especially in morbid obesity are the important sources for the development of adipose tissue inflammation. This inflammation is mediated by producing a large number of cytokines and chemokines, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and regulated upon activation, normal T-cell expressed and secreted (RANTES). Of note, these cytokines and chemokines produced by adipocytes during hypertrophy and hypoxia are crucially involved in the initiation and development of obesity-associated inflammatory response in adipose tissue. The capacity of constitutive and regulated release of immune mediators from adipocytes demonstrates a causal link between the biology of adipocytes and immune cells, such as macrophages and T cells. Moreover, the synergistic effect of hypertrophic, hypoxia adipocytes, and adipose tissue immune cells has also been implicated in the development of obesity-induced insulin resistance. This chapter provides the overall review and update evidence to highlight the important role and possible underlying mechanism of adipocyte hypertrophy and hypoxia in the development of obesity-associated adipose tissue (AT) inflammation and insulin resistance.

Keywords: adipocyte, hypertrophy, hypoxia, adipose tissue inflammation, insulin resistance

1. Introduction

Adipose tissue inflammation has been suggested to be crucially involved in the pathological mechanisms of obesity-associated cardiometabolic complications, including insulin resistance, type 2 diabetes, atherosclerosis, and non-alcoholic fatty liver disease (NAFLD). However, the underlying mechanisms of this process are still under investigation.

Adipocytes in an obesity setting, especially in morbid obesity, are characterized by hypertrophy and hypoxia, and they are the important sources to initialize adipose tissue inflammation. This inflammation is mediated by producing a large number of cytokines and chemokines, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and regulated upon activation, normal T-cell expressed and secreted (RANTES). These cytokines and chemokines produced by adipocytes during hypertrophy and hypoxia significantly contribute to the development of obesity-associated adipose tissue inflammation. The capacity of constitutive and regulated release of immune mediators from adipocytes demonstrates a causal link between the biology of adipocytes and immune cells, such as macrophages and T cells. Moreover, the interplay of hypertrophic, hypoxia adipocytes and adipose tissue immune cells has been speculated to play the key regulatory role in the development of obesity-induced insulin resistance.

This review provides update evidence to emphasize the important role of adipocyte hypertrophy and hypoxia in the development of obesity-associated adipose tissue (AT) inflammation and insulin resistance and also discusses possible underlying mechanism.

2. Main subjects

2.1. Adipose tissue inflammation crucially contributes to the pathogenesis of obesity-associated insulin resistance and type 2 diabetes mellitus (DM)

According to the World Health Organization, the worldwide prevalence of obesity and its metabolic complications have increased substantially in recent decades. More than 1.9 billion adults were overweight and over 600 million of these were obese in 2014 [1]. Excess adiposity and adipocyte dysfunction in the state of obesity result in dysregulation of a wide range of adipose tissue-derived secretory factors, which may contribute to the development of various metabolic diseases via altered glucose and lipid homeostasis as well as inflammatory responses. Two important publications in 2003 [2,3] have demonstrated the crucial role of adipose tissue macrophage infiltration in obesity-associated adipose tissue inflammation and associated insulin resistance [4]. Progression of morbid obesity is closely linked to a phenotype switch of the macrophage activation state in adipose tissue. In the obese insulin-resistant state, anti-inflammatory M2 macrophages initially resided in adipose tissue would be progressively replaced by pro-inflammatory M1 macrophages [5]. On the other hand, in the previous issue of Nature Medicine, three different groups published the related aspects of an important link between adaptive immunity (T-cell mediated) in obesity-induced adipose tissue inflammation and insulin resistance in mice. Their results implicate that the alteration in the infiltrated adipose tissue T cells occurs early in obesity and shows the causal relationship between immunity and metabolism. For instance, Nishimura et al. [6] analyzed the dynamics of the inflammatory infiltrate in the visceral fat of C57Bl/6 mice with diet-induced obesity. They used mice with immunological and genetic depletion of CD8⁺ T cells (lose and gain of function) to and demonstrated that these T cells are critical mediators of systemic metabolic dysfunction. In addition, obesity alters the balance between Th1 and Th2 stimulation in fat, perhaps through the depletion of Th2 and Treg T cells, and subsequently inducing the increase in

CD8⁺ and Th1 T cells [6–8]. Thereby, these findings suggest that phenotype switch and immune cell infiltration in adipose tissue are crucial for the development of obesity-related adipose tissue inflammation and metabolic dysfunction [3,9,10].

