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REVIEW ARTICLE

Subcutaneous adipose tissue: Implications in dermatological diseases and beyond

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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]

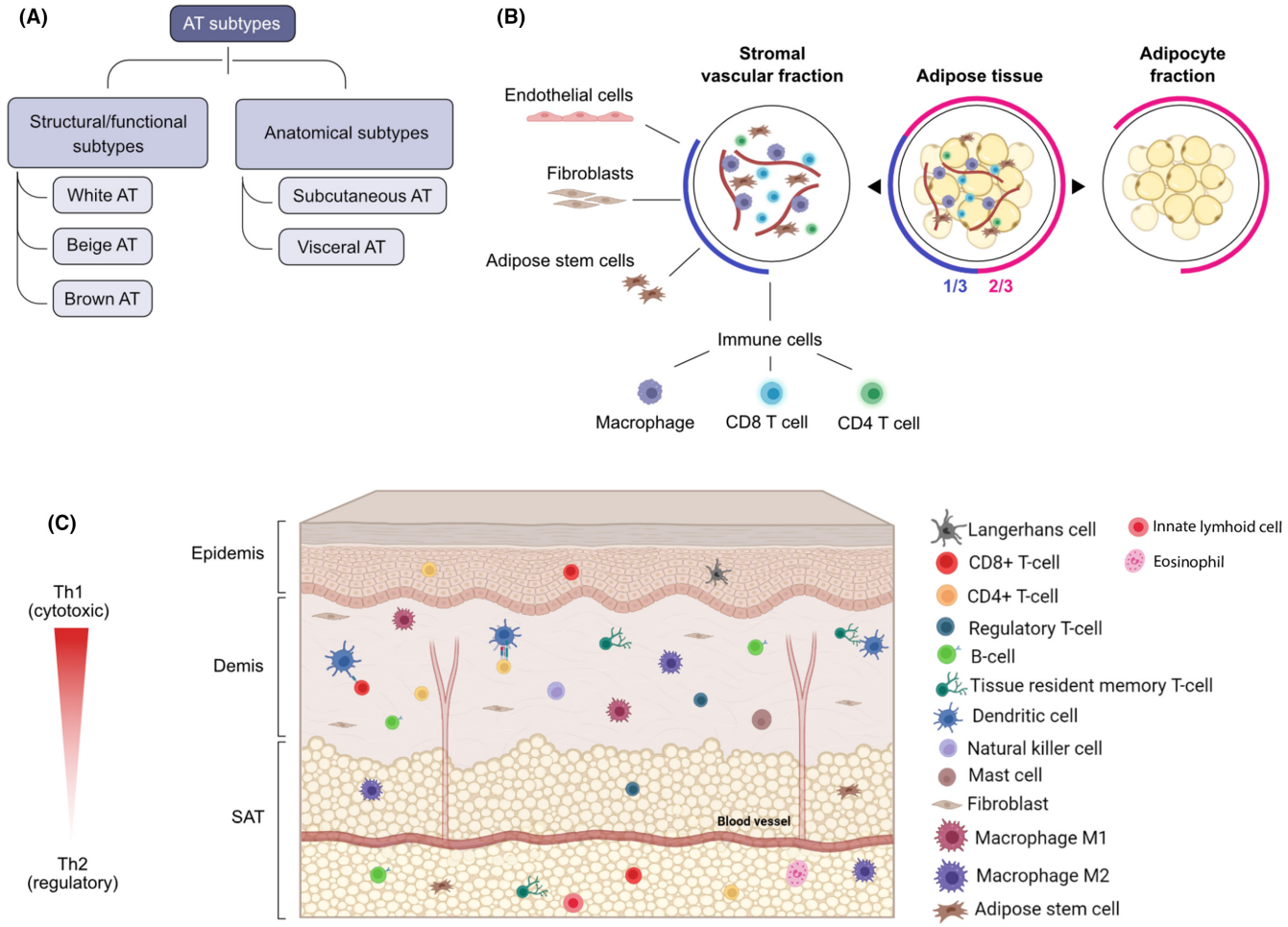

FIGURE 1 Structural and cellular composition of adipose tissue (AT). (A) Different structural and anatomical subtypes of AT (B) Cellular components of AT. AT consists of a 2/3 adipocyte fraction and a 1/3 of stromal vascular fraction (C) Immune cells in the three-layered cutaneous integument, which consists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

