Contents available at **PubMed**
www.clinicalandtranslationalinvestigation.com

Check for updates

Rev Invest Clin. 2024;76(2):65-79 IN-DEPTH REVIEW

Adipose Tissue Immunometabolism: Unveiling the Intersection of Metabolic and Immune Regulation

Aida X. Medina-Urrutia[1,2#], Ivan Torre-Villalvazo[3#], and Juan G. Juárez-Rojas[4*]

[1]Department of Endocrinology, Instituto Nacional de Cardiología Ignacio Chávez (INCICh), Mexico City, Mexico; [2]Postgraduate Program in Biological Sciences, Postgraduate Unit, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico; [3]Department of Nutrition Physiology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [4]Department of Pharmacology, INCICh, Mexico City, Mexico

[#]Both authors are the first authors and they contributed equally.

ABSTRACT

Excess body weight has become a global epidemic and a significant risk factor for developing chronic diseases, which are the leading causes of worldwide morbidities. Adipose tissue (AT), primarily composed of adipocytes, stores substantial amounts of energy and plays a crucial role in maintaining whole-body glucose and lipid metabolism. This helps prevent excessive body fat accumulation and lipotoxicity in peripheral tissues. In addition, AT contains endothelial cells and a substantial population of immune cells (constituting 60-70% of non-adipocyte cells), including macrophages, T and B lymphocytes, and natural killer cells. These resident immune cells engage in crosstalk with adipocytes, contributing to the maintenance of metabolic and immune homeostasis in AT. An exacerbated inflammatory response or inadequate immune resolution can lead to chronic systemic low-grade inflammation, triggering the development of metabolic alterations and the onset of chronic diseases. This review aims to elucidate the regulatory mechanisms through which immune cells influence AT function and energy homeostasis. We also focus on the interactions and functional dynamics of immune cell populations, highlighting their role in maintaining the delicate balance between metabolic health and obesity-related inflammation. Finally, understanding immunometabolism is crucial for unraveling the pathogenesis of metabolic diseases and developing targeted immunotherapeutic strategies. These strategies may offer innovative avenues in the rapidly evolving field of immunometabolism. (REV INVEST CLIN. 2024;76(2):65-79)

Keywords: Immunometabolism. Adipose tissue functionality. Inflammation.

***Corresponding author:**
Juan G. Juárez-Rojas
E-mail: gaboyk2@gmail.com

Received for publication: 13-10-2023
Approved for publication: 09-02-2024
DOI: 10.24875/RIC.23000231

INTRODUCTION

Excess body weight has emerged as a global epidemic and a significant risk factor for the development of chronic diseases, including diabetes, metabolic dysfunction-associated steatotic liver disease, coronary artery disease, and cancer – leading causes of morbidity and mortality worldwide[1]. While population-based studies have established a clear connection between body weight and the prevalence of conditions such as hypertension, dyslipidemia, and diabetes, it is noteworthy that up to 40% of overweight individuals exhibit no metabolic abnormalities[1]. This suggests that adipose tissue (AT) functionality, rather than total body weight or body fat content, plays a crucial role in determining the development of metabolic alterations.

It has been observed that AT contains 4-6 million stromal cells per gram of mass, with 60-70% being immune cells. There is evidence of a complex interrelationship between adipocytes and immune cells, where the latter regulates energy homeostasis, and adipocytes modulate the immune response through the release of adipocytokines – a process defined as immuno-metabolism[2]. This narrative review aims to describe the regulatory mechanisms through which immune cells and adipocytes influence each other's activities and their impact on immunity and energy homeostasis. Integrating the crosstalk between AT and the immune system in health and during obesity is crucial for identifying therapeutic molecular targets and developing novel strategies for immunomodulation.

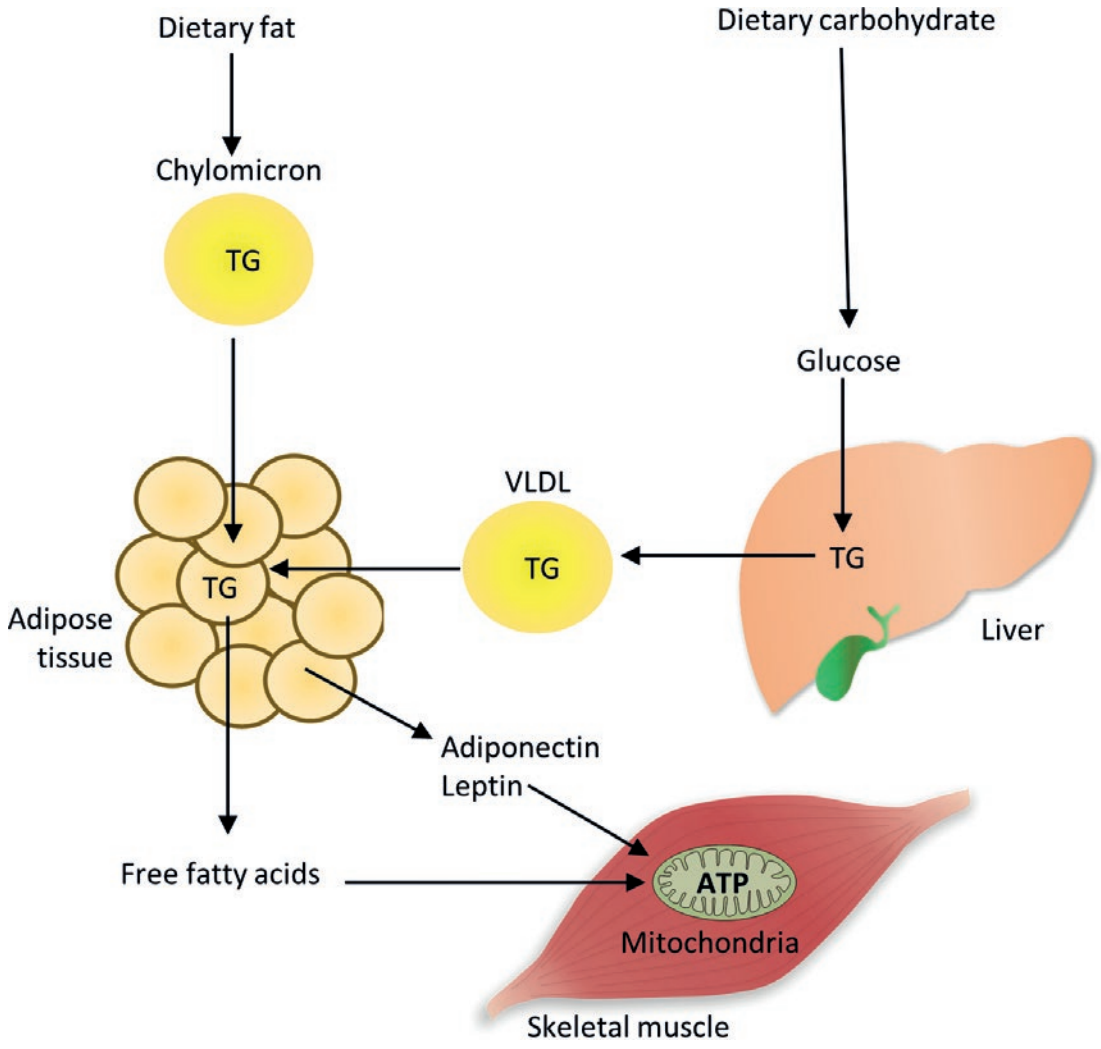
THE PHYSIOLOGICAL ROLE OF ADIPOSE TISSUE

After skeletal muscle, AT is the body's second-largest organ, constituting 15-30% of total body weight. AT is composed mainly of adipocytes, unique cells capable of storing large amounts of energy as triglycerides (TG), which features a single lipid vacuole occupying 90% of their volume. Adipocytes play a crucial role in maintaining whole-body energy homeostasis, a process tightly regulated by hormones and cytokines. During fasting conditions, glucagon, cortisol, and epinephrine activate lipolytic enzymes, triggering the hydrolysis of TG. This releases fatty acids as an energy source for the muscle, heart, and other tissues (Fig. 1). Conversely, food intake promotes the release of pancreatic insulin[3]. Within the adipocyte, insulin binds to its receptor, initiating autophosphorylation and recruiting additional proteins necessary for insulin receptor activation. This process triggers an intracellular signaling pathway mediated by phosphatidylinositol 3-kinase and protein kinase B (AKT). The pathway promotes the translocation of the glucose transporter 4 receptor to the cell membrane, facilitating the entry of glucose into the cell for use as an energy substrate (Fig. 2). The phosphatidylinositol 3-kinase-AKT pathway also inhibits lipolytic enzymes and stimulates lipoprotein lipase secretion and activity[4]. In addition, adipocytes release metabolic hormones such as leptin and adiponectin, known as adipokines. These adipokines increase glucose uptake and lipid oxidation in skeletal muscle, heart, and liver, while regulating satiety and energy expenditure in the central nervous system (Fig. 1)[3]. The coordinated activities of these hormones and enzymes enable adipocytes to efficiently capture lipoprotein-derived lipids and esterify them into TG, preventing the lipotoxic effects of lipid over-accumulation in non-ATs[4]. Thus, the metabolic switch exerted by AT in the transition from fed to fasting periods allows skeletal muscle to efficiently oxidize glucose during feeding while providing fatty acids for energy production during fasting or exercise. Adequate AT functionality maintains whole-body glucose and lipid metabolism, preventing excessive body fat accumulation and lipotoxicity in peripheral tissues. Notwithstanding the foregoing, AT is highly dynamic and can adapt to increase in energy intake. Excessive lipids are buffered by AT expansion through increases in cell volume (hypertrophy) or the number of adipocytes (hyperplasia) (Fig. 3). Hyperplasia is mediated by the differentiation of mesenchymal stem cells into mature adipocytes, in a process named adipogenesis[5]. Subcutaneous AT is the physiological energy reservoir, tightly regulated by the transcription factor peroxisome proliferator-activated receptor gamma (PPARγ), which promotes AT expansion. On the other hand, metabolic alterations such as dyslipidemia and insulin resistance (IR) are related to AT hypertrophy[6].

