Chapter

Adipose Tissue Inflammation and Metabolic Disorders

Felipe Henriques, Alexander H. Bedard and Miguel Luiz Batista Júnior

Abstract

Adipose tissue not only possesses an important role in the storage of excess nutrients but also acts as a critical immune and endocrine organ. Researchers and clinicians now consider adipose tissue to be an active endocrine organ that secretes various humoral factors called "adipokines," which imparts important systemic metabolic effects, from food intake to glucose tolerance. Along with its production of specialized adipokines, adipose tissue also secretes proinflammatory cytokines that likely contributes to the low-level systemic inflammation that has become a hallmark of various metabolic syndrome-associated chronic pathologies, such as obesity and cancer cachexia. These systemic effects may be mediated by communication networks arising from the multitude of resident adipose cells, including adipocytes, endothelial cells, neuronal cells, stem cells and other precursors, and a wide variety of immune cell populations that recent studies have demonstrated play a crucial role in the development of adipose inflammation and systemic metabolic abnormalities. In this chapter, we detail various molecular pathways linking excess adipose lipid storage to chronic inflammation and review the current knowledge as to what triggers obesity- and cachexia-associated inflammation in adipose tissue. Finally, we describe how the cross talk between adipose tissue inflammation and the non-adipocyte resident cells present in tissue is involved in this metabolic disruption.

Keywords: adipokines, remodeling, cross talk, cachexia, obesity

1. Introduction

In recent years, adipose tissue has rapidly emerged as a critical player in maintaining an organism's metabolic homeostasis through its canonical role in storing excess energy, as well as its emerging role in facilitating communication modalities critical to maintaining systemic metabolism. These diverse abilities possessed by adipose tissue directly results from its heterogeneous composition which allows for the integration and propagation of signals that influence whole-body homeostasis. To be effective in reacting to alterations within the organism, the adipose tissue must be dynamic and remodel itself in order to preserve the health of the organism. While remodeling allows for the maintenance of homeostasis, this mechanism may become compromised in certain metabolic diseases, such as cancer cachexia and obesity. Here, the influence of adipose heterogeneity on tissue remodeling in the context of cancer cachexia and obesity will be further discussed.

2. The adipose tissue

2.1 Adipose heterogeneity

Adipose tissue, or fat tissue, is classified in morphofunctional term into two distinct groups; (1) white adipose tissue (WAT), composed predominantly of unilocular adipocytes, with low mitochondrial density and low oxidative capacity, and (2) brown adipose tissue (BAT), predominantly composed of multilocular adipocytes, high mitochondrial density and oxidative capacity for the uptake and oxidation of fatty acids and glucose related to the maintenance and regulation of body temperature [1]. Other differences between the two types of adipose tissues are the depot localization, profile of secreted molecules, cell population, vascularization and also innervation [2–4]. While both of these adipose tissue groups contribute a significant role in maintaining systemic homeostasis, WAT is the primary site of metabolic dysregulation in many metabolic diseases [5, 6].

WAT is divided into two large depots, subcutaneous adipose tissue (scWAT) and visceral adipose tissue (vWAT). scWAT is present in the innermost layers of the skin (hypodermis), while vWAT is located in the internal organs [7]. In addition, it is well described, both in experimental and clinical research, that adipose tissue is a heterogeneous tissue, that presents different gene and protein expression profiles, as well as cellular composition depending on the location of the tissue [8, 9]. scWAT represents approximately 80% of the total fat mass in healthy individuals, while vWAT accounts for between 10 and 20% of the total body fat of lean men, and between 5 and 10% of total fat in women [10]. vWAT has been shown to be more metabolically responsive, and its accumulation has a higher correlation with obesity-related mortality [11].