On the other hand, the excess fat accumulation promotes the release of free fatty acids from adipose tissue into the circulation and affects many other tissues, including the liver, skeletal muscle, and heart. [11]. The detrimental effects of fatty acids and their metabolites, such as acyl-coenzyme A, ceramides, and diacylglycerol, on insulin signaling through activating protein kinases such as protein kinase C, mitogen-activated protein kinases (MAPK), c-Jun N-terminal kinase (JNK), and the inhibitor of nuclear factor- κ B kinase B have been reported [12]. Moreover, free fatty acids serve as ligands for the Toll-like receptor 4 (TLR4) complex [13] and stimulate cytokine production of macrophages [14], thereby modulating inflammation of adipose tissue which also significantly contributes to obesity-associated metabolic complications.

2.2. The development of adipocyte hypertrophy and hypoxia in adipose tissue inflammation

Adipose tissue can respond rapidly and dynamically to alterations in nutrient deprivation and excess through adipocyte hypertrophy and hyperplasia [15]. Especially in morbid obesity, in contrast to adipose tissue expansion in health obesity consisting of an enlargement of adipose tissue through effective recruitment of adipogenic precursor cells to the adipogenic programs, the pathogenic adipose tissue expansion consists of massive enlargement of existing adipocytes and limited angiogenesis and ensuring hypoxia [16]. For instance, adipocytes become hypertrophic during the development of obesity, and their size increases up to 140–180 μ m in diameter, but the diffusion limit of oxygen is at most 100 μ m [17]. On the other hand, it is possible that the blood supply to adipocytes may be reduced during the progressive adipocyte enlargement with consequent hypoxia [18].

2.3. The hypothesis and evidence about the effect of adipocyte hypertrophy and hypoxia on the development of adipose tissue inflammation and insulin resistance

Recent studies have demonstrated that adipose tissue during the development of morbid obesity is characterized by adipocyte hypertrophy followed by hypoxia, immune cell infiltration, and pro-inflammatory adipocytokines during progress of chronic inflammation. In addition, the concomitant development of reduced blood flow perfusion, lipotoxicity, and adipocyte cell death would also further deteriorate the progress of adipose tissue inflammation (**Figure 1**).

2.3.1. Effect of adipocyte hypertrophy on adipose tissue hypoxia

Obesity as excess of adipose tissue is attributed to hypertrophy and hyperplasia of adipocytes. Adipocytes have a limited capacity for hypertrophy. One explanation is considered the diffusion limit of oxygen, which is at most 100 μ m [17]. Therefore, it is possible that hypertrophic adipocytes might endure less than adequate oxygen supply. On the other hand, it has been demonstrated that hypoxia of obese mice may occur in the areas within adipose tissue as a result of adipocyte hypertrophy compromising effective O₂ supply from the vascular and then