DYSFUNCTIONAL ADIPOSE TISSUE

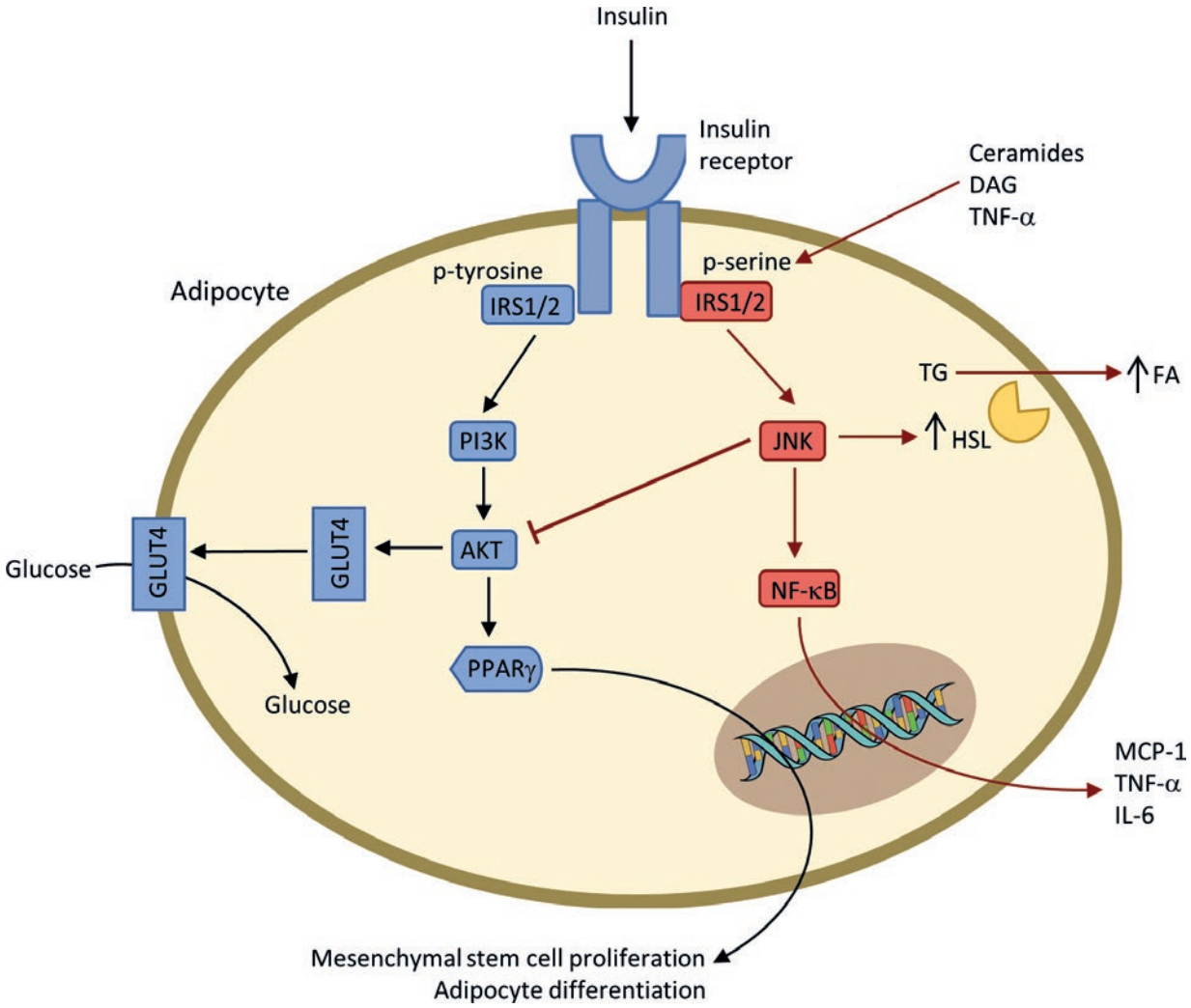
Energy balance in the body results from the ratio of energy intake to energy expenditure. The intake of

Figure 1. Metabolic and endocrine functions of adipose tissue. TG: triglycerides; VLDL: very-low-density lipoproteins.



high-calorie diets, accompanied by low physical activity, produces a positive energy balance and weight gain through adipogenesis and hyperplasic AT growth[3]. However, pro-inflammatory dietary patterns characterized by high saturated and trans fats, lipoperoxidated vegetable oils, high-fructose corn syrup, xenobiotics, excessive sodium, and low fiber and antioxidant intake are the main factors driving AT dysfunction, resulting in hypertrophic growth[7]. All these dietary compounds promote the accumulation of ceramides and diacylglycerols, potent lipotoxic and pro-inflammatory agents capable of disrupting the insulin signaling pathway, impairing glucose uptake and PPARγ activity, while increasing pro-inflammatory cytokine secretion (Fig. 2). These events impede adipocyte proliferation, leading to hypertrophy that limits oxygen diffusion within AT, resulting in hypoxia and activation of hypoxia-inducible factor 1α (HIF-1α)[8]. Reduced oxygen availability to adipocytes can lead to mitochondrial dysfunction and reactive oxygen species (ROS) release, causing oxidative stress and, eventually, cell death. Pro-inflammatory diets also lack antioxidant polyphenols and immunomodulatory fatty acids, such as eicosapentaenoic fatty acid (EPA) and docosahexaenoic fatty acid (DHA)[9]. Consequently, the inflammatory response initiated in adipocytes may lead to a chronic low-grade systemic inflammatory profile, characterized by a high release of free fatty acids, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α), or interleukin (IL)-6, as observed in most individuals with body weight excess (Fig. 3).

Figure 2. Activation and resolution of the inflammatory response. GLUT4: glucose transporter; IRS: insulin receptor substrate; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase; B; PPARγ: peroxisome proliferator-activated receptor gamma; JNK: c-Jun N-terminal kinase; NF-κB: nuclear factor kappa B; TG: triglycerides; HSL: hormone-sensitive lipase; DAG: diacylglycerol; TNF-α: tumor necrosis factor-alpha; FA: fatty acids, MCP-1: monocyte chemoattractant protein-1; IL: interleukin.



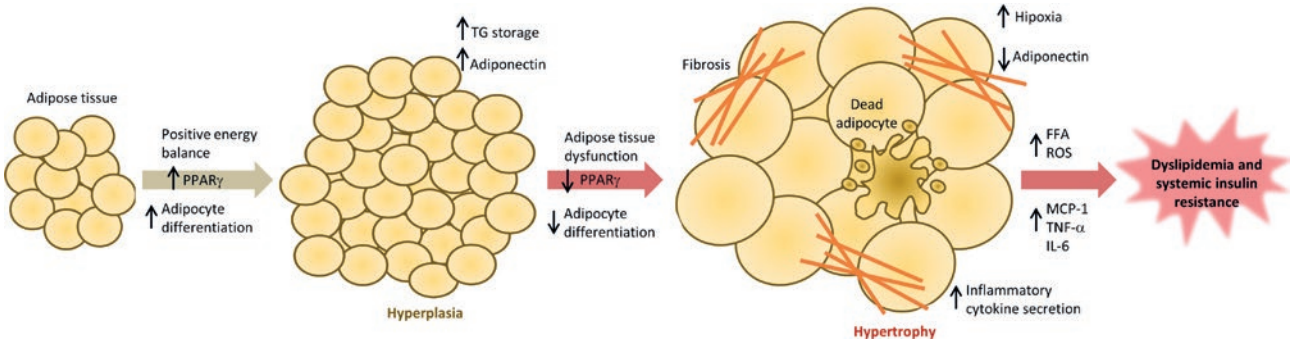
THE EMERGING FIELD OF IMMUNOMETABOLISM

Although AT primarily comprises adipocytes, it is a heterogeneous organ housing a diverse array of immune cell types[2,10]. This unique composition has led to the hypothesis that AT could serve as a reservoir of immune cells, offering an evolutionary advantage by facilitating a quick response to tissue damage. Adipocytes modulate the immune response by releasing free fatty acids and adipokines, influencing immune cell activity and cytokine profiles. This dynamic interaction is referred to as immunometabolism[2]. Understanding the impact of AT function on immunometabolism is pivotal to comprehend metabolic health, as it is directly related to the development of chronic metabolic diseases.