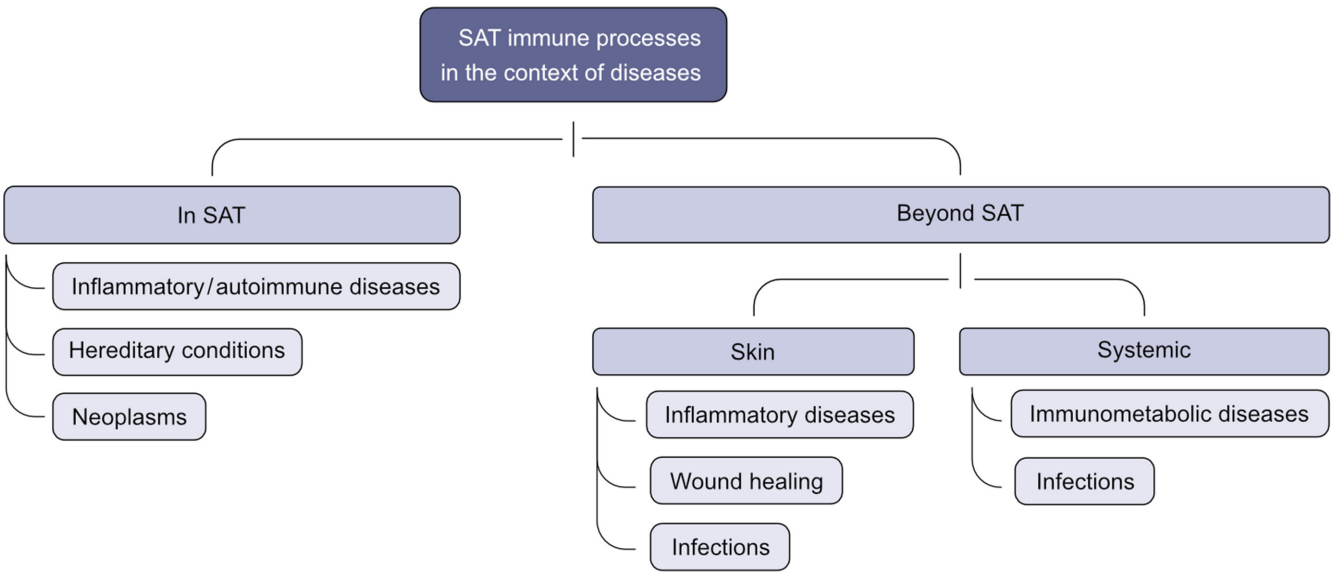

FIGURE 2 Subcutaneous adipose tissue (SAT)-mediated immune processes in clinical conditions.

