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REVIEW ARTICLE

Subcutaneous adipose tissue: Implications in dermatological diseases and beyond

Reihane Ziadlou[1,2,3,4] | Ganesh N. Pandian[5] | Jürg Hafner[1,2] | Cezmi A. Akdis[1,3,4] | Georg Stingl[6] | Emanual Maverakis[7] | Marie-Charlotte Brüggen[1,2,3]

[1]Faculty of Medicine, University of Zurich, Zurich, Switzerland

[2]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

[3]Christine Kühne Center for Allergy Research and Education CK-CARE, Davos, Switzerland

[4]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Zurich, Switzerland

[5]Institute for Integrated Cell-Material Science (WPI-iCeMS), Kyoto University, Kyoto, Japan

[6]Department of Dermatology, Medical University of Vienna, Vienna, Austria

[7]Department of Dermatology, University of California, Davis, California, USA

Correspondence
Marie-Charlotte Brüggen, Department of Dermatology, University Hospital Zürich, CK Care Davos, Rämistrasse 100, 8091 Zürich, Switzerland.
Email: marie-charlotte.brueggen@usz.ch

Abstract

Subcutaneous adipose tissue (SAT) is the deepest component of the three-layered cutaneous integument. While mesenteric adipose tissue-based immune processes have gained recognition in the context of the metabolic syndrome, SAT has been traditionally considered primarily for energy storage, with less attention to its immune functions. SAT harbors a reservoir of immune and stromal cells that significantly impact metabolic and immunologic processes not only in the skin, but even on a systemic level. These processes include wound healing, cutaneous and systemic infections, immunometabolic, and autoimmune diseases, inflammatory skin diseases, as well as neoplastic conditions. A better understanding of SAT immune functions in different processes, could open avenues for novel therapeutic interventions. Targeting SAT may not only address SAT-specific diseases but also offer potential treatments for cutaneous or even systemic conditions. This review aims to provide a comprehensive overview on SAT's structure and functions, highlight recent advancements in understanding its role in both homeostatic and pathological conditions within and beyond the skin, and discuss the main questions for future research in the field.

KEYWORDS
clinical immunology, inflammation, interleukins, macrophages

1 | INTRODUCTION

Adipose tissue (AT) has traditionally been viewed as an inert energy storage site.[1] However, research over the past decades has uncovered its dynamic nature, revealing AT as a highly active organ with metabolic, endocrine, immune, and biomechanical functions.[2] AT plays a central role in the pathogenesis of various diseases, including diabetes, cardiovascular disease, osteoarthritis, and cancer.[3–5] Situated throughout the body, AT encompasses the deepest layer of the cutaneous integument, known as subcutaneous adipose tissue (SAT), along with the epidermis and dermis.[6] SAT's involvement in both immune and metabolic processes has been insufficiently explored.

Given that obesity has become a worldwide pandemic,[7] additional attention to SAT physiology is necessitated, especially its contributions to conditions like diabetes and immune-mediated skin diseases such as hidradenitis suppurativa and psoriasis. In these diseases, adipokines, and saturated fatty acids (FA) contribute towards the polarization to an IL-17-mediated immune response.[6,8–12]

This review aims to focus on the current understanding of SAT structure and functions, emphasizing its association with various diseases. Additionally, we will discuss the immunological functions of SAT in the context of both cutaneous and systemic diseases, examining its potential role in immune-mediated skin infections.

1.1 | AT types: structures and cellular composition

AT subtypes can be organized by their anatomical localization in mammals, that is, subcutaneous, visceral and ectopic. SAT is found beneath the skin, while visceral adipose tissue (VAT) lines internal organs.[13] Ectopic AT is a non-physiologic accumulation of adipocytes adjacent to non-adipose organs, such as the liver and heart.[14]

Structural and functional features can also be used to divide AT into three subtypes: white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue (Figure 1A).

WAT is mainly known for its role in energy storage and immune regulation.[15] It is the main constituent of visceral, ectopic, and subcutaneous AT (SAT). In rodents, a striated muscle layer, the panniculus carnosus, subdivides SAT into two functionally distinct compartments, namely subcutaneous and dermal AT.[16] This muscle layer enables animals to move their skin without involving underlying tissues. This is, at least partially, the reason why such a barrier is missing in human SAT.[16,17]

In contrast to WAT, BAT are highly specialized for thermogenesis, capable of dissipating stored energy as heat to maintain optimal body temperature.[18] BAT is abundant and broadly distributed in newborns. In adults, BAT is limited to cervical, supraclavicular, paravertebral, mesenteric, and pericardial areas and is present in SAT. Beige AT emerges through "browning" of WAT, induced by external stimuli, such as low temperature or exercise.[19,20] In this process, white adipocytes acquire the morphology of brown adipocytes, characterized by small vacuoles and several mitochondria. This results in a functional shift from energy storage towards thermogenic activity.

In all AT types, approximately one-third of the cellular content consists of adipocytes. The remaining two-thirds constitute the stromal vascular fraction (SVF) (Figure 1B). The stromal component of AT contains adipose stem cells (ASCs), preadipocytes, fibroblasts, endothelial cells, and immune cells. ASCs serve as precursor cells for preadipocytes,[21,22] specialized progenitors committed to becoming adipocytes and residing in a unique perivascular tissue niche.[23–25] Fibroblasts in the SVF provide support to preadipocytes and help to maintain the adipose tissue homeostasis.[26] In SAT, cells from both the innate (adipose tissue macrophages [ATM], natural killer cells [NK], innate lymphocytes [ILC]) and the adaptive lineage (T cells, B-lymphocytes, dendritic cells [DC]) are present.[27,28]