Activation and resolution of the inflammatory response: a dynamic balancing act

The immune system comprises a vast array of specialized cells that work in concert to protect the host from invading pathogens, repair damaged tissues, and clear malignant cells. These critical activities are performed by recognizing pathogen-associated molecular patterns that are present in the membrane of

Figure 3. Intracellular signals and biochemical pathways in adipocytes that interact with immune cells. PPARγ: peroxisome proliferator-activated receptor gamma; TG: triglycerides; FFA: free fatty acids; ROS: Reactive oxygen species; MCP-1: monocyte chemoattractant protein-1; IL: interleukin.



infectious pathogens. However, the immune response is also activated by damage-associated molecular patterns (DAMPs), which are endogenous antigens derived from damaged or necrotic cells. This activation is known as sterile inflammation, a form of immune response triggered by non-infectious insults that represent a critical aspect of the immune system's ability to maintain tissue homeostasis.

At the cellular level, stressors such as oxidative and endoplasmic reticulum stress, as well as mitochondrial dysfunction, promote plasma membrane instability, leading to the leakage of DAMPs and triggering a local inflammatory response[11]. The resolution of inflammation involves a shift from pro-inflammatory to anti-inflammatory signals. Anti-inflammatory cytokines, such as IL-10, downregulate immune cell activation, reducing the production of pro-inflammatory mediators. Specialized pro-resolving mediators terminate the inflammatory response and stimulate the release of growth factors and matrix metalloproteinases that promote tissue repair mechanisms, including angiogenesis and fibroblast activation[5,7]. Thus, the adequate and timely shift from pro-inflammatory to anti-inflammatory signals is critical, as an exacerbated inflammatory response or inadequate resolution may result in chronic systemic low-grade inflammation, triggering the development of metabolic alterations such as IR and the onset of chronic diseases[12].

Metabolic pathways influencing immune response

The adequate immune response depends on the reprogramming of immune cells from a pro-inflammatory activity to a pro-resolution secretome. Immune cells, particularly lymphocytes and macrophages, undergo distinct metabolic reprogramming upon activation to meet the demands of proliferation, cytokine production, and effector functions[13]. Anaerobic glycolysis, which converts glucose into pyruvate and lactate, is central to immune cell activation. Upon stimulation, immune cells rapidly up-regulate glucose uptake and its metabolism to lactate for cell proliferation and pro-inflammatory cytokine production. In human immune cells, the increase in cytokine secretion in response to pathogenic stimulation is proportional to the increase in lactate release[14]. Conversely, fatty acid oxidation is vital for the differentiation and functioning of regulatory T cells (Tregs) and dendritic cells[15,16]. The oxidative phosphorylation of fatty acids at the mitochondria is essential for memory T-cell formation. Indeed, effector T-cells switch from glycolysis to fatty acid oxidation to establish long-lasting immune memory[15]. Immune cells also rely on specific fatty acids to produce pro-resolution mediators derived from long-chain omega-3 fatty acids (EPA and DHA), generating lipoxins, resolvins, protectins, and maresins[17]. These lipid mediators are synthesized for the resolution phase to quench inflammation and promote the restoration of tissue homeostasis.

The short-chain fatty acid β-hydroxybutyrate (BHB) is a ketone released by the liver during fasting, exercise, and low-carbohydrate diets, exerting immunomodulatory activities in macrophages and other immune cells. BHB acts as a ligand for the cell surface G-protein-coupled receptor, hydroxycarboxylic acid receptor 2, also called GPR109A, which polarizes macrophages and other immune cells into an anti-inflammatory phenotype[18]. Thus, ketone bodies

arising from hepatic metabolism of free fatty acids released from AT favor immune response resolution during energy-demanding situations.

Amino acids are also crucial for several immune cell functions. Immune cells mainly depend on certain amino acids, notably glutamine and arginine. Glutamine is a vital carbon and nitrogen source for nucleotide and protein synthesis, making it indispensable for rapidly dividing immune cells. Arginine, on the other hand, is involved in the synthesis of nitric oxide (NO) and polyamines, which are crucial for macrophage effector functions and host defense. Amino acids regulate immune cell function through several signaling pathways, including activating the rapamycin pathway that controls T-cell activation and differentiation[19]. Innate and adaptive immune cell activities are also modulated by the insulin receptor, adding an important layer to the immune-metabolic crosstalk in the body. Insulin binding to its receptor in macrophages and monocytes favors pro-inflammatory polarization in response to inflammatory stimuli such as lipopolysaccharides (LPS)[20]. Insulin receptor activation in dendritic cells also induces an inflammatory metabolic reprogramming while preventing autophagy-induced antigen presentation, thus impairing an adequate adaptive response[21]. Insulin signaling increases ROS production and the release of neutrophil extracellular traps from neutrophils, enhancing their pathogen-clearance activities but also sustaining a pro-inflammatory milieu, preventing the resolution of inflammation[22]. Thus, nutrient availability and metabolism modulate immune cell function, cytokine secretion, and cytokine profiles; in turn, it modulates nutrient consumption in metabolic organs, such as AT. This crosstalk between immune cells and AT is critical for immunomodulation and metabolic homeostasis (Fig. 4).

IMMUNE CELL POPULATIONS IN INFLAMED ADIPOSE TISSUE

Macrophages

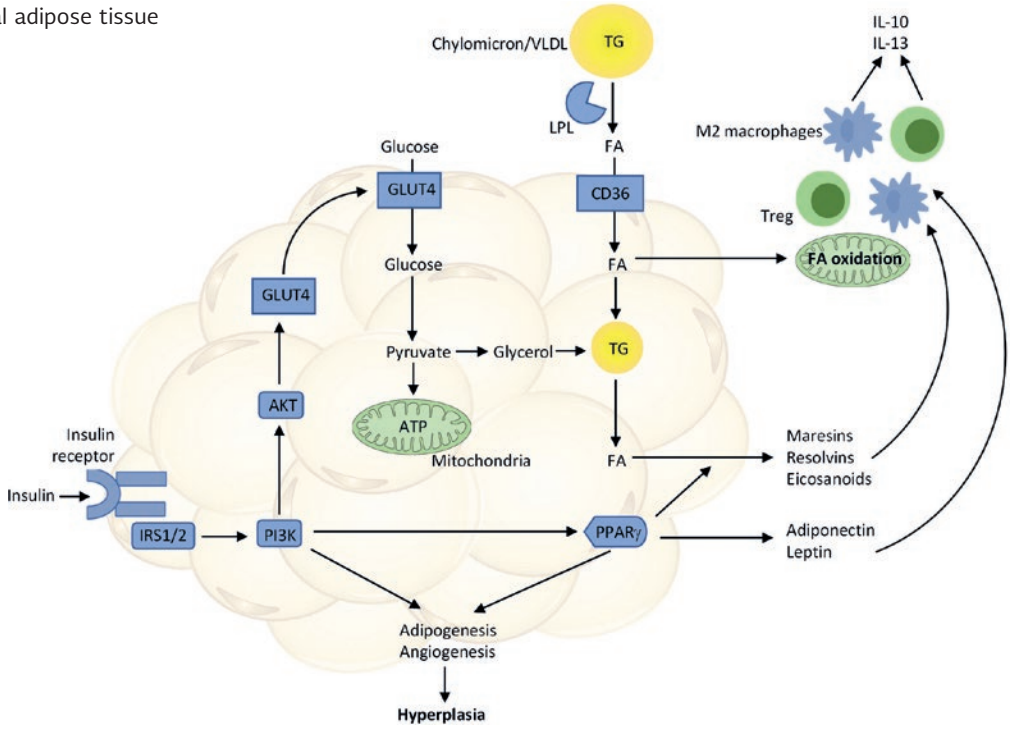
Macrophage (MCF), integral component of the myeloid lineage within the innate immune system, is distributed throughout various body tissues, swiftly responding to acute infections and diverse internal or external threats. In murine models of obesity, MCFs constitute as much as 50% of the total immune cell population[23]. Conversely, in healthy humans with normal weight, MCFs make up approximately 4% of the stromal fraction in AT, predominantly originating embryonically and capable of local regeneration[24]. Among overweight individuals, hypertrophy and the release of damage signals prompt the recruitment and differentiation of circulating monocytes into MCFs, resulting in a threefold increase in the MCF ratio within AT[25].