The morphological composition of adipose tissue plays an important role in the homeostatic maintenance and tissue development. Adipose tissue is a special type of connective tissue composed of different cell types composed of approximately 50–70% adipocytes and 30–50% of stromal vascular fraction (SVF) cells, where the mesenchymal precursor cells, pre-adipocytes, fibroblasts, leukocytes, blood vessels, lymph nodes and nerves are present (**Figure 1**) [12–14]. Numerous studies have shown the cellular heterogeneity of adipose tissue is a critical component in the

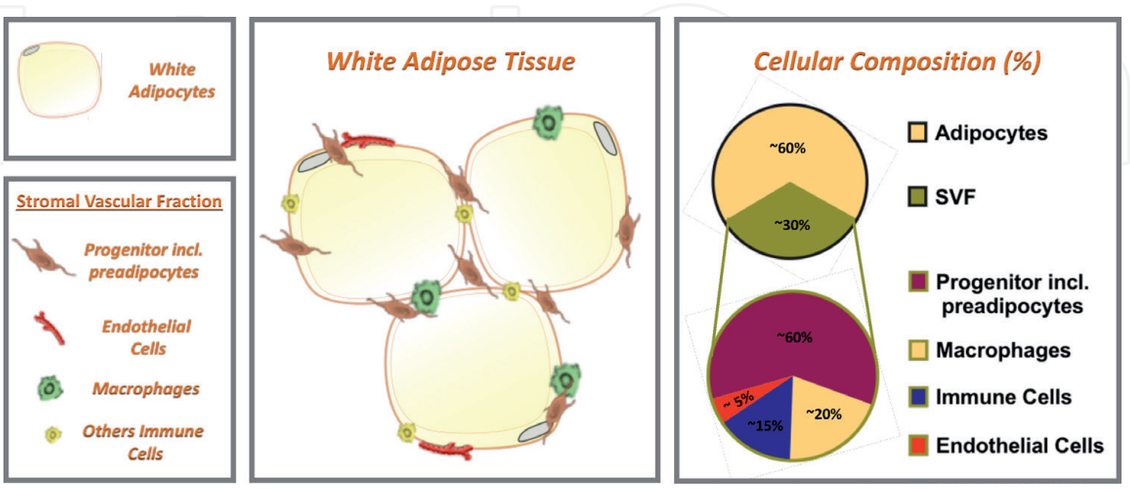

Figure 1.
Adipose tissue cellularity. The vast majority of the adipose tissue mass is composed of adipocytes (approximately 60%). There are many other cell types present in the adipose tissue. This specific portion of non-adipocytes is called the stromal vascular fraction (SVF) that is approximately 30% of the total cells in the tissue. In this portion are present mesenchymal precursor cells, pre-adipocytes, macrophages, others immune cells and endothelial cells.

tissue's ability to act as a hub of metabolic equilibrium [8, 15, 16]. Discovering and understanding the role of each cell present in adipose tissue leads to a greater chance in the development of possible therapeutics targeting metabolic disorders, which places a greater emphasis on studies of adipose cellularity.

2.2 Adipose tissue as an endocrine organ

This endocrine role of adipose tissue is best characterized by leptin [17, 18]. In 1994, with the discovery of leptin, the perception of WAT evolved from simply an energy storage compartment, mechanical protector and thermal insulation, but also an endocrine organ due the identification of a multitude of adipocyte-secreted factors that can act on distal tissues to regulate systemic functions, such as immunological and inflammatory responses, regulation of appetite, vascular events, control of reproductive functions, and insulin sensitivity [17, 19]. Total deficiency or insensitivity to leptin causes hyperphagia, morbid obesity, diabetes, a variety of neuroendocrine abnormalities, and autonomic and immunologic dysfunction [20].

Studies show that adipose tissue-derived hormones, fatty acids, lipids and signaling molecules, act by exerting endocrine, autocrine and paracrine effects. These factors are part of the large family of proteins and small molecules released by adipose tissue, which collectively are called adipokines [17, 21]. This tremendous diversity of signaling molecules enables the adipose tissue to engage in a wide array of signaling modalities that allows for systemic regulation of an organism's physiology (**Figure 2**). In instances of whole-body metabolic dysregulation, such as cancer cachexia and obesity, alterations to adipose tissue composition may have drastic effects on adipokine production. These effects are of critical importance in understanding the manifestation of metabolic syndromes. One example of such a dysregulation in adipokine profile is the release of pro- and anti- inflammatory adipokines during pathophysiological processes. This adipokine dysregulation

