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# Adipose Tissue in Health and Disease

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## Abstract

Obesity, being an epidemic these days, is the trigger of metabolic disturbances such as cardiovascular disease, type 2 diabetes, and insulin resistance. Defined as an increase in fat storage, adipose tissue has been put under the spotlight as the culprit of these conditions, as it is composed not only by adipocytes but of any immune system cell and a singular extracellular matrix. Its behavior under acute and chronic hypercaloric states is quite different; persistent hypertrophy in the latter creates hypoxia, resulting in the release of reactive oxygen species and proinflammatory cytokines that impact on the immune response type of the resident leucocytes, mainly macrophages. Hypertrophy over hyperplasia, adipose tissue macrophages-M1 phenotype polarization, and the adipokines/myokines profile are thought to be regulated by foreign microRNAs, delivered from surrounding or distant cells by exosomes through the bloodstream. In this chapter, we focus on adipose tissue immunometabolism and how obesity causes the chronic inflammatory state, and, subsequently, this establishes a pathologic adiposity, characterized by dyslipidemia and insulin resistance (IR).

**Keywords:** obesity, adipose tissue, adipose tissue macrophages-M1 phenotype, exosomes, microRNAs, insulin resistance, pathologic adiposity

## 1. Introduction

Novel findings on the immune-regulatory processes and metabolic mechanisms may open new avenues in the complex diseases as well as obesity; research on basic and clinical advances in immunometabolism has evolved rapidly during the past years, and the emergence of new tools for the detection and characterization of regulation of inflammation in systemic inflammatory diseases with metabolic comorbidity may play an imperative role.

Interplay in regulation of inflammation and metabolic risk factors are a complex cluster. The inflammatory condition associated with adipose tissue represents a triggering factor in the etiology of the obesity pathological-mechanism and mainly contributes to the related disease outcomes.

The purpose of this chapter is to address recent findings in metabolic, molecular biology, function, and pathology of the immune response to inflammation on the

role of the immunometabolism in obesity. That containing significant new findings in the field, presenting the state of the art findings, will offer the new insights into interplay in the regulation of inflammation, especially in the tools of the comorbidity, in order to know their mechanisms by metabolic and immune response that cause disease.

## 2. Healthy adipose tissue

### 2.1 Morphology and cellular biology

Adipose tissue (AT) is a type of specialized connective tissue, and as such, it consists of two main components: a cellular population and a specialized extracellular matrix (ECM) [1].

The cellular population is integrated not only by adipocytes (the main cell type, by which receives its name) but also by preadipocytes, mesenchymal stem cells (MSCs), fibroblasts, endothelial and smooth muscle cells of blood vessels and any immune system cell, and adipose tissue macrophages (ATMs) with relevance [2, 3].

Its ECM, as any other, is composed of a wide type of collagens (fibrillar (I and III) and nonfibrillar (IV, VI, and VIII)), laminins, fibronectin, and proteoglycans; especially the external membrane contains a large complex of collagen IV and VIII as well as heparan sulfate proteoglycans and laminins [4]. AT ECM possesses the highest collagen VI concentration compared to any other body tissue [5, 6]. Altogether, the ECM and the non-adipocyte cellular population receive the name of stromal-vascular fraction (SVF) [7].

#### 2.1.1 Classification

Histologically, AT is classified according to adipocyte microscopic characteristics as white (WAT), brown (BAT), and beige. White adipocytes are big oval cells with a single lipid droplet that fills the whole cytoplasm, displacing the nucleus and other organelles through periphery; its main function is the storage of energy in the form of triglycerides (TG) and lipolysis. Brown adipocytes are oval cells with multilocular lipid droplets uniformly distributed over the cytoplasm and have a high number of mitochondria, each one with several cristae expressing uncoupling protein 1 (UCP-1), characteristics that reflect an important thermogenic property. Beige adipocytes are cells with brown phenotype within WAT, that is why they are also called brite (brown-in-white) adipocytes; under basal conditions they express low quantity of UCP-1 but can overexpress it upon  $\beta$ -adrenergic stimulation and thus acquire thermogenic function [8–10].

Moreover, adipose tissue has an important endocrine function, as it is capable to secrete own specific hormones called adipokines [11].

#### 2.1.2 Fat depots

In humans WAT constitutes close to 5–10% of total human body weight and is located in two main compartments: intra-abdominal, named visceral AT (VAT), and subcutaneous AT (SCAT), also called hypodermis. VAT coats internal organs and protects them from mechanical friction and damage and can be divided into omental, mesenteric, retroperitoneal, gonadal and pericardial; SCAT is designated according to its superficial or deep situation regarding to the fascia superficialis as lamellar or areolar [12]. Moreover, abdominal and gluteofemoral regions are more relevant regarding of functional properties [13, 14].

It is remarkable to note that gender-related differences in distribution and quantity exist. While women have more SCAT (especially in gluteofemoral and peripheral regions), men have more VAT because SCAT has higher levels of estrogen and progesterone receptors, while VAT has more androgen receptors [15, 16].

In rodents, the main SCAT pads are anterior, from the neck to the axillae running through the interscapular area, and posterior, from the dorsolumbar to the gluteal region running through the inguinal region. Also, the striated muscle called *panniculus carnosus* clearly separates two layers of WAT depots: one directly underlying the reticular dermis and SCAT as such [17]; the former compartment is designated as dermal WAT (DWAT), composed primarily by intradermal adipocytes. These two terms were proposed as a redefinition of the nomenclature of skin-associated adipocytes, as it more accurately reflects their immediate developmental origin and anatomical location; humans, although not having a *panniculus carnosus*, possess functional and morphological distinctions between DWAT and SCAT [18, 19].

Differentiation, lipolytic and endocrine activity, and leucocyte population differ between VAT and SCAT, conferring them distinct metabolic properties and, in case of VAT, attribution of metabolic disturbances like dyslipidemia, glucose intolerance, and insulin resistance (IR) [20].

## 2.2 Immunometabolism

As an interdisciplinary field, immunometabolism emerged from discoveries of interdependent functions and mechanisms between the immune system and parenchymal cells of metabolic organs, which confer adaptive processes in homeostasis or disease at cellular, tissue, and systemic level [21, 22]. AT is the most studied in this field.

### 2.2.1 Immune response

Immune system has an important role on the control of AT homeostatic state, where its main functions are keeping an anti-inflammatory environment and remodeling of the extracellular matrix [8].

Under physiologic state, AT leucocyte population is integrated by eosinophils, mast cells, group 2 innate lymphoid cells (ILC2), invariant natural killer T cells (iNKT), regulatory T lymphocytes (Treg), and, of particular interest, adipose tissue macrophages (ATMs). It is proposed that these immune cells contribute to the maintenance of AT integrity through secretion of cytokines such as IL-4, IL-5, IL-13, and IL-10 (a Th2-type immune response) and that under hypercaloric state, macrophage accumulation may be a protective mechanism of the body to cope metabolic disturbances [23].