In 1882, Elie Metchnikoff characterized MCFs as sentinel cells adept at internalizing microbes through phagocytosis. More recently, their role in maintaining tissue integrity and homeostasis by facilitating the clearance of apoptotic cells through the anti-inflammatory process of efferocytosis has been recognized[19,25]. Within AT, efferocytosis manifests as the formation of distinctive structures known as crown-like structures (CLS). In response to DAMPs produced by aged or apoptotic adipocytes, resident MCFs undergo proliferation stimulated by IL-4. This proliferation is attributed to the smaller size of MCFs compared to adipocytes (≈ 20μm vs. ≈ 120 μm in diameter), necessitating synergistic action to clear damaged adipocytes effectively[25]. In addition, during AT dysfunction, hypertrophic adipocytes release MCP-1, promoting the recruitment of circulating monocytes and their subsequent differentiation into inflammatory MCFs[26]. While establishing the contribution of recruited peripheral cells to the total MCFs in dysfunctional AT remains challenging, it has been observed that up to 90% of resident MCFs are concentrated within CLS[27].

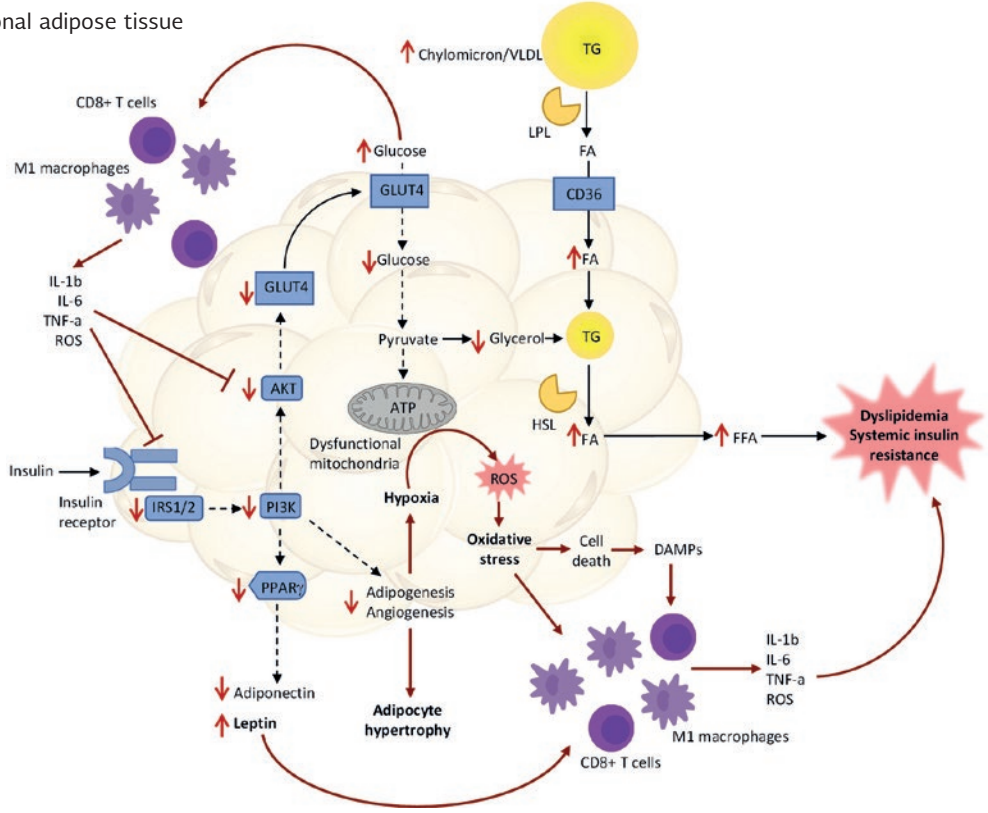
Two pivotal studies conducted in 2003 shed light on the integral role of MCFs in energy metabolism[27,28]. Weisberg et al. established a direct correlation between the body weight of various mouse models of obesity and the abundance of MCFs in AT, identified by the F4/80 marker. Notably, this research unveiled a direct association between the F4/80 cell ratio, adipocyte size, and the expression of inflammatory genes. An insightful conclusion drawn from this study was that TNF-α production originates primarily from AT-resident MCFs, challenging the initial hypothesis attributing it to adipocytes or other stromal cells. Some of these findings were corroborated in humans, where a direct link emerged between body mass index (BMI) and the expression of CD68, a marker for MCFs in AT[27].

Figure 4. **A:** adipose tissue expansion and **B:** the role of the immune system in the dysfunction of adipose tissue in response to an inflammatory dietary pattern. TG: triglycerides; LPL: lipoprotein lipase; CD36: lipid transporter; FA: fatty acids; IL: interleukin; Treg: regulatory T cells; PPARγ: peroxisome proliferator-activated receptor gamma; GLUT4: glucose transporter; AKT: protein kinase B; PI3K: phosphatidylinositol 3-kinase; IRS: insulin receptor substrate, TNF-a: tumor necrosis factor-alpha, ROS: reactive oxygen species, VLDL: very lowdensity lipoproteins, HSL: hormone-sensitive lipase, DAMPs: damage-associated molecular patterns.

A Functional adipose tissue



B Dysfunctional adipose tissue



Xu et al. conducted a parallel investigation, reporting increased expression of genes associated with inflammation in a murine obesity model. Their analysis included scrutinizing the temporal relationship between the onset of glucose and insulin metabolism alterations and the production of inflammatory mediators. Intriguingly, they observed that inflammation precedes elevated blood glucose and insulin concentrations, suggesting that the recruitment of MCFs serves as a triggering factor for IR[28,29]. However, it is essential to note the controversy surrounding this point, since conflicting studies propose that IR might precede inflammation[27]. It is crucial to acknowledge that these insights are derived from animal models under specific conditions and may not directly extrapolate to human scenarios. Nevertheless, consistent reports indicate that mitigating the inflammatory response holds promise in preventing the development of IR and diabetes[30].

The accumulation of MCFs in AT can be initially viewed as a protective physiological response. However, if stressors, such as an imbalance in calorie intake, persist, this phenomenon can turn pathogenic[2]. MCFs exhibit remarkable plasticity, capable of adopting various phenotypes depending on their microenvironment (Fig. 4). As weight increases and MCFs proliferate, their expression of membrane molecules and the production of cytokines and chemokines undergo modifications[31].

Conventionally, MCFs were categorized into two primary phenotypes based on their response to infection or damage, referred to as M1 (pro-inflammatory) or classically activated MCFs. Activation of M1 macrophages occurs in response to LPS from bacteria and inflammatory cytokines like interferon-gamma (IFNγ). Characterized by F4/80+CD11c+ expression, M1 macrophages function as antigen-presenting cells, releasing pro-inflammatory cytokines such as TNF-α, IL-6, IL-12, IL-1β, and IL-23. They are associated with oxidative stress due to their ability to produce ROS and NO, contributing to their bactericidal effect[32]. In contrast, alternatively activated macrophages, or M2, are induced in response to anti-inflammatory cytokines such as IL-4 or IL-13 (Fig. 4B). Identified in lean mice expressing F4/80+CD206+CD301+CD11, M2 macrophages play a role in tissue regeneration and repair. They secrete anti-inflammatory molecules such as IL-10 and transforming growth factor-beta, and unlike M1 macrophages, they are not as efficient in antigen presentation[33].

In the context of obesity in humans, the inflammatory process is more complex than in animal models. Cells with M1 characteristics are positive for CD11c and CD206 but exhibit high production of inflammatory cytokines. When stimulated by LPS and IFNγ, human MCFs express high levels of major histocompatibility complex class II and CD80/86 costimulatory molecules. Meanwhile, M2 macrophages in humans are characterized by increased expression of CD206, CD163, and transglutaminase 2 but have a limited capacity as antigen-presenting cells[34].

The inflammatory response to progressive weight gain in humans differs from that in infection. It is proposed that chronic overconsumption of nutrients promotes gradual weight gain, parallel polarization of M2 to M1 macrophages, and the development of IR[33,34]. The microenvironment surrounding MCFs exposed to an obesogenic environment differs from that during infection. Consequently, Kratz et al. proposed a model of metabolic activation in which they analyzed monocytes isolated from peripheral blood exposed to a medium that mimics the metabolic conditions of obesity (high concentrations of palmitic acid, glucose, and insulin). Using this model, they defined a new type of macrophage called metabolically activated (MMa). Through proteomic analysis, they observed that MMa was characterized by the expression of molecules related to lipid transport, such as CD36, the type 1 scavenger receptor, the adenosine triphosphate (ATP)-dependent transporter ABCA1, and the adipocyte differentiation-related protein perilipin 2. The study suggests that PPARγ regulates this activation. While MMa showed higher expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), they did not express surface markers related to M1 macrophage activation (CD38, CD274, and CD319)[35].