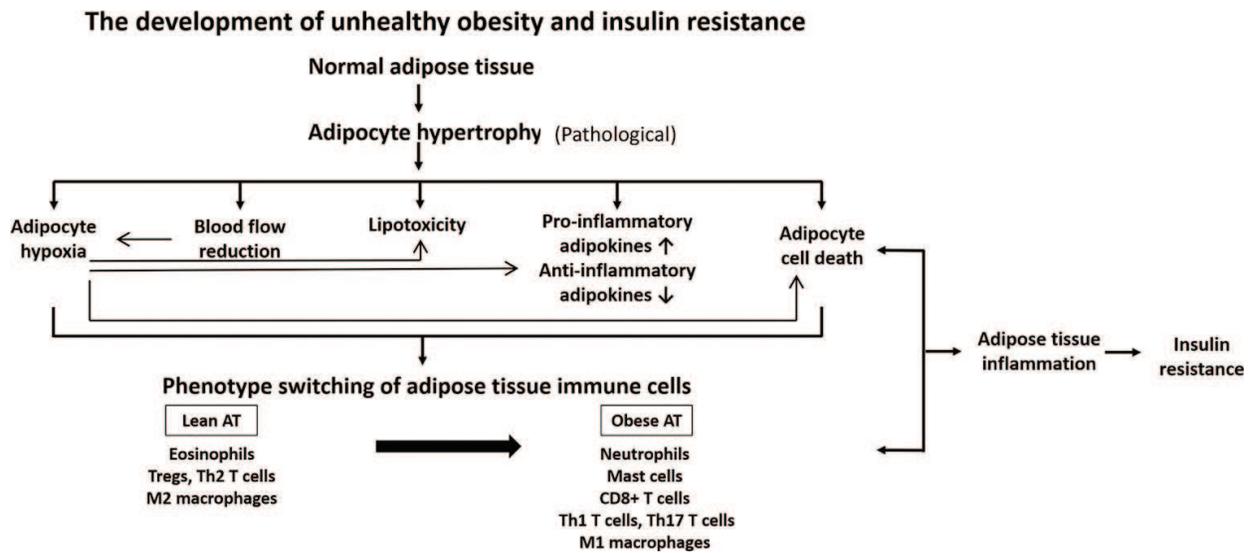


Figure 1. The development of unhealthy obesity and insulin resistance.

initialize an inflammatory responses indicated by pimonidazole hydrochloride adduction (physical evidence) as well as lactate concentration (physiological evidence) [19]. Moreover, it has also been reported that hypoxia results in inflammation in adipose tissue and insulin resistance *in vitro* and in animal studies [19–21].

The hypoxia is able to induce inflammation in adipose tissue by the induction of hypoxia-related gene expression in adipocytes and macrophages. An important and well-characterized key regulator of the adaptive response to alterations in oxygen tension is hypoxia-inducible factor-1 α (HIF-1 α), a transcription factor that accumulates during hypoxia and activates the nuclear factor- κ B pathways, leading to increased inflammation and stimulation of angiogenesis [19].

Of note, hypoxia-inducible factor-1 α (HIF-1 α), which plays a pivotal role in the response to hypoxia [20], is regarded as the master regulator of O₂ homeostasis. HIF-1 α has been identified in human adipose tissue and is reported to be increased in obesity [21]. In addition, several rodent studies have shown that the increased gene expression of HIF-1 α , more hypoxic areas, and lower PO₂ were detected in white adipose tissue of *ob/ob*, *KKAy*, and dietary-induced obese mice [22–24]. Reduced oxygen tension has been directly measured in obese fat depots in mouse models and human subjects [23]. Overexpression of HIF-1 α in the adipocyte has also been proved to be more pro-fibrotic and pro-inflammatory than pro-angiogenic [25]. Adipocyte-specific deletion of HIF-1 α limited high-fat diet-induced adipose tissue inflammation and insulin resistance, and the tissue was equally vascularized as wild-type controls [26]. Thereby, the augmentation of HIF-1 α expression could contribute to a localized inflammation in adipose tissue that propagates an overall systemic inflammation associated with the development of obesity-related comorbidities [27].

2.3.2. Effect of adipocyte hypertrophy on production of free fatty acids (lipotoxicity)

Hypertrophic adipocytes are subjected to multiple cytotoxic stressors including lipotoxicity [27]. Impaired insulin action in adipocytes during the development of hypertrophy and

hypoxia is associated with elevated lipolysis and increased release of free fatty acids leading to ectopic fat deposition in liver and skeletal muscle. Subsequently, it will cause the progress of systemic insulin resistance [27]. Chronic hypoxia has been suggested to be part of the pathological mechanisms causing dysfunction of adipocytes [20,25]. For instance, chronic hypoxia leads to derangements in lipid metabolism and reduced lipoprotein clearance by decreasing lipoprotein lipase activity in mice [28] and diminished subcutaneous adipose tissue lipolysis by decreased efficiency of lipolytic signaling driving by the lipolytic signaling of beta-adrenergic nervous system, growth hormone, and parathyroid hormone in humans [29]. Moreover, the increment of circulating free fatty acids (FFA) could be triggered by acute hypoxia in an ischemia model of adult rats [24]. Acute hypoxia was also shown to increase lipolysis by activation of adipocyte protein kinase A via increased epinephrine and norepinephrine release following sympathetic nervous system stimulation [30]. In addition, the study conducted with *ob/ob* mice showed that adipose tissue hypoxia caused free fatty acid release and inhibited glucose uptake in adipocytes by inhibition of the insulin-signaling pathway [24].

Nevertheless, the increase in fatty acid flux into the fat cells also results in greater synthesis of the FFA into triglycerides, which would lead to endoplasmic reticulum (ER) stress activating the JNK pathway and thus further increasing insulin resistance in the fat cells [31].