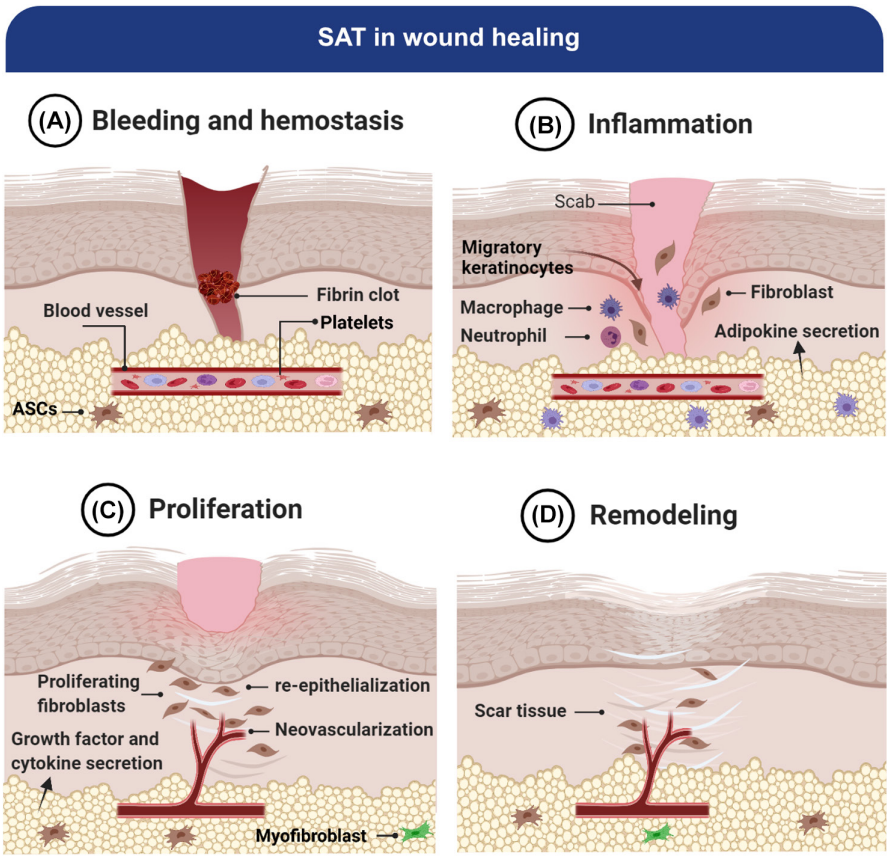

FIGURE 3 The role of SAT in wound healing. Wound healing consists of several regenerative phases (A): Bleeding and hemostasis lead to platelet aggregation and coagulation (B) Inflammatory cells, such as neutrophils, macrphages are recruited to the site of injury to clear debris and microbes. Fibroblast 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

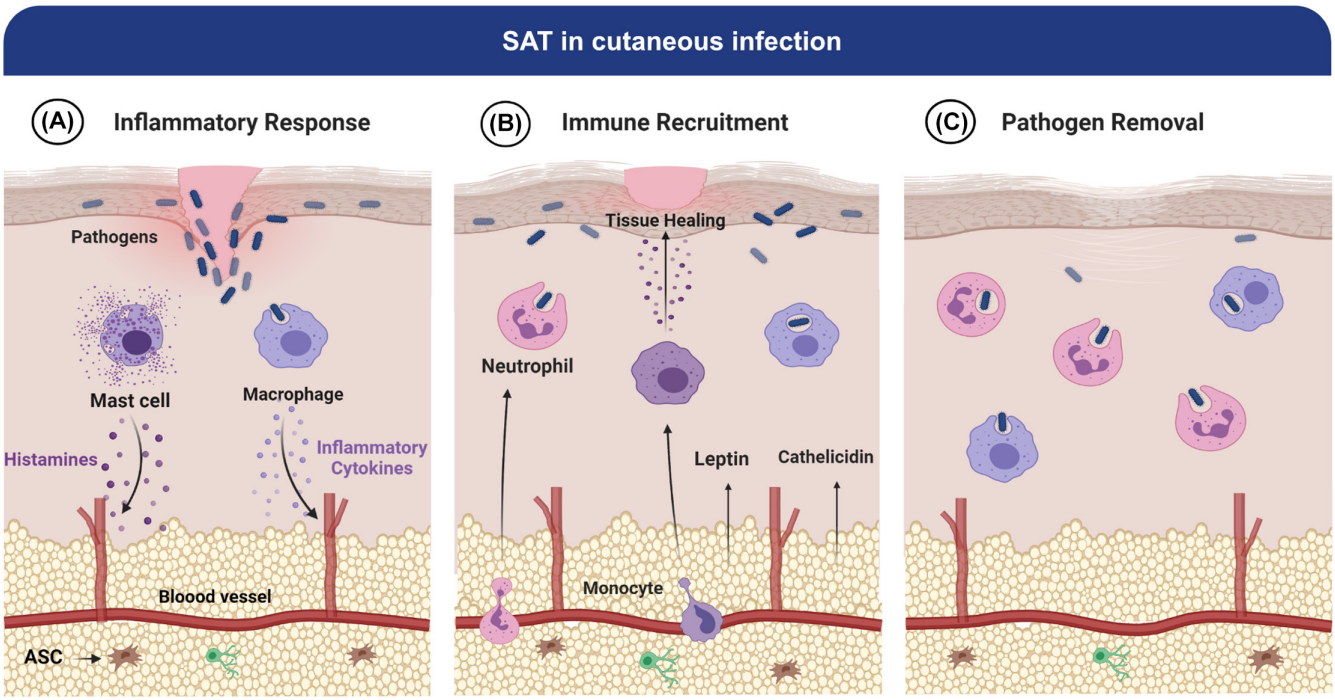

FIGURE 4 SAT in cutaneous infection. (A) Inflammatory cytokines and histamine are released by macrophages and recruit monocytes and neutrophils to the site of infection. (B) Adipocytes secret antimicrobial peptide cathelicidin and leptin adipokine (C) Pathogens are removed from the site of infection.

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.