IL-33 produced by endothelial stromal cells has a key role in homeostatic maintenance and function of ECM. It is ligand of ST2 receptor, which is expressed in mast cells, Treg, eosinophils, ILC2s, and iNKT cells, practically the whole resident leucocyte population [24, 25].

In vitro and in vivo studies have demonstrated important effects of IL-33: production of IL-5 and IL-13 by Th2 lymphocytes and macrophages, eosinophil IL-4 production and survival, as well as ILC2s survival and expansion, the latter similar for Tregs [26]. iNKT cells express the transcriptional factor E4BP4; in adipose tissue produce anti-inflammatory cytokines, such as IL-2, IL-4, and IL-10; and participate in control of the homeostasis of Treg cells and macrophages in this tissue [27].

IL-25 promotes lipid metabolism and energy production, improves mitochondrial respiratory capacity, and alleviates lipid accumulation in the liver and AT via M2 macrophages and its interaction with adipocytes.

As we can observe, AT leucocytes produce the Th2-type cytokines, profile that favors the maintenance of ATMs in an anti-inflammatory M2 phenotype, known for the expression of arginase-1 (Arg-1, which inhibits iNOS activity) and production of IL-10 and IL-1Ra. ATMs also play an important lipid “buffering” activity, as they engulf free fatty acids (FFA) coming from adipocytes that have surpassed their lipid storage capacity and unchain lipolysis. Moreover, ATMs engulf death adipocytes that have reached a critical death size (CDS) [28] by a process named efferocytosis [29].

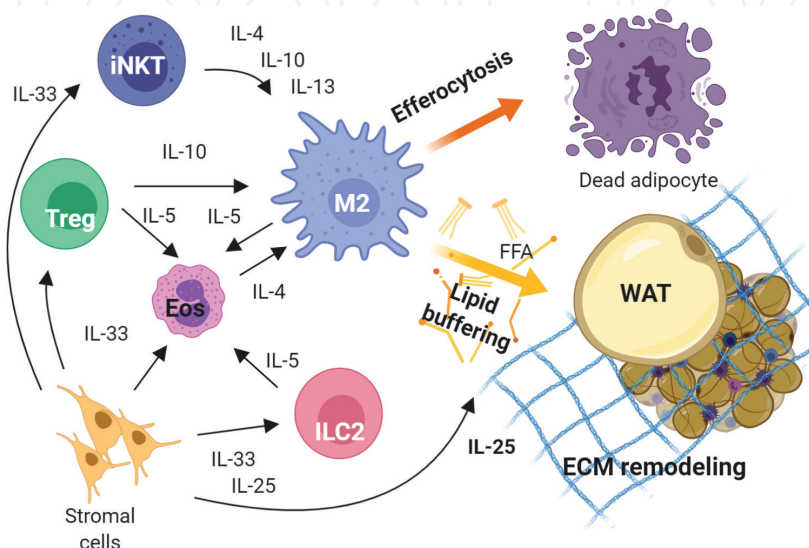
Thus, ATM is the fundamental leucocyte for correct AT functionality, as it engulfs apoptotic cell debris, and, FFA released whether by lipolysis or adipocyte death, promotes ECM reconstruction [30] and provides ECM components as scaffolds for its remodeling in the same way as under wound healing process; all these mechanisms promote adipogenesis and hyperplastic AT expansion. It is worth noting that these beneficial functions take place only under an anti-inflammatory M2 phenotype (**Figure 1**).

### 2.2.2 ECM remodeling

The ECM of any specialized connective tissue is essential not only for mechanic and structural sustain but also for providing a network that permits inter- and extracellular communication that enables proper growth and differentiation [1]. AT ECM is no exception, and its remodeling is regulated by resident leucocytes and own adipocytes.

WAT can undergo remodeling in response to changes in energy balance, like ECM degradation by members of the matrix metalloproteinase (MMP) family during adipocyte enlargement (hypertrophy) and allowing expansion by adipogenesis, under a positive energy balance [31, 32]; on the other hand, MMP activity counter-regulation is mediated by their tissue inhibitors (TIMPs). The balance between MMPs and TIMPs is critical for ECM integrity and function, and alterations in this proteolysis balance may contribute to many pathological states [33].

Secreted protein, acidic, and rich in cysteine complex (SPARC)/osteonectin and its C and N isoforms contribute to AT ECM remodeling; they modulate cell-ECM contact, cell-cell interaction, ECM deposition, and adipose stem cells (ASCs) migration and posterior incorporation into expanding neovasculature



**Figure 1.**  
*Adipose tissue homeostatic immunometabolism.*

accompanying WAT growth [34]. A study showed that serum concentrations of SPARC and MMP-2 after bariatric surgery decreased, SMAC correlated with HOMA-IR, and MMP-9 inversely correlated with serum adiponectin levels [35].

Regarding vasculature, AT ECM remodeling is influenced by a variety of angiogenic molecules, and it is triggered by transient hypoxia as a result of enlarged adipocytes under a positive energy balance. Hypoxia stimulates the production of angiogenic factors to compensate low perfusion rate; vascular endothelial growth factor (VEGF) is known as a master regulator of angiogenesis and plays crucial roles in the neovascular development of AT with obesity [36]. Hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) binds to the proximal hypoxia response element in the *VEGF* gene promoter [37]; nevertheless, it also has a role in regulation of ECM remodeling, as overexpression of a constitutively active form of HIF-1 $\alpha$  in adipose tissue forced the expression of pro-fibrotic genes, including *Col I* and *III*, *elastin*, *lysyl oxidase*, and *Timp1* [38].

This shows that detrimental ECM component deposition occurs under chronic hypoxic conditions. Transforming growth factor beta (TGF $\beta$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are released under acute hypoxia state and act as proangiogenic factors [39, 40], and the latter activates expression of preadipocyte genes in 3T3-L1 adipocytes [41]. This is in contrast to the belief that AT inflammation exerts a fundamentally negative impact on metabolism, postulating the concept “healthy inflammation” under overnutrition, requiring an acute local inflammation in order to prevent lipotoxicity and ectopic lipid accumulation; in this regard, a report showed the analysis of three animal models with constitutive or inducible expression of anti-inflammatory factors and revealed their inability to expand AT, leading to ectopic lipid deposition and deteriorated metabolic profile [42].