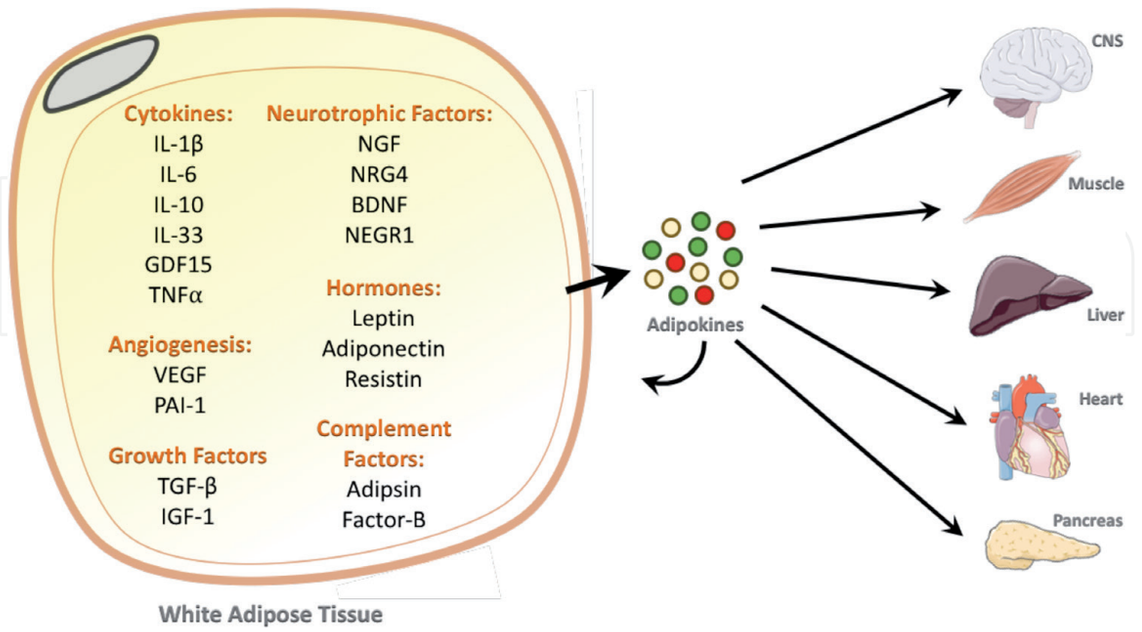

Figure 2.
Adipose tissue as endocrine organ. Endocrine factors released by white fat may signal to distant issues, including the brain, muscle, liver, heart and pancreas that regulate glucose and fatty acid metabolism in peripheral tissues, energy homeostasis, inflammatory response, and blood pressure, among others. Imbalanced secretion of some of these adipokines is associated with metabolic disorders. These factors released by white adipose tissue may target itself in an autocrine and paracrine manner, and also activate distant tissues in an endocrine manner (e.g., brown adipose tissue). Abbreviations see appendices and nomenclature section.

contributes significantly to the disruption of adipose tissue homeostasis in these diseases. Excessive secretion of potentially harmful adipokines (e.g., PAI-1, TNF-α and IL6) and hyposecretion of potentially beneficial adipokines, (e.g., adiponectin), may play an important role in the major mechanisms involved in during metabolic diseases. Thus, understanding the mechanism of various metabolic diseases calls for a deep understanding of the relationship between adipose tissue cellular composition and function.

2.3 Adipose tissue remodeling

Adipose tissue can respond rapidly and dynamically depending on the situation involved, thus fulfilling its major role in preserving whole-body energy homeostasis [22, 23]. Adipose tissue remodeling is a continuous process that is involved in some metabolic syndromes, such as reduction of vascular remodeling [24], overproduction of extracellular matrix [25], altered immune cell populations, and inflammatory responses are classic tissue response to such metabolic imbalances [26]. However, not all remodeling of adipose tissue is necessarily associated with pathological changes. A classic example is a concept of "metabolically healthy obesity" [27, 28], suggesting that some individuals may preserve systemic insulin sensitivity based on the "healthy" expansion of adipose tissue, avoiding the pathological consequences associated with obesity. Among the various consequences that can arise from adipose tissue remodeling is a state of local inflammation. This inflammatory state has been implicated in the progression of systemic dysregulation of metabolism in instances of "metabolically unhealthy obesity" [29]. Thus, comprehending the role of inflammation in the remodeling process of the adipose tissue is essential in understanding the main pathological alterations of this tissue.