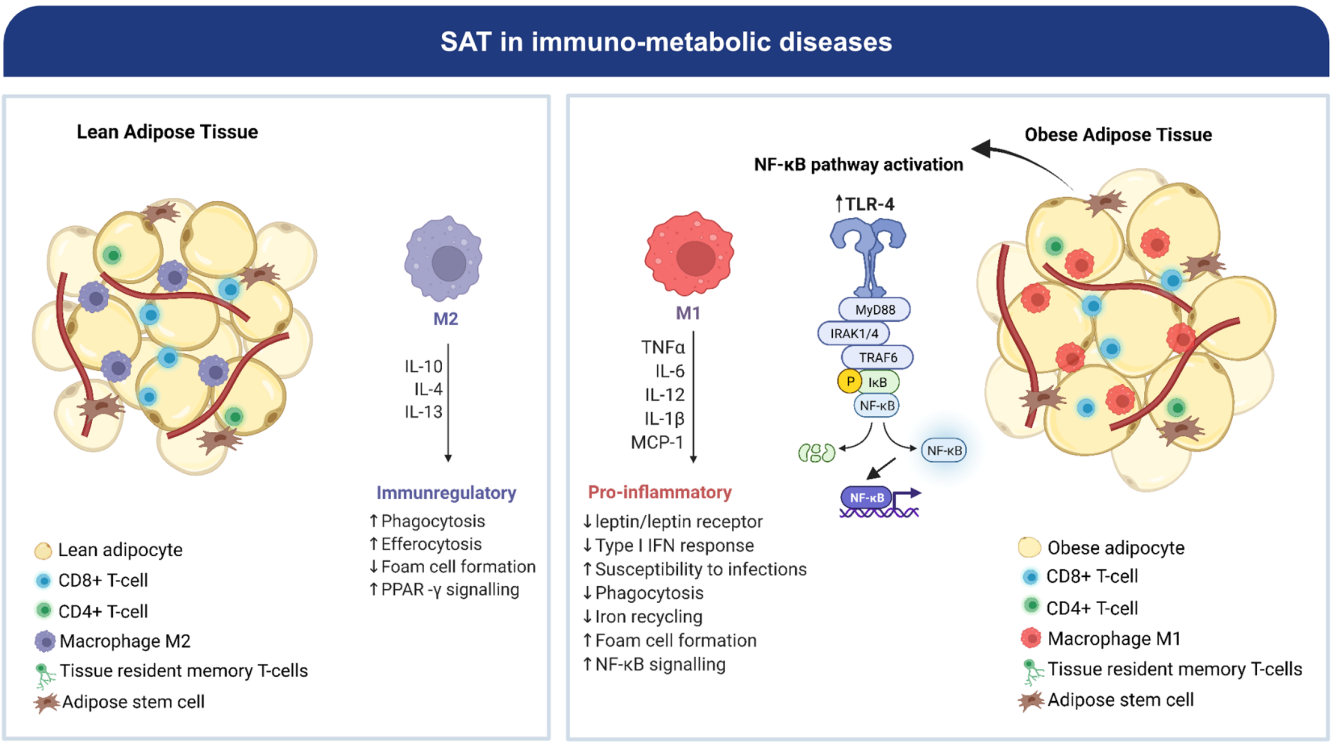

FIGURE 5 Lean and obese adipose tissue immune function. In obesity macrophages are polarized towards M1 phenotype with pro-inflammatory properties, while M2 macrophages with immunoregulatory properties are predominant in lean AT. In obese AT, NFk-B signaling pathway will be activated upon overexpression 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