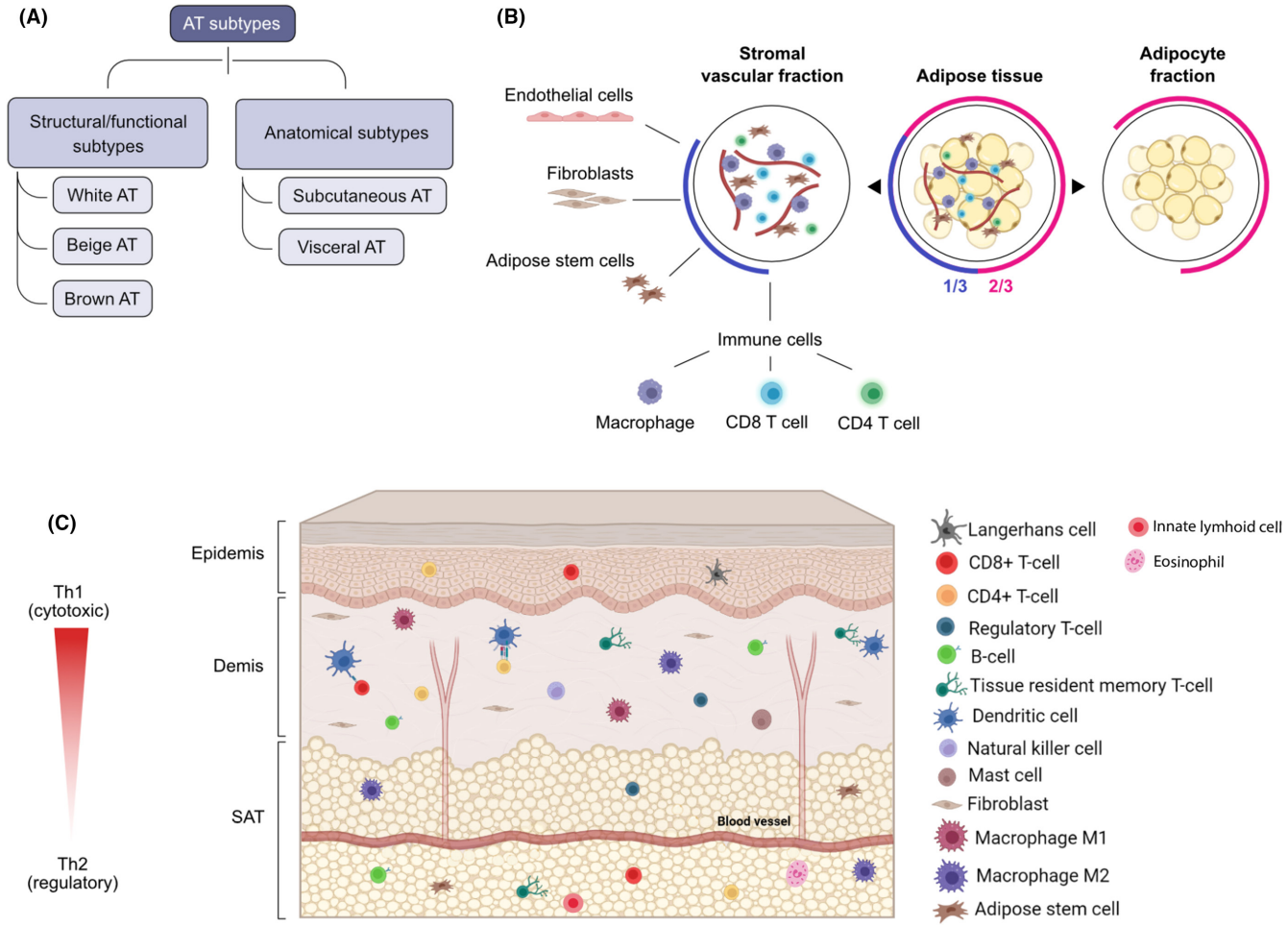

FIGURE 1 Structural and cellular composition of adipose tissue (AT). (A) Different structural and anatomical subtypes of AT (B) Cellular components of AT. AT consists of a 2/3 adipocyte fraction and a 1/3 of stromal vascular fraction (C) Immune cells in the three-layered cutaneous integument, which consists of epidermis, dermis and subcutaneous adipose tissue (SAT).

1.2 | SAT immune homeostasis: A type 2-predominated milieu

In healthy individuals, T cells, ATM, and ILCs in SAT tend to favor a type 2 and regulatory phenotype.[29–32] T cells in epidermis and dermis generally adopt a T-helper 1 (Th1) phenotype, acting as the primary defense line in homeostatic conditions.[29] T cells in SAT may function as counter-regulators (Figure 1C). A similar functional stratification could characterize the innate immune system arm. Little is known about presence of these cells in SAT, but in visceral WAT ILC2s recruit eosinophils, which in turn skew ATM towards an anti-inflammatory phenotype. This axis is at the interplay between immune response and metabolic homeostasis.[33]

1.3 | Immune responses in the context of cutaneous and systemic diseases in the SAT

The skin acts as a physical barrier, orchestrating a complex interplay of structural, and cellular elements. Resident and migrating immune cells not only protect against pathogens, but also, under certain conditions, can trigger pathologic responses. This can contribute to autoimmune, autoinflammatory, and allergic conditions including atopic dermatitis, allergic contact dermatitis, and IgE-mediated food allergies.[34–36] In this context the role of SAT in the cutaneous immune system and its impact under homeostatic and pathogenic conditions has been poorly characterized.

Evidence suggests that SAT's reservoir of immune and stromal cells may direct metabolic and immunologic processes.[34–36] SAT-mediated pathologic responses can manifest within SAT itself, the overlying dermis or epidermis, or extracutaneous sites throughout the body (Figure 2). Examples demonstrating SAT's involvement in immunoregulation include: (i) cutaneous wound healing,[30,37,38] (ii) induction of a protective immune responses,[35] (iii) modulation of immunologic and metabolic processes, (iv) regulation of cutaneous inflammatory diseases, (v) promotion of neoplastic processes, and (vi) and influence on the phenotype of various genodermatoses[39,40] (Figure 2). However, much of this evidence is derived from animal studies, necessitating further investigations to understand SAT-mediated pathologies in humans and its communication with superficial skin layers.

1.3.1 | SAT in wound healing

Wound healing consists of several regenerative phases (Figure 3), in which keratinocytes act as the main effectors by supporting fibroblasts, leukocytes, and mesenchymal cells.[41] SAT-based processes play an essential role in all phases of wound healing via the secretion of glucocorticoids, adipokines (e.g., interleukins [IL]-1β, −6, −8, −10; leptin, adiponectin, MCP-1, TNF), and array of growth factors (e.g., vascular endothelial growth factor [VEGF], basic fibroblast growth factor [bFGF], transforming growth factor beta [TGFβ]).[42–45] In a mouse model, dermal adipocytes were crucial for initiating inflammation post-injury contributed to wound repair by dedifferentiating into myofibroblasts, for extracellular matrix (ECM) production.[37,46] A particularly important role in wound healing has been attributed to ASCs residing in SAT. ASCs promote cutaneous neovascularization and re-epithelialization through secretion of growth factors and cytokines.[47–49] Interestingly, they may also promote muscle healing after muscle injuries.[50] Several pre-clinical studies have shown the potential therapeutic effect of ASCs in wound repair.[51,52] Despite ASCs being considered a relatively safe source of stem cells, their widespread therapeutic application is currently hindered by barriers such as cost and the absence of highly standardized cell preparation methodologies.[51] As an alternative to ASC-based cell therapy, the administration of ASC-derived exosomes[53–55] has been explored,