Platelet-derived growing factor B (PDGF-B), usually produced by endothelial cells, activates an intracellular signaling cascade binding to its receptor (PDGFR $\beta$ ) and promotes pericyte detachment and migration around new-forming vessels for maturation, playing key roles in vascular development and wound healing in adults via angiogenic actions [43]. Surprisingly, Onogi Y. and colleagues found that M1 macrophages were a major type of cells expressing PDGF-B in obese adipose tissue and correlated with elevated pericyte detachment in a dose-dependent manner; in contrast, inducible knockout *pdgfrb* mice presented reduced M1 macrophages and CLS formation but increased M2 macrophages. Additionally, they were protected from body weight gain, accumulation of SCAT, VAT, and ectopic fat in muscle and liver and showed improved whole-body glucose metabolism under high-fat diet (HFD) condition. The expression of hypoxic and proinflammatory factors (*Hif1a*, *Emr1*, *Itgax*, *Mrc1*, *Tnfa*, and *Ccl2*) was significantly increased by HFD feeding mice, whereas the increasing effects were attenuated in HFD-fed *PDGFRB*-KO mice [44]. Also, increased adipogenic capacity of PDGFR $\beta$ + precursors through *PPARG* overexpression in pericytes resulted in healthy VAT expansion in obesity and adiponectin-independent improvements in glucose homeostasis, in contrast with knockout *PPARG* counterparts; moreover, the ability of the thiazolidinedione (TZD) class of antidiabetic drugs to promote healthy visceral WAT remodeling is dependent on mural cell *PPARG* [45].

An experimental in vivo study consisting of brown adipogenesis by  $\beta$ 3-adrenergic receptor (ADRB3) activation caused crown-like structures (CLSs) formation: white adipocyte death recruited M2-polarized macrophages with high expression of osteopontin (OPN), which in turn attracted a subpopulation of PDGFR $\alpha$ + CD44+ (OPN receptor) progenitors that underwent adipogenesis, in contrast with knockout OPN [46]. It is important to highlight that recruited M2 macrophages also showed upregulation of *Arg1* and *Il10* without significant changes

in proinflammatory markers, indicating that ADRB3-mediated adipogenesis involves recruitment of macrophages that mediate non-inflammatory tissue repair [47]. Another study combining experiments in mouse models and human conditions reported that PDGFR $\alpha$  + CD9<sup>high</sup> cells originate pro-fibrotic cells, while their CD9<sup>low</sup> counterparts harbored pro-adipogenic potential; frequency of PDGFR $\alpha$  + CD9<sup>high</sup> in omental WAT (oWAT) correlated not only to oWAT fibrosis level but also to the severity of insulin resistance and T2D [48].

Adipokines can also help regulate angiogenesis, a sustained and progressive increase in leptin resulting from hypoxic conditions could induce VEGF and receptor (VEGFR2) expression, activate sirtuin 1 (SIRT1), and subsequent HIF-2 $\alpha$  stabilization promoting its activity [49].

### 2.2.3 Glucose and lipid metabolism

A steady and continuous energy supply is necessary for all cells' survival; the production of the principal high-energy molecule, the adenosine triphosphate (ATP), is primarily obtained by the metabolism of such molecules as glucose and fatty acids. In the case of carbohydrates, these are the main source of energy in almost every living organism, from archaea to humans. It is not only the supply of these molecules, but also the intricate mechanism of regulation of pathways that control the consumption and storage of these biomolecules.

For example, after a meal, or what is called a post absorptive state, there is an increment of plasmatic glucose concentration which results in the secretion of hormones such as insulin by the pancreas; this contributes to the regulation of glucose metabolism as well, and the physiological response varies on every tissue, as can be seen in muscle and liver, where insulin favors glycolysis and glycogenesis. Nevertheless, this hormone not only alters the carbohydrates metabolism, but also promotes cholesterol synthesis and lipogenesis (or TG synthesis) in hepatic and adipose tissues [50].

In the case of glycolysis, it represents the central path for glucose metabolism and provides multiple intermediate products. On aerobic conditions, it starts in the cytoplasm of the cell, with glucose as a substrate, which is partially oxidized by 10 enzymatic reactions, obtaining two pyruvate molecules, reducing equivalents such as NADH (nicotinamide adenine dinucleotide in reduced form) and a net production of 2 ATPs for each glucose [51].

Afterward, the pyruvate molecules will be transformed into acetyl-CoA and transported into the mitochondria to continue their oxidation in the tricarboxylate cycle to produce two CO<sub>2</sub> molecules, three NADH and one FADH (flavin adenine dinucleotide in reduced form). The latter will transfer their electrons to the mitochondrial complexes of the electron respiratory chain; a series of redox transformation and the aid of molecular oxygen will finally converge in the synthesis of ATP by the ATP synthase complex.

Both ATP, NADH, and acetyl-CoA are metabolites that are shown to be thermodynamically favorable and are indicated as the protagonists in cellular energy metabolism [52].

After glycogen, the body stores energy in the form of TG in adipose tissue; nevertheless, diverse types of lipids are required for the maintenance of cellular functions, not only for energetic ones, but also structural (such as phospholipids) or for the formation of specialized products like steroid hormones. These are obtained from diet, absorbed and subsequently transported by lipoproteins such as the very high-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), all of these ensembled by the liver. FFAs are a major source of acetyl-CoA molecules by  $\beta$ -oxidation, these molecules continue their oxidation in

the tricarboxylate cycle and the electron respiratory chain, providing a significant amount of energy at the cellular level.

Due to the importance of these biomolecules, there is a narrow regulation that includes transcription factors such as sterol regulatory element-binding proteins (SREBPs) and hormonal control for an adequate function [53].

Although these regulatory mechanisms are recognized, the possible regulatory activity that miRNAs may have in lipid and cholesterol homeostasis has recently been suggested, particularly for miR-122 and miR-33 [54].

### **3. Adipose tissue and disease**

#### **3.1 Insulin resistance**

##### *3.1.1 Obesity as a trigger*

Obesity is a disease of multifactorial origin with a worldwide increasing prevalence; it entails an injurious health status for individuals, which represents a serious public health issue. This condition is associated to diverse diseases and has a complex treatment, being the reason why it must be assessed in a multidisciplinary context by healthcare professionals.

It is defined as an abnormal or excessive fat accumulation that can be detrimental for health [55]. It originates from the interrelation of inadequate food intake and/or overfeeding, sedentary lifestyle, and psychological, genetic, and ambient factors. The excessive adiposity status hinders the disease reversion because of the difficulty to perform physical activity and the metabolic and satiety dysregulation [56].

Obesity develops a diversity of somatic complications such as respiratory, mechanic, cardiovascular, and metabolic, as well as psychological and social, which make its assessment, prognosis, and intervention even more complicated. Diagnosis is preceded by an anthropometric evaluation, which correlates adiposity with a total body weight of individuals [57].

