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Visceral Versus Subcutaneous Adipose Tissue: Immune Microenvironment and Metabolic Consequences

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Abstract: ***The immune microenvironment exhibits significant differences between visceral white adipose tissue (vWAT) and subcutaneous white adipose tissue (sWAT), a disparity that serves as a fundamental mechanism underlying their distinct metabolic outcomes. vWAT is predominantly associated with a pro-inflammatory profile, wherein the release of inflammatory cytokines and free fatty acids (FFAs) promotes insulin resistance (IR) via the portal venous system, thereby contributing to the pathogenesis of type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases (CVDs). Conversely, sWAT is characterized by an anti-inflammatory phenotype and provides a metabolic buffering effect, partially through hyperplastic expansion. Nevertheless, this protective function is compromised when its capacity for expansion is exceeded. A comprehensive analysis of the immune differences characteristic of these two adipose depots, along with an elucidation of the transition from homeostasis to pathological states, will enhance the precise identification of early intervention points for metabolic disorders and offer a theoretical foundation for the development of immune-modulatory strategies targeting specific adipose depots.***

Keywords: Visceral white adipose tissue, Subcutaneous white adipose tissue, Immune microenvironment, Free fatty acids, Metabolic diseases**.**

1. Introduction

In recent years, metabolic diseases have become increasingly prevalent on a global scale, presenting a significant public health challenge worldwide [1]. Dysfunction of adipose tissue is a critical factor in the pathogenesis of obesity-related metabolic disorders. This dysfunction often precedes the onset of obesity, instigating a shift in adipokine secretion towards a pro-diabetic profile and propagating local disturbances to the systemic level through mechanisms such as adipocyte hypertrophy, hypoxia, and immune cell infiltration. These processes disrupt glucose and lipid metabolism, thereby contributing to the development of metabolic diseases [2]. Adipose tissue is an organ system comprising multiple anatomically distinct and functionally specialized fat depots. In addition to its traditional role in energy storage, adipose tissue also performs specific functions related to signal regulation and immune defense. Mammalian adipose tissue predominantly consists of white adipose tissue (WAT) and brown adipose tissue (BAT). WAT, serving as the principal form of fat storage, can be further subdivided into visceral WAT (vWAT) and subcutaneous WAT (sWAT). VWAT is primarily located within the abdominal cavity, enveloping internal organs such as the omentum, mesentery, and retroperitoneal space, whereas sWAT is distributed beneath the skin throughout the body, with a higher concentration in the gluteal and femoral regions [3]. Research indicates that under equivalent systemic metabolic stress, vWAT and sWAT exhibit significant differences in immune-inflammatory responses and metabolic phenotypes. An excessive accumulation of vWAT is associated with an elevated risk of insulin resistance, hypertension, and hypertriglyceridemia. Conversely, individuals with increased lower-body sWAT accumulation tend to have a reduced metabolic risk [4]. The differential impact on systemic metabolism can be attributed to the distinct immune microenvironments they establish. Adipose tissue contains a diverse array of immune cells that interact with adipocytes, preadipocytes, and stromal vascular cells through a complex network of signaling molecules, including cytokines and chemokines, which collectively maintain local immune and metabolic homeostasis [5]. Consequently, a comprehensive analysis and comparison of the compositional and functional differences in the immune microenvironments of vWAT and sWAT, as well as the elucidation of the mechanisms leading to their divergent metabolic outcomes, are crucial for understanding the pathogenesis of obesity-related metabolic diseases and for identifying specific therapeutic targets.

2. Composition and Function of the Adipose Tissue Immune Microenvironment

The immune microenvironment of adipose tissue comprises a complex network of immune cells, adipocytes, stromal cells, and the signaling molecules they produce. This microenvironment operates as a dynamic entity that either sustains adipose tissue homeostasis or contributes to its functional abnormalities. Alterations in the adipose tissue immune microenvironment often precede the development of metabolic disorders, with the ensuing pathological state of metabolic dysfunction further aggravating disruptions in the immune microenvironment, thereby establishing a vicious cycle [6].