2.3.3. Effect of adipocyte hypertrophy on adipose tissue blood flow reduction

The growing fat mass, in particular, the abdominal adipose tissue, is associated with unfavorable changes in adipose tissue blood flow and the development of metabolic disorders in state of obesity. The diminished blood flow shown in enlarged fat mass might mainly attribute to the development of adipocyte hypertrophy.

A decrease in adipose tissue perfusion is a common feature in obesity. West et al. [32] demonstrated that blood flow to adipose tissue, measured with radiolabeled microsphere, was reduced in Zucker obese rats. In humans, the levels of adipose tissue blood flow were measured with positron emission tomography using [¹⁵O]-labeled water [33] and the ¹³³Xe washout method [34] and were lower in obese compared with non-obese subjects. In addition, the disturbances in the regulation of adipose tissue blood flow have been linked to obesity and insulin resistance [35]. This study demonstrated a close relationship between insulin sensitivity and the regulation of postprandial adipose tissue blood flow, independent of adiposity. Therefore, impaired regulation of adipose tissue blood flow by adipocyte hypertrophy could also be a significant and independent contributor for the development of insulin resistance in the state of obesity [35].

2.3.4. Effect of adipocyte hypertrophy on adipocyte death

As mentioned above, adipocyte hypertrophy could directly and indirectly cause adipocyte hypoxia. Hypoxia may be a potential risk factor for adipocyte death in adipose tissue of obese subjects. An increase in adipocyte death was reported in adipose tissue of obese subjects and was proposed to induce macrophage infiltration [36]. The cell death may also promote lipolysis and release of FFA into blood stream under insulin resistance. This will significantly contribute to the increase in plasma FFA in obesity. Moreover, it has been demonstrated that

the frequency of adipocyte death was significantly associated with the adipose gene expressions of TNF- α , IL-6, and MCP-1 in adipose tissue and the development of whole-body insulin resistance [37].

Macrophages are extremely proficient in the removal of numerous molecules, ranging from small lipids to colonies of pathogens to dead cells. Necrosis of adipocytes, driven by hypertrophy and accelerated by obesity, is a prominent phagocytic stimulus that attracts macrophage infiltration into adipose tissue [18]. Using a transgenic animal model of inducible lipoatrophy, Pajvani et al. demonstrated that massive adipocyte death can indeed drive rapid accumulation of adipose tissue macrophages (ATMs) as an integral element in the remodeling of fat pads [38]. These observations implicate an important role of adipocyte hypertrophy in the development of adipocyte death and associated inflammatory changes in AT and obesity complication.

2.3.5. Effect of adipocyte hypertrophy on adipokine production

Elevation of pro-inflammatory cytokines in fat and circulation such as TNF- α , IL-1, IL-6, MCP-1, and PAI-1 has been documented in obesity [23,25,39]. The increase in adipokine production in adipocyte hypertrophy and hypoxia has been suggested to underlie the development of the inflammatory response in adipose tissue, which occurs in the obese state [11,40]. It has been clearly indicated that adipocyte size is an important determinant for the secretion of several inflammatory adipokines, such as leptin, IL-6, and MCP-1, thereby providing another link between adipocyte size and inflammation in obesity [41]. In the same study, there was a tendency to reduce the release of anti-inflammatory adipokines such as IL-10 and adiponectin with increasing adipocyte size [41].

On the other hand, hypoxia has been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue, which subsequently results in the dysregulation of the production of inflammation-related adipokines such as leptin, adiponectin, TNF- α , IL-6, and vascular endothelial growth factor (VEGF) [40,42]. Recently, hypoxia has also been reported to induce the production of PAI-1 and to inhibit the synthesis of adiponectin by 3T3-L1 adipocytes [39]. It is also reported to induce the expression of visfatin in these cells [43]. The expressions of other major adipokine production from murine or human adipocytes including angiopoietin-like protein 4 (Angptl4), interleukin-6 (IL-6), macrophage migration inhibitory factor (MIF), and VEGF [23,40,44] are also stimulated by hypoxia. Accordingly, Wang et al. mimicked hypoxia in human adipocytes for 24 h using cobalt chloride (CoCl₂). It is shown that HIF-1 α along with oxidative stress markers, inflammatory markers, and leptin was increased, but conversely adiponectin was decreased during hypoxia [42].