MMas also express lipid-degrading hydrolytic proteins independently of lipase-related lipolytic activity. These hydrolases are located in the lysosomes of resident MCFs, and clear excess TG released by hypertrophic adipocytes through exophagy[36]. A similar macrophage subclass has been described in humans, characterized by the expression of CD9. These cells secrete exosomes rich in TG and are identified as lipid-laden foam cells in obese individuals[33,34].

These studies suggest that MCFs regulate lipid homeostasis, which has evolved to favor metabolic health. In addition to clearing apoptotic adipocytes, they are activated to degrade excess lipids in hypertrophic adipocytes. Given the plasticity of MCFs in response to the AT microenvironment, it is essential to characterize changes in protein expression under different metabolic stimuli to describe their metabolic-functional heterogeneity.

The functional heterogeneity of MCFs, as well as the need for a rapid response to damage, requires these cells to rapidly produce energy in the form of ATP and reprogram their metabolism to respond appropriately to the microenvironment surrounding them. One of the first differences identified between the MCFs was the metabolites produced from arginine, since inducible NO synthase acts in the M1 type and produces NO and citrulline, while in the M2 type, arginase-1 acts and synthesizes proline and polyamines[19].

It has been observed that the inflammatory environment surrounding the M1 macrophage converges on the activation of nuclear factor kappa B and HIF-1α[8], modulating their energy metabolism. On the one hand, inflammation increases the expression of GLUT1, raising up to 10 times the contribution of glucose to the MCFs[37]. In addition, it stimulates the activity of some enzymes of the glycolytic pathway and lactate dehydrogenase, promoting the conversion of pyruvate to lactate and limiting oxidative phosphorylation (FOx). A high concentration of glycolytic intermediates favors the pentose phosphate pathway and maintains the production of nicotinamide adenine dinucleotide phosphate, which is essential for ROS production. Finally, there is also decreased activity of the enzyme isocitrate dehydrogenase, which is why M1 macrophages accumulate citrate, which is transformed into acetyl coenzyme A and promotes the accumulation of fatty acids and produces itaconate. This substrate functions as an inhibitor of the enzyme succinate dehydrogenase, promotes succinate accumulation, stabilizes HIF-1α, and decreases mitochondrial respiration, leading to more ROS. Although the glycolytic pathway is inefficient for producing ATP, it is the fastest way to obtain energy. It promotes a high production of ROS, which constitutes one of the leading defense mechanisms of M1 macrophages against pathogens and increases the release of chemokines that exacerbate the inflammatory response[37].

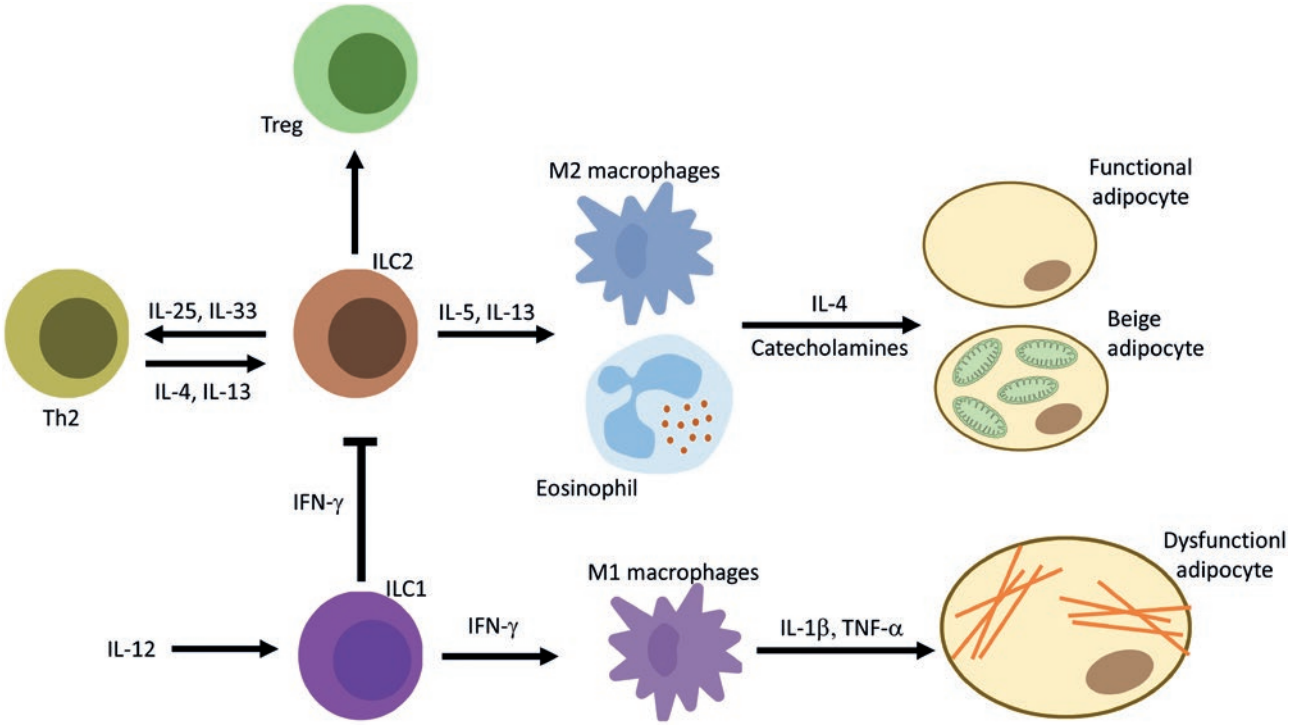
M2 macrophages primarily derive energy from the lipolytic pathway (Fig. 4A). On the other hand, glucose is metabolized to pyruvate, and in conjunction with the efficient oxidation of fatty acids, produces acetyl coenzyme A, which enters the tricarboxylic acid cycle. This cycle generates nicotinamide-adenine dinucleotide and flavin-adenine dinucleotide, serving as electron donors essential for ATP production through FOx. This metabolic pathway stimulates both phagocytic and lysosomal activity, crucial for the clearance of apoptotic cells and lipids – the primary function of M2 macrophages. The precise mechanisms by which energy metabolism is reprogrammed in obese subjects and its relationship with dysfunctional AT have not been fully elucidated. However, observations suggest active involvement of both the glycolytic pathway and FOx[14]. Alongside MCFs, healthy AT also houses other innate immune cells that contribute to maintaining an anti-inflammatory environment. These cells include eosinophils (EOSs), class 2 innate lymphoid cells (ILC2), and cytokines IL-4, 5, 13, and 33. In response to excess stored nutrients and lipids, dysfunctional AT triggers a type 1 inflammatory response, as previously described, which is associated with low-grade chronic inflammation and systemic metabolic disturbances. In such cases, the number of eosinophils decreases, while class 1 innate lymphoid cells (ILC1), NK cells, and the production of inflammatory cytokines such as IL-1β, 8, 18, and TNF-α increase[10].

Eosinophils

Eosinophils are versatile granulocytes originating in the bone marrow. Their maturation is driven by cytokines such as IL-5 and granulocyte colony-stimulating factor, releasing differentiated cells into the circulation. Known for their vital roles in allergic responses and defense against parasitic infections, eosinophils can migrate into tissues in response to chemokines like eotaxin 1 and induce the expression of the Siglec-F surface molecule (Fig. 5)[38].

An intriguing discovery hinting at the participation of resident eosinophils in AT homeostasis was made when Siglec-F+ eosinophils in the rat epididymis exhibited the highest expression of IL-4, a cytokine pivotal in the differentiation of M2 macrophages. This observation suggested that eosinophils contribute to AT health by promoting the activation of M2

Figure 5. Altered hormonal signaling and biochemical pathways in adipocytes leading to pro-inflammatory immune cells activation and its metabolic consequences. Treg: regulatory T cells; Th2: type 2 helper T cells; IL: interleukin; ILC2: class 2 innate lymphoid cells; IFN-γ: interferon-gamma; ILC1: class 1 innate lymphoid cells; IL-1β: interleukin 1 beta; TNF-α: tumor necrosis factor-alpha. *Adapted from Saetang J. et al., 2018*[10].



macrophages. However, efforts to recruit eosinophils through IL-5 administration did not enhance insulin signaling or increase energy expenditure in an obese mouse model[39]. Conversely, mice on a high-fat diet experienced a reduction in eosinophil numbers in the epididymis and an increase in M1 macrophages. This effect reversed when the mice transitioned to a low-fat diet, leading to weight loss. Notably, macrophages can also stimulate eosinophil recruitment, complicating the regulatory mechanisms between these cells[39]. In contrast to previous findings, another study reported that eosinophils, in the presence of oxidized low-density lipoproteins, induced the activation of M1 macrophages, producing pro-inflammatory cytokines[40].