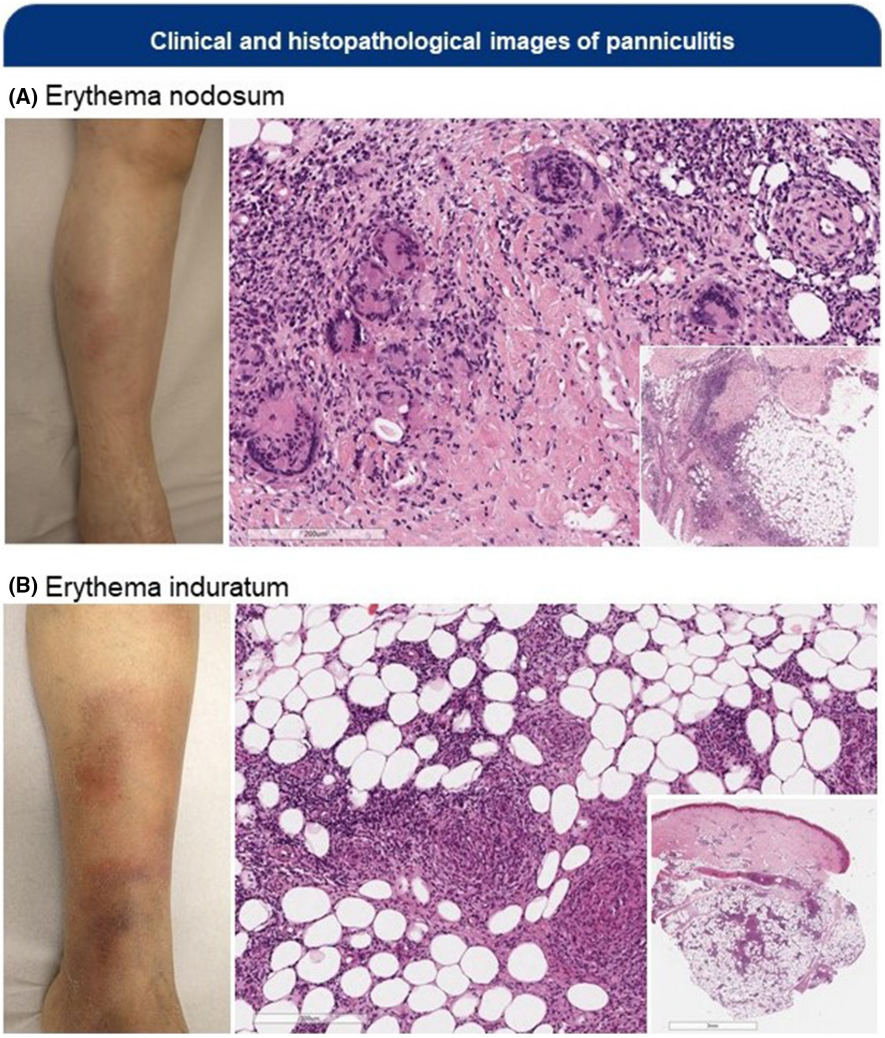

FIGURE 6 Clinical and histopthological images of panniculitis. (A) Septal panniculitis (erythema nodosum). H&E stain shows the inflammatory infiltrate is predominatly confinded to the thickened and fibrotic septa of the subcutis. The inflammatory infiltrate is mostly lymphocytic, with admixture of eosinophilic 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

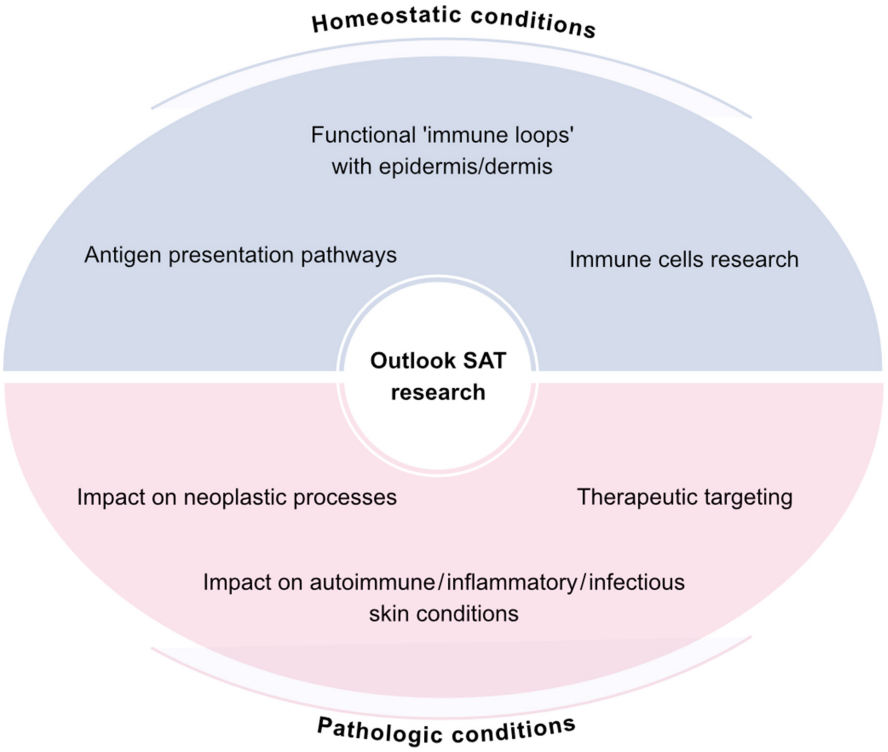

FIGURE 7 Future perspectives in SAT translational/clinical research.