2.4. The interaction of adipocytes under hypertrophy and hypoxia and infiltrated immune cells in development of adipose tissue inflammation and obesity complications

Adipocyte hypertrophy and hypoxia are crucially involved in adipose tissue inflammation via induction of pro-inflammatory cytokines, as well as of chemokines that attract immune cells in the early development of obesity. It has long been known that adipose tissue in obesity is in a heightened state of inflammation. Recently, it has been transformed by the knowledge that immune cells such as macrophages and T cells can infiltrate adipose tissue and are responsible

for the majority of inflammatory cytokine production and adipose tissue inflammation. It has also been suggested that adipocytes could act as antigen-presenting cells to immune cells in adipose tissue inflammation [45].

2.4.1. Macrophages

Some of the consequences of adipocyte hypertrophy include fatty acid flux, vascularization, increased adipokine secretion, hypoxia, and adipocyte cell death. These adipocyte-related consequences of adipose tissue expansion are important contributors to the initiation of macrophage recruitment in morbid obesity. Macrophage infiltration in the inflamed adipose tissue results from blood monocyte influx, mainly attracted by the chemokine MCP-1, which is mainly secreted by hypertrophic adipocytes [46]. Adipose tissue macrophages (ATMs) accumulate in both the subcutaneous and visceral expanding fat depots [46]. Apart from increasing in numbers, adipose tissue macrophages are also phenotypically changed during obesity from the anti-inflammatory M2 macrophages to pro-inflammatory M1 macrophages dominantly in that of obese mice [5]. Activated M1 ATMs are the prominent source of pro-inflammatory cytokines such as TNF- α and IL-6, which can block insulin action in adipocytes via autocrine/paracrine signaling and also cause systemic insulin resistance via endocrine signaling. Of note, adipokine production during adipocyte hypertrophy and hypoxia such as free fatty acids and TNF- α has been reported to facilitate M1 phenotype switch in the state of obesity [47].

2.4.2. T cells

In addition to macrophages, recent studies have revealed a growing list of other immune cells that are involved in the regulation of adipose tissue remodeling in state of obesity. It has been demonstrated that RANTES release is dependent on adipocyte size and is higher than those of obese donors. Hypoxia could also cause an increase in RANTES release [48,49]. Human adipocytes express the chemokine RANTES and are thus identified as one of the novel cellular sources of the immune mediator. Wu et al. [50] found higher RANTES mRNA levels in visceral compared with subcutaneous adipose tissue in obese humans. Elevated RANTES expression in the adipose tissue of diet-induced obese male mice is associated with increased T-cell infiltration, suggesting paracrine chemotactic effects [50]. Recently, it has been suggested that adipocytes could act as antigen presenting cells to T cells during adipose tissue inflammation [45]. Major histocompatibility complex (MHC) class II molecules on adipocytes can functionally activate CD4⁺ T cells in an antigen-specific and contact-dependent manner [45]. Therefore, adipocytes seem to act as key regulatory cells in the control of adipose tissue inflammation through cytokine secretion and antigen presentation. The interaction involves several T lymphocyte lineages including CD4⁺ and CD8⁺ T cells, regulatory T cells, and mast cells [6,51]. In particular, the levels of CD8⁺ T cells are enriched in the early stages of obesity before the accumulation of ATMs [6]. It implicates a potential role for CD8⁺ T cells in the initiation of the subsequent inflammatory cascade. It is also suggested that adipose tissue inflammation is the coordinated inflammatory responses involving hypertrophic, hypoxic adipocytes, recruitment of ATMs, the accumulation of pro-inflammatory T cells (CD8⁺ and Th1 CD4⁺ T cells), and the loss of anti-inflammatory regulatory T cells, Th2 CD4⁺ T cells as well as the appearance of B cells, natural killer (NK) cells, eosinophils, neutrophils, and mast cells [6,51–53].

Furthermore, the recently discovered T helper 17 (Th17) cells represent a novel subset of CD4⁺ T cells, defined by their production of interleukin 17 (IL-17) [54]. Interestingly, serum IL-17 is upregulated in obese human patients [55], and obesity is positively correlated with enhanced IL-17 expression in T cells isolated from spleen [56]. Zúñiga et al. revealed that IL-17 secreted by T cells in adipose tissue is an important negative regulator of adipogenesis via suppressing the expression of several pro-adipogenic transcription factors, including PPAR- γ and C/EBP- α [57] and also glucose metabolism to aggravate insulin resistance [58]. Thereby, increased IL-17 secretion by Th17 cells inhibits the differentiation of adipocyte-derived stem cells (ASCs) to adipocytes and also suppresses the insulin responsiveness of the adipocytes. Eljaafari et al. [59] provide intriguing evidence by using the co-culture of human ASCs with human mononuclear cells (MNCs), ASCs from obese donors augment the differentiation of naïve CD4⁺ T cells toward Th17 cells and change the phenotype of MNCs via increased the secretion of IFN- γ by Th17 cells. Taken together, these observations suggest an important role of IL-17 and Th17 cells in obesity-related adipose tissue dysfunction and systemic complications.