While studies analyzing the association between the number of circulating eosinophils and BMI in humans present contradictory results, beneficial metabolic effects have been observed by inducing eosinophilia in patients with diabetes infected with non-pathogenic parasites[41]. This underscores the need for further research to clarify the role of eosinophils in different physiological contexts. Much of the evidence regarding their involvement in AT homeostasis comes from murine models, and the results may not necessarily apply to humans.

Innate lymphoid cells (ILCs)

In recent years, ILCs have garnered significant attention. Emerging from lymphoid progenitor cells in the fetal liver and adult bone marrow, ILCs constitute a family of effector cells within the immune system, playing crucial roles in metabolism, homeostasis, tissue repair, and regeneration. These cells are distributed across various tissues, including AT, as well as parenchymal organs such as the kidneys and liver. ILCs are categorized into five types: natural killer (NK) cells, ILC1, ILC2, ILC3, and lymphoid tissue-inducing cells[10].

ILC2s play a crucial role in maintaining AT homeostasis by fostering a type 2 inflammatory environment

and promoting thermogenesis. This activity enables AT to enhance energy expenditure by converting surplus energy into heat, involving beige adipocytes that are more prevalent in lean individuals and are characterized by a rich mitochondrial content[42]. It is hypothesized that ILC2 cells facilitate the differentiation of beige adipocytes by increasing the activity of mitochondrial uncoupling protein-1, possibly mediated through the production of the opioid penta-peptide met-enkephalin, thereby enhancing uncoupling protein-1 expression in adipocytes[43].

The recruitment of ILC2s into AT is contingent on the presence of IL-33, although the source of this cytokine remains a topic of debate. Some studies propose that stromal cells in AT, including fibroblasts and endothelial cells, are responsible for IL-33 production[43]. AT mesenchymal cells have been suggested as primary IL-33 producers, with IL-33 potentially playing a role in beige adipocyte differentiation. In addition, IL-5 production by ILC2s in AT is pivotal for EOS recruitment and retention, and this mechanism is also IL-33 dependent[44]. The collaboration between EOS, ILC2s, and their secretion of IL-4 and IL-13 collectively supports the presence of M2 macrophages, contributing significantly to AT homeostasis[43,44].

The number of AT-resident ILC2 cells in humans tends to decrease with increasing BMI, likely due to reduced IL-33 production[42]. In mice, studies suggest that a high-fat diet can increase IL-33 protein expression associated with programmed cell death, leading to decreased ILC2 cell numbers and reduced production of IL-5 and IL-13. This shift creates a type 1 inflammatory environment and promotes IR. Moreover, the infiltration of IFNγ-producing cells into AT has been observed to alter IL-33 production and ILC2 numbers (Fig. 5). Although the mechanisms behind the decrease in ILC2s during obesity are not fully defined, it is worth noting that the detrimental effects of a high-fat diet in obese animals can be reversed by administering IL-33, resulting in improved insulin sensitivity and blood glucose levels[45]. Previous reports have indicated that obesity induced by a high-fat diet can increase IL-12 expression and IFNγ release, leading to the proliferation of ILC1s in AT and the development of IR[46]. These findings have been corroborated in humans, where a direct correlation was found between the number of circulating and resident ILC1 cells in AT. In addition, ILC1 cells were more abundant in obese individuals and even more so in those with diabetes. This study also revealed a significant association between AT's number of ILC1 cells and IR-related variables. Moreover, the number of ILC1 cells and IR were independent predictors of AT fibrosis[47].

NK cells, a subset of ILCs, exhibit a classic effector function of cytotoxicity, crucial for eliminating tumor cells. This function is finely regulated by the expression of germline-encoded inhibitory receptors, primarily of the killer cell immunoglobulin-like receptor type, which recognizes major histocompatibility system molecules on target cells. *In vitro* studies have suggested that the cytotoxic capacity of NK cells from obese individuals is diminished due to decreased expression of granzymes and perforins, impairing their ability to eliminate damaged cells[48].

While morbidly obese individuals have been found to have fewer circulating NK cells than lean subjects, a recent study in overweight or moderately obese subjects did not report this effect[49]. Interestingly, another study by Li et al. demonstrated a higher number of NK cells in individuals with excess adiposity, suggesting that population demographics and the number of subjects studied may account for these discrepancies[50]. NK cells are considered contributors to the amplification and sustainment of type 1 inflammation, constituting over 40% of total IFNγ production in AT. They play a role in promoting the differentiation of MCFs toward the M1 phenotype. In addition, NK cells produce IL-15 and IL-12, which stimulate their activation and proliferation at sites of tissue damage, thereby contributing to the loss of insulin sensitivity. This feedback loop between NK cells and MCFs has primarily been observed in visceral AT. Paradoxically, NK cells have been found to exert their cytotoxic activity primarily on M2 MCFs, suggesting that NK cells may eliminate MCFs that have fulfilled their physiological function. This complex interplay between NK cells and MCFs and their potential effects on metabolically activated macrophages (MMa) warrants further investigation. The interaction between NKG2D and RAE-1 (NK receptor and MCFs ligand) plays a crucial role in regulating inflammation. The reduced expression of RAE-1 in MCFs of obese individuals makes them less susceptible to the regulatory cytotoxic action of NK cells[50].

Inflammatory response in dysfunctional adipose tissue

Most research on the immune response and its relationship with AT homeostasis has predominantly focused on MCFs, as they are the most abundant cells in murine models, serving as central regulators of the inflammation-IR relationship. However, in healthy humans, lymphocytes constitute approximately 50% of AT's total resident immune cells[23]. Lymphocytes have been observed to infiltrate hypertrophic adipocytes with crown structures. CD4+ and Tregs are present in healthy AT, maintaining a type 2 inflammatory environment. In contrast, hypertrophic AT contains CD4+ and CD8+ cytotoxic effector T lymphocytes designed to specifically eliminate damaged cells by secreting perforin and granzyme B. These responses favor the differentiation of M1 MCFs and the development of IR[10].

CD4+ T lymphocytes, also known as T helper (Th) cells, recognize antigens presented by cells expressing major histocompatibility complex class II, such as MCFs and dendritic cells. When activated, they amplify immune responses through proliferation and cytokine production. These cells are categorized into Th1 lymphocytes, activated by IFNγ, and known for producing IFNγ and TNF-α; Th2 lymphocytes, activated by IL-4, and known for producing ILs 1, 4, 5, 10, and 13; and Th17 and Th22 lymphocytes, which secrete IL-17 and IL-22, respectively[10]. Studies characterizing the profile of T cells in human AT provide essential information regarding their relationship with metabolic abnormalities. Fabbrini et al. obtained subcutaneous AT biopsies from lean and obese subjects, with and without metabolic abnormalities. Compared with metabolically healthy lean and obese subjects, obese individuals with metabolic abnormalities had increased AT CD4+ lymphocyte counts and CCL-5 and IL-17 expression. CD4+ cells from dysmetabolic subjects were positive for IL-22 and 17, accompanied by higher plasma concentrations of these cytokines. The authors of this work demonstrated through *in vitro* assays that IL-22 and 17 induce insulin resistance in the liver and muscle, altering glucose uptake in these tissues[51]. The accumulation of CD4+ cells that produce IL-22 and 17 was confirmed in a study carried out in patients with diabetes, in which it was shown that the MCFs have receptors for these cytokines and that the interaction between these cells favors the increased production of IL-1β. Considering this background and results from other studies[52], we can conclude that subjects with obesity are characterized by presenting a higher proportion of Th17, Th22, and CD4+ cells in AT, which favors a pro-inflammatory environment and the development of metabolic abnormalities.

Treg cells, characterized by the expression of FOXP3, play a crucial role in maintaining tolerance toward self. Evidence from a mouse model in which the FOXP3 gene was deleted demonstrated the importance of Treg cells, as their absence resulted in lymphoproliferative disease and premature death. Although Treg cells originate in the thymus, they can also be found as resident lymphocytes. Visceral AT in mice was one of the first tissues where these resident Treg cells were discovered, colonizing the area within the first 4 days of life. These resident Treg cells are characterized by high expression of neuropilin-1 and IL-33[53]. Their main function is to balance the inflammatory response by suppressing effector T cells and inflammatory MCFs through several mechanisms, including the expression of suppressor molecules such as CTLA4, consumption of IL-2, and secretion of transforming growth factor-beta and IL-10[54]. Multiple studies in animal models characterized by obesity and IR have reported fewer Treg cells than in healthy animals. Similar observations have been made when comparing obese and IR individuals to healthy lean subjects, suggesting a potentially protective metabolic effect of these cells[55].