Among the immune cell populations, adipose tissue macrophages (ATMs) are the most prevalent and play a pivotal role, serving as the central hub of metabolic inflammation. The phenotypic characteristics of ATMs are notably heterogeneous, traditionally categorized into the pro-inflammatory M1 type and the anti-inflammatory M2 type [7]. Recent advancements in single-cell sequencing have

further delineated ATMs within adipose tissue into distinct subsets, including perivascular macrophages (PVMs), lipid-associated macrophages (LAMs), and monocyte-derived macrophages [8, 9]. Under physiological conditions, ATMs predominantly exhibit an anti-inflammatory M2 phenotype, which plays a crucial role in maintaining tissue repair and insulin sensitivity through the secretion of factors such as interleukin-10 (IL-10), thereby contributing to the homeostasis of healthy adipose tissue [10]. However, this equilibrium is perturbed in the context of obesity. Empirical studies have demonstrated that bone marrow-derived monocytes are recruited to adipose tissue via a CCR2-dependent mechanism, subsequently differentiating into pro-inflammatory M1-type macrophages. Concurrently, novel pro-inflammatory subsets, such as $F4/80^{+}CD11c^{+}$ cells, emerge within the adipose tissue [11]. This phenotypic transition from M2 to M1 underlies the development of chronic low-grade inflammation in adipose tissue and constitutes a fundamental mechanism contributing to IR [10].

The equilibrium of T lymphocyte subsets within the immune cell population is of paramount importance. In adipose tissue, T lymphocytes predominantly comprise $CD8^{+}$ T cells, $CD4^{+}$ T cells, regulatory T cells (Tregs), and natural killer T (NKT) cells [12]. Tregs play a pivotal role in maintaining metabolic homeostasis. In a healthy physiological state, Tregs are particularly abundant in adipose tissue, especially in vWAT, where they effectively mitigate local inflammation through various mechanisms. These include the secretion of anti-inflammatory cytokines such as IL-10, inhibition of the pro-inflammatory activities of conventional T cells, and preservation of the anti-inflammatory phenotype of ATMs, thereby positively influencing systemic insulin sensitivity [13]. In contrast, during metabolic disorders such as obesity, there is a marked infiltration and accumulation of pro-inflammatory effector cells, notably $CD8^{+}$ T cells, facilitated by chemotactic processes, while the population of protective Tregs diminishes. A critical upstream factor driving this alteration is the functional transformation of adipose-derived stem cells (ASCs). Upon activation, these cells secrete substantial quantities of the chemokine CCL5 in the early stages of obesity, thereby mediating the recruitment of T cells. Ultimately, the accumulation and activation of T cells exacerbate chronic inflammation and IR within adipose tissue [14].

Neutrophils, as key immune cells, infiltrate adipose tissue during the initial stages of obesity. While their presence is minimal in normal adipose tissue, it increases significantly in the early phases of obesity, preceding the accumulation of ATMs. The infiltration of neutrophils is contingent upon upstream signaling and can further recruit ATMs through the secretion of various chemokines, such as CCL3. This process establishes an inflammatory amplification loop that transitions the immune microenvironment of adipose tissue from a homeostatic state to one of chronic inflammation [15].

Adipocytes are not solely energy-storing entities, they also serve as crucial endocrine and immunomodulatory cells. Under physiological conditions, they play a systematic role in regulating inflammation, energy expenditure, and insulin sensitivity, primarily through the secretion of adipokines such as leptin and adiponectin. Simultaneously, adipocytes exhibit a stable capacity for cellular turnover and possess a favorable adaptability for volume expansion, thereby dynamically sustaining their metabolic buffering and endocrine regulatory functions [16, 17]. In the context of metabolic dysregulation, adipocytes undergo hypertrophy due to triglyceride accumulation, accompanied by a decrease in adiponectin secretion. They actively recruit ATMs by secreting chemokines such as monocyte chemoattractant protein-1 (MCP-1), collectively contributing to a local chronic inflammatory state driven by TNFα. This inflammatory milieu inhibits peroxisome proliferator-activated receptor gamma (PPARγ), a pivotal regulator of adipocyte function, resulting in a diminished capacity for triglyceride storage and enhanced lipolysis, thereby releasing excessive FFAs into the circulation. These alterations shift adipocytes from a role in sustaining metabolic equilibrium to one that exacerbates systemic metabolic dysregulation [18–20].

Beyond the primary cellular components previously discussed, the integrity of the adipose tissue immune microenvironment is contingent upon the collaboration of various cell types. For example, under homeostatic conditions, eosinophils predominantly exert anti-inflammatory and metabolic regulatory effects through the secretion of cytokines such as IL-4 [21]. In contrast, under pathological conditions, certain pro-inflammatory subsets of B cells can intensify local inflammation by producing inflammatory cytokines [22]. Furthermore, stromal cells, including fibroblasts and endothelial cells, along with sympathetic nerve fibers, collectively constitute the physical framework and source of initial signals within the microenvironment [23]. Through intricate interactions, these cells establish a dynamic and mutually regulatory functional network.