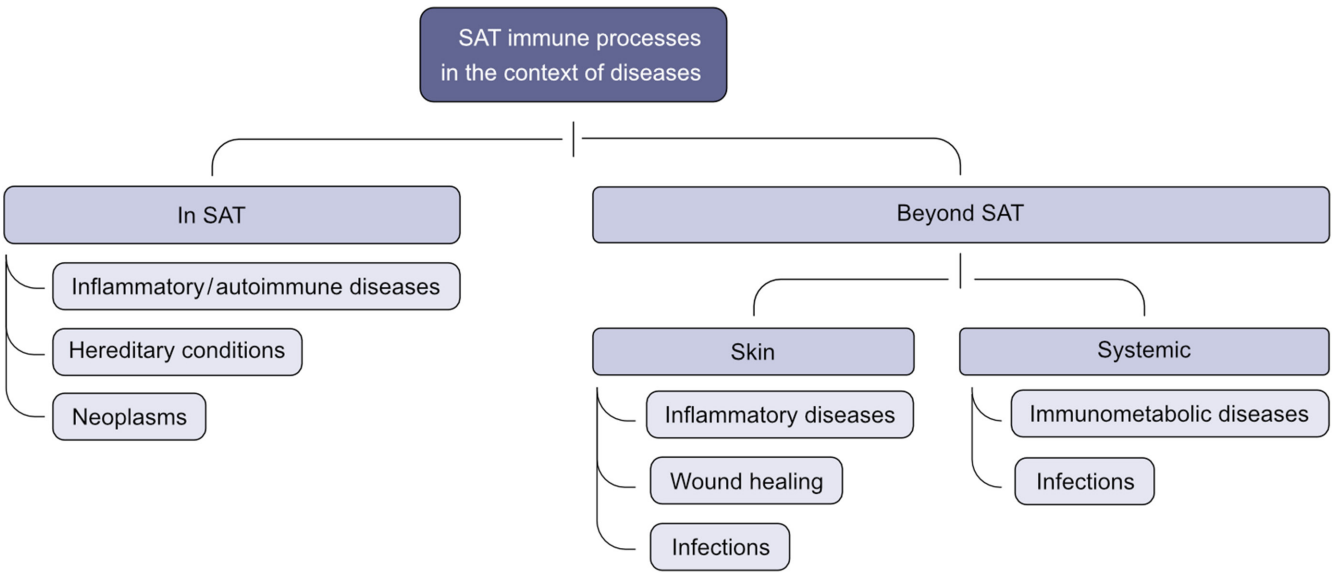

FIGURE 2 Subcutaneous adipose tissue (SAT)-mediated immune processes in clinical conditions.

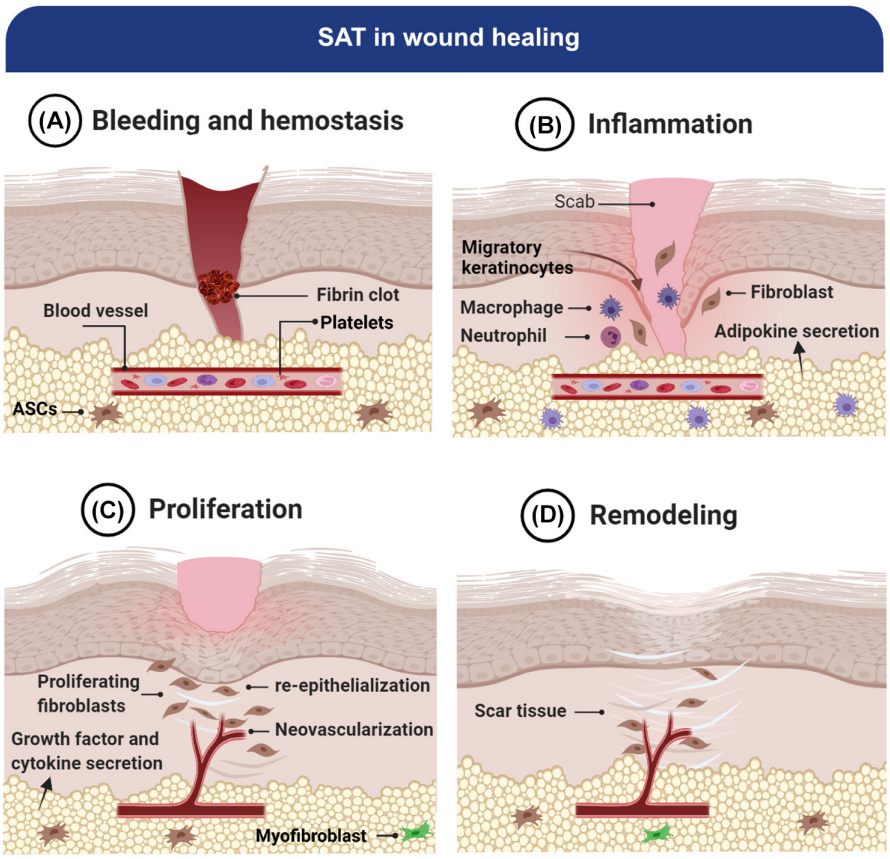

FIGURE 3 The role of SAT in wound healing. Wound healing consists of several regenerative phases (A): Bleeding and hemostasis lead to platelet aggregation and coagulation (B) Inflammatory cells, such as neutrophils, macrphages are recruited to the site of injury to clear debris and microbes. Fibroblast and macrophages support the migration of keratinocytes and adipocytes secret adipokines such interleukins, leptin and adiponectin. (C) Secretion of growth factors and cytokines from adipocytes promotes fibroblast proliferation, re-epithelialization and neovascularization. Administration of ASC-derived exosomes can promote angiogenesis and re-epithelization (D) Adipocytes de-differentiate to myofibroblasts, which contributed to wound repair by producing extracellular matrix (ECM) which serve as scaffold.

demonstrating immunomodulatory effects and the ability to promote angiogenesis and re-epithelization[56,57] (Figure 3A).

1.3.2 | The role of SAT in induction of a protective immune response against pathogens

The skin serves as the primary defense against pathogen invasion. It provides both a physical barrier and an intrinsic warning system to trigger innate and adaptive immune responses when the physical barrier is breached. The role of epidermal/dermal leukocytes, keratinocytes, and other non-leukocyte populations in antimicrobial defense has been well investigated. In contrast, the contribution of underlying SAT to this process remains largely unexplored.[58]

One avenue through which adipocytes can participate in antimicrobial defense is through the release of soluble mediators. Adipokines released by adipocytes, as shown in a series of mouse studies, have the ability to recruit immune cells to infection sites and modulate their effector functions.[59,60] Leptin, a well-characterized adipokine known for its role in hunger regulation, also exhibits immunomodulatory properties, contributing to antimicrobial immune responses.[61–63] Studies on leptin/leptin receptor-deficient mice have revealed increased susceptibility to viral or bacterial infections.[64–66] In obese individuals, elevated blood levels of leptin lead to leptin resistance, which in turn induces a reduced type I interferon (IFN) response and increased susceptibility to viral infection.[67,68] This also contributes to the increased susceptibility to viral infections in patients with type 2 diabetes (T2D).[69]

Adipocytes are also a major secretor of cathelicidins, short cationic antimicrobial peptides[35,70] (Figure 4). Obese animals produce fewer cathelicidins, thereby contributing to compromised infection control[71] (Table 1). Beyond adipocytes, one finding that links AT to the immune system is that WAT harbors a significant number of resident memory T-cells. This population can be rapidly reactivated to provide protection against pathogens.[72] Studies in mice and humans indicate that obesity is associated with impaired memory T-cell responses and reduced natural killer cell cytotoxicity.[73–81] Furthermore, systemic viral infections have been shown to alter SAT immune-metabolic functions in mice, notably by inducing AT expansion.[82–84] Unraveling the specific mechanisms through which SAT contributes to immune defense may open avenues for therapeutic interventions targeting both metabolic and immunologic aspects, with potential implications for preventing and managing infectious diseases.