Progressive AT expansion in the organism, given by a positive energy balance from excessive macronutrients and calorie intake, entails an elevated number of circulating FFA that triggers a deregulation in the organism, from changes in body structure to changes at local and systemic levels [58]. This excessive AT induces a chronic inflammatory state, also named lipoinflammation, causing hypoxia of adipocytes [59]. AT hypoxia and inflammation correlate with the risk of developing insulin resistance (IR), type 2 diabetes (T2D), and cardiovascular disease (CVD).

When the organism is under positive energy balance, energy excess accumulates in AT, giving place to SCAT hyperplasia until a physiologic allowed limit as energy reservoir is reached. When energy excess prevails, it is now stored at VAT; unfortunately this depot does not possess a great capacity as SCAT, resulting in adipocyte hypertrophy and subsequent android, central, or visceral adiposity [60, 61].

Central obesity is highly associated with T2D and CVD. AT is the pathogenic site where obesity-induced local IR originates before being systemic; its secretory genetic expression profile of endocrine and paracrine bioactive substances reflects a generalized inflammatory local state, the reason why adipocyte is referred to as key to the onset and development of obesity-induced inflammation and to macrophages as amplifiers of this process [62].

As aforementioned, AT initially plays a role in energy reservoir but also has a significant function in metabolism and immune system. Resident ATMs are key in IR onset, as they produce proinflammatory molecules which can explain more than



50% of secretion of TNF- $\alpha$ , by the action of insulin on adipocytes and on peripheral organs of the body [63].

Other implicated adipokines are resistin and IL-6, which stimulate hormone-sensitive lipase (HSL) activity resulting in triglycerides cleavage and subsequent glycerol and FFA release; these high circulating FFA levels are the cause and consequence of IR and T2D [64].

We can broadly elucidate that adipocytes and ATMs synthesize proinflammatory molecules and that weight increase at the expense of AT will contribute in turn to the perpetuation of chronic inflammation by increasing the levels of circulating cytokines. Required actions to help reverse the IR process should be focused on establishing a healthy diet accompanied by exercise; these will help to reduce the proinflammatory state, while downregulation of TNF- $\alpha$  and IL-6 expression of adipocytes occur. Meanwhile, exercise by its own will enhance mitochondrial FFA metabolism, avoiding their storage [65].

Other factors involved in IR and inflammation are implicated by diet and related to gut microbiota, which in turn demonstrates how an excessive saturated fat consumption can drive an important bacterial lipopolysaccharide (LPS) production, which impacts on systemic inflammation [58].

Initial steps that launch the inflammatory response are less well elucidated. On experimental studies with HFD-induced obesity murine models, HIF-1 $\alpha$  levels are observed before the onset of a significant adiposity status; under this situation, adipocyte hypoxia and HIF-1 $\alpha$  act as early triggers of inflammation and IR [59].

### 3.1.2 Inflammatory pathway

Adipose tissue complex and diverse functions have implications in the whole body, and cytokines are involved in his physiologic response. In obesity condition the major cytokines expressed by AT are leptin, resistin, TNF $\alpha$ , chemerin, MCP-1 and IL-6 [66, 67]. On the other hand, the adipose cells are both hyperplastic and hypertrophic, and in this state induce the inflammatory process. Dysregulation of adipose tissue promotes incorrect remodeling and subsequent inflammation, according to recruitment of macrophages and expression of chemotactic cytokines like MCP-1, TNF $\alpha$  and chemerin, to mention some of them. The phenotype involved is the M1 pro-inflammatory and evidence shows that this situation is not only local, but also systemic and this promotes further inflammation explaining how obesity can be the etiologic cause of other diseases [68, 69].

In addition, it is well known that this mechanism promotes insulin resistance, which is the previous phase before the development of T2D. However, the adipocyte is in a very close communication with the macrophage making the inflammatory process redundant and more complex. Nevertheless, in lean adipose tissue, it is typically the opposite, meaning that macrophages differentiate into a M2 anti-inflammatory phenotype, releasing IL-10, TGF $\beta$ , IL-4, and other regulatory cytokines [70]. Otherwise other mechanisms that can promote the anti-inflammatory pathway, like the consumption of Omega 3 fatty acids, exist [71].

Taking it all together, obesity results from genetic, epigenetic, physiological, behavioral, molecular and environmental factors that lead the proinflammatory phenotype [72, 73].

### 3.1.3 Molecular mechanism

It is described that adipose cells derive from a stem cell that can differentiate into adipocytes, chondrocytes, osteoblasts, and myocytes [74].

In a first phase, adipoblasts can be addressed to the adipogenic lineage and become preadipocytes. If the stimuli in the tissue continue, these cells mature to become mature adipose cells with lipid storage capacity [75].

There are two main transcription factors that are involved in the differentiation of the adipocyte, CCAAT/enhancer-binding protein  $\alpha$  (C/EBP- $\alpha$ ), and peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ). PPAR- $\gamma$  is the most described transcriptional factor, and its expression is regulated by the co-factor PGC1 $\alpha$  and the production of adiponectin [76, 77].

Transcription factors that belong to the C/EBP family also have a crucial play in the differentiation, and there are reports that this factor can be activating more early than PPAR- $\gamma$  (Figure 2) [78].

The dysfunction in the capacity of generating healthy adipose tissue has several metabolic consequences, like dyslipidemia, hypertension, and insulin resistance among others [79].

Many molecular mechanisms are involved since the adipocytes have different gene expression patterns, leading to the expression of different types of adipokines depending the phenotype induced in the tissue. Healthy expansion of adipocytes depends on the plasticity of the extracellular matrix, but in obesity there is a limiting in the oxygen diffusion, and it becomes hypoxic [80].

### 3.1.4 Role of adipokines and myokines

Skeletal muscle compounds 40% of total body weight in healthy individuals. The muscle is the major site for the insulin-stimulated glucose uptake and lipid metabolism, so it is an important part of metabolism maintenance [81].

Adipose tissue possesses more than 600 potentially secretory proteins, which means that more adipokines and myokines are still in line for discovery and characterization [82].

Additionally in adipokines there is a cross talk between these and myokines, which are synthesized by the muscle. Nevertheless, both tissues can express the same cytokines creating a regulation process with a strong communication. The most characterized cytokines are chemerin, TNF $\alpha$ , MCP-1 and IL-6. It is demonstrated that WAT deposits exist in skeletal muscle and facilitate communication, also, these tissues usually are in close anatomical proximity.