2.4.3. Others

The development of adipocyte hypertrophy and hypoxia plays an important trigger to initialize immune cells infiltration, either directly or indirectly. As mentioned above, adipocytes act as key regulatory cells in the control of adipose tissue inflammation through cytokine secretion and antigen presentation. Immune cells such as macrophages, T cells, mast cells, and eosinophils have all been implicated to substantially participate into the process of adipose tissue inflammation [60]. Besides ATMs and T cells, increased infiltration of neutrophils into adipose tissue has also been documented in high-fat diet (HFD)-induced obese mice [61]. Neutrophils secrete various proteases, such as neutrophil elastase. The depletion of neutrophil elastase in HFD-fed mice improves adipose tissue inflammation, implicating that secreted elastase from neutrophil is the key mediator of adipose tissue inflammation [61]. In addition, it has been demonstrated that eosinophil regulated macrophage activation in adipose tissue and also plays a crucial role in metabolic homeostasis. Alternatively activated (M2) macrophages induced by Th2 cytokines IL-14, which is major secreted from eosinophils. Alternatively activation of ATMs in adipose tissue is impaired in the absence of IL-4 or eosinophils [60]. Mast cells have been shown to accumulate in the visceral adipose tissue of obese mice. Mast cell Kit^{W-sh/W-sh}-deficient mice without mature mast cells are resistant to high fat diet-induced obesity and exhibit significant reduction in pro-inflammatory cytokines and chemokines and also in macrophage number in visceral adipose tissue [62]. Therefore, it appears that mast cell arrival in adipose tissue precedes the release of pro-inflammatory mediators that attract macrophages [62].

In addition, our recent study [63] has further demonstrated that COX-2 mediated PGE₂ EP3 signaling during the development of adipocyte hypertrophy and hypoxia is important to recruit and interact with adipose immune cells to amplify the inflammatory responses in adipose tissue, which is also causally linked to the development of systemic insulin resistance.

2.5. The regulatory mechanisms of adipocyte hypertrophy in the development of obesity

The pathogenic change of adipocyte hypertrophy during obesity is determined by two distinct processes of adiposity: adipocyte differentiation (adipogenesis) and lipogenesis. They are

dependent on both of genetic predisposition and environmental surroundings. During persistent positive caloric intake, adipocyte hypertrophy might result in adipocyte dysfunction while adipogenesis is impaired [64,65].

On the other hand, the mechanisms of adipocyte differentiation have been extensively studied in recent decades. A number of key transcription factors and adipokines in adipocyte differentiation have been identified [66]. For instance, they are included peroxisome proliferator-activated receptor (PPAR) family proteins [67], CCAAT/enhancer-binding protein (C/EBP) [68], adipocyte differentiation determination-dependent factor 1 (ADD1) [69], and sterol response element-binding protein 1 (SREBP 1) family proteins [70]. In addition, the tyrosine phosphorylated Dok1 has also been demonstrated to promote adipocyte hypertrophy by counteracting the inhibitory effect of extracellular signal-regulated kinase (ERK) on PPAR- γ [71].

In addition, sustained energy excess could facilitate the storage of energy through lipogenesis and hypertrophy of existed adipocytes than through adipogenesis with recruitment and differentiation of new adipocytes from pre-adipocytes. Eventually, it would lead to pathologic adipocyte hypertrophy that contributes to the development of adipose tissue inflammation and obesity-associated metabolic disorders [72,73].

2.6. The therapeutic implications

In this chapter, we discuss the recent advance about the role of adipocytes in the control of development, growth, and remodeling of obesity-associated adipose tissue. This review article further highlights the important role of adipocytes during hypertrophy and hypoxia in the development of adipose tissue inflammation and following insulin resistance. Furthermore, the understanding of regulatory mechanism of adipocyte hypertrophy during the development of obesity could provide better strategy for the prevention and treatment of obesity-associated type 2 diabetes and metabolic syndrome.

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