B lymphocytes have also been found to participate in the regulation of energy homeostasis. Several animal models of diet-induced obesity have shown increased infiltration of B cells in visceral AT, particularly immunoglobulin (Ig)G-producing lymphocytes. In addition, one study demonstrated that inoculating IgG produced in obese animals accelerates inflammation and IR[56]. Interestingly, the administration of polyclonal IgG in patients with common variable immunodeficiency, characterized by low IgG concentrations, decreased inflammation, improved insulin sensitivity, and enhanced endothelial function. Peripheral blood B cells obtained from patients with diabetes were shown to induce a pro-inflammatory phenotype, characterized by increased production of IL-6 and TNF-α and decreased IL-10[57].

TARGETING IMMUNOMETABOLISM FOR OBESITY INTERVENTION

Immunomodulatory drugs and their potential in obesity treatment

The resolution of inflammation is a primary strategy to combat the deleterious effects of chronic immune cell activation. Several immunomodulatory agents have been tested for obesity treatment, offering promising pathways for intervention. These emerging therapeutic compounds exhibit immunomodulatory activities by suppressing the synthesis and secretion of pro-inflammatory cytokines by immune cells, enhancing anti-inflammatory signaling, and rebalancing the immune milieu. They may also stimulate a shift from M1 to M2 macrophages and regulate the activity of T cell subsets, promoting anti-inflammatory Tregs while inhibiting pro-inflammatory T cell responses. These mechanisms lead to the resolution of inflammation and improvement in insulin sensitivity. Some examples of these compounds include salicylates, which increase insulin sensitivity by reducing pancreatic inflammation and insulin clearance; etanercept and infliximab, TNF-α inhibitors that improve insulin sensitivity; canakinumab, an IL-1β inhibitor that has demonstrated beneficial effects on glycemic control; tofacitinib, a Janus kinase inhibitor that may reduce AT inflammation; and metformin, widely used as a diabetes medication that exhibits immunomodulatory effects, including reducing macrophage infiltration and inflammation in AT[58].

Lifestyle interventions influencing adipose tissue immunometabolism

While immunomodulatory drugs are effective in preventing and resolving low-grade chronic inflammation associated with dysfunctional AT, their accessibility and cost may limit their widespread use. Therefore, lifestyle modification remains the most effective strategy for the long-term prevention and treatment of inflammatory diseases. Anti-inflammatory dietary patterns, such as the Mediterranean and Dietary Approaches to Stop Hypertension (DASH), have demonstrated significant immunomodulatory activities in individuals with metabolic syndrome[59,60]. Key components of an immunomodulatory dietary pattern include long-chain omega-3 fatty acids EPA and DHA from marine sources, antioxidant, and immunomodulatory polyphenols (such as genistein, resveratrol, quercetin, epigallocatechin, and kaempferol), prebiotic fermentable fiber, probiotic bacteria and yeast, branched-chain amino acids, as well as vitamins A and D, selenium, and zinc[59,60]. These components, naturally present in various foods, contribute to reducing inflammation and improving metabolic health.

In addition to dietary changes, other lifestyle modifications play crucial roles in regulating inflammation and maintaining metabolic health. Regular physical exercise has well-documented anti-inflammatory effects and can help improve insulin sensitivity. Adequate sleep patterns and effective stress-coping mechanisms also contribute to reducing inflammation and supporting overall health.

FUTURE DIRECTIONS

The immune system plays a pivotal role in maintaining AT homeostasis and influencing the development of metabolic abnormalities. The burgeoning field of immunometabolism focuses on unraveling these intricate connections and exploring novel treatment strategies for inflammatory diseases associated with metabolic dysfunction. While substantial research has been conducted on various immune cell types and their involvement in energy metabolism, much of this work has been carried out in animal models. However, significant differences in the proportion of these cells and their responses to various stimuli pose challenges in extrapolating findings to human contexts. A wealth of information exists regarding the polarization of immune cells in response to classic inflammatory processes induced by LPS or IFNγ, contributing substantially to the field of immunometabolism. Nevertheless, many aspects remain to be understood about the involvement of diverse immune cell types in inflammation induced by metabolic alterations, their interactions in response to metabolic stimuli, and the regulatory mechanisms maintaining healthy AT.

The interactions and functional dynamics of immune cell populations within AT are critical for preserving the delicate balance between metabolic health and inflammation associated with obesity. A comprehensive understanding of the roles and regulatory mechanisms of immune cells in AT is essential for decoding

the pathogenesis of metabolic diseases and formulating targeted immunotherapeutic strategies. AT emerges as a dynamic immunological niche with profound implications for both metabolic and immune regulation. Exploring interventions that manipulate glucose and insulin pathways holds promise for enhancing host defense, mitigating inflammation, and advancing immunotherapies within the realm of immunometabolism.

ACKNOWLEDGMENTS

This article serves as a fulfilment of Dr Aida X. Medina-Urrutia, for obtaining a Doctoral degree in the *Posgrado en Ciencias Biológicas,* Universidad Nacional Autónoma de México. The authors would like to thank Froylan David Martínez-Sánchez (Internal Medicine Department, Hospital General Dr. Manuel Gea González, Mexico City, Mexico), for supporting the final restructuring of the manuscript and revision of the english version.

REFERENCES

1. Tsatsoulis A, Paschou SA. Metabolically healthy obesity: criteria, epidemiology, controversies, and consequences. Curr Obes Rep. 2020;9:109-20.
2. Trim WV, Lynch L. Immune and non-immune functions of adipose tissue leukocytes. Nat Rev Immunol. 2022;22:371-86.
3. Rosenbaum M, Leibel RL. Adaptive thermogenesis in humans. Int J Obes (Lond). 2010;34(Suppl 1):S47-55.
4. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest. 2016;126:12-22.
5. Sakers A, De Siqueira MK, Seale P, Villanueva CJ. Adipose-tissue plasticity in health and disease. Cell. 2022;185:419-46.
6. Hammarstedt A, Gogg S, Hedjazifar S, Nerstedt A, Smith U. Impaired adipogenesis and dysfunctional adipose tissue in human hypertrophic obesity. Physiol Rev. 2018;98:1911-41.
7. Saghafi-Asl M, Mirmajidi S, Asghari Jafarabadi M, Vahid F, Shivappa N, Hébert JR, et al. The association of dietary patterns with dietary inflammatory index, systemic inflammation, and insulin resistance, in apparently healthy individuals with obesity. Sci Rep. 2021;11:7515.
8. Fujisaka S, Usui I, Ikutani M, Aminuddin A, Takikawa A, Tsuneyama K, et al. Adipose tissue hypoxia induces inflammatory M1 polarity of macrophages in an HIF-1α-dependent and HIF-1α-independent manner in obese mice. Diabetologia. 2013;56:1403-12.
9. Tristan Asensi M, Napoletano A, Sofi F, Dinu M. Low-grade inflammation and ultra-processed foods consumption: a review. Nutrients. 2023;15:1546.
10. Saetang J, Sangkhathat S. Role of innate lymphoid cells in obesity and metabolic disease (Review). Mol Med Rep. 2018; 17:1403-1412.
11. Shim YR, Jeong WI. Recent advances of sterile inflammation and inter-organ cross-talk in alcoholic liver disease. Exp Mol Med. 2020;52:772-80.
12. Lee YS, Olefsky J. Chronic tissue inflammation and metabolic disease. Genes Dev. 2021;35:307-28.
13. Altun I, Yan X, Ussar S. Immune cell regulation of white adipose progenitor cell fate. Front Endocrinol (Lausanne). 2022; 13:859044.
14. Vrieling F, van Dierendonck XA, Jaeger M, Janssen AW, Hijmans A, Netea MG, et al. Glycolytic activity in human immune cells: inter-individual variation and functional implications during health and diabetes. Immunometabolism (Cobham). 2022; 4:e00008.
15. Zhang S, Gang X, Yang S, Cui M, Sun L, Li Z, et al. The alterations in and the role of the Th17/treg balance in metabolic diseases. Front Immunol. 2021;12:678355.
16. Liu R, Pugh GH, Tevonian E, Thompson K, Lauffenburger DA, Kern PA, et al. Regulatory T cells control effector T cell inflammation in human prediabetes. Diabetes. 2022;71:264-74.
17. Chiurchiù V, Leuti A, Maccarrone M. Bioactive lipids and chronic inflammation: managing the fire within. Front Immunol. 2018;9:38.
18. Fu SP, Li SN, Wang JF, Li Y, Xie SS, Xue WJ, et al. BHBA suppresses LPS-induced inflammation in BV-2 cells by inhibiting NF-κB activation. Mediators Inflamm. 2014;2014:983401.
19. Yurdagul A Jr., Subramanian M, Wang X, Crown SB, Ilkayeva OR, Darville L, et al. Macrophage metabolism of apoptotic cell-derived arginine promotes continual efferocytosis and resolution of injury. Cell Metab. 2020;31:518-33.e10.
20. Ratter JM, van Heck JI, Rooijackers HM, Jansen HJ, van Poppel PC, Tack CJ, et al. Insulin acutely activates metabolism of primary human monocytes and promotes a proinflammatory phenotype. J Leukoc Biol. 2021;110:885-91.
21. Xuan NT, Hoang NH, Nhung VP, Duong NT, Ha NH, Hai NV. Regulation of dendritic cell function by insulin/IGF-1/PI3K/Akt signaling through klotho expression. J Recept Signal Transduct Res. 2017;37:297-303.
22. Thimmappa PY, Vasishta S, Ganesh K, Nair AS, Joshi MB. Neutrophil (dys)function due to altered immuno-metabolic axis in type 2 diabetes: implications in combating infections. Hum Cell. 2023;36:1265-82.
23. Laparra A, Tricot S, Le Van M, Damouche A, Gorwood J, Vaslin B, et al. The Frequencies of immunosuppressive cells in adipose tissue differ in human, non-human primate, and mouse models. Front Immunol. 2019;10:117.
24. Gautier EL, Yvan-Charvet L. Understanding macrophage diversity at the ontogenic and transcriptomic levels. Immunol Rev. 2014;262:85-95.
25. Boutens L, Stienstra R. Adipose tissue macrophages: going off track during obesity. Diabetologia. 2016;59:879-94.
26. Amano SU, Cohen JL, Vangala P, Tencerova M, Nicoloro SM, Yawe JC, et al. Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation. Cell Metab. 2014;19:162-71.
27. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112:1796-808.
28. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003; 112:1821-30.
29. Semnani-Azad Z, Connelly PW, Johnston LW, Retnakaran R, Harris SB, Zinman B, et al. The macrophage activation marker soluble CD163 is longitudinally associated with insulin sensitivity and β-cell function. J Clin Endocrinol Metab. 2020; 105:e285-94.
30. Hamjane N, Benyahya F, Nourouti NG, Mechita MB, Barakat A. Cardiovascular diseases and metabolic abnormalities associated with obesity: what is the role of inflammatory responses? A systematic review. Microvasc Res. 2020;131:104023.
31. Huber J, Kiefer FW, Zeyda M, Ludvik B, Silberhumer GR, Prager G, et al. CC chemokine and CC chemokine receptor profiles in visceral and subcutaneous adipose tissue are altered in human obesity. J Clin Endocrinol Metab. 2008;93:3215-21.
32. Chávez-Galán L, Olleros ML, Vesin D, Garcia I. Much more than M1 and M2 macrophages, there are also CD169(+) and TCR(+) macrophages. Front Immunol. 2015;6:263.
33. Russo L, Lumeng CN. Properties and functions of adipose tissue macrophages in obesity. Immunology. 2018;155:407-17.
34. Zeyda M, Farmer D, Todoric J, Aszmann O, Speiser M, Györi G, et al. Human adipose tissue macrophages are of an anti-inflammatory phenotype but capable of excessive pro-inflammatory mediator production. Int J Obes (Lond). 2007;31:1420-8.
35. Kratz M, Coats BR, Hisert KB, Hagman D, Mutskov V, Peris E, et al. Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages. Cell Metab. 2014;20:614-25.
36. Coats BR, Schoenfelt KQ, Barbosa-Lorenzi VC, Peris E, Cui C, Hoffman A, et al. Metabolically activated adipose tissue macrophages perform detrimental and beneficial functions during diet-induced obesity. Cell Rep. 2017;20:3149-61.