2.3.1 An overview of adipose tissue inflammation

The adipose tissue plays host to a variety of immune cell populations that are intimately involved in the remodeling state of the tissue. Adipose tissue resident cells can secrete several proinflammatory cytokines that can orchestrate the inflammatory state of the tissue by influencing these immune cell populations within the tissue itself [21]. These inflammatory mediators have several metabolic and endocrine functions (immunity, metabolism, energy balance, among others), which is intimal related to the inflammatory process and immune system response [30, 31].

Inflammation in adipose tissue rose to prominence in the mid-1990s, shortly after obesity was recognized as an inflammatory disease in a study conducted with rats, which demonstrated greater expression of the gene encoding the proinflammatory cytokine TNF-α in adipose tissue, as well as a reduction in insulin sensitivity after exposure to a weight-gain diet [32]. In recent decades, data from human studies and transgenic animal models have strongly suggested correlative but also causative associations between the activation of proinflammatory pathways and insulin resistance [33, 34]. Particularly, chronic inflammation in adipose tissue appears to play an important role in the development of insulin resistance related to obesity and others metabolic diseases [33, 35]. The following potential mechanisms of adipose tissue inflammation and how this state is involved during the pathological process of cancer-associated cachexia and obesity are discussed.

2.3.2 Adipose tissue inflammation during cancer cachexia

Cancer cachexia syndrome is characterized by systemic inflammation, body weight loss, adipose tissue remodeling, and skeletal muscle wasting that cannot be

fully reversed by conventional nutritional support and leads to progressive functional impairment [36]. Interesting, that adipose tissue of cachectic cancer patients is a possible relevant systemic source of inflammatory molecules during the development of the disease [37]. Moreover, it is now well described in both experimental and clinical research that these changes are dependent on the location of adipose tissue (e.g., visceral versus subcutaneous), which is involved in differential depot response to the disease [8, 38]. WAT also secretes and responds to pro-inflammatory mediators, as it also expresses several receptors for these secreted cytokines, chemokines, complement and growth factors [39]. These mediators act locally in an autocrine and/or paracrine manner, as well as distally in an endocrine fashion that can regulate appetite, modulate energy expenditure and affect a range of physiological processes, including insulin sensitivity and inflammatory responses [40].

Some interesting studies proposed that an imbalance between catabolic and anabolic processes in WAT is associated with the progression of cachexia. The proinflammatory cytokines interleukin 1-beta (IL-1β), interferon gamma (IFN-γ), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) appear responsible for the activation of WAT catabolism in experimental models [37, 41–44]. Additionally, studies have demonstrated a predominance of an inflammatory profile in the terminal phase of the cachexia syndrome, notably within vWAT [45]. The presence of an important macrophage infiltration in this depot in rats with cancer cachexia was verified, which has been shown to contribute to the secretion of inflammatory factors [45]. More recently, in the same model of cancer cachexia, Batista et al. [41] showed an increase of macrophages around the adipocytes that were are polarized to a proinflammatory state in the vWAT simultaneously with the activation of the inflammasome pathway in this specific depot [43]. This event was immediately preceded by an increase in neutrophil density within the depot, which usually occurs in the intermediate phases of the syndrome. Therefore, depending on the inflammatory phase, distinct cell types can be observed. In fact, in several inflammatory processes, chronic inflammation is characterized by the presence of mononuclear cells that is usually preceded by tissue infiltration of neutrophils, which are cells that characterize acute inflammation [46].

In addition to animal models of cachexia, a study has recently demonstrated the presence of an exacerbated inflammatory profile in the WAT of humans with cancer cachexia [38]. In particular, an increase in CD68 positive cells, indicative of macrophages, and the clustering of the classic "crown-like structure" around the adipocyte were described. This morphological characteristic, although well-detailed in an obesity model, was described for the first time in cachexia. In the same study, an increase in CD3, a lymphocyte marker, and total collagen-positive cells in the WAT of these patients with cachexia was also detected. Taken together, the data indicate the presence of morphological alterations that suggest WAT remodeling in the presence of cachexia in humans [38].