1.3.3 | SAT in immuno-metabolic diseases

Obesity is associated with a state of low-grade inflammation in SAT. This poses a heightened risk for the development of various health conditions, including T2D, autoimmune, and autoinflammatory diseases, cardiovascular disease, asthma, and cancer.[5,85–94] The systemic low-grade inflammation associated with obesity contributes to insulin resistance in skeletal muscle and liver[95,96] and ATMs along with innate lymphoid cells ILCs1 promote AT fibrosis

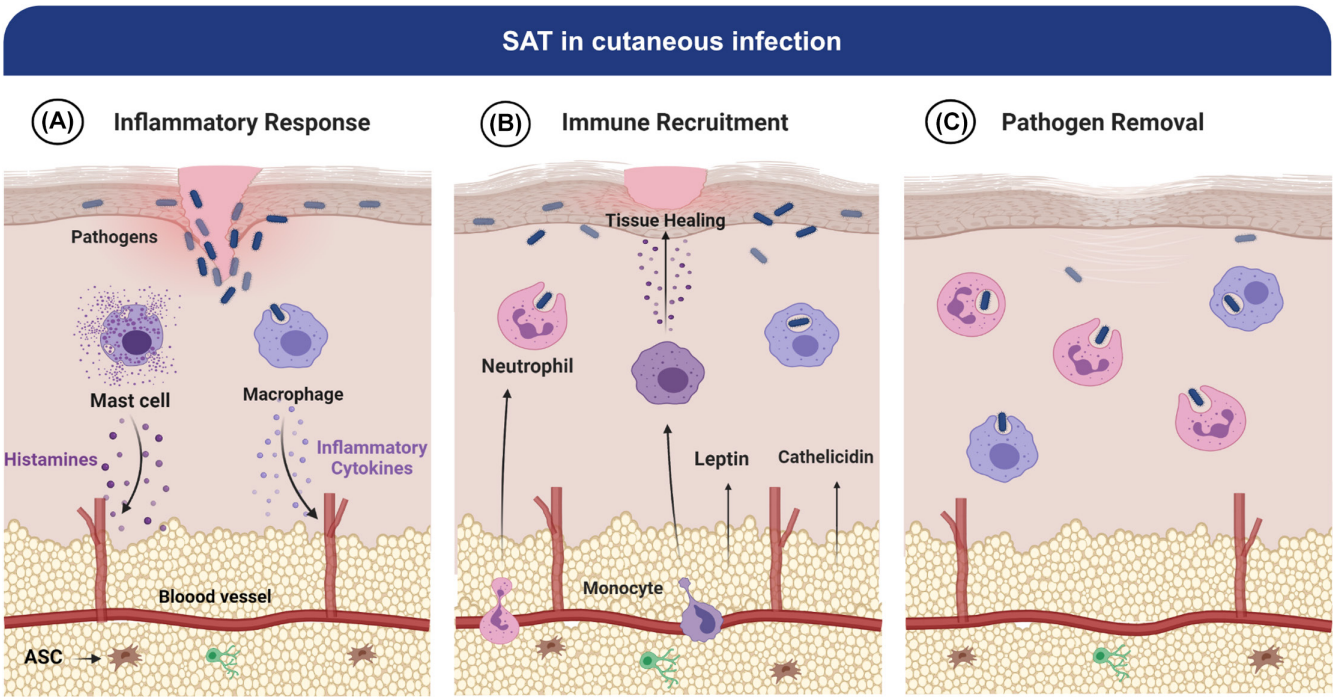

FIGURE 4 SAT in cutaneous infection. (A) Inflammatory cytokines and histamine are released by macrophages and recruit monocytes and neutrophils to the site of infection. (B) Adipocytes secret antimicrobial peptide cathelicidin and leptin adipokine (C) Pathogens are removed from the site of infection.

TABLE 1 Secreted antimicrobial molecules, adipokines, and cytokines in obese adipose tissue.

Antimicrobial peptides	
↓Cathelicidin	Anti-bacterial
Adipokines	
↑Leptin	Immunomodulatory effects
↑Resistin	Immunomodulatory effects
↓Adiponectin	Increase insulin sensitivity and glucose tolerance, anti-inflammatory
↑Visfatin	Regulate insulin secretion, pro-inflammatory effects
Cytokines	
↑IL-6	Pro-inflammatory
↑TNF-α	Pro-inflammatory
↑IL-1β	Pro-inflammatory
↑MCP-1	Pro-inflammatory

Abbreviations: IL-1β, interleukin-1β; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein1; TNF-α, tumor necrosis factor-α.

by inducing ECM deposition, which contributes to insulin resistance and T2D.[97,98] Inhibition of AT fibrosis may be a mechanism to improve glucose intolerance.[99]

In obese asthmatic patients, excessive AT correlates with increased levels of inflammation and cell infiltration in the lung.[100] Asthma patients undergoing bariatric surgery demonstrated significantly higher mRNA levels of CD68 and leptin and downregulation of adiponectin in VAT. Similar tendencies were observed in subcutaneous in SAT.[101] Later studies demonstrated increased numbers of ATM, with predominance of M1 subset in VAT of obese asthmatic subjects. The presence of anM1 population and an increased M1:M2 ratio negatively correlated with certain lung function parameters.[102] These data were confirmed by another study demonstrating increased levels of hypoxic death among adipocytes and elevated secretion of IL-6, TNF-α, IL-1β, and MCP-1in obese asthmatic subjects.[103]

The inflammatory state linked to obesity stems from multiple mechanisms. In individuals with obesity, the expansion of adipocytes leads to increased release of adipokines like leptin and resistin, alongside decreased levels of the anti-inflammatory adiponectin.[104,105] This directly promotes a phenotypic shift of AT-resident immune cells toward a pro-inflammatory state[62,106,107] (Figure 5). ATM with an M1 phenotype increase and tightly correlate with the number of $CD8^+$ T cells. Th1, Th17, and $CD8^+$ T cells expand, while of Th2 and regulatory T cells decrease.[108] SAT-resident helper T cells in obese individuals are skewed towards a Th1 phenotype[108–110] (Figure 5), with an increase of IFNγ-producing $CD4^+$ T cells.[111,112] The TCR diversity of $CD8^+$ T cells in mice on high-fat diet seems to be reduced.[113] Interestingly, MHC class II antigen presentation regulates effector/memory $CD4^+$ T cells and insulin responsiveness in AT of obese mice.[114]

Regulatory $CD4^+$ T cells (Treg) on the other hand are decreased in obese SAT.[115] Treg depletion in lean mice leads to increased mRNA expression of TNF-α, IL-6, MMP-3, RANTES, and impaired insulin signalling.[116] Natural killer T cells (iNKT cells) are also reduced in obese AT. These cells have a highly conserved TCR recognising a glycolipid antigen (α-galactosylceramide) in the context of tCD1.

