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Posted Date: 23 May 2025

doi: 10.20944/preprints202505.1869.v1

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Review

Phenotypic Switch of Adipose Tissue Macrophages as a Target to Reduce Obesity-Associated Metabolic Risk

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Abstract: Obesity, a chronic inflammatory disease, is caused by a positive balance between energy intake and energy expenditure. Adipose tissue (AT) inflammation is the main cause of local and systemic inflammation and oxidative stress and is the link between systemic inflammation and obesity-associated metabolic abnormalities, such as dyslipidemia, hypertension, insulin resistance (IR), fatty liver disease, and dysfunction of pancreatic β -cells. AT macrophages are derived from bone marrow and blood monocytes that, upon arrival and under the pressure of the AT microenvironment, are differentiated into AT-associated macrophages (ATMs). The AT microenvironment in obesity causes the activation of transcription factors that control the expression of a number of inflammatory genes, leading to an ATM M1 phenotype or classically activated ATM. These M1 macrophages express a number of proinflammatory genes and are the main cause of AT inflammation. Herein, we reviewed recently published information on the molecular mechanisms leading to the phenotypic switch of macrophages under the pressure of obese AT. This information is needed to develop novel mechanism-based therapeutics to reduce AT inflammation and thus the metabolic risk associated with obesity.

Keywords: obesity; adipose tissue; metaflammation; microenvironment; metabolic risk; macrophage phenotype; polarization

Introduction

Macrophages are cells of the innate immune system that are characterized by the detection, phagocytosis and destruction of bacteria and/or other invading microorganisms[1]. These cells are involved in the presentation of antigens for the development of the adaptive immune response and can secrete cytokines and chemokines to initiate the inflammatory process against injury[2].

The phenotypic heterogeneity of macrophages can be divided into two main subtypes: M1-type macrophages and M2-type macrophages[3]. M1 macrophages are described as the proinflammatory type and are important for direct host defense against pathogens, including phagocytosis and the secretion of proinflammatory cytokines and microbicidal molecules[4]. M2 macrophages have

opposite functions, regulating the resolution phase of inflammation and repairing damaged tissues[5]. More recent *in vitro* and larger *ex vivo* studies have shown that macrophage phenotypes are much more diverse, overlapping with one another in terms of gene expression and function, revealing that these many hybrid states form a continuum of activation states that depend on the microenvironment[6]. There is great diversity in the gene expression profiles of different populations of tissue macrophages, which is why the activation spectrum of macrophages is considered broader and involves a complex regulatory pathway that responds to many different signals from the adipose environment[7,8].

Systemic inflammation plays a crucial role in the development of metabolic risks associated with obesity[9]. Chronic low-grade inflammation, often referred to as "metaflammation", is a hallmark of obesity resulting from the expansion of AT[10]. This expansion leads to hypoxia, mechanical stress on adipocytes, and the release of proinflammatory cytokines[11]. These factors collectively trigger an immune response that recruits inflammatory cells such as macrophages and T cells into the AT, perpetuating the inflammatory state[12]. This systemic inflammation not only exacerbates IR but also contributes to the progression of metabolic disorders such as type 2 diabetes (T2D) and cardiovascular disease (CVD)[13]. Recent research highlights that the interplay between metabolic dysregulation and immune activation is central to the pathogenesis of these obesity-related conditions, underscoring the importance of targeting inflammation in therapeutic strategies for obesity and its associated metabolic risks[14].

In this review, we summarize the most recent findings concerning AT inflammation and obesity, highlighting the physiological, cellular, and molecular mechanisms through which AT inflammation contributes to AT dysfunction, systemic inflammation and obesity-associated metabolic abnormalities.

Macrophage Polarization: M1 and M2 Phenotypes

Circulating monocytes in the blood come from the bone marrow through a process known as hematopoiesis, where hematopoietic stem cells differentiate into myeloid progenitors. In response to growth factors such as GM-CSF or G-CSF, these cells generate granulomonocytic progenitors and then monoblasts, which in turn also give rise to premonocytes in the presence of these growth factors; thus, they ultimately differentiate into mature monocytes, which leave the bone marrow and enter the bloodstream[15]. There are different populations of monocytes in the circulation; classical monocytes represent 85% of circulating monocytes and present CD14⁺⁺ and CD16⁻ as surface markers; intermediate monocytes represent 5% of monocytes in the blood and have CD14⁺ and CD16⁺ surface markers; and nonclassical monocytes present CD14⁺ and CD16⁺⁺ surface markers and constitute the remaining 10% of circulating monocytes (**Figure 1**)[16,17]. These immune cells migrate to peripheral tissues in response to some stimulus; within these tissues, they differentiate into macrophages or dendritic cells and trigger specific responses owing to the tissue microenvironment in which they are found; these responses occur owing to the phenotypic heterogeneity presented by macrophages owing to the previous polarization of monocytes[3,18].