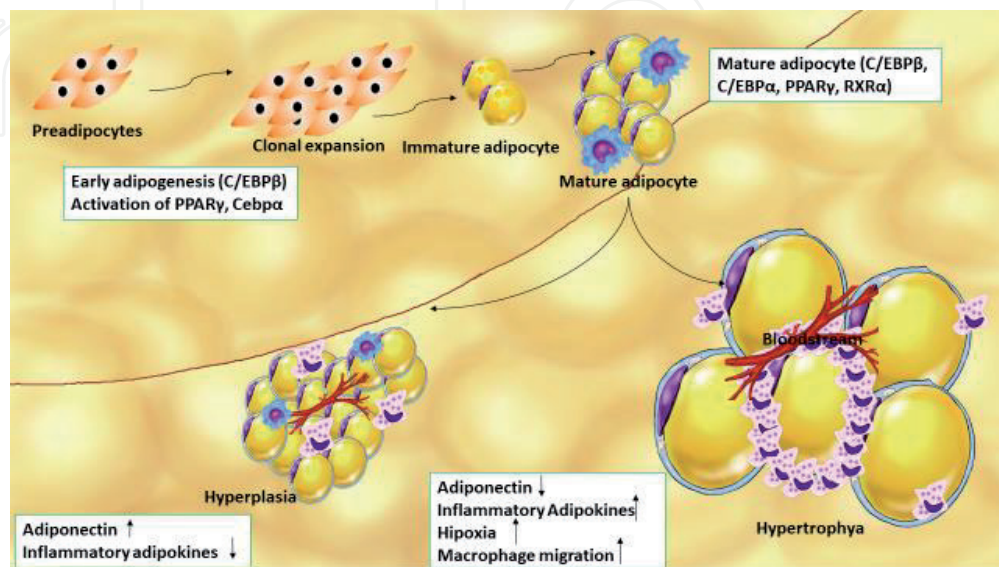


Figure 2.  
Adipose tissue differentiation and hyperplasia and hypertrophy consequences.

The knowledge of the most important characterized myokines is as follows:

IL-6: this increases in favor of the exercises, but it is recognized that it has a controversial role in the inflammatory or anti-inflammatory pathway.

Il-15: it mediates a beneficial effect on physical activity.

Irisin: it stimulates the development of brown adipose tissue activating MPK and ERK molecular ways, and it is regulated by the age and gender. This molecule has also a controversial role, because it has been reported to increase obesity.

Myonectin: it has a homology worth the sequence of adiponectin and promotes fatty acid uptaking in mice [82, 84–86].

Principally, the major role of the adipomyokines is contributing to metabolism, angiogenesis, blood vessel regulation, adipogenesis, myogenesis, and immune response [82]. On the other hand, it is important to remark the impact that macrophages have in metabolism, since they induce a response in both tissues. For example, when circulating monocytes respond to chemoattractant molecules, they migrate into adipose and muscle tissue, and then develop a phenotype depending on environmental necessities (**Table 1**) [94].

Finally, there is another terminology newly adopted by the scientist called organokines, because it has been suggested that all proteins secreted in various tissues or organs (liver, adipose tissue, muscle, and bone) have an intimate relationship in the context of the communication and regulation for the maintaining of homeostasis and that they are involved in a network of paracrine and endocrine cross talk [84].

### 3.1.5 Emerging role of microRNAs in obesity

In the context of complex diseases, obesity is the prototype of immuno-metabolic disease; it is considered a major factor that triggers metabolic risk and the development of secondary chronic illness<sup>2</sup>, insulin resistance (IR), and metabolic syndrome (MS). The susceptibility of a subject to develop obesity will depend on different factors such as the repertoire of individual variations in an ensemble of relevant genes, their history of exposure to environmental risk factors, and the interaction between the lifestyle and metabolism, which is also modulated by the gene regulators [95–97].

Meanwhile, obesity presents many subclinical manifestations, characterized by alterations in lipids and carbohydrate metabolism at different levels; most of these changes is due to a low-grade systemic chronic inflammation [98, 99] that favors the development of IR. Adipose tissue is the primary anatomical site where IR disease takes place; in early stage this tissue became inflamed.

IL-6	[87]
IL-8	[88]
MCP-1	[89]
Irisin	[82]
PAI-1	[90]
PEDF	[91]
FGF21	[92]
Fstl 1	[93]

**Table 1.**  
*Best characterized adipomyokines.*

Novel findings on the immune-regulatory processes and metabolic mechanisms may open new avenues in the treatment of the common complex diseases as well as inflammatory component; research on basic and clinical advances in immunometabolism has evolved rapidly during the past years, and the beginning of new tools for the detection and characterization of regulation of inflammation in metabolic diseases with comorbidity may play an imperative role; nevertheless, the precise mechanisms mediating this relationship remains poorly understood.

Interplay in the regulation of inflammation and metabolic risk factors are a complex cluster. The inflammatory condition associated with adipose tissue represents a triggering factor in the etiology of the obesity pathological mechanisms and mainly contributes to the related disease outcomes.

In the early stages of obesity, in white adipose tissue, primed immune cells are recruited as adiposity increases, and these cells became resident cells (mainly macrophages) and secrete proinflammatory adipokines that promote further recruitment of circulating monocytes [100–103]. Later, they polarize toward M1 macrophages, favoring a subclinical chronic inflammatory state [102, 104–106] secondary to irregular increase and distribution of fat depots [107]. In IR, the expression of genes implicated in glucose and lipid absorption and metabolism in liver and adipose tissue is dysregulated, at the same time, insulin signaling pathway in peripheral tissues is also disturbed [108]; this IR scenario precedes the development of T2D and other related diseases.

The identification of diverse molecular mechanisms related to energy metabolism has allowed the definition of strategies for searching genes implied in obesity and IR.

In the decade that precedes us, experimental reports show the existence of small noncoding RNAs, which are identified as microRNAs, (miRs) with the function of regulating cellular processes through modulating the expression of genes that code for functional proteins.

The insulin signaling pathways may be regulated by microRNAs (miRNA) that modulate the stability and translation of messenger RNAs (mRNA) by a particular mechanism of binding seeding sequences located in target genes, resulting in protein decay [109, 110].

Once synthesized, some miRNA can be released into circulation via exosomes, vesicular bodies, lipoproteins, simple extrusion, or apoptotic bodies. Most researches in the field have assessed the presence of circulating miRNA in many body fluids, being related to their impaired expression in tissues under physiological and pathological conditions. Several studies have shown a correlation of particular circulating miRNA with the development of different pathologies, positioning them as valuable biomarkers in silent diseases such as obesity, IR, and MS [111, 112].

Although rapid progress is being made in research on miRs, there is little availability of experimental tools with scientific value and mechanisms that lead from the discoveries of miRs to the therapeutic application in diseases. Therefore, the current demand is to explore the expression and biological function of miRs in the development of diseases *in vivo*.