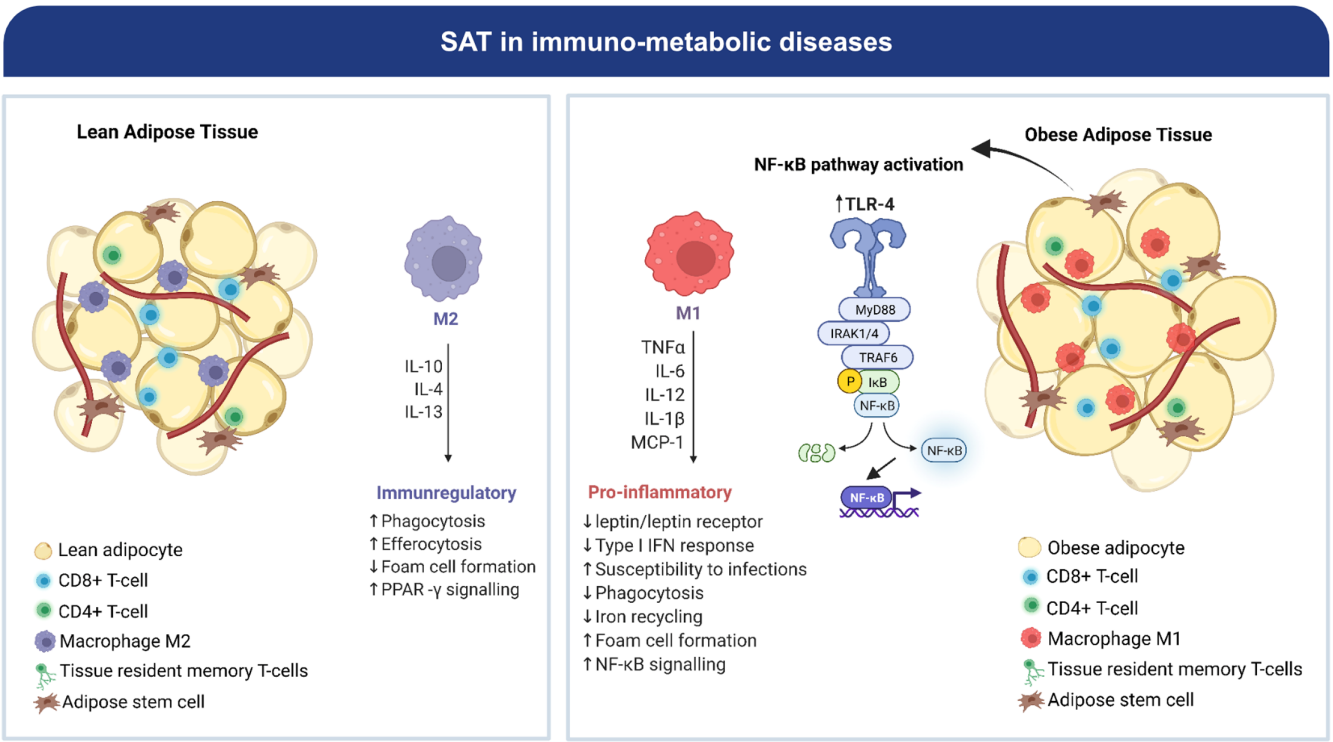

FIGURE 5 Lean and obese adipose tissue immune function. In obesity macrophages are polarized towards M1 phenotype with pro-inflammatory properties, while M2 macrophages with immunoregulatory properties are predominant in lean AT. In obese AT, NFk-B signaling pathway will be activated upon overexpression of Toll-like receptor 4 (TLR-4). Upon activation of NFk-B signaling, monocyte chemoattractant protein-1 (MCP-1) and pro-inflammatory markers such as interleukins β, 6, 12 (IL1β IL-6, IL-12) and tumor necrosis factor-α (TNF-α) will be expressed.

Adoptive transfer and in vivo activation of iNKT cells induced type 2 cytokine production and decreased metabolic dysfunction in obese mice.[76] This highlights the role of glycolipid antigens in the regulation of inflammatory responses in AT. Obesity also affects γδ T cells, known regulators and protectors against bacterial infection. γδ T cells (mostly expressing Vγ4+ TCR) expand in obesity, promoting accumulation of proinflammatory ATM.[117] In contrast, obese patients have diminished circulating Vγ9Vδ2 T cells with a reduced ability to produce IFN-γ in response to viruses.[118]

SAT adipocytes of obese patients express all 10 Toll-like receptors (TLRs), with TLR-4 exhibiting the highest expression.[119,120] TLR4 activation triggers the NF-κB signaling pathway in adipocytes and monocytes/macrophages, subsequently leading to the release of monocyte chemoattractant protein-1 (MCP-1) and pro-inflammatory cytokines such as IL1β, tumor necrosis factor-α (TNF-α), IL-6.[121,122] Elevated MCP-1 levels further prompt the infiltration of monocytes into SAT, where they differentiate into pro-inflammatory (M1) ATM (Figure 5).[123,124] Increased levels of TNF-α have significant effects in induction of lipolysis, the breakdown of fat stored in AT. TNF-induced lipolysis is a complex process involving the activation of inflammatory pathways, lipolytic enzyme activity and release of free fatty acids (FFAs).[125,126] Elevated levels of FFAs released during lipolysis can impair insulin signaling in peripheral tissues such as muscle and liver, contributing to insulin resistance and metabolic dysfunction.[127] Understanding these mechanisms is important for elucidating the role of SAT-derived TNF in metabolic disorders and inflammatory conditions associated with dysregulated lipid metabolism.

Excessive caloric intake in obesity also leads to increased reactive oxygen specious (ROS) production in adipocytes, causing mitochondrial dysfunction.[128] Abnormal mitochondrial function in adipocytes leads to lipid accumulation, ultimately contributing to metabolic syndrome.[129] Therefore, mitigating excessive ROS production and chronic inflammation in SAT of obese individuals present a novel approach to address obesity-related immunometabolic disorders.

1.3.4 | SAT in autoimmune diseases

Disbalance and dysfunction of resident immune cells in dermis and epidermis are well-described features in various autoimmune diseases of the skin. For SAT, such a tendency is best described for resident ATM and T-regs. Dysregulation of the latter leads to excessive cytokine production and autoimmune diseases.[130–132] This disrupted balance can be originated within SAT. Adipocytes secrete various pro-inflammatory cytokines and chemokines and thereby create an environment conductive to immune dysregulation. Furthermore, imbalances in adipokine levels may contribute to the dysregulation of immune responses and exacerbate autoimmune conditions.[133,134] A focused investigation into the specific roles of resident T-regs and

ATM along with exploration of the involvement of cytokines and adipokines in this dysregulation is crucial for understanding the pathways leading to autoimmune diseases.

Lipid antigen presentation may be a particularly important, although not exclusive feature of SAT involvement in autoimmune diseases. Lipid antigens are mostly presented via highly conserved MHC class I-like molecule, CD1d.[135,136] Several studies suggest a possible role of AT-derived CD1-presented lipid antigens in autoimmunity. For example, adipocytes from obese mice express CD1d, contributing to the induction of an autoreactive immune response.[137] A better understanding of the interplay between adipocytes, lipid autoantigens, and CD1 presentation will elucidate a new, and potentially targetable, pathway in autoimmunity. In healthy human skin, appears to be competition between permissive and blocking lipids for presentation by CD1a, the balance of which can modulate T cell responses.[138] Specifically, presentation of very long chain FAs, such as 42:2 sphingomyelin lipids, by CD1a has been observed to impede the engagement of CD1a-directed autoreactive T-cells.[139] A disruption of this balance may favor the development of autoimmune processes. Therefore, it is intriguing to explore the CD1a-related functions and pathways as potential targets in the prevention and treatment of autoimmune conditions.