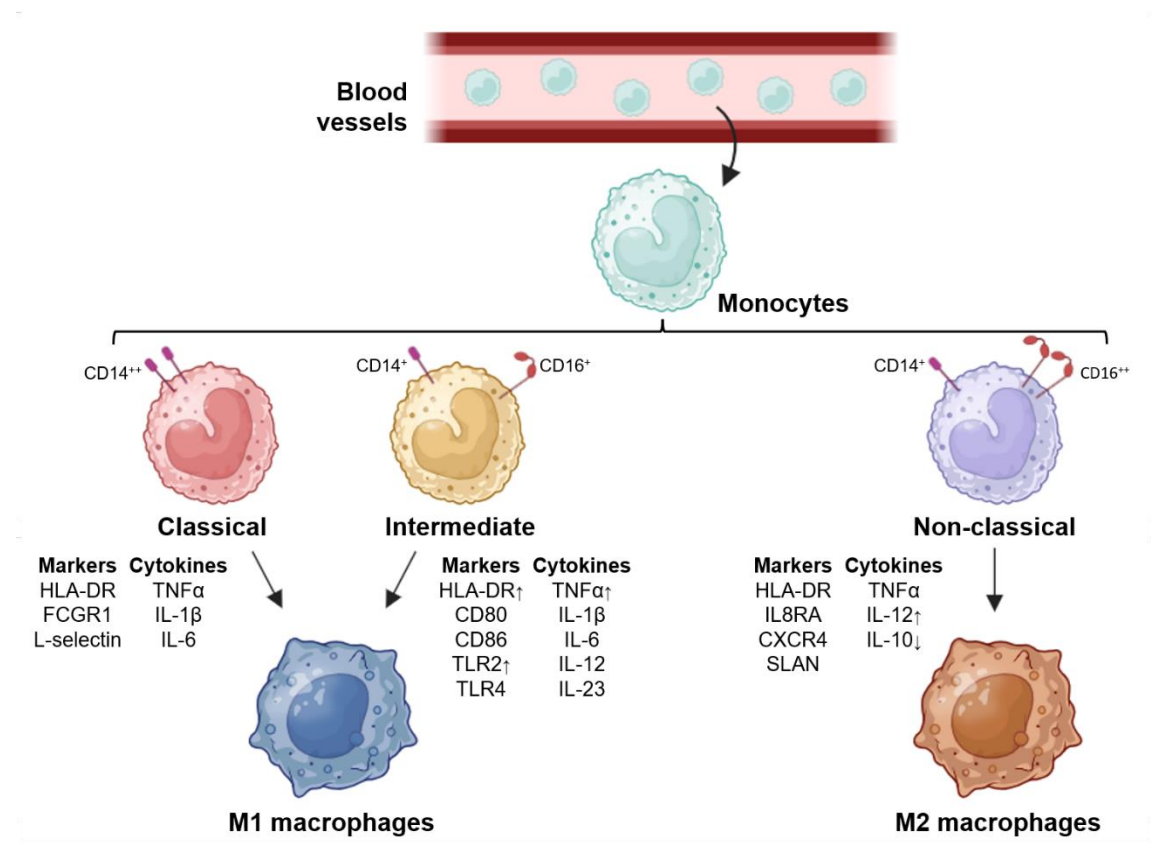


Figure 1. Monocyte differentiation and polarization. Differentiation of circulating monocytes into three subsets: classical (CD14⁺⁺, CD16⁻), intermediate (CD14⁺, CD16⁺), and nonclassical (CD14⁺, CD16⁺⁺) monocytes. Classical and intermediate monocytes can differentiate into M1 proinflammatory macrophages, whereas nonclassical monocytes can differentiate into M2 anti-inflammatory macrophages. HLA-DR, major histocompatibility complex class II antigen DR; FCGR1, Fc gamma receptor 1; TNF α , tumor necrosis factor alpha; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; CD80, macrophage antigen CD80; CD86, CD80 antigen; TLR2, Toll-like receptor 2; TLR4, Toll-like receptor 4; IL-12, interleukin-12; IL-23, interleukin-23; IL8RA, interleukin-8 receptor A; CXCR4, C-X-C motif chemokine receptor 4; SLAN, selenocysteine insertion sequence-binding protein 2-like; IL-10, interleukin-10.

Macrophage polarization is a process by which macrophages produce different functional programs in response to microenvironment signals[5]. Macrophage phenotypes have multiple functions in the body: powerful effector cells of the innate immune system, removal of cellular waste, tissue homeostasis and repair, and embryonic development[19]. Macrophages can be polarized into the M1 and M2 phenotypes, so they perform different functions under certain conditions of the cellular environment; these phenotypes differ in their biological functions owing to their surface markers and secreted cytokines[16].

M1 Macrophage’s Phenotype

The M1 macrophage phenotype is activated by the “classical pathway” through the recognition of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS); inflammatory cytokines, such as interferon gamma (IFN γ) and tumor necrosis factor alpha (TNF α); and reactive oxygen species (ROS) and reactive nitrogen (RNS) species[16]. The surface markers expressed in this macrophage phenotype are CD80 antigen (CD80), CD86 antigen (CD86), Toll-like receptor 2 (TLR-2), Toll-like receptor 4 (TLR-4), major histocompatibility complex class II (HLA-DR) and interferon gamma receptor (IFN γ R)[20].

M1-activated macrophages are produced because the activation of signaling pathways leads to the activation of transcription factors; high expression of nuclear factor kappa light polypeptide gene enhancer in B cells (NF- κ B) and signal transducer and activator of transcription 1 (STAT1); and the upregulation of signal transducer and activator of transcription 5 (STAT5), interferon regulatory factor 5 (IRF5), interferon regulatory factor 3 (IRF3), activator protein (AP-1), and hypoxia-inducible factor 1 alpha (HIF-1 α)[2,8]. The induction of these transcription factors enhances the inflammatory, bactericidal, viricidal and antitumor capacity of these cells via the secretion of high levels of proinflammatory cytokines such as TNF α , interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), interleukin-12 (IL-12), interleukin-1 alpha (IL-1 α), interleukin-23 (IL-23), interleukin-18 (IL18), and chemokines such as C-X-C motif chemokine ligand 9 (CXCL9), C-X-C motif chemokine ligand 10 (CXCL10), C-X-C motif chemokine ligand 11 (CXCL11), C-C motif chemokine ligand (CCL5), C-C motif chemokine receptor 7 (CCR7), C-X-C motif chemokine ligand 16 (CXCL16), and granulocyte-macrophage colony-stimulating factor (GM-CSF) (**Figure 2**); these cytokines and chemokines can induce chronic inflammation and lead to disease pathogenesis[21,22].

In addition, to increase their ability to eliminate pathogens, M1 macrophages produce greater amounts of nitric oxide (*NO) and citrulline from arginine, products of inducible nitric oxide synthase (iNOS) pathway metabolism[23]. Owing to their ability to fight pathogens, M1 macrophages are present during acute infectious diseases[24]. Several studies have shown that bacterial infection, the early stage of inflammation and chronic inflammatory processes induce macrophage polarization toward the M1 phenotype, resulting in phagocytosis and the intracellular killing of bacteria as well as the removal of damaged or dead body cells[24–26]. Inadequate control of the inflammatory response triggered by M1 macrophages can lead to alterations in tissue homeostasis and prevent injury repair[27].

M2 Macrophage's Phenotype

The M2 macrophage phenotype is activated by the “alternative or nonclassical pathway”, also known as anti-inflammatory macrophages; activation is produced by high levels of interleukin-4 (IL-4) and interleukin-13 (IL-13) and other ligands, such as interleukin-10 (IL-10), interleukin-33 (IL-33), transforming growth factor beta (TGF β), interleukin-21 (IL-21) and interleukin-25 (IL-25)[23]. The surface markers expressed in this macrophage phenotype are macrophage-associated antigen (CD163), macrophage scavenger receptor 1 (CD204), mannose receptor type-1 (CD206), CD209 antigen (CD209) and interleukin-4 receptor alpha (IL-4R α)[2,23].

The activation of M2 macrophages triggers the regulation of signaling pathways that produce the following transcription factors: signal transducer and activator of transcription 6 (STAT6), signal transducer and activator of transcription 3 (STAT3), interferon regulatory factor 4 (IRF4), Krüppel-like factor 4 (KLF4), peroxisome proliferator activated receptor delta (PPAR δ) and peroxisome proliferator activated receptor gamma (PPAR γ)[22,28]. M2-polarized macrophages secrete interleukins such as IL-10 and IL-4; the chemokines C-C motif chemokine ligand 1 (CCL1), C-C motif chemokine ligand 17 (CCL17), C-C motif chemokine ligand 18 (CCL18), C-C motif chemokine ligand 22 (CCL22), C-C motif chemokine ligand 24 (CCL24), and C-X-C motif chemokine ligand 13 (CXCL13); the growth factors TGF β and vascular endothelial growth factor (VEGF); and other components involved in humoral immunity, wound healing and tolerance of autoantigens and neoantigens[29–31]. Thus, M2 macrophages govern functions at the interfaces of immunity, infection prevention, tissue development, removal and repair, angiogenesis and immunomodulation (**Figure 2**)[16,21].