The primary function of the adipose tissue immune microenvironment is to preserve tissue homeostasis. Under physiological conditions, it plays a crucial role in regulating lipid storage and mobilization, insulin sensitivity, and the repair and remodeling of adipose tissue through signaling interactions among immune cells, adipocytes, and stromal cells [24]. However, in the context of obesity, the homeostasis of adipose tissue is disrupted. Dysfunctional adipocytes emit stress signals, which are accompanied by the activation of stromal cells. These signals facilitate the recruitment and polarization of ATMs and activate T cells via pathways such as the NLRP3 inflammasome activation. This process ultimately drives the adipose tissue into a state of persistent chronic low-grade inflammation [25]. The sustained inflammatory state contributes to insulin resistance and abnormalities in lipid metabolism, which eventually extend local metabolic disturbances to systemic metabolic dysfunction [26].

3. Characteristic Differences in Immune Microenvironment Between Visceral and subcutaneous Adipose Tissue

While both vWAT and sWAT function as reservoirs for fat storage, their immune microenvironments differ markedly, which has significant implications for the onset and progression of obesity-related metabolic disorders. Predominantly, vWAT is characterized by a pro-inflammatory immune milieu, whereas sWAT generally

maintains a state of immune and metabolic equilibrium.

In terms of immune cell composition, vWAT demonstrates a more substantial infiltration of ATMs. The recruitment of ATMs is notably pronounced, with their density in vWAT being considerably higher than in sWAT under conditions of obesity, a disparity that intensifies with increasing obesity severity [27]. This recruitment is closely linked to the elevated expression of MCP-1 and cell adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), in vWAT, which collectively facilitate monocyte chemotaxis and retention [28]. ATMs in vWAT exhibit heterogeneity and predominantly exhibit pro-inflammatory functions. Under obese conditions, the balance between anti-inflammatory and pro-inflammatory activities is disrupted, with anti-inflammatory IL-10 expression being preserved only in specific ATM subsets. In contrast, the accumulation of pro-inflammatory ATMs in sWAT is significantly lower than in vWAT. Additionally, the proportion of anti-inflammatory ATMs remains stable with obesity, thereby maintaining a predominance of the anti-inflammatory phenotype [29]. Initial research predominantly concentrated on the overall increase in ATM numbers. However, recent advancements in single-cell sequencing have elucidated that the pro-inflammatory transformation of ATMs in vWAT during obesity is not exclusively driven by M1-type infiltration. Instead, it also involves alterations in the self-renewal patterns of tissue-resident ATMs and their in situ polarization [30]. Moreover, immune dysregulation in vWAT is characterized by an explosive nature involving significant infiltration of $CD8^+$ effector T cells and Th1 cells, a marked reduction in the proportion of Tregs, and the rapid formation of crown-like structures (CLS) during the early stages of obesity. Conversely, the onset of immune imbalance in sWAT is considerably delayed, with only mild recruitment of T cells under prolonged metabolic stress, and the typical formation of CLS is infrequent [31]. Notably, the pro-inflammatory transformation of vWAT is challenging to completely reverse following weight loss. In contrast, the immune microenvironment of sWAT exhibits greater plasticity [32]. This disparity in dynamic response patterns indicates that vWAT is a rapidly reactive and difficult-to-reverse pro-inflammatory tissue, whereas sWAT is a homeostatic tissue characterized by gradual dysregulation and the capacity for reversible repair.

The variation in cellular infiltration results in distinct inflammatory factor secretion profiles between vWAT and sWAT. vWAT is characterized by a pro-inflammatory state, evidenced by significantly elevated levels of IL-6 secretion compared to sWAT. This pro-inflammatory state is closely linked to systemic inflammation and IR [33], with vWAT serving as a principal source of circulating pro-inflammatory factors, such as MCP-1 [34]. Obesity markedly suppresses total adiponectin secretion from vWAT, and the release of TNF-α from the mesenteric subtype is notably higher than that from other adipose depots, further reinforcing its pro-inflammatory phenotype [35]. Conversely, the inflammatory factor secretion profile of sWAT demonstrates an anti-inflammatory inclination. The TNF-α release from its mesenteric subtype is lower than that of vWAT, with minimal net release into the circulation and a relatively stable microenvironment [36]. Evidence indicates that abdominal sWAT is a more consistent source of adiponectin in humans, its adiponectin secretion is significantly less reduced compared to vWAT, even under conditions of obesity or severe obesity [37]. Consequently, vWAT acts as a primary source of pro-inflammatory factors, while sWAT functions as a stable reservoir for anti-inflammatory factors.