The main considerations that are known are that the process of its biogenesis is governed by regulatory checkpoints, based on the fact that the sequence of the primary transcript does not correspond linearly to mature miR. The abundance or scarcity of a miR indicates its level of regulation.

Under physiological conditions, it has been shown that miRs modulate gene expression; however pathological stress increases or decreases its function. Therefore, its function will be defined by the effect on the expression of the genes to which it is directed. Predictions indicate that 60% of target mRNA genes have

similar binding sequences in the 3'UTR region for single or multiple miRs. These miRs exert their silencing function through two different mechanisms: translation inhibition (initiation or elongation) and target mRNA degradation. In the target genes for miRs, it is observed that 3'UTR regions have binding sites for multiple miRs; this suggests cooperation and redundancy of the effect on gene expression between the different miRs.

Currently, there are 1917 human miRNAs listed in the miRNA database miRBase (<http://www.mirbase.org>), representing 1% of all genes in the human genome. These miRNAs are predicted to target approx. 30% of the human gene pool.

From the extraction of plasma and blood serum miRs from human and mammalian animal samples, they have been proposed as diagnostic biomarkers in the diseases. The attributes that stand out are that the miRs extracted from the serum have stability, and the results in the quantification are reproducible and consistent among individuals of the same species.

The logical sequence in the integral investigation of miRs is firstly to identify the presence in a given sample. The experimental tools used to measure the expression profile of miRs have been by microarray analysis or deep sequencing, while the determination of the level of expression of individual miRs has been performed by RT-PCR, in situ hybridization or northern blot.

However, the investigations carried out can be categorized from two conceptual points, the determination of the level of expression in which the most used methodological tool is real-time PCR analysis and global expression assays. The former stand out for their specificity while confirming the latter, while the latter provide a broad view of the presence and regulation of miRs.

Properly identifying the functionality and level of expression of a specific miR is limited due to the high degree of sequence homology between some miRs and the size of the molecule; the parallel application of different molecular tools strengthens the identification or quantification process of the level of expression. However, an unfavorable factor is the combined regulation of multiple genes or small changes in gene regulation that are lost in biological noise.

Enhancing the work of performing research surrounding these novel gene regulators will advance our understanding of miRNAs and their specific functions and will augment the opportunities to safely follow them as therapeutic targets [113].

### 3.2 IR in muscle and liver

Conventionally, insulin acts directly on the WAT under the cascade of the IRS1 axis, PI3K, and AKT, for glucose absorption, with a possible positive feedback of the phosphorylation of Ser<sup>388</sup> from IRS2, by cyclin-dependent kinase 4 (CDK4) [114], culminating with lipolysis regulation. However, as described in previous sections of the chapter, inflammatory processes and alternative activation of macrophages favor the pathogenic adiposity in which the action of insulin is not carried out correctly and therefore does not slow the lipolysis process.

Although the mechanism of signaling pathways that links pathogenic adiposity to insulin resistance in skeletal muscle and liver has not been well defined due to the difficulty of modeling in vitro systems that allow cell coordination as in a complex organism, the process of understanding molecular bases has lagged behind the direct action of insulin in an organ or cell. The best way to associate it is the chronic surplus of energy that favors the accumulation of ectopic lipids in the liver and skeletal muscle that trigger the activation of pathways that impair insulin signaling, causing the decrease in glucose absorption in muscle cells and of glycogenesis in liver [115].

### 3.2.1 Liver

In a physiological stage with food withdrawal, the main source of glucose in the bloodstream is the liver. On the other hand, after absorption of nutrients by the intestine, the production of hepatic glucose should be interrupted in coordination with hyperinsulinemia.

The most assertive explanations of how insulin acts to promote glucose homeostasis by inhibiting both glycogenolysis and hepatic gluconeogenesis have focused on the canonical pathway of insulin interacting directly in the liver by activating the insulin receptor (InsR) and the substrate of insulin receptor (IRS) and the phosphoinositol 3-kinase signaling cascade (PI3K/Akt/mTOR pathway) by inhibiting transcription of the forkhead box class O-1FOXO1 factor and thus gene transcription and activation of gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PCK1) and glucose 6 phosphatase (G6PC) [116, 117].

However, it has been observed that suppression of hepatic glucose production is not totally dependent on the Akt activation pathway, for which remote insulin actions that interact indirectly with the physiological process of hepatic glucose have been studied. On one hand, the reduction of PCK1 and glucose 6-phosphatase (G6Pase) through cerebral insulin action activates the ATP-sensitive potassium channels ( $K_{ATP}$ ) of hypothalamus and stimulate the vagal transmission and STAT3 activation [118, 119], blocking the *de novo* glucose formation by the liver and therefore regulating serum hyperglycemia.

On the other hand, insulin action in WAT suppresses lipolysis and reduces the fatty acids flow into the liver, therefore, reduction of both acetyl-CoA concentration and pyruvate-to-glucose conversion occur, corresponding with the cessation of glycerol supply, observing a decrease in pyruvate carboxylase (PC) enzyme activity [120].

However, when WAT is in an inflammatory process and insulin resistance, it constantly increases the supply of gluconeogenic substrates, such as non-esterified fatty acids (NEFAS), and glycerol favors hepatic glucose production [121]. In stages with normal insulin levels, fatty acids in the bloodstream compete with glucose to internalize cells independent of hyperglycemia; however when insulin concentration or activity is deficient, fatty acids contribute directly to the production of glucose [122]. The ectopic accumulation of fatty acids in liver increases the content of acetyl-CoA allosterically activating PC and increasing gluconeogenesis; this increase in glucose and the presence of pro-inflammatory cytokines lead to inadequate insulin signaling in liver and subsequently, IR [123].

According to current knowledge of the importance of indirect insulin pathways in the liver to maintain the homeostatic glucose process, research groups will follow some therapeutic targets associated with the signaling pathways of G-protein-coupled receptors (GPCRs) [124] as well as inhibitors of the enzyme acetyl-CoA carboxylase [125, 126] for the treatment of metabolic diseases. Similarly there is evidence that proves that the diet with low calorie concentrations can reverse hyperglycemia [127].

### 3.2.2 Muscle

The skeletal muscle is responsible for 70% of the elimination of total body glucose, associated with its capacity and energy need. Therefore, insulin sensitivity of skeletal muscle is critically important in maintaining homeostasis of blood glucose [128].

Many studies propose molecules related to the deterioration in insulin signaling; however, they agree that these molecules accumulate when the energy supply exceeds the demand in the body. Therefore, it suggests that the IR in the

muscle not only has intrinsic problems as a reference. One of the main mechanisms proposed to elucidate the pathogenic process of IR in skeletal muscle is mitochondrial compromise due to the bioenergetic imbalance present mainly in pathological adiposity. However, the molecular pathways to describe this event are not entirely elucidated.