M2 macrophages have regulatory or wound-healing functions[2]. Regulatory functions show anti-inflammatory and phagocytic properties, which are important in the resolving phases of inflammation, producing the immunosuppressive cytokine IL-10, and can be triggered by immune complexes, prostaglandins, apoptotic cells, and IL-10[32]. On the other hand, wound-healing functions produce IL-4 and positively regulate the activity of the arginase pathway, obtaining

ornithine and urea as products from arginine; this enzyme is involved in the production of polyamines and collagen, thus regenerating damaged tissue[33,34].

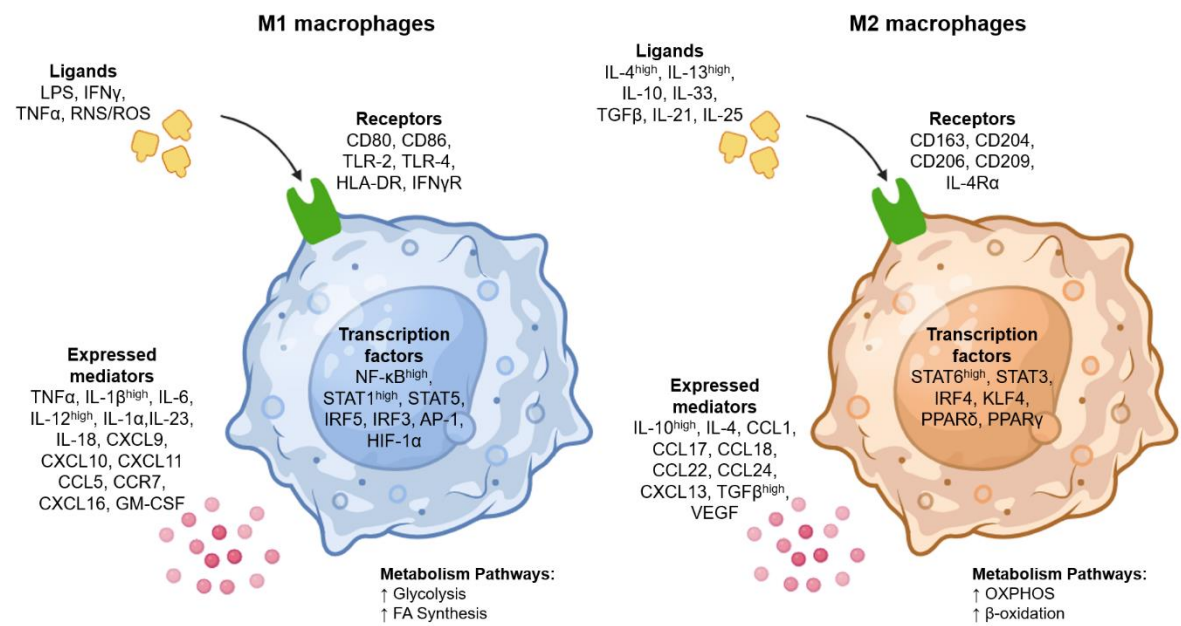


Figure 2. Mediators secreted during macrophage polarization. The different stimuli or ligands, receptors, transcription factors and metabolism pathways of M1 and M2 macrophages are summarized.

Recently, M2 macrophages have been subclassified into subtypes, which leads to more complex systematization: M2a, M2b and M2c[8]. M2a macrophages are activated by IL-4 and IL-13, leading to upregulated expression of arginase-1 (Arg-1) and CD206, impact presentation by the MHC II system, and production of IL-10 and TGF β , leading to tissue regeneration and the internalization of proinflammatory molecules to prevent the inflammatory response[35]. M2b macrophages produce IL-1, IL-6, IL-10, and TNF α in response to immune complexes or bacterial LPS, leading to Th2 cell activation and anti-inflammatory activity; however, they can inhibit the polarization of naive macrophages into M1 macrophages, thus promoting the survival of microorganisms or tumor cells [36]. M2c macrophages are activated by IL-10, TGF β , and glucocorticoids[20]. These cells express CD206 and CD163 surface markers and then produce large amounts of IL-10, TGF β and chemokines, leading to suppression of the inflammatory response. These macrophages are involved in tissue homeostasis due to their high phagocytic capacity[35,37]. Another subtype is M2d macrophages, which respond to IL-6, agonist TLRs and adenosine stimuli[38]. These macrophages are characterized by heterogeneous macrophage populations and pro- and anti-inflammatory functions and are also known as tumor-associated macrophages (TAMs) because of their immunosuppressive capacity and ability to promote angiogenesis in cancer (**Table 1**)[29].

Although the activation state of M2-type macrophages involves heterogeneous macrophage populations, some markers are shared between subtypes, so the strict division of macrophages into subtypes has not been fully elucidated[36]. Tissues contain a diverse range of stimuli that give rise to mixed populations of M2 macrophages, so these cells are of scientific interest because of their broad spectrum of activation states[6].

Table 1. Stimuli, surface markers, secreted cytokines and biological functions of different types of macrophages. Arg-2, arginase type-2; Arg-1, arginase type-1; CSF-1, colony stimulating factor 1; ILT3R, immunoglobulin-like transcript 3.

Phenotype	Stimuli	Surface markers	Expressed mediators	Functions	References
M1	LPS IFN γ TNF α	CD80, CD86, TLR2, TLR4, HLA-DR, IFN γ R	TNF α , IL-1 β ^{high} , IL-6, IL-12 ^{high} , IL-1 α , IL-23, IL-18, CXCL9, CXCL10, CXCL11,	Pro-inflammatory Th1 response Anti-tumor capacity	[2,20,21]

	RNS/ROS		CCL5, CCR7, CXCL16, GM-CSF Arg-2, iNOS		
M2a	IL-4, IL-13	CD163, CD206, Arg-1	IL-10, TGFβ, CCL17, CCL24, CSF-1	Anti-inflammatory Tissue remodeling	[15,35]
M2b	IL-1β, TLR ligands, immune complex	CD86	TNFα, IL-1β, IL-6 IL-10, CCL1	Th2 activation, Pro- and anti-inflammatory Immunoregulation	[15,36]
M2c	Glucocorticoids, IL-10, TGFβ	CD206, CD163 Arg-1	IL-10, CCL18, CXCL13, TGFβ, CCL16	Anti-inflammatory Phagocytic and apoptotic capacity	[35,37]
M2d	IL-6, adenosine receptor ligands, TLR ligands	VEGF, ILT3R	IL-10, CCL18, CCL22, VEGF	Pro- and anti-inflammatory Angiogenesis, Immunosuppressive Tumor progression	[20,29]

Inflammation of the Adipose Tissue in Obesity

Obesity is considered a global epidemic that, as a consequence, reduces quality of life, presents a lower life expectancy and increases health care costs[39]. This disease is a risk factor for the development of IR, T2D, hyperlipidemia, CVD, hyperuricemia and disorders of the immune system[40,41]. Obesity is a multifactorial chronic disease that cannot be considered only the result of an energy imbalance between caloric intake and expenditure; however, a series of metabolic abnormalities, oxidative stress, mitochondrial and immunological dysfunction, and chronic inflammation in obese individuals have also been identified[10,42]. Although AT is well known to generate an immune response to the excessive presence of nutrients, there is still no knowledge about the initial inflammatory trigger involved[43]. Therefore, more attention is currently being devoted to the study of endogenous anti-inflammatory mediators and other important therapeutic targets in AT inflammation.