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.

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REFERENCES

1. Ottaviani E, Malagoli D, Franceschi C. The evolution of the adipose tissue: a neglected enigma. *Gen Comp Endocrinol*. 2011;174(1):1-4.
2. Scheja L, Heeren J. The endocrine function of adipose tissues in health and cardiometabolic disease. *Nat Rev Endocrinol*. 2019;15(9):507-524.
3. Khan S, Chan YT, Revelo XS, Winer DA. The immune landscape of visceral adipose tissue during obesity and aging. *Front Endocrinol*. 2020;11:267.
4. Singh GM, Danaei G, Farzadfar F, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS One*. 2013;8(7):e65174.
5. Collins KH, Lenz KL, Pollitt EN, et al. Adipose tissue is a critical regulator of osteoarthritis. *Proc Natl Acad Sci USA*. 2021;118(1):e2021096118.
6. Leung DYM, Berdyshev E, Goleva E. Cutaneous barrier dysfunction in allergic diseases. *J Allergy Clin Immunol*. 2020;145(6):1485-1497.
7. Nyberg ST, Batty GD, Pentti J, et al. Obesity and loss of disease-free years owing to major non-communicable diseases: a multicohort study. *Lancet Public Health*. 2018;3(10):e490-e497.
8. Campanella G, Gunter MJ, Polidoro S, et al. Epigenome-wide association study of adiposity and future risk of obesity-related diseases. *Int J Obes*. 2018;42(12):2022-2035.
9. Jensen P, Skov L. Psoriasis and obesity. *Dermatology*. 2016;232(6):633-639.
10. Coimbra S, Oliveira H, Reis F, et al. Circulating levels of adiponectin, oxidized LDL and C-reactive protein in Portuguese patients with psoriasis vulgaris, according to body mass index, severity and duration of the disease. *J Dermatol Sci*. 2009;55(3):202-204.
11. Kromann CB, Ibler KS, Kristiansen VB, Jemec GB. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. *Acta Derm Venereol*. 2014;94(5):553-557.
12. Krajewski PK, Matusiak Ł, Szepietowski JC. Adipokines as an important link between hidradenitis suppurativa and obesity: a narrative review. *Br J Dermatol*. 2023;188(3):320-327.
13. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev*. 2010;11(1):11-18.
14. De Munck TJI, Soeters PB, Koek GH. The role of ectopic adipose tissue: benefit or deleterious overflow? *Eur J Clin Nutr*. 2021;75(1):38-48.
15. Chen SX, Zhang L-J, Gallo RL. Dermal white adipose tissue: a newly recognized layer of skin innate defense. *J Invest Dermatol*. 2019;139(5):1002-1009.
16. Zhang Z, Shao M, Hepler C, et al. Dermal adipose tissue has high plasticity and undergoes reversible dedifferentiation in mice. *J Clin Invest*. 2019;129(12):5327-5342.
17. Driskell RR, Jahoda CAB, Chuong C-M, Watt FM, Horsley V. Defining dermal adipose tissue. *Exp Dermatol*. 2014;23(9):629-631.
18. Jung SM, Sanchez-Gurmaches J, Guertin DA. Brown adipose tissue development and metabolism. *Handb Exp Pharmacol*. 2019;251:3-36.
19. Whitehead A, Krause FN, Moran A, et al. Brown and beige adipose tissue regulate systemic metabolism through a metabolite interorgan signaling axis. *Nat Commun*. 2021;12(1):1905.
20. Sidossis L, Kajimura S. Brown and beige fat in humans: thermogenic adipocytes that control energy and glucose homeostasis. *J Clin Invest*. 2015;125(2):478-486.
21. Cai X, Lin Y, Hauschka PV, Grottkau BE. Adipose stem cells originate from perivascular cells. *Biol Cell*. 2011;103(9):435-447.
22. Si Z, Wang X, Sun C, et al. Adipose-derived stem cells: sources, potency, and implications for regenerative therapies. *Biomed Pharmacother*. 2019;114:108765.
23. Andersen E, Ingerslev LR, Fabre O, et al. Preadipocytes from obese humans with type 2 diabetes are epigenetically reprogrammed at genes controlling adipose tissue function. *Int J Obes*. 2019;43(2):306-318.
24. Sengenès C, Lolmède K, Zakaroff-Girard A, Busse R, Bouloumié A. Preadipocytes in the human subcutaneous adipose tissue display distinct features from the adult mesenchymal and hematopoietic stem cells. *J Cell Physiol*. 2005;205(1):114-122.