1.3.5 | SAT in inflammatory skin diseases

Inflammatory processes within the SAT of the skin differ from those in the epidermis and dermis. There is limited research on this subject and most evidence comes from studies on psoriasis.[140] Psoriasis is associated with an increased risk of cardiovascular and immunometabolic disorders, notably obesity.[141,142] The increased production of pro-inflammatory adipokines and decreased production of anti-inflammatory adiponectin in obesity may predispose individuals to develop psoriasis.[143,144] Animal models also indicate that diets high in saturated FA can promote IL-17-mediated immune responses, leading to increased susceptibility to psoriasis.[145,146]

Dermal sclerosis is another pathogenic process that might be aided by aberrant responses in AT. Recent studies suggest the involvement of ECM produced by WAT-derived myofibroblasts in scleroderma pathogenesis.[147,148] As of yet, other neutrophilic and fibrotic diseases such as hidradenitis suppurativa (HS) have not yet been linked to AT; clinical evidence, namely the high incidence of obesity in HS patients and the distribution of inflammatory infiltrates in the follicular epithelium, strongly suggest a role of SAT.[149,150]

Inflammatory conditions primarily originating and taking place in SAT are grouped under the term "panniculitis." Panniculitides encompass a range of heterogeneous etiologies, including infection, trauma, connective tissue diseases, vasculitis, and certain types of cancer (Table 2). Their classification considers location, lesion etiology, and histopathology. The latter considers whether SAT infiltration is septal or lobular and whether it is accompanied by vasculitis.[151–153] Despite diverse etiologies, the cellular and molecular pathomechanisms underlying panniculitis remain poorly characterized. Therapeutic approaches remain widely nonspecific.[154–158] Nonsteroidal anti-inflammatory drugs (NSAID) are often used as first line option. NSAID block cyclooxygenase enyzmes, thus blocking the downstream generation of lipid inflammatory mediators such as prostaglandins. Although its exact mechanism of action is unknown, oral potassium iodide has an anti-inflammatory effect in panniculitis, possibly by inhibiting neutrophil chemotaxis.[159] Dapsone mainly exerts its anti-inflammatory properties by dampening the neutrophil response.[160] hydroxychloroquine.[161] The respective effects on SAT inflammation however have not been specifically investigated.

Panniculitides can originate either as primary pathologies within AT or as secondary manifestations of systemic diseases. For instance, erythema nodosum (EN), the most common type of panniculitis, may be idiopathic or triggered by infections, sarcoidosis, Crohn's disease, or other conditions.[162] In rare cases, neutrophilic dermatoses or pregnancy can induce an EN eruption.[163] The pathogenesis of EN is postulated to involve type III or IV hypersensitivity reactions. There is evidence suggesting a pathogenic role of neutrophils via their production of reactive oxygen intermediates, which induce tissue damage.[164–167] This process ultimately results in increased expression of adhesion molecules, VEGF, and cytokines (i.e., TNF-α, IL-6, and IL-8) both locally and systemically, facilitating immune cell migration to the SAT septae[168] (Figure 6A).

Erythema induratum of Bazin (EIB) is a lobular panniculitis with lymphocytic vasculitis.[169] It is recognized as a multifactorial disease associated with several triggers, including infection with tuberculosis.[170] Similar to EN, type III and IV hypersensitivity reactions are hypothesized to play a role in EIB[169] (Figure 6B).

Lupus panniculitis is also a predominantly lobular process with lymphocytic vasculitis and mucin or calcium deposition. The infiltrating cells consist mainly of T-cells, B-cells, and macrophages.[171] Partial deficiency in complement component, C4, which causes defective opsonization of immune complexes and disease pathogenesis has been linked to some cases of early-onset lupus.[172]

1.3.6 | Neoplastic processes in SAT

Beyond inflammatory processes, SAT can also harbor neoplasms, originating either from SAT-resident cells or secondary infiltration/metastasis. The most common primary SAT neoplasms are benign lipoma,[173] while malignant liposarcoma is quite rare.[174,175]

Most primary cutaneous lymphomas, whether of the T cell-(CTCL) or B-cell-lineage (CBCL),[176–178] typically develop in the dermis and may subsequently extend to the SAT. In contrast, certain lymphomas, such as intravascular B-cell lymphoma, can have their primary origin in different target organs, including SAT.[179] However, only a few lymphomas have their primary origin in SAT. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) specifically involves the subcutis, characterized by neoplastic T-cells rimming fat cells.[177,180] Two distinct types of SPTCL have been identified: (i) SPTCL with an α/β T-cell receptor (SPTCL-AB), which is characterized by a $CD4^{-}CD8^{+}CD56^{-}$ phenotype, and (ii) the highly aggressive

TABLE 2 Classification of panniculitis.

Type	Etiology	Pathogenesis	Reference
Predominantly septal panniculitis without vasculitis			
Erythema nodosum	Idiopathic, Streptococcal infections, viral upper respiratory tract infection, Coccidioidomycosis, Sarcoidosis, drugs, inflammatory bowel disease	Hypersensitivity type III/IV reaction	206
Scleroderma	Idiopathic, an overproduction and accumulation of collagen in connective tissue due to immune system complications	Lymphocyte- and plasma cell-mediated reaction	206
α1-antitrypsin deficiency panniculitis	α1-antitrypsin deficiency	Neutrophil-mediated	207
Predominantly septal panniculitis with vasculitis			
Cutaneous polyarteritis nodosa	Ideopathic, Group A β hemolytic Streptococcus infection, hepatitis B infection, inflammatory bowel disease	Type III hypersensitivity reaction, medium-sized vessel vasculitis	208
Erythema nodosum leprosum	Mycobacterium leprae Type 2 reaction	Type II hypersensitivity reaction, small-sized vessel vasculitis	209
Leukocytoclastic vasculitis	Infection, inflammatory disease, medication or drugs	Type III hypersensitivity reaction, small-sized vessel vasculitis	210
Superficial thrombophlebitis	Thrombosis in superficial vein, trauma, venos statis, malignancy, pregnancy	Inflammation of superficial veins, large-sized vein vasculitis	211
Lobular and mixed septal-lobular panniculitis without vasculitis			
Lupus panniculitis (lupus profundus)	Autoimmune connective tissue disease	Infiltration of T-lymphocytes and macrophages, Type III hypersensitivity in patients with C4 deficiency, interferon-driven Th1 immune response	212
Sclerosing panniculitis (lipodermatosclerosis)	Venous insufficiency, obesity	Lymphocytic infiltration, lipomembranous changes and thickened membrane	213,214
Sclerema neonatorum	Hypothermia, asphyxia, dehydration	Inflammation sparse to absent, crystallization of fat due to an increased saturated: unsaturated fatty acid ratio	215
Neonatal subcutaneous fat necrosis	Hypercalcemia, hypothermia, hypoglycemia	Infiltration of neutrophils, lymphocytes and macrophages	216
Pancreatic panniculitis	Pancreatic disorders	Elevated enzyme levels (lipase, amylase, and trypsin), infiltration of neutrophils, macrophages, and multinucleated giant cells	217
Infection-induced panniculitis	Infectious agents such as "bacteria, mycobacteria, coxiella, borrelia, fungi and helminths," vascular proliferation, hemorrhage, necrosis	Neutrophilic infiltration	218
Traumatic panniculitis	External injury such as cold in infants, injections, radiation in deep tissue, self-injection of oily materials on the male genitalia, adipocyte necrosis	Infiltration of lymphocytes, neutrophils, foamy macrophages, plasma cells, eosinophils	219–221
Factitious panniculitis	Self-induction of unknown substances	Unknown	222
Subcutaneous sarcoidosis	Systemic sarcoidosis	Granulomatous infiltration	223
Post-steroid panniculitis	Follows rapid corticosteroid withdrawal	Neutrophilic infiltration	224
Panniculitis like T-cell lymphoma	Malignancy-related panniculitis-like infiltrates	Neoplastic T-cells ($CD8^+$ cells) and macrophages infiltration	204
Weber–Christian disease	Idiopathic nodular panniculitis	Unknown	
Lobular and mixed septal-lobular panniculitis with vasculitis			
Erythema induratum of Bazin	« Id-reaction » to mycobacterium tuberculosis infection	Hypersensitivity type III/IV reaction	170
Neutrophilic lobular panniculitis	Hematologic malignancies, rheumatoid arthritis	Predominant neutrophils infiltration and macrophages	225,226
Erythema nodosum leprosum	Lepromatous leprosy, reaction to mycobacterium leprae	Type II reaction, neutrophil infiltration	209