However, despite the relevance of local inflammation, notably in WAT, the mechanisms that result in this process still require further detailing. Another important aspect is the characterization and understanding of the inflammatory process in this condition and its possible relation with the metabolic disorders, in order to answer if this process is secondary or the "trigger" for the development of the syndrome. Understanding the basic mechanisms of cancer cachexia that orchestrate WAT remodeling is relevant for the development of new pharmacological and nutritional therapies for anti-cachectic purposes. In this context, further demonstrating an intimate correlation between inflammation and the prognosis of cancer-associated cachexia, it was demonstrated that a genetic and pharmacological (atorvastatin) model of Toll-like receptor 4 (TLR4) inhibition, one of the primary inflammatory mediators, was able to attenuate classic symptoms of cachexia in an

animal model [47]. This suggests that an important inflammatory pathway may be considered a promising target for therapeutic actions. It also further elucidates the mechanism by which cancer cachexia is manifested [47].

2.3.3 Adipose tissue inflammation during obesity

The incidence of overweight and obesity has increased substantially in the last decades worldwide is considered a worldwide epidemic, reducing the quality of life due to an increase in the physical and metabolic disability of individuals [48]. This occurs, at least partially, because of the obesity-induced insulin resistance and the fact that adipose tissue is not only an energy reservoir but also a secretory endocrine organ of cytokines, hormones, and proteins that affect the functionality of cells and tissues all over the body [49].

Recent studies have established association between obesity and systemic chronic low-grade inflammation [30, 50]. This association is characterized by, among other things, higher levels of circulating proinflammatory cytokines and fatty acids that can contribute to the development of the metabolic dysfunctions involved in the pathogenesis of its comorbidities [51].

It is well known that during this inflammation state in the adipose tissue, the tissue starts an intense remodeling in the adipose cell types present in the tissue. A major type of cell that plays an important role in the adipose tissue is the macrophages. Adipose tissue macrophage can be characterized in two different classes based on the expression of particular markers [52]. M1 macrophages or classically activated macrophages are characterized by *nitric oxide* synthase (*iNOS*) and CD11c surface expression, and expression of pro-inflammatory cytokines [53]. On the other hand, M2 macrophages or alternatively activated macrophages, are characterized by *Arginase* 1 (Arg1) and CD206 surface expression, and secrete anti-inflammatory cytokines predominates [53].