AT, commonly known as body fat, is a complex loose connective tissue composed of mature adipocytes, which are the cells responsible for fat storage; preadipocytes; fibroblasts; mesenchymal cells; vascular endothelial cells; pericytes; the stromal vascular fraction; immune cells, including macrophages and T cells; and the supportive matrix of extracellular proteins[44,45]. Its functions include storing energy in the form of lipids and protecting and insulating vital organs of the body[46]. This tissue has endocrine activity and secretes various bioactive molecules, including adipokines, cytokines, and hormones, such as leptin, adiponectin, resistin, estradiol and TNFα[47,48]. There are two types of AT, white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is composed of 5–50% of the body weight, stores energy in the form of triglycerides and plays an important role in endocrine signaling by releasing hormones. WAT can be divided into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT acts as a thermal insulator and protector, whereas VAT is more related to metabolic processes. BAT is located in the neck and large blood vessels of the thorax, plays an important role in adaptive thermogenesis and decreases with age[49,50].

Adipocytes, the main cells present in the AT, can develop through two processes: hypertrophy, described as an increase in cell size, and hyperplasia, which is the increase in the number of cells from a precursor cell—preadipocyte—that manage to differentiate until its final stage, becoming a mature adipocyte[51]. Both processes of adipocyte development occur under healthy conditions; adipocytes begin to grow at a certain time, increasing their fat volume, and when they reach the critical threshold in size, the hyperplasia process occurs; the hypertrophied cell stimulates a preadipocyte, thus generating a new adipose cell[52]. During the development of adipocytes by hypertrophy, a transient inflammatory state occurs, which is considered necessary to carry out this process[51]. The problem arises when in a state of obesity, this situation is continuous, since a larger size of the adipose cell together with the concomitant inflammation compromises the integrity and functionality of the adipocyte by being excessively hypertrophied, which modifies the metabolic behavior of the cell,

generating alterations in the tissue and even triggering the apoptosis of the adipocytes[53]. Under these circumstances, obese AT has an altered secretory profile with greater production of leptin and less adiponectin, lower sensitivity to insulin in tissues, mitochondrial dysfunction and greater stress in the endoplasmic reticulum; these disruptions increase basal lipolysis and decrease de novo lipogenesis, which results in alterations in the cellular structure of adipocytes[54].

In healthy individuals, adipocytes help maintain an adequate energy balance and a normal body temperature[55]. Lipids are predominantly stored in the SAT, but in obese individuals, the SAT can reach its expansion limit or cannot expand adequately to store excess energy [55]. When adipocytes reach their triglyceride storage limit, they begin to be deposited ectopically in other tissues involved in metabolic homeostasis, that is, skeletal muscle, liver and VAT; this is due to the increase in basal lipolysis, a process known as the “*overflow hypothesis*”, thus altering the metabolic balance, which is associated with the development of chronic inflammation and lipotoxicity[56,57]. The increase in the flow of free fatty acids and the release of inflammatory factors act together as triggers of IR and local inflammation to later cause systemic IR and metaflammation[58]. Furthermore, BAT is often reduced under obesogenic conditions, decreasing the body's ability to burn calories and increasing the risk of metabolic diseases[59]. Overall, the hypertrophy capacity of SAT and fat storage in VAT are critical factors in the development of obesity, IR, and their associated complications[60].

Functions of Macrophages in the Healthy Adipose Tissue

The microenvironment of healthy AT is a complex and dynamic system that plays a crucial role in maintaining energy balance and metabolic homeostasis[61]. In a healthy state, the cells that compose this tissue interact in a balanced manner, promoting an anti-inflammatory and metabolically active environment[62]. The AT microenvironment is characterized by a well-regulated balance in the secretion of adipokines, cytokines, and hormones, which are essential for normal metabolic processes such as glucose and lipid metabolism, insulin sensitivity and immune responses[63]. These adipokines, such as leptin and adiponectin, are in charge of regulating appetite, increasing insulin sensitivity and regulating systemic inflammation[64]. Adiponectin has anti-inflammatory effects and promotes insulin sensitivity, helping to maintain efficient regulation of metabolism[65]. Furthermore, the vascular network within the AT is crucial for nutrient and oxygen supply, supporting the high metabolic activity of adipocytes[66]. In healthy AT, this vasculature is well developed, allowing for efficient transport of lipids and glucose into adipocytes and facilitating the removal of waste products[45]. Additionally, the presence of immune cells, such as macrophages, in healthy AT is tightly regulated by cytokines and transcription factors[67]. These immune cells play a role in tissue remodeling and maintaining a balance between proinflammatory and anti-inflammatory signals, which is critical for preventing chronic inflammation and associated metabolic disorders[67,68]. Anti-inflammatory cytokines such as IL-10 and TGF β predominate, maintaining controlled immune activity[69]. Macrophages in the AT of healthy individuals are usually of the M2 type, which promotes tissue repair and the resolution of inflammation[70]. Furthermore, transcription factors such as PPAR γ and CCAAT/enhancer binding protein α/β (C/EBP α/β) are essential for adipocyte differentiation and lipid metabolism; *e.g.*, PPAR γ plays a key role in the formation of new adipocytes and in regulating insulin sensitivity[71,72]. On the other hand, the extracellular matrix (ECM), an important factor in healthy AT, provides structural support and regulates cell signaling, which influences the cell differentiation, proliferation, and survival of resident cells[73]. The ECM components are constantly remodeled to adapt to changes in the size and function required by adipocytes, especially during periods of weight gain or weight loss[74]. A healthy ECM ensures that AT remains flexible and capable of expanding or contracting as needed without triggering fibrosis or other pathological changes[75]. Overall, the microenvironment of healthy AT is finely tuned by a network of cellular and molecular signals that support metabolic health, where the tissue can respond to nutritional changes and interact with other organs through endocrine signaling[76]. Disruptions to this microenvironment, such as excessive adipocyte hypertrophy, chronic inflammation, or impaired angiogenesis, can lead to metabolic diseases or

initiate metabolic syndrome[77]. Therefore, maintaining the integrity of the AT microenvironment is essential for overall health and well-being[76].