25. Rodeheffer MS, Birsoy K, Friedman JM. Identification of white adipocyte progenitor cells in vivo. *Cell*. 2008;135(2):240-249.
26. Zhang R, Gao Y, Zhao X, et al. FSP1-positive fibroblasts are adipogenic niche and regulate adipose homeostasis. *PLoS Biol*. 2018;16(8):e2001493.
27. Anderson EK, Gutierrez DA, Hasty AH. Adipose tissue recruitment of leukocytes. *Curr Opin Lipidol*. 2010;21(3):172-177.
28. Soedono S, Cho KW. Adipose tissue dendritic cells: critical regulators of obesity-induced inflammation and insulin resistance. *Int J Mol Sci*. 2021;22(16):8666.
29. Brüggen MC, Strobl J, Koszik F, et al. Subcutaneous white adipose tissue of healthy young individuals harbors a leukocyte compartment distinct from skin and blood. *J Invest Dermatol*. 2019;139(9):2052-2057.
30. Li Y, Yun K, Mu R. A review on the biology and properties of adipose tissue macrophages involved in adipose tissue physiological and pathophysiological processes. *Lipids Health Dis*. 2020;19(1):164.
31. Bolus WR, Hasty AH. Contributions of innate type 2 inflammation to adipose function. *J Lipid Res*. 2019;60(10):1698-1709.
32. Hildreth AD, Ma F, Wong YY, Sun R, Pellegrini M, O'Sullivan TE. Single-cell sequencing of human white adipose tissue identifies new cell states in health and obesity. *Nat Immunol*. 2021;22(5):639-653.
33. Brestoff JR, Kim BS, Saenz SA, et al. Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. *Nature*. 2015;519(7542):242-246.
34. Brestoff JR, Artis D. Immune regulation of metabolic homeostasis in health and disease. *Cell*. 2015;161(1):146-160.
35. Zhang LJ, Guerrero-Juarez CF, Hata T, et al. Innate immunity. Dermal adipocytes protect against invasive *Staphylococcus aureus* skin infection. *Science*. 2015;347(6217):67-71.
36. Nguyen AV, Soulika AM. The dynamics of the skin's immune system. *Int J Mol Sci*. 2019;20(8):1811.
37. Shook BA, Wasko RR, Mano O, et al. Dermal adipocyte lipolysis and myofibroblast conversion are required for efficient skin repair. *Cell Stem Cell*. 2020;26(6):880-895.e6.
38. Shook B, Xiao E, Kumamoto Y, Iwasaki A, Horsley V. CD301b^{+} macrophages are essential for effective skin wound healing. *J Invest Dermatol*. 2016;136(9):1885-1891.
39. Wong Y, Nakamizo S, Tan KJ, Kabashima K. An update on the role of adipose tissues in psoriasis. *Front Immunol*. 2019;10:1507.
40. Raud B, McGuire PJ, Jones RG, Sparwasser T, Berod L. Fatty acid metabolism in CD8^{+} T cell memory: challenging current concepts. *Immunol Rev*. 2018;283(1):213-231.
41. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: a cellular perspective. *Physiol Rev*. 2018;99(1):665-706.
42. Salgado AJ, Reis RL, Sousa NJ, Gimble JM. Adipose tissue derived stem cells secretome: soluble factors and their roles in regenerative medicine. *Curr Stem Cell Res Ther*. 2010;5(2):103-110.
43. López JF, Sarkanen JR, Huttala O, Kaartinen IS, Kuokkanen HO, Ylikomi T. Adipose tissue extract shows potential for wound healing: in vitro proliferation and migration of cell types contributing to wound healing in the presence of adipose tissue preparation and platelet rich plasma. *Cytotechnology*. 2018;70(4):1193-1204.
44. Cui L, Yin S, Liu W, Li N, Zhang W, Cao Y. Expanded adipose-derived stem cells suppress mixed lymphocyte reaction by secretion of prostaglandin E2. *Tissue Eng*. 2007;13(6):1185-1195.
45. Wang M, Crisostomo PR, Herring C, Meldrum KK, Meldrum DR. Human progenitor cells from bone marrow or adipose tissue produce VEGF, HGF, and IGF-I in response to TNF by a p38 MAPK-dependent mechanism. *Am J Physiol Regul Integr Comp Physiol*. 2006;291(4):R880-R884.