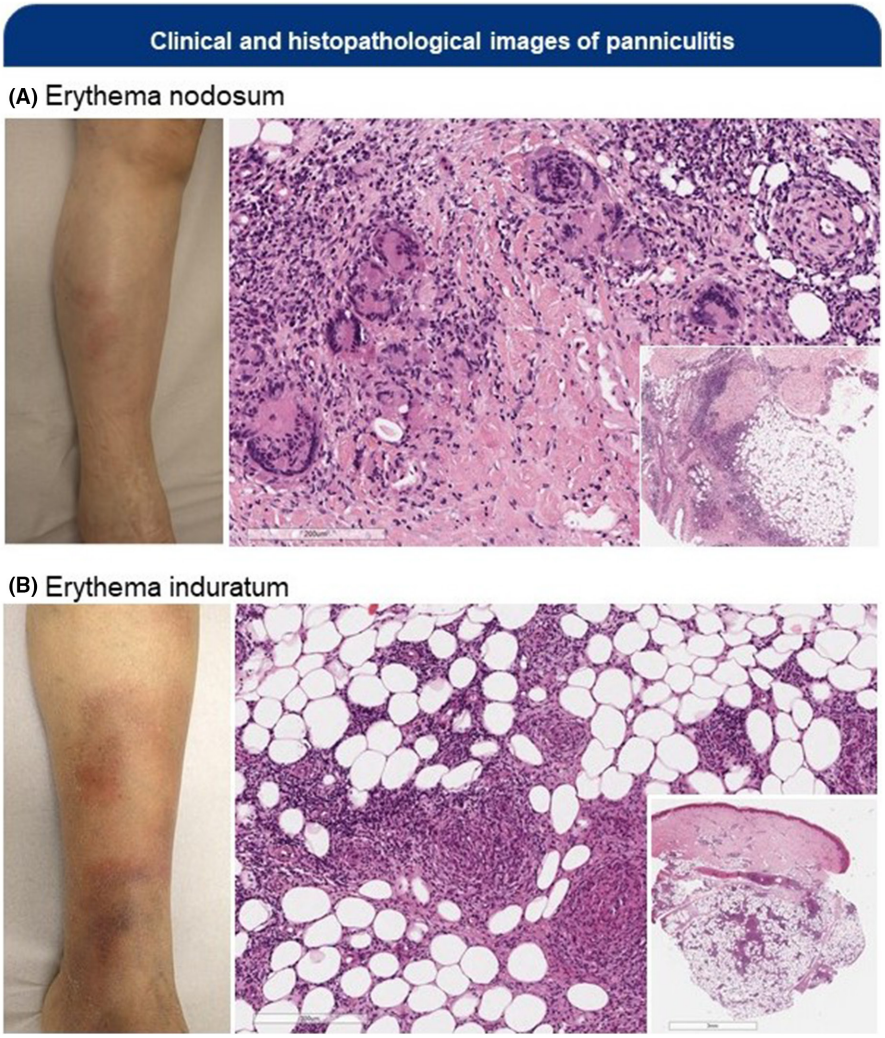

FIGURE 6 Clinical and histopthological images of panniculitis. (A) Septal panniculitis (erythema nodosum). H&E stain shows the inflammatory infiltrate is predominatly confinded to the thickened and fibrotic septa of the subcutis. The inflammatory infiltrate is mostly lymphocytic, with admixture of eosinophilic granulocytes, plasma cells and many multinucleate giant cells. The vessels are inconspicious. (B) Lobular panniculitis (erythema induratum). H&E stain shows nodular vasculitis with granuloma formation and vasculitis.

SPTCL with a γδ T-cell phenotype (SPTCL-GD), characterized by a $CD4^{-}CD8^{-}$ phenotype with variable CD56 expression.[180] An investigation of SPTCL skin samples showed significantly increased expression of the tolerogenic enzyme indoleamine 2,3-dioxygenase (IDO-1) and Th1-specific cytokine, INFγ.[166] It is suggested that IDO-1 overexpression creates an immunosuppressive environment conductive to SPTCL development.[166] However, the clonal specificity and underlying mechanisms of SPTCL development remain largely unknown.

1.3.7 | Hereditary SAT diseases

Hereditary SAT disorders such as lipedema, multiple symmetric lipomatosis (MSL), Dercum's disease, and familial partial lipodystrophy (FPLD) are characterized by a disproportional SAT hypertrophy that can be associated with systemic symptoms.[181] Unlike obesity, hereditary SAT disorders are resistant to dietary changes or physical exercise.[181] Among them, lipedema is the most prevalent, marked by the enlargement and deposition of subcutaneous adipocytes.[181–185] The occurrence of lipedema during hormonal changes in women, such as puberty, pregnancy, or menopause suggests a potential involvement of estrogen in its pathogenesis. However, the underlying pathomechanisms of lipedema development remain unclear.[186] Clinical and histological studies do not show any morphological alterations of the vascular/lymphatic system.[187] However, recent evidence suggests an immune-related origin, as observed through macrophage infiltration in lipedema AT.[187] Furthermore, lipedema-derived ASCs express proliferative markers (Ki67 and CD34) and show an increased adipogenic differentiation potential in 2D cultures.[188–190] The specific roles of these cells and their pathophysiological significance remain to be elucidated.