Macrophages in the Microenvironment of Obese Adipose Tissue

Obesity creates a unique AT microenvironment characterized by chronic inflammation and altered immune responses[77]. This environment plays a key role in metabolic dysfunction and can contribute to several metabolic health issues, including IR, T2D and cancer[78].

AT has a great capacity to adapt to the body's excess energy[63]. AT is a fundamental characteristic of the development of a state of metaflammation due to increases in the size and number of adipocytes[79]. Excess lipid storage leads to adipocyte hypertrophy, resulting in hypoxia, dysfunction and cellular stress. TLR2 is activated by the presence of free fatty acids, which leads to the development of an inflammatory state caused by cellular hypertrophy, causing adipocytes and resident macrophages to secrete proinflammatory cytokines such as $\text{TNF}\alpha$, IL-6, IL-1 β and monocyte chemoattractant protein-1 (MCP-1); these biomolecules induce the infiltration of immune cells, mainly macrophages[80–82]. When macrophages begin to accumulate in the tissue in response to cellular stress, they acquire the M1 phenotype, and together with adipocytes, they secrete a greater amount of proinflammatory cytokines and recruit a greater number of immune cells; the release of these inflammatory factors into the bloodstream can be directed to other tissues, where more alterations are generated at the functional level, which leads to the development of a cycle of perpetual systemic inflammation[10,83,84]. Furthermore, adipokines play a crucial role in the complications associated with obesity[85]. The inflammation produced in AT, known as lipo-inflammation, is also associated with an imbalance in the adipokine-secretory profile, where the relationship between leptin and adiponectin is altered[86,87]. Leptin is known to have an immunomodulatory role, and adiponectin acts as an insulin sensitizer and has an anti-inflammatory role at the systemic level[88]. However, in obese individuals, serum leptin levels are increased, and adiponectin levels are decreased[89]. This abnormal secretory profile of adipokines may be one of the causes of metabolic irregularities associated with obesity[90]. In addition, the structure of the ECM and its angiogenic capacity are altered and seem to be involved as underlying factors in the abnormal expansion capacity of AT (abnormal hypertrophy) in obesity, producing a fibrotic and hypoxic state in AT, which further affects the deregulation of adipocyte function and aggravates the inflammatory state; however, this phenomenon has not been widely studied[74,91].

Adipocytes, which have limited hyperplastic capacity, greater hypertrophy and metaflammation in AT, decrease lipolysis by inhibiting the response to insulin in metabolically active tissues and preventing glucose uptake, contributing to the development of IR and glucose intolerance[92,93]. This is why VAT becomes the main store of triglycerides because the SAT becomes incompetent to continue storing excess energy[94]. Therefore, these alterations in the microenvironment of obese AT and the increase in fat deposition at the visceral level play a central role as significant risk factors because of the increased incidence of metabolic syndrome, IR, T2D, CVD, and certain types of cancer, among others[95,96]. To mitigate these health risks, it is essential to understand the mechanisms that link lipo-inflammation to obesity-associated diseases and thus be able to develop therapies targeting these pathologies[97]. On the other hand, the ease of storing fat in the gluteal–femoral region in women, compared with the accumulation of fat at the central level in men, explains, to some extent, the lower incidence of cardiovascular events in women than in men[98].

Phenotypic Switch of Macrophages in the “Obese” Adipose Tissue

Studies have shown that a high-fat diet leads to dynamic infiltration of innate and adaptive cells into the AT during the onset of IR and obesity[99]. The immune cells that infiltrate AT are macrophages, lymphocytes, foam cells, mast cells, eosinophils and neutrophils. These immune cells secrete inflammatory factors that alter the adipose microenvironment and may play a key role in

metabolic disruption, shifting from an anti-inflammatory to an inflammatory profile[100]. Macrophages play crucial roles in regulating inflammation and metabolic balance in AT; in turn, AT plays an important role in regulating the immune system, particularly in influencing macrophage polarization[101]. The macrophages present in this tissue are referred to as ATMs[49]. ATMs are key modulators of energy metabolism and mitochondrial function in adipocytes; they originate from circulating monocytes that accumulate in ATs via MCP-1 action, differentiate into macrophages in VAT and SAT, and self-renew from ATMs already present in the tissue[49,102].

Impact of Macrophage Polarization in Obesity

The phenotype, quantity and activation state of ATMs have a major impact on the development of obesity-induced metabolic diseases[103]. In lean AT, ATMs acquire the M2 phenotype, promoting an anti-inflammatory response and tissue repair in AT[101]. The main function of M2 macrophages in the tissue is to regulate systemic glucose homeostasis by inhibiting preadipocyte proliferation through the CD206/TGF β signaling pathway, which induces IL-10 release[104,105]. Furthermore, IL-25 stimulates M2 macrophage polarization and enhances their interaction with adipocytes, promoting energy metabolism, improving mitochondrial functions in adipocytes and regulating lipid accumulation in WAT, VAT and the liver[106]. However, under conditions of energy excess and obesity, the ATM M2 phenotype polarizes to the M1 phenotype, which is the main actor in the initiation and maintenance of the inflammatory state by releasing cytokines that contribute to the infiltration of circulating monocytes attracted by chemoattractants, resulting in greater accumulation of macrophages and the development of chronic low-grade local inflammation; this inflammatory state in AT not only affects its function but also extends to a systemic level[107,108]. It has been shown that inositol-requiring enzyme 1 α (IRE1 α) is an important protein in the development of obesity and metabolic syndrome because its activation decreases the population of M2 ATMs and increases M1 ATMs through the action of obesogenic factors such as stearic, palmitic and myristic fatty acids and LPS; the IRE1 α pathway affects BAT activity and prevents WAT browning[109,110]. Furthermore, the inhibition of factors involved in AT browning and homeostasis, such as fibroblast growth factor 21 (FGF21) and NAD-dependent sirtuin-1 deacetylase (SIRT1), increases miR-34a levels in obese AT[49,111]. miR-34a is released into ATMs by lipid-rich exosomes from hypertrophic adipocytes, which decreases the expression of KLF4, a transcription factor involved in M2 polarization; it also releases miR-155, which regulates M1 macrophage polarization[112,113]. However, preadipocyte-derived SVF exosomes transactivate Arg-1 to drive M2 macrophage polarization by inhibiting miR-34a and miR-155, and these macrophages further promote preadipocyte hyperplasia and AT browning[49,114]. On the other hand, continuous exposure to hyperglycemia activates macrophages through the JNK and ERK pathways, which induce monocyte infiltration in the tissue to differentiate into M1 macrophages[115]. In addition, a high number of macrophages infiltrating AT is positively correlated with the development of obesity in human AT and several mouse models[83,116,117]. This finding indicates that macrophages could be among the most important cells involved in the growth of fat mass, which is why macrophages that infiltrate the AT of obese patients are of greater interest for the study of the interaction between immune cells and metabolism[118].