The stromal vascular fraction (SVF) within adipose tissue, comprising preadipocytes, endothelial cells, and immune cells, also demonstrates distinct depot-specific roles [38]. The SVF of vWAT exhibits an enhanced ability to secrete pro-inflammatory cytokines and chemokines, and its endothelial cells adopt a pro-inflammatory phenotype that contributes to local inflammatory processes [28]. Furthermore, the expansion of vWAT readily induces local hypoxia, which further exacerbates inflammatory responses [39]. In addition, preadipocytes in vWAT possess a reduced replicative capacity, hindering their ability to form new adipocytes through proliferation and differentiation. This limitation predisposes existing adipocytes to hypertrophy, thereby activating inflammatory pathways [40]. The elevated concentrations of TNF-α, IL-6, and transforming growth factor-beta (TGF-β) within vWAT synergistically promote the differentiation of adipose progenitor cells (APCs) into myofibroblast-like cells. This differentiation results in excessive extracellular matrix (ECM) deposition and subsequent tissue fibrosis. The fibrotic tissue, in turn, activates ATMs via integrin signaling, thereby establishing a self-perpetuating “inflammation-fibrosis” cycle [41, 42]. Conversely, the SVF of sWAT exhibits a diminished capacity for pro-inflammatory factor secretion [33]. Moreover, preadipocytes, particularly those derived from the gluteofemoral region, demonstrate enhanced proliferative and differentiative potential. This facilitates sWAT expansion through adipocyte hyperplasia rather than hypertrophy, a process conducive to the preservation of local metabolic and immune homeostasis [43]. The fundamental distinction between these tissues is that the immune microenvironment of vWAT is predisposed to a persistent cycle of inflammation and remodeling, whereas sWAT sustains a comparatively reversible state of homeostasis.

The variations in the immune microenvironments between these two adipose tissue depots are modulated by the expression of distinct receptors and transcription factors. The expression of the glucocorticoid receptor (GR) is elevated in vWAT, where it is associated with the regulation of lipolytic activity [44]. Nonetheless, the function of the glucocorticoid receptor in adipose tissue immune cells is characterized by functional heterogeneity. Boullu-Ciocca et al. [45] demonstrated in rat models that GR is highly expressed in mesenteric fat, significantly promoting the release of pro-inflammatory factors. Conversely, research conducted by Lee et al. [46] indicated that GR within the stromal vascular fraction of human adipose tissue can exert anti-inflammatory effects by suppressing the expression of pro-inflammatory cytokines and downregulating inflammatory pathway. Additionally, vWAT exhibits high expression of the androgen receptor, which can intensify local immune activation by upregulating the transcription of pro-inflammatory cytokines [47]. In contrast, sWAT preferentially expresses receptors such as estrogen receptor-beta, which contribute to the

inhibition of local inflammatory responses [48]. Simultaneously, sWAT is enriched with PPARγ, a pivotal transcription factor involved in adipogenesis and a crucial regulatory element for maintaining M2 macrophage polarization and Treg function [49]. These variations in the distribution of receptors and transcription factors underscore the distinct immune characteristics of the two adipose tissue depots.

Ultimately, these differences result in divergent pathological outcomes. The pro-inflammatory microenvironment of vWAT, along with the FFAs and inflammatory mediators it releases, serves as a central driver of IR, NAFLD, and CVDs [50]. Conversely, sWAT, particularly peripheral sWAT, exhibits a protective effect to some extent due to its relatively healthy immune and metabolic properties, with dysfunction manifesting only under extreme conditions such as severe obesity [51]. Therefore, a comprehensive understanding of the distinctive immune microenvironments of these two adipose depots is of paramount importance for elucidating the heterogeneity of obesity-related complications and for the development of targeted therapeutic strategies.

4. Immune Microenvironmental Variations in Visceral vs. Subcutaneous Fat and Their Metabolic Effects.

The immune microenvironments of vWAT and sWAT exhibit distinct characteristics that result in divergent systemic metabolic outcomes. VWAT, characterized by its pro-inflammatory nature, is a significant contributor to various metabolic diseases, whereas sWAT generally provides a protective metabolic effect, albeit with limitations.