FPLD is a rarer hereditary lipodystrophy associated with the development of metabolic syndromes and cardiovascular disease in affected patients.[191,192] Investigating the pathomechanisms underlying hereditary lipodystrophies in the context of metabolic syndrome can contribute to a better understanding of obesity related metabolic diseases (Table 3).

1.4 | Challenges in SAT research

Investigations of human SAT are challenged by tissue availability and technical difficulties. Adipocyte size (50–200 μm) and fragility,

challengean in-depth analysis. However, modern flow cytometers can analyze cells with a large dimeter (150–250 μm) while exerting minimal shear stress. However, cell sorting still presents the danger of cell lysis occurrence.[193] This problem was overcome by developing new techniques for the analysis of cellular components of AT.[194,195] SAT for in situ analyses requires a different processing than epidermis and dermis, since adipocytes are not stable under "normal" cutting conditions (OCT, −20°C). AT-infiltration with sucrose and tissue cutting at −50°C has yielded better morphological results.[29] New approaches such as imaging mass cytometry or spatial genomics now allow a more in-depth analysis of SAT (Ziadlou et al., unpublished data). Finally, extravascular vesicles (EV) now allow a more comprehensive analysis of AT cellular components. Human and mice EVs derived from obese AT were successfully used to study inflammatory.[196,197]

2 | CONCLUSION AND CLINICAL PERSPECTIVES

There is a growing body of evidence highlighting the intricate and crucial immune functions of AT.[27,29,30] Understanding the specific contributions of SAT in both homeostatic and pathological states remain a central challenge. Key questions need to be addressed to unravel immune loops between SAT and the skin or other organ systems.

Primarily, there is a need for a better understanding of the immunological reservoir within SAT in humans under homeostatic conditions (Figure 7). This necessitates a through characterization and functional exploration of both cellular (leukocytic and non-leukocytic) and molecular immune components within SAT. Also, characterizing the distinctions in SAT resident immune cells across various topographical locations of the body is crucial for elucidating their impact on skin homeostasis.

A pivotal aspect of this exploration is deciphering antigen presentation in SAT, including the identification of antigen-presenting cells (APC) and the nature of presented antigens. While ATM are the primary APC population in mice,[198] obesity models have shown adipocytes MHC class II and activating $CD4^+$ T-cells.[199–201] The involvement of unconventional APCs in humans remains unclear, necessitating further research to develop novel therapeutic strategies for SAT-based immune diseases.

TABLE 3 Hereditary SAT disease characteristics.

Hereditary SAT	Inheritance pattern	Associated comorbidities
Lipedema	Autosomal dominant, receive penetrance	Painful SAT, depression, joint pain, arthritis, vascular dysfunction
MSL	Autosomal dominant or recessive	Hyperlipidemia, hyperuricemia, hypothyroidism, T2D, neuropathy
Dercum's disease	Autosomal dominant	Gastrointestinal problems, joint pain, vascular dysfunction, asthenia, painful SAT
Familial partial lipodystrophy	Autosomal dominant	Metabolic syndrome, T2D, insuline resistance, cardiovascular disease
Congenital generalized lipodystrophy	Autosomal recessive	Metabolic syndrome, T2D, hepatosplenomegaly

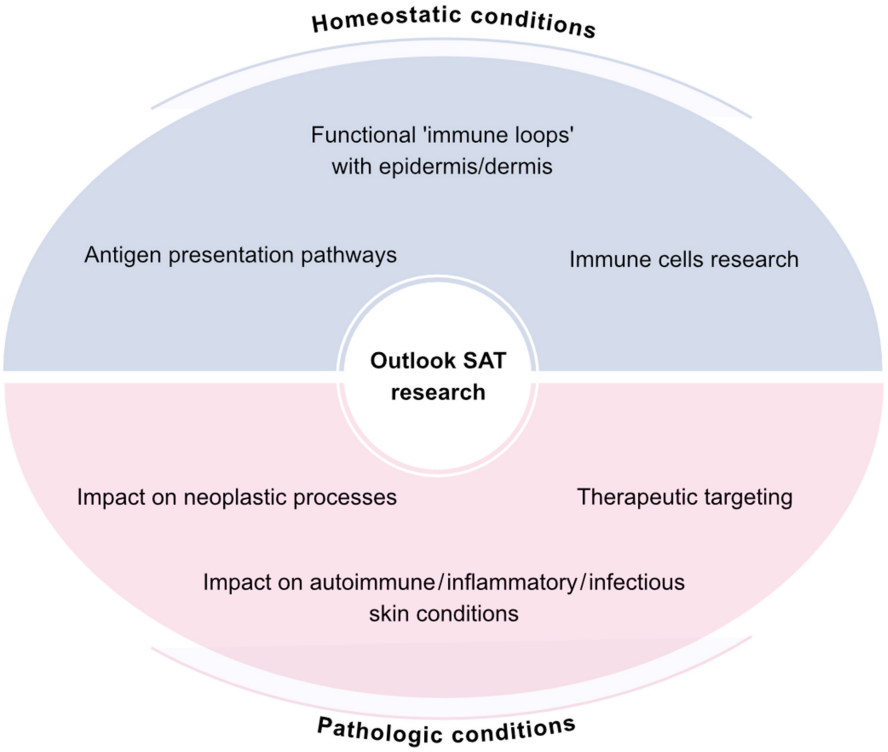

FIGURE 7 Future perspectives in SAT translational/clinical research.

In addition to comprehending immune dynamics under homeostatic conditions, it is crucial to delve into the pathomechanisms of SAT inflammation, using panniculitis as a representative model. The investigation of "immune loops" connecting SAT with the superficial skin layers or the systemic level, as observed in psoriasis and potentially other inflammatory conditions holds significant importance.[39] Moreover, understanding the impact of SAT-based processes on both inflammatory and neoplastic conditions, as illustrated by data from breast cancer and SPCTL, is crucial.[202–204] Additionally, the potential contribution of leaky barriers to increased inflammation in AT,[205] along with the migration of proinflammatory cells (DC and ATM) from the AT to inflammatory organs, warrants exploration.

To investigate specific antigens and signaling pathways, and cell–cell interactions in various contexts, the development of full thickness skin models, comprising SAT, dermis, and epidermis is warranted. A detailed understanding of SAT-based pathomechanisms facilitates the development of small molecule inhibitors targeting immunogenic antigens to mitigate inflammatory-driven complications. Moreover, considering the potential impact of obesity on these conditions, modulating SAT immune responses emerges as a promising avenue for developing targeted therapies against cutaneous/systemic immune-related diseases and obesity (Figure 7).

AUTHOR CONTRIBUTIONS

R.Z. and M.C.B. drafted the manuscript and figures. R.Z. and M.C.B. developed the main conceptual ideas. All authors critically reviewed and edited concepts described in the manuscript. All authors edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in relation to this work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Reihane Ziadlou https://orcid.org/0000-0001-7016-6725
Ganesh N. Pandian https://orcid.org/0000-0002-5531-1995
Cezmi A. Akdis https://orcid.org/0000-0001-8020-019X
Marie-Charlotte Brüggen https://orcid.org/0000-0002-8607-6254

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