Hypoxia as the Main Driver of Adipose Tissue Dysfunction

Hypoxia in obesity is a key factor driving metabolic dysfunction and chronic inflammation in AT. As AT expands in response to excessive caloric intake, the increasing distance between adipocytes and the vascular network does not increase proportionally, leading to inadequate oxygen delivery or hypoxia, particularly in hypertrophic adipocytes. The hypoxic environment, tissue hypertrophy, and hyperinsulinemia impede proteasome degradation of HIF-1 α , triggering the stabilization and upregulation of this transcription factor in adipocytes and macrophages through the IGF receptor-activated PI3K–Akt pathway, promoting a cascade of proinflammatory and metabolic changes. In turn, HIF1 α , by binding to its coactivator p300/CBP, positively regulates the expression of a wide range of genes involved in glycolysis, angiogenesis and inflammation, including

GLUT1 (glucose transporter 1), VEGF and NF- κ B. This adaptation aims to support AT survival under low-oxygen conditions, but in obesity, chronic activation of HIF-1 α contributes to the deregulation of adipocyte function, promotes IR, inhibits PPAR γ and alters adipokine secretion. For example, hypoxia is one of the main causes of an altered adiponectin/leptin balance. Furthermore, early inflammation and hypoxia have been shown to activate NF- κ B and induce increased expression of HIF-1 α , thereby increasing the production of proinflammatory cytokines, such as TNF α and IL-6, downstream and enhancing macrophage infiltration, driving their polarization toward the proinflammatory M1 phenotype. This exacerbates local and systemic inflammation, worsening IR and metabolic disease. Furthermore, HIF-1 α activity impairs adipocyte differentiation and promotes fibrosis in ATs, thereby compromising their ability to store lipids properly, leading to ectopic deposition in the liver and muscle. Hypoxia also increases the expression of ECM components such as collagen, impairing AT flexibility and further exacerbating metabolic dysfunction. Consequently, persistent activation of HIF1 α in obese AT is a major contributor to the development of metabolic syndrome, making it a critical area of research for understanding and addressing obesity-related complications.

GLUT1 and GLUT4 are key glucose transporters involved in regulating glucose uptake in various tissues, and their dysregulation plays an important role in the development of glucose intolerance and IR. In obesity, HIF1 α upregulates GLUT1 expression in response to hypoxia, enhancing basal glucose uptake in a noninsulin-dependent manner in hypoxic AT. This is part of a metabolic shift known as the “Warburg effect,” where cells rely more on glycolysis (anaerobic metabolism) rather than oxidative phosphorylation to produce energy to maintain their elevated metabolic activity. The upregulation of GLUT1 in the hypoxic environment not only fuels adipocytes but also M1-phenotype macrophages, as these immune cells rely on increased glucose uptake to maintain their proinflammatory activities. However, this shift toward active glucose metabolism often coincides with impaired GLUT4 function due to the resulting IR. As insulin signaling becomes defective by HIF-1 α in obese AT and skeletal muscle, the ability of GLUT4 to translocate to the cell membrane in response to insulin is decreased, leading to decreased glucose uptake in these tissues and contributing to hyperglycemia. This creates a vicious cycle: hypoxia promotes HIF1 α activation, which supports GLUT1 upregulation and proinflammatory responses, whereas the resulting IR decreases GLUT4 activity, impairing insulin-mediated glucose uptake in AT and skeletal muscle. The contrasting roles of GLUT1 and GLUT4 in obesity highlight the complex metabolic environment in obese individuals. While GLUT1 helps cells survive hypoxia by increasing glucose uptake, it also exacerbates immune cell activation and inflammation; moreover, downregulation or dysfunction of GLUT4 contributes to impaired systemic glucose homeostasis. Therefore, targeting HIF1 α to alleviate hypoxia and inflammation, modulating GLUT1 activity, and restoring GLUT4 function in adipose and immune cells could be potential therapeutic strategies to reduce hypoxia-induced inflammation and restore proper insulin sensitivity.

VEGF plays a crucial role in regulating angiogenesis, particularly in response to the increased metabolic demands of AT differentiation and expansion in obesity. As AT expands, the oxygen demand increases due to insufficient vascularization, stimulating VEGF production to promote new blood vessel formation. However, in obese individuals, persistent activation of HIF-1 α elevates VEGF levels, leading to excessive and abnormal angiogenesis that fails to adequately oxygenate the tissue. This ongoing hypoxic state exacerbates inflammation, fibrosis, and metabolic dysfunction in obese AT. In addition to HIF-1 α , VEGF transcription is controlled by STAT3, PCG-1, and PPAR γ . The VEGF-HIF1 α pathway contributes to the recruitment of immune cells that further aggravate inflammation. Thus, while VEGF and HIF1 α are initially activated to combat hypoxia to maintain healthy AT expansion, their dysregulation in obese patients plays a key role in AT dysfunction, systemic inflammation, and the pathogenesis of metabolic diseases. Targeting VEGF signaling to restore normal vascular function without promoting excessive or abnormal angiogenesis could offer therapeutic strategies to improve tissue oxygenation and reduce inflammation in obese patients.

The important role of platelet-derived growth factor receptor (PDGFR) in regulating AT remodeling and fibrosis in obese patients under hypoxic conditions has recently been revealed. PDGFR exists in two forms, PDGFR α and PDGFR β , both of which are expressed in adipose progenitor and stromal cells. PDGFR α is crucial for AT expansion, as it regulates the development of new adipocytes from progenitor cells. The PDGFR/HIF-1 α relationship is an interesting area of study that highlights the interplay between this growth factor signaling pathway and hypoxia-induced responses in AT. PDGFR and HIF-1 α are key players in AT remodeling, inflammation, and fibrosis, which are critical processes in metabolic dysfunction. PDGFR downstream signaling enhanced by HIF-1 α drives the proliferation and differentiation of fibroblasts and preadipocytes, contributing to impaired adipogenesis and excessive ECM deposition; these abnormalities lead to reduced flexibility and expandability of AT. As the ability to safely store lipids in adipocytes is impaired, a “spillover effect” is created where excess lipids are deposited in ectopic tissues. Furthermore, increased PDGFR activity under hypoxic conditions has been associated with the recruitment and activation of proinflammatory macrophages, which promote the activation of inflammatory pathways in obese AT. On the other hand, a study revealed that the PDGFR β ⁺ pathway inhibits PPAR γ through the release of HIF-1 α -driven factors that limit the adipogenic capacity of adipose cells. Inhibition of HIF-1 α in PDGFR β ⁺ preadipocytes promotes adipogenesis and healthy WAT remodeling and improves glucose tolerance in a PPAR γ activation-dependent manner. Thus, the PDGFR/HIF-1 α axis plays a pivotal role in pathological WAT remodeling during obesity. Targeting this relationship could provide novel therapeutic approaches to improve metabolic health in obese individuals by mitigating fibrosis, promoting adipogenesis, and reducing WAT inflammation.