In the physiological process of insulin/IR interaction in skeletal muscle, you can activate two signaling pathways with the phosphorylation of IRS1 and, on the one hand, the PI3K/AKT pathway that induces glycogen synthesis and glucose uptake by recruiting the transporter protein of glucose (GLUT-4) to the plasma membrane, while the activation of the MAPK pathway favors the growth and differentiation of skeletal muscle [129].

The presence of pathological adiposity provides high concentrations of fatty acids and cytokines that activate signaling pathways linked to obesity that converge with insulin signaling. As plasma FFA increase, they accumulate in muscle. Intramuscular diacylglycerol (DAG) and ceramides levels rise, compounds that might act as second messengers in alternative signaling pathways that interfere with IRS-1 adequate phosphorylation [108, 130].

The presence of TAG and DG in muscle activates Ser<sup>307</sup> phosphorylation in IRS-1, resulting in the activation of PKC- $\theta$ . These changes in turn result in a decrease in the tyrosine phosphorylation of IRS-1 and a lower activation of the PI3K associated with IRS-1, resulting in a decrease in insulin-stimulated glucose transport activity. Intramolecular lipids (IMCL) have been observed to be elevated when lipid oxidation is poor and lipid supply to the muscle is exceeded [120, 131, 132].

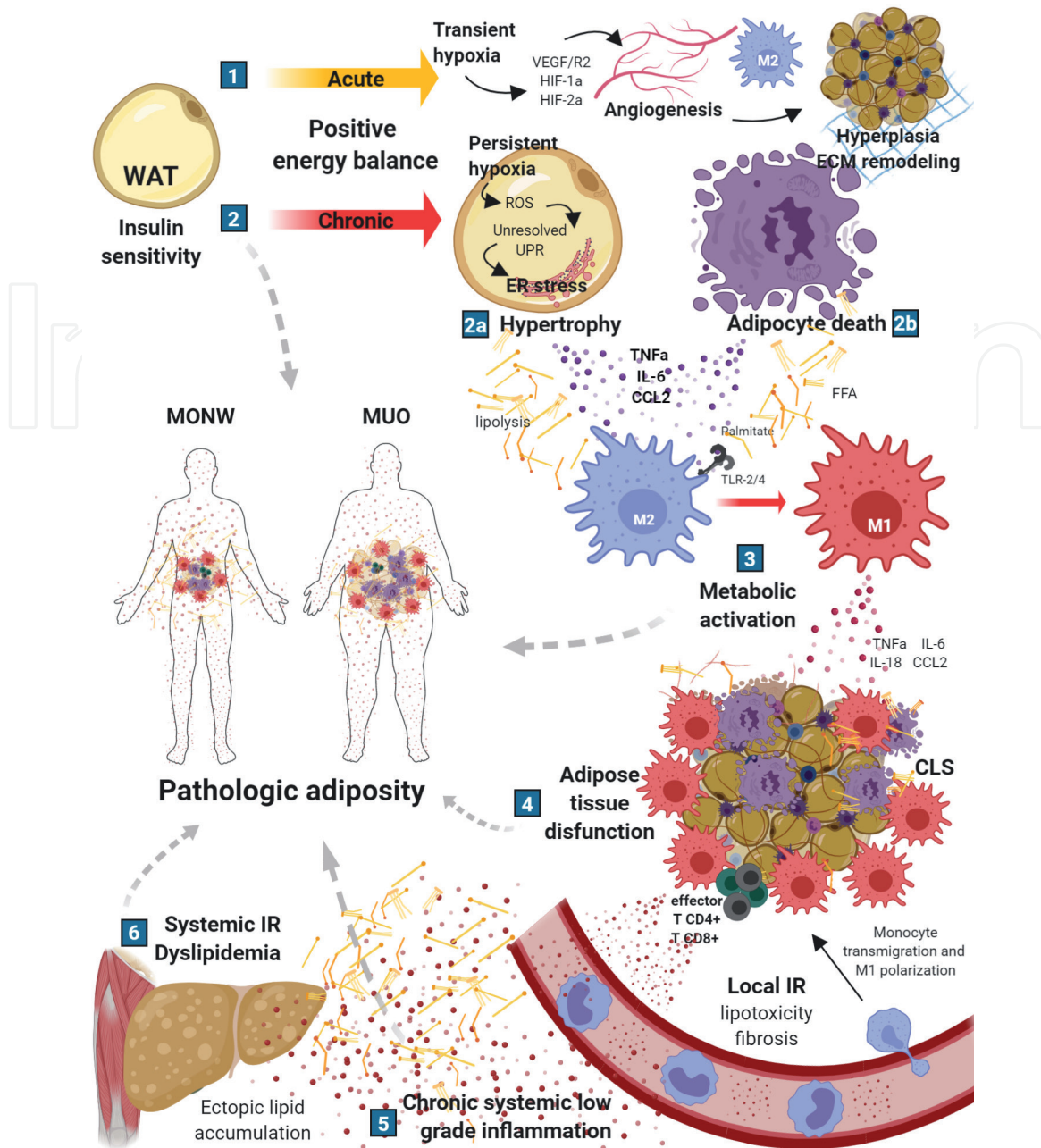
The bioenergetic imbalance favors mitochondrial beta oxidation, although incompletely which can increase the concentration of reactive oxygen species (ROS) mainly H<sub>2</sub>O<sub>2</sub>, this reactive species is responsible for the inhibition of PP2A causing the activation of JNK and ERK, and these inhibit serine phosphorylation in IRS1. When the energy demand is exceeded, skeletal muscle mitochondria stimulate lipid biosynthesis that redundantly increases the concentration of ROS and myocellular lipids [133–135].

Although the process by which ROS and fatty acids trigger insulin resistance is not yet elucidated, it can be deduced that energy imbalance is the fundamental key.

#### **4. A new terminology: pathologic adiposity**

Total adipose mass, fat depot location, and particular AT type function are the predominant factors that explain high metabolic risk in individuals with obesity, since number, distribution, and leucocyte population differ between SCAT and VAT from lean and obese individuals; VAT has higher a macrophage number, and adipocyte size is smaller and has less lipid storage capacity. These differences suggest VAT can undergo subclinical inflammation and metabolic disease [136]; actually, central obesity associates with higher CVD, metabolic disorders, and early death, in contrast with gynecoid obesity at the expense of SCAT accumulation in the gluteofemoral region [13].