37. Freemerman AJ, Johnson AR, Sacks GN, Milner JJ, Kirk EL, Troester MA, et al. Metabolic reprogramming of macrophages: glucose transporter 1 (GLUT1)-mediated glucose metabolism drives a proinflammatory phenotype. J Biol Chem. 2014; 289:7884-96.
38. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, et al. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science. 2011;332:243-7.
39. Bolus WR, Peterson KR, Hubler MJ, Kennedy AJ, Gruen ML, Hasty AH. Elevating adipose eosinophils in obese mice to physiologically normal levels does not rescue metabolic impairments. Mol Metab. 2018;8:86-95.
40. Qin M, Wang L, Li F, Yang M, Song L, Tian F, et al. Oxidized LDL activated eosinophil polarize macrophage phenotype from M2 to M1 through activation of CD36 scavenger receptor. Atherosclerosis. 2017;263:82-91.
41. Hays R, Esterman A, Giacomin P, Loukas A, McDermott R. Does Strongyloides stercoralis infection protect against type 2 diabetes in humans? Evidence from Australian aboriginal adults. Diabetes Res Clin Pract. 2015;107:355-61.
42. Brestoff JR, Kim BS, Saenz SA, Stine RR, Monticelli LA, Sonnenberg GF, et al. Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. Nature. 2015;519:242-6.
43. Molofsky AB, Van Gool F, Liang HE, Van Dyken SJ, Nussbaum JC, Lee J, et al. Interleukin-33 and interferon-γ counter-regulate group 2 innate lymphoid cell activation during immune perturbation. Immunity. 2015;43:161-74.
44. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB, et al. Type 2 innate lymphoid cells control eosinophil homeostasis. Nature. 2013;502:245-8.
45. Bénézech C, Jackson-Jones LH. ILC2 orchestration of local immune function in adipose tissue. Front Immunol. 2019;10:171.
46. O'Sullivan TE, Rapp M, Fan X, Weizman OE, Bhardwaj P, Adams NM, et al. Adipose-resident group 1 innate lymphoid cells promote obesity-associated insulin resistance. Immunity. 2016; 45:428-41.
47. Wang H, Shen L, Sun X, Liu F, Feng W, Jiang C, et al. Adipose group 1 innate lymphoid cells promote adipose tissue fibrosis and diabetes in obesity. Nat Commun. 2019;10:3254.
48. Tobin LM, Mavinkurve M, Carolan E, Kinlen D, O'Brien EC, Little MA, et al. NK cells in childhood obesity are activated, metabolically stressed, and functionally deficient. JCI Insight. 2017; 2:e94939.
49. Keilen J, Gar C, Rottenkolber M, Fueessl LU, Joseph AT, Draenert R, et al. No association of natural killer cell number and function in peripheral blood with overweight/obesity and metabolic syndrome in a cohort of young women. Physiol Rep. 2022;10:e15148.
50. Li Y, Wang F, Imani S, Tao L, Deng Y, Cai Y. Natural killer cells: friend or foe in metabolic diseases? Front Immunol. 2021; 12:614429.
51. Fabbrini E, Cella M, McCartney SA, Fuchs A, Abumrad NA, Pietka TA, et al. Association between specific adipose tissue CD4+ T-cell populations and insulin resistance in obese individuals. Gastroenterology. 2013;145:366-74.e1.
52. Bertola A, Ciucci T, Rousseau D, Bourlier V, Duffaut C, Bonnafous S, et al. Identification of adipose tissue dendritic cells correlated with obesity-associated insulin-resistance and inducing Th17 responses in mice and patients. Diabetes. 2012;61:2238-47.
53. Kolodin D, van Panhuys N, Li C, Magnuson AM, Cipolletta D, Miller CM, et al. Antigen- and cytokine-driven accumulation of regulatory T cells in visceral adipose tissue of lean mice. Cell Metab. 2015;21:543-57.
54. McLaughlin T, Ackerman SE, Shen L, Engleman E. Role of innate and adaptive immunity in obesity-associated metabolic disease. J Clin Invest. 2017;127:5-13.
55. Eller K, Kirsch A, Wolf AM, Sopper S, Tagwerker A, Stanzl U, et al. Potential role of regulatory T cells in reversing obesity-linked insulin resistance and diabetic nephropathy. Diabetes. 2011; 60:2954-62.
56. Tam CS, Viardot A, Clément K, Tordjman J, Tonks K, Greenfield JR, et al. Short-term overfeeding may induce peripheral insulin resistance without altering subcutaneous adipose tissue macrophages in humans. Diabetes. 2010;59:2164-70.
57. DeFuria J, Belkina AC, Jagannathan-Bogdan M, Snyder-Cappione J, Carr JD, Nersesova YR, et al. B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. Proc Natl Acad Sci U S A. 2013;110:5133-8.
58. Kuryłowicz A, Koźniewski K. Anti-inflammatory strategies targeting metaflammation in type 2 diabetes. Molecules. 2020; 25:2224.
59. Tieu S, Charchoglyan A, Wagter-Lesperance L, Karimi K, Bridle BW, Karrow NA, et al. Immunoceuticals: harnessing their immunomodulatory potential to promote health and wellness. Nutrients. 2022;14:4075.
60. Reneau J, Goldblatt M, Gould J, Kindel T, Kastenmeier A, Higgins R, et al. Effect of adiposity on tissue-specific adiponectin secretion. PLoS One. 2018;13:e0198889.