The Role of PPAR γ in Macrophage Polarization

PPAR γ is an important transcription factor in AT that is involved in adipocyte lipid metabolism and anti-inflammatory responses[119,120]. PPAR γ -regulated metabolic adaptation leads to subcutaneous and brown fat deposition in adipocytes, reduced circulating lipids, and decreased lipotoxicity[121]. Alterations in PPAR γ expression decrease fatty acid uptake and change the metabolic programming of adipocytes and ATMs[122]. The presence of lipid molecules plays a role in macrophage polarization and is influenced by the PPAR γ signaling pathway[121,123]. This regulatory pathway promotes the anti-inflammatory M2 metabolic program and inhibits M1 polarization[124]. The metabolic features displayed by PPAR γ -regulated ATMs include increased amino acid metabolism by Arg-1, inhibition of glycolysis, increased lipolysis, elevated β -oxidation of fatty acids, and increased mitochondrial biogenesis[124,125]. Studies have shown that elevated IL-4 induces the expression of fatty acid translocase (CD36/FAT), a receptor that transports long-chain fatty acids and oxidizes low-density lipoproteins (ox-LDL); moreover, IL-4 further increases PPAR γ expression[126]. Therefore, fatty acid metabolism and PPAR γ expression are necessary for anti-inflammatory ATM polarization[122]. The inhibition of PPAR γ in ATMs of obese individuals induces an M1 proinflammatory metabolic program via IFN γ , which is characterized by increased aerobic glycolysis and fatty acid synthesis, decreased lipid transport, and amino acid metabolism that is regulated by iNOS and generates a greater amount of ROS[123,127].

In recent years, the role of mammalian target of rapamycin (mTOR) in relation to PPAR γ in the metabolic program of adipocytes and macrophages has been studied[128]. Induction of mTOR in AT is associated with adipocyte hypertrophy, but its inhibition results in a decrease in the size and number of adipose cells, resulting in probable protection against obesity[128,129]. However, the inhibition of mTOR, despite decreasing lipid uptake and storage, produces hypertriglyceridemia, which is why mTOR and PPAR γ also modulate lipid metabolism in the plasma[130]. In obesity, under conditions of excess energy, mTOR enhances the transcriptional activity of PPAR γ and increases the synthesis of proteins involved in lipid metabolism, such as lipoprotein lipase (LPL) and glycerol kinase (GyK)[129]. Therefore, mTOR activation is important for maintaining plasma lipid homeostasis and increasing lipid uptake and storage by activating PPAR γ [131]. mTOR acts on PPAR γ depending on metabolic and nutritional status to execute metabolic responses (*e.g.*, synthesis

of cholesterol, fatty acids and proteins involved in lipid metabolism) and responses associated with inflammation in ATMs[132]. Recently, semaphorin-6D (Sema6D) was shown to link the mTOR and PPAR γ pathways in ATM polarization[133]. Sema6D, acting as a receptor (reverse signaling), is activated by mTOR and binds to protein kinase C-Abl; this induces the transcription of PPAR γ , allowing the polarization of anti-inflammatory macrophages and the regulation of fatty acid metabolism. c-Abl also activates the differentiation of preadipocytes (hyperplasia)[133,134]. The inhibition of mTOR or Sema6D decreases the expression and activity of PPAR γ ; as a consequence, the polarization of ATMs toward M2 is affected, their metabolic programming and lipid uptake decrease, the expression of CD36 is also affected, and inflammatory polarization is improved[135].

Adiponectin, a plasma protein secreted by adipocytes, protects the body against CVD and metabolic diseases[136]. There is also a regulatory cycle between PPAR γ and adiponectin; the increase in adiponectin available in the blood is associated with greater activation of PPAR γ , and this factor further stimulates the synthesis and release of bioavailable adiponectin[137]. A study showed that modified mice that overexpress adiponectin present with hypotriglyceridemia and that lipids are stored in the SAT[138]. On the other hand, this adipokine also exerts a regulatory effect on the polarization of macrophages toward an anti-inflammatory phenotype[139]. Animal studies have revealed that modified mice that do not express adiponectin exhibit increased production of the inflammatory cytokines TNF α , IL-6, and MCP-1 in ATMs, whereas the number of M2 macrophages and their markers, such as Arg-1 and IL-10, decreases[140]. In addition, another study reported that the levels of markers and polarization of M2 macrophages increase and that the level of ROS and polarization toward the M1 phenotype decrease in macrophages treated with recombinant adiponectin[141]. The stimulation of adiponectin expression decreases the progression of obesity and other associated metabolic diseases by promoting the resolution of the low-grade inflammatory state in AT[142].

Studies related to microRNAs have been very important and useful in recent years. One known regulator of inflammation and IR is miR-223[143]. The expression of miR-223 is regulated downstream by PPAR γ ; consequently, the PPAR γ /miR-223 axis regulates the polarization of macrophages toward an anti-inflammatory phenotype to maintain homeostasis in AT and ameliorate insulin sensitivity[144,145]. Investigating the mechanisms by which mTOR-Sema6D and adiponectin modulate PPAR γ and by which PPAR γ regulates miR-223 expression may be highly important for the development of therapeutic approaches related to PPAR γ activity, safe lipid storage, ATM polarization, and metabolic reprogramming of adipocytes and macrophages[146].

Macrophages in the Crown-like Structures (CLS)

ATMs exhibit high proliferative capacity and decreased cell apoptosis in the early stages of WAT hypertrophy following a high-fat diet[147]. However, continuous intake of a high-fat diet leads to the development of glucose intolerance and IR because adipocytes upregulate the endoplasmic reticulum stress pathway C/EBP α / β , resulting in an altered WAT microenvironment[148,149]. Alterations and stress in the microenvironment and elevated lipid storage in adipocytes lead to adipose cell death, and cell debris is removed by ATMs. The large size and volume of apoptotic adipocytes cannot be phagocytosed and engulfed by a single macrophage, and as a result, monocytes infiltrate and subsequently differentiate into macrophages, which aggregate around the adipose cell, forming a crown-shaped structure (CLS), and can eliminate dead adipocytes by lysosomal exocytosis, a hallmark of AT remodeling in obesity. As alterations in adipocyte function and stress progress, lysosomal exocytosis abruptly decreases, and excessive lipid accumulation results in increased tissue damage in AT.

CLS is a primary/key histological feature in the inflammatory and apoptotic process of AT. The dominant macrophages in CLSs are of the M1 phenotype and release proinflammatory factors (NF- κ B, iNOS, IL-1 β , IL-6, and TNF α) and free fatty acids, which contribute to increased hyperinsulinemia and IR. Furthermore, ATMs of the M1 phenotype activate the transcription factor HIF-1 α ; as a result, these hypoxic ATMs agglomerate to form CLSs and express elevated iNOS and IL-1 β as obesity

progresses. These CLSs are the main site of hypoxia and local inflammation in the later stages of obesity. Recently, estrogen receptor beta (ER β) was shown to be key for the initiation of CLS formation by acting on HIF-1 α . A recent study confirmed that CLS formation in SAT and VAT is increased in obese ER β -/- mice. Obese mice treated with an ER β agonist show decreased CLS formation in SAT and VAT, as well as decreased HIF-1 α activation. Stimulating ER β in macrophages that compose CLSs and infiltrating macrophages may help reduce the amount of CLSs, decreasing the degree of IR in ATs[150].