T2DM is the most prevalent clinical manifestation of this immune disparity. Numerous studies have demonstrated that vWAT accumulation is a more robust predictor of T2DM than general obesity. A meta-analysis has revealed that the visceral adiposity index (VAI) is linearly and positively associated with T2DM risk, with individuals in the highest VAI group exhibiting a 105% increased risk compared to the reference group. Additionally, each one-unit increase in VAI is associated with a 44% elevated risk, independent of body mass index and subcutaneous fat mass [52]. This epidemiological relationship is underpinned by well-defined immune mechanisms. Under physiological conditions, Tregs, type 2 innate lymphoid cells (ILC2s), eosinophils, and M2-type ATMs in vWAT collectively sustain an anti-inflammatory microenvironment, thereby facilitating normal insulin signal transduction [53]. Single-cell sequencing studies have demonstrated that obesity is associated with a marked reduction of Tregs in visceral adipose tissue, alongside a notable increase in M1-type ATMs, NKT cells, type 1 innate lymphoid cells (ILC1s), and pro-inflammatory B cells [30]. The TNF-α produced by these pro-inflammatory cells activates the JNK1/2 and IKKβ/NF-κB signaling pathways, leading to serine/threonine phosphorylation of insulin receptor substrate-1 (IRS-1), which disrupts insulin signaling. This mechanism has been consistently validated in numerous in vitro and animal studies [54]. In contrast, during systemic metabolic stress, the extent of immune dysregulation in sWAT is considerably less severe than in vWAT. Research indicates that the baseline levels of Bregs and their IL-10 secretion are significantly higher in sWAT compared to vWAT, effectively mitigating pro-inflammatory immune responses in adipose tissue. Even when obesity impairs their function, subcutaneous Bregs maintain a relatively stronger anti-inflammatory regulatory capacity [55]. Moreover, immune regulatory networks involved in thermogenesis and the browning of sWAT, such as the eosinophil-M2 macrophage-mediated IL-4/IL-13 pathway, remain active and can enhance systemic glucose and lipid metabolism by promoting lipid oxidation and thermogenic energy dissipation [56]. Clinical cohort studies have corroborated that obese individuals with predominant abdominal sWAT accumulation exhibit a significantly lower risk of developing T2DM compared to those with predominant vWAT accumulation [57]. Collectively, this evidence suggests that the pro-inflammatory immune microenvironment of vWAT is a central driver of IR, whereas sWAT provides metabolic protection through its relatively anti-inflammatory immune characteristics.

NAFLD further underscores this disparity from an anatomical perspective. The unique anatomical relationship between vWAT and the liver amplifies the impact of immune dysregulation in vWAT. Specifically, because venous blood from vWAT drains directly into the portal vein, the FFAs and pro-inflammatory factors released by vWAT reach the liver without being diluted by the systemic circulation [58]. Numerous cross-sectional and longitudinal imaging studies have demonstrated that visceral fat area and liver fat content exhibit a stronger correlation with the severity of NAFLD compared to subcutaneous fat [59, 60]. Mechanistic investigations have further elucidated that FFAs released by vWAT, along with IL-6 secreted by its enriched ATMs, are directly transported to the liver via the portal vein. FFAs contribute to hepatic insulin resistance, while IL-6 exacerbates hepatic inflammation, with both processes occurring independently of hepatic steatosis [61]. Simultaneously, excessive FFAs released by hypertrophic adipocytes are directly deposited into hepatocytes, promoting the progression of hepatic steatosis [62]. Conversely, the immune microenvironment of sWAT is predominantly anti-inflammatory. sWAT contains a higher proportion of M2-type ATMs, and Treg cells within adipose tissue can synergize with M2-type ATMs to inhibit lipolysis and reduce FFA release [13, 63, 64]. Additionally, sWAT secretes significantly more leptin than vWAT and produces fewer pro-inflammatory and metabolically disruptive cytokines, thereby reducing ectopic fat deposition in the liver and mitigating lipotoxicity, ultimately exerting a protective effect on the liver [65]. Nevertheless, this protective capacity is not without limits. Once sWAT reaches its maximum storage capacity and becomes inflamed, lipids are redirected to the liver, thereby accelerating the progression of NAFLD [66]. This phenomenon elucidates why some individuals with obesity maintain normal liver function, while others experience significant hepatic injury even at the early stages of obesity.