With the aforementioned, we can state that not every obese individual is affected by the common metabolic abnormalities associated with obesity. Approximately 10–25% of obese and a smaller fraction of morbidly obese persons are “metabolically healthy” (metabolically healthy obese, MHO), as they are insulin sensitive and normotensive and possess a favorable lipid profile; furthermore, they present less VAT and hepatic lipids and possess normal glucose metabolism. On the other hand, a subgroup of normal weight individuals suffers obesity characteristic metabolic abnormalities, whereby they are denominated as “metabolically healthy



**Figure 3.**  
 A series of unfortunate events that leads to a pathologic adiposity status.

but with normal weight” (MONW). It is suggested that MHO individuals own a less detrimental metabolic profile and better prognosis compared to normal weight individuals with metabolic syndrome [137–139].

As stated before in this chapter, under acute caloric excess, enlarged adipocytes suffer hypoperfusion and mechanic stress owing to its surrounding ECM, which causes transient hypoxia and triggers angiogenesis and release of stress signals so that AT could undergo healthy remodeling and maintenance [140].

Nonetheless, obesity is a chronic caloric excess state, which means adipocyte enlargement surpasses angiogenesis, whereby hypoxia and stress signals perpetuate and cause fibrosis and cell death with eventual necrosis; this scenario causes local lipotoxicity, as ATM lipid buffering function is surpassed by the increased FFAs levels caused by overfeeding or adipocyte lipolysis and death [141, 142]. Thus, ATMs undergo metabolic activation, as lipids like palmitate are TLR-2/4 ligands, therefore initiating a proinflammatory response and polarization towards a M1 phenotype, losing all pro-homeostatic functions that we have previously discussed [143–145].



Furthermore, the other resident leucocytes will change in number and function as ATMs did, towards a Th1-type immune response.

The activation of NF- $\kappa$ B pathway with cytokine/chemokine release and the contribution of harmful metabolites (i.e., ceramide and sphingosine 1-phosphate, S1P) interfere with proper insulin signaling, therefore establishing a local AT IR [146–148].

After the AT IR is established, non-suppressive lipolysis now perpetuates and triggers high circulating FFA levels giving place to peripheral/systemic lipotoxicity: ectopic fat accumulation in liver and muscle; additionally, the proinflammatory cytokine, adipokine, and chemokine profile will circulate through the bloodstream, establishing metaflammation. Eventually, the high ectopic lipid concentration in this tissues will unleash similar detrimental effects that took place at AT, establishing now peripheral/systemic IR and dyslipidemia [132, 149].

The ensemble of this AT dysfunction and its harmful metabolic repercussions is what we call pathologic adiposity: the adiposity status that determinates metabolic systemic dysfunction (IR and dyslipidemia), whether in an obese or normal weight individual, “metabolically unhealthy obese” (MUO), or “metabolically obese normal weight” (MONW) person, respectively (**Figure 3**).

## 5. Conclusions

Metaflammation can be defined as the systemic metabolic inflammation derived from obese adipose tissue in which innate and adaptive immune system cells have changed in number and function, from a lean and homeostatic to a pro-inflammatory state, and whose cytokine and adipokine proinflammatory profiles cause metabolic syndrome. Some authors consider metaflammation as the result of dysfunctional adipose tissue that consists of unhealthy expansion (hypertrophy) and angiogenesis, hypoxia, and detrimental ECM remodeling, which in turn limit adipocyte lipid storage capacity; altogether, these deleterious scenarios cause lipolysis and ectopic fat accumulation in the liver and muscle.

The knowledge developed in recent years in relation to the homeostatic interaction between immune system and the energetic metabolism along with the role of miRs allows that in a state in imbalance such as obesity, new biomarkers that show clinical information about the state are sought health of individuals and the early detection of the risk of developing metabolic complications is derived from the state of pathological adiposity.

### Conflict of interest

The authors declare no conflict of interest.

### Acronyms and abbreviations

ADRB3	$\beta$ 3-adrenergic receptor
AKT	protein kinase B
ASCs	adipose stem cells
AT	adipose tissue
ATMs	adipose tissue macrophages
ATP	adenosine triphosphate
BAT	brown adipose tissue
C/EBP- $\alpha$	CCAAT/enhancer-binding protein $\alpha$

CDK4	cyclin-dependent kinase 4
CDS	critical death size
CVD	cardiovascular disease
DWAT	dermal WAT
ECM	extracellular matrix
ERK	extracellular signal-regulated kinase-1
FADH	flavin adenine dinucleotide in reduced form
FFA	free fatty acids
FGF21	fibroblast growth factor 21
FOXO1	forkhead box class O-1
Fstl 1	follistatin-related protein 1
G6PaseC	glucose 6 phosphatase
GLUT	transporter protein of glucose
HDL	high-density lipoproteins
HFD	high-fat diet
HIF-1 $\alpha$	hypoxia-inducible factor-1 $\alpha$
HSL	hormone sensitive lipase
IL	interleukin
ILC2	group 2 innate lymphoid cells
IMCL	intramolecular lipids
iNKT	invariant natural killer T cells
IR	insulin resistance
IRS1	substrate of insulin receptor 1
IRS2	substrate of insulin receptor 2
K <sub>ATP</sub>	ATP-sensitive potassium channels
LDL	low-density lipoprotein
LPS	lipopolysaccharide
MCP-1	monocyte chemoattractant protein-1
miRs	microRNAs
MPK	mitogen-activated protein kinase
mRNA	messenger RNAs
MS	metabolic syndrome
MSCs	mesenchymal stem cells
NADH	nicotinamide adenine dinucleotide in reduced form
NEFAS	non-esterified fatty acids
OPN	osteopontin
PAI-1	plasminogen activator inhibitor-1
PCK1	phosphoenolpyruvate carboxy kinase
PC	pyruvate carboxylase
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PEDF	pigment epithelium-derived factor
PI3K	phosphoinositide 3-kinases
PPAR- $\gamma$	peroxisome proliferator-activated receptor $\gamma$
RT-PCR	real-time polymerase chain reaction
SCAT	subcutaneous adipose tissue
SIRT 1	sirtuin 1
SPARC	secreted protein, acidic, and rich in cysteine complex
SREBPs	sterol regulatory element-binding proteins
STAT3	signal transducer and activator of transcription 3
SVF	stromal-vascular fraction
S1P	sphingosine-1-phosphate
TZD	thiazolidinediones

TIMP	tissue inhibitor of matrix metalloproteinases
T2D	type 2 diabetes
TG	triglycerides
TGF $\beta$	transforming growth factor beta
TNF $\alpha$	tumor necrosis factor alpha
Treg	regulatory T lymphocytes
UCP-1	uncoupling protein 1
VAT	visceral adipose tissue
VLDL	very-low-density lipoprotein
WAT	white adipose tissue

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