Tetraspanin-29 (CD9) macrophages represent a distinct ATM population and have gained attention for their role in metabolic dysfunction. They are cells that, owing to the expression of the surface marker CD9, are able to form CLSs around dead or dying adipocytes, thus playing a role in the removal of apoptotic adipocytes; they also present increased lipid accumulation through exosome formation, are metabolically active and are responsible for amplifying inflammatory signaling in obese ATs. CD9⁺ ATMs co-express elevated levels of the surface markers CD11c, CD16, and CD206, which express inflammatory transcription factors such as AP-1 and NF- κ B, and these induce the release of the proinflammatory mediators IL-6, IL-18, and TNF α , which promote IR and exacerbate AT dysfunction. Research has shown that CD9⁺ ATMs express genes involved in lipid handling and fibrosis, further implicating them in AT remodeling and metabolic complications.

On the other hand, other subpopulations of CD11c⁺/CD163⁺ ATMs are part of the CLS in VAT and SAT and have special relevance because of their dual or transitional role in regulating the local inflammatory and metabolic environment and in processes of remodeling or resolution of inflammation, which adds complexity to the immune response in obesity. CD11c⁺/CD163⁺ macrophages actively participate in the response to adipocyte death and in the regulation of inflammation in expanded AT. CD11c expression is related to the proinflammatory M1 profile, while CD163 expression could be involved in the modulation of inflammation and protection against excessive tissue damage due to its anti-inflammatory profile. Targeting CD9⁺ macrophages as well as hybrid M1/M2 macrophage subtypes could offer a novel therapeutic approach to reduce inflammation and improve metabolic outcomes in obese individuals.

Recently, a subpopulation of macrophages known as lipid-associated macrophages (LAMs) was discovered within the CLS; these macrophages have the main functions of lipid catabolism and modulate the inflammatory response of the AT through the loss of homeostasis and death of hypertrophic adipocytes[151]. The LAM that forms the CLS are the only immune cells in obese AT that express lipid receptor trigger receptor expressed on myeloid cells 2 (Trem2)[152]. Studies have shown that LAM-Trem2⁻ increases hypertrophy in adipocytes and leads to hypercholesterolemia, inflammation, glucose intolerance and IR; therefore, metabolism in obese individuals is further impaired[153,154]. However, LAM-Trem2⁺ CLSs formed in obese adipocytes can locally contain lipid droplets, decrease AT inflammation and hypertrophy, and prevent the loss of lipid homeostasis at the systemic level, since the transcriptional profile triggered by Trem2 induces the expression of mediators involved in lipid handling, such as CD36 and PLIN2[153,155]. These findings suggest that the downstream pathway of Trem2 is activated by recognition signals, indicating the loss of homeostasis in adipocytes and lipid accumulation in the ECM[156]. Although CLS formation has been reported to be positively correlated with increased severity of obesity and metabolic syndrome, these studies identify Trem2⁺ CLSs as a new potential therapeutic target in obesity.

Obesity-Associated Metabolic Risk and Macrophage Phenotypic Switch

Obesity-related inflammation is a critical factor in the development of several chronic diseases. One of the primary diseases associated with this condition is T2D. Inflammation impairs insulin signaling pathways, leading to IR, a hallmark of T2DM[157]. Cardiovascular diseases (CVDs) are also closely linked to obesity-induced inflammation. Proinflammatory cytokines contribute to the formation of atherosclerotic plaques and promote endothelial dysfunction, increasing the risk of heart attack and stroke[158]. Nonalcoholic fatty liver disease (NAFLD) is another condition exacerbated by inflammation in obese individuals. The accumulation of fat in liver cells triggers inflammation, which

can progress to nonalcoholic steatohepatitis (NASH), fibrosis, and even cirrhosis[159]. Additionally, certain cancers, such as breast, colorectal, and pancreatic cancer, are associated with chronic inflammation stemming from obesity. The inflammatory environment promotes tumor initiation, progression, and metastasis. Understanding the intricate relationships among obesity, inflammation, and these diseases is essential for developing effective prevention and treatment strategies[97].

Interestingly, contrary to studies showing that inflammatory signals mainly exert a negative impact on metabolism, there is new evidence that proinflammatory signaling in the tissue is necessary for proper remodeling and expansion of AT in healthy individuals and could be important in the treatment of obesity[107]. Authors have shown that, in mice, a specific reduction in AT in a proinflammatory state reduces the adipogenic capacity *in vivo*; this finding is associated with a decrease in the ectopic accumulation of lipids, improved glucose tolerance and decreased systemic inflammation[160]. However, other studies suggest that triggering an inflammatory state of AT can generate a response in SAT that allows safe storage and expansion against excess nutrients, thus decreasing lipid accumulation in VAT, and AT could be protected against metabolic and inflammatory disruptions[161].

Concluding Remarks

The phenotypic switch of macrophages in the obese adipose microenvironment has become a critical therapeutic target for addressing obesity-related inflammation and metabolic dysfunction. Recent advances in understanding the underlying mechanisms of this switch, including the role of hypoxia, lipid signaling, and the interplay of cytokines and adipokines, have paved the way for innovative therapeutic strategies. Emerging approaches include the use of small molecules and biologics aimed at modulating key signaling pathways, such as inhibitors of NF- κ B and HIF-1 α or activators of PPAR γ and STAT6, to promote the anti-inflammatory M2 phenotype. Additionally, nanoparticle-based drug delivery systems are being developed to selectively target macrophages within obese adipose tissue, offering precision in reprogramming their polarization without affecting systemic immunity. Immunotherapy approaches, such as adoptive transfer of engineered macrophages or the use of monoclonal antibodies against proinflammatory cytokines such as TNF- α and IL-6, also show promise. Another exciting avenue is the application of metabolic reprogramming agents, which aim to shift macrophage metabolism from glycolysis (associated with M1 polarization) to oxidative phosphorylation (favoring M2 polarization). Furthermore, therapies targeting the gut-adipose axis, such as prebiotics and probiotics, are being explored to indirectly influence macrophage function by modulating systemic inflammation and lipid metabolism. While these novel therapies show significant potential, challenges remain in optimizing their safety, efficacy, and delivery, emphasizing the need for continued research and clinical trials to bring these approaches closer to widespread application in managing obesity and its associated diseases.

Acknowledgments: This study was supported by PICT-2021-I-A-0147 from the FONCYT, Agencia Nacional para la Promoción de la Ciencia y la Tecnología, Ministerio de Capital Humano, Gobierno de la República Argentina.

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