CVDs are also significantly affected by the immunological differences between adipose depots, with effects mediated through both local and systemic pathways. The local pathway primarily involves perivascular adipose tissue, a critical subtype of vWAT. Under physiological conditions,

eosinophils within perivascular adipose tissue contribute to its anti-contractile effect on local blood vessels. However, in the context of obesity, research has demonstrated that eosinophils in perivascular adipose tissue are largely depleted, while M1-type ATMs secrete vasoconstrictive factors such as TNF-α. This results in the loss of the anti-contractile function of perivascular adipose tissue and an increase in peripheral vascular resistance, thereby contributing to hypertension [67]. The systemic pathway is characterized by damage to the vascular endothelium, attributable to inflammatory mediators released from vWAT. Extensive cohort studies have demonstrated that visceral fat volume serves as an independent predictor of myocardial infarction and stroke, with this association remaining significant even after controlling for traditional cardiovascular risk factors [68]. IL-6, persistently secreted by abdominal fat, enters the systemic circulation and may induce endothelial dysfunction, thereby facilitating the formation and destabilization of coronary atherosclerotic plaques [69]. Conversely, sWAT does not exhibit a direct regulatory relationship with vascular function, and its immune microenvironment does not exert any discernible adverse effects on the cardiovascular system. Evidence suggests that sympathetic nerves within sWAT establish a thermoregulatory network with innate immune cells, primarily ATMs, which can enhance lipid oxidation and reduce lipid accumulation in the bloodstream, thus potentially lowering the risk of atherosclerosis [70]. This observation aligns with epidemiological findings indicating that increased subcutaneous fat volume, especially in the lower body, is linked to a favorable cardiometabolic profile and reduced cardiovascular mortality [71].

T2DM, NAFLD, and CVDs each support, from unique perspectives, the central conclusion that the pro-inflammatory immune microenvironment of visceral fat significantly contributes to systemic metabolic dysfunction. In contrast, subcutaneous fat confers a protective metabolic effect due to its relatively anti-inflammatory immune properties. Understanding this disparity elucidates why individuals with different fat distribution patterns exhibit varying risks for metabolic disorders.

5. Conclusions and Perspectives

The immune microenvironments of vWAT and sWAT exhibit marked differences in cellular composition, secretion of inflammatory mediators, and tendencies for tissue remodeling. vWAT is characterized by an abundance of pro-inflammatory components, including M1-type ATMs and $CD8^+$ T cells, while regulatory T cells are relatively underrepresented. This composition results in a microenvironment marked by pro-inflammatory activity, hypoxia, and fibrosis. Conversely, sWAT is predominantly composed of M2-type ATMs, Tregs, and eosinophils, which collectively sustain a relatively anti-inflammatory immune homeostasis. These immunological distinctions underpin the divergent roles of these adipose depots in systemic metabolic regulation. The pro-inflammatory milieu of vWAT facilitates the pathogenesis of T2DM, NAFLD, and CVDs through mechanisms such as the secretion of inflammatory factors, increased lipolysis, and reduced adiponectin secretion. In contrast, sWAT contributes to metabolic homeostasis through its anti-inflammatory properties and enhanced capacity for lipid storage; however, this protective role is compromised when its expandability is exceeded and immune homeostasis is disrupted.

Future research should explore several avenues in greater depth. Current studies predominantly consider vWAT as a uniform entity, however, it remains unclear whether immune characteristics vary among distinct visceral depots, such as mesenteric versus omental fat, and whether these differences contribute to varying levels of systemic metabolic damage, due to a lack of direct comparative studies. Consequently, further investigations into the immune characteristics of different visceral fat sub-depots are necessary. Establishing that mesenteric fat is more pathogenic due to its portal drainage could provide a theoretical basis for shifting imaging assessments from measuring “total visceral fat volume” to distinguishing specific sub-depots, thereby enabling more accurate prediction of metabolic disease risk. Simultaneously, the protective role of sWAT is not unlimited, determining the critical threshold at which its healthy expansion transitions to pathological remodeling, and identifying early markers of this transition, are essential questions that need to be addressed for effective clinical prevention. To address this challenge, future research should incorporate longitudinal cohort studies with multi-omics approaches to identify immune markers indicative of sWAT decompensation. This integration will provide an objective framework for determining optimal early intervention periods in clinical settings. Additionally, the influence of sex, age, and genetic background on adipose tissue immune responses is not well understood, and the applicability of current research findings to diverse populations remains uncertain. Therefore, subsequent studies should include diverse population samples to systematically evaluate how host factors influence the adipose immune microenvironment. This approach will facilitate the shift from universal prevention strategies to population-specific and individualized precision management of obesity-related metabolic disorders.

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