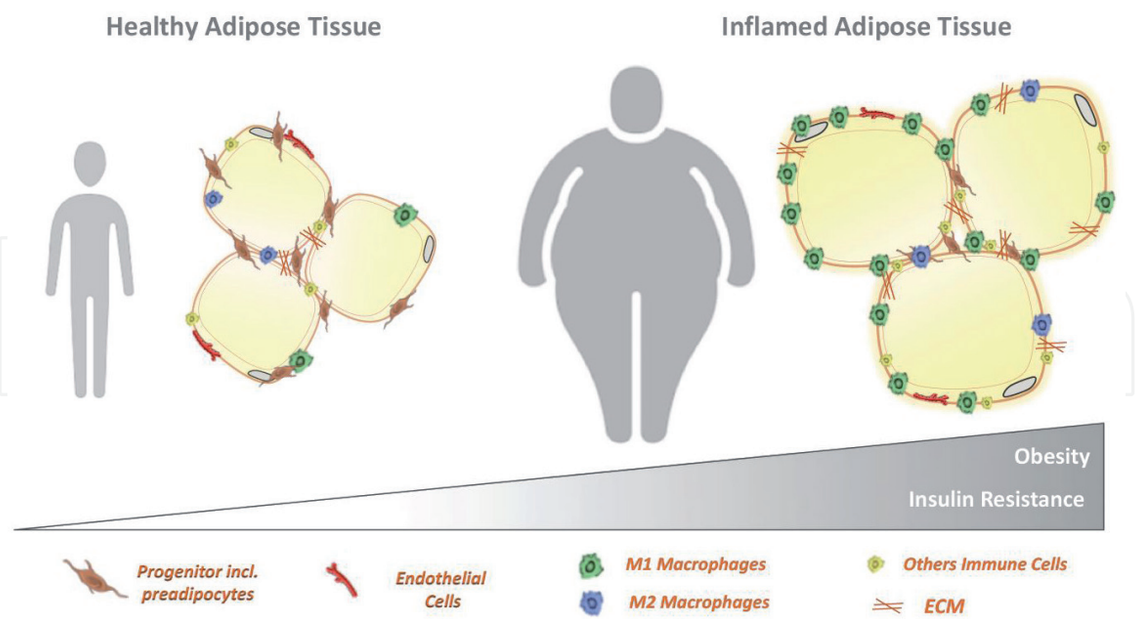

Figure 3.
Features in adipose tissue inflammation. Healthy adipose tissue displays high insulin sensitivity and is characterized by an anti-inflammatory state marked by elevated levels of adipocyte progenitor cells and M2 macrophages, sufficient vasculature to support tissue expansion and adipocyte hyperplasia. In an obese state, the adipose tissue contains hypertrophic adipocytes and a state of chronic inflammation exists within the tissue. A large increase in the populations of M1 proinflammatory macrophages, along with several other inflammatory leukocytes, begins to infiltrate the inflamed tissue. In addition, it is possible to observe a reduction in the vascularization of this unhealthy fat, resulting in a hypoxic state. Chronic inflammation results in the development of fibrotic structures in the form of increased extracellular components, such as collagen. Such events contribute to the development of insulin resistance.

A proposed model was defined as "phenotypic switching" that means an enhanced adipose tissue macrophage infiltration aggravates the environment of obesity-related inflammation [54]. This model emphasized that obesity starts to induced a polarization in these macrophage cells present in the tissue, that now the ratio M1/M2 macrophage are dysregulated and the M1 macrophage population are predominate in the adipose tissue [54]. Interesting that some studies showed that M1 macrophage population demonstrates a positive correlation with insulin resistance and an increase in proinflammatory responses [55]. Therefore, these studies suggest a sophisticated balance in relation to the diversity of macrophages population is necessary to sustain the adipose tissue homeostasis.

In addition to this deregulation in macrophages infiltration, other major changes also appear in the inflamed adipose tissue during obesity. Modifications in the composition of the extracellular matrix, decreased in the vascularization and alterations in the composition of immune cells in tissue are classic features of this adipose tissue remodeling [24, 26, 56] (**Figure 3**).

3. Concluding remarks

In summary, certain metabolic disease states, such as cancer cachexia and obesity, may alter the heterogeneous composition of adipose tissue, resulting in a remodeled tissue that is unable to properly respond to the systemic needs of the organism. We know that the adipose heterogeneity cells present in the tissue are the extremely importance in to regulate the homeostasis, and in the time that adipose tissue is affected to some metabolic syndrome this cross talk is deregulated and the homeostasis is compromised. After the adipose tissue is committed by a metabolic syndrome, the tissue starts to react in several ways. Several studies using cachexia and obesity experimental models have consistently indicated that a classic response to this imbalance, showed an intense adipose tissue remodeling in which the tissue begins to present numerous alterations in the morphology and also genetic alterations where its function ends up being extremely compromised. Finally, a deeper understanding of the initial stimulus and also who are the main types of cells involved in adipose tissue remodeling is essential for understanding the basic mechanisms in which adipose tissue performs. Once we have managed to obtain the answers to these important issues, we will be able to advance and have the chance to achieve some possible therapeutic target to these severe metabolic diseases.

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Conflict of interest

The authors declare no conflicts of interest.

Appendices and nomenclature

BAT	brown adipose tissue
BDNF	brain-derived neurotrophic factor

ECM	extracellular matrix
GDF15	growth differentiation factor 15
IGF-1	insulin-like growth factor 1
IL6	interleukin 6
IL1β	interleukin 1β
IL10	interleukin 10
IL33	interleukin 33
NEGR1	neuronal growth regulator 1
NGF	nerve growth factor
NRG4	neuregulin 4
PAI-1	plasminogen activator inhibitor-1
scWAT	subcutaneous adipose tissue
SVF	stromal vascular fraction
TGF-β	transforming growth factor β
TLR4	Toll-like receptor 4
TNFα	tumor necrosis factor α
UCP1	uncoupling protein 1
vWAT	visceral adipose tissue
VEGF	vascular endothelial growth factor
WAT	white adipose tissue

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