46. Merrick D, Seale P. Skinny fat cells stimulate wound healing. *Cell Stem Cell*. 2020;26(6):801-803.
47. Raghuram AC, Yu RP, Lo AY, et al. Role of stem cell therapies in treating chronic wounds: a systematic review. *World J Stem Cells*. 2020;12(7):659-675.
48. Fujiwara O, Prasai A, Perez-Bello D, et al. Adipose-derived stem cells improve grafted burn wound healing by promoting wound bed blood flow. *Burns Trauma*. 2020;8:tkaa009.
49. Kuo Y-R, Wang C-T, Cheng J-T, Kao G-S, Chiang Y-C, Wang C-J. Adipose-derived stem cells accelerate diabetic wound healing through the induction of autocrine and paracrine effects. *Cell Transplant*. 2016;25(1):71-81.
50. Sastourné-Arrey Q, Mathieu M, Contreras X, et al. Adipose tissue is a source of regenerative cells that augment the repair of skeletal muscle after injury. *Nat Commun*. 2023;14(1):80.
51. Kokai LE, Marra K, Rubin JP. Adipose stem cells: biology and clinical applications for tissue repair and regeneration. *Transl Res*. 2014;163(4):399-408.
52. Gimble JM, Guilak F, Bunnell BA. Clinical and preclinical translation of cell-based therapies using adipose tissue-derived cells. *Stem Cell Res Ther*. 2010;1(2):19.
53. An Y, Lin S, Tan X, et al. Exosomes from adipose-derived stem cells and application to skin wound healing. *Cell Prolif*. 2021;54(3):e12993.
54. Golchin A, Hosseinzadeh S, Ardeshirylajimi A. The exosomes released from different cell types and their effects in wound healing. *J Cell Biochem*. 2018;119(7):5043-5052.
55. Baglio SR, Pegtel DM, Baldini N. Mesenchymal stem cell secreted vesicles provide novel opportunities in (stem) cell-free therapy. *Front Physiol*. 2012;3:359.
56. Hu L, Wang J, Zhou X, et al. Exosomes derived from human adipose mensenchymal stem cells accelerates cutaneous wound healing via optimizing the characteristics of fibroblasts. *Sci Rep*. 2016;6(1):32993.
57. Wang L, Hu L, Zhou X, et al. Exosomes secreted by human adipose mesenchymal stem cells promote scarless cutaneous repair by regulating extracellular matrix remodelling. *Sci Rep*. 2017;7(1):13321.
58. Mahlakõiv T, Flamar AL, Johnston LK, et al. Stromal cells maintain immune cell homeostasis in adipose tissue via production of interleukin-33. *Sci Immunol*. 2019;4(35):eaax0416.
59. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: an update. *Clin Endocrinol*. 2006;64(4):355-365.
60. Rajesh Y, Sarkar D. Association of adipose tissue and adipokines with development of obesity-induced liver cancer. *Int J Mol Sci*. 2021;22(4):2163.
61. Bates SH, Stearns WH, Dundon TA, et al. STAT3 signalling is required for leptin regulation of energy balance but not reproduction. *Nature*. 2003;421(6925):856-859.
62. Procaccini C, Jirillo E, Matarese G. Leptin as an immunomodulator. *Mol Asp Med*. 2012;33(1):35-45.
63. Klein J, Perwitz N, Kraus D, Fasshauer M. Adipose tissue as source and target for novel therapies. *Trends Endocrinol Metab*. 2006;17(1):26-32.
64. Mancuso P, Gottschalk A, Phare SM, Peters-Golden M, Lukacs NW, Huffnagle GB. Leptin-deficient mice exhibit impaired host defense in gram-negative pneumonia. *J Immunol*. 2002;168(8):4018-4024.
65. Maurya R, Bhattacharya P, Dey R, Nakhasi HL. Leptin functions in infectious diseases. *Front Immunol*. 2018;9(2741):2741.
66. Milner JJ, Beck MA. The impact of obesity on the immune response to infection. *Proc Nutr Soc*. 2012;71(2):298-306.
67. Terán-Cabanillas E, Hernández J. Role of leptin and SOCS3 in inhibiting the type I interferon response during obesity. *Inflammation*. 2017;40(1):58-67.
68. Schaab M, Kratzsch J. The soluble leptin receptor. *Best Pract Res Clin Endocrinol Metab*. 2015;29(5):661-670.
69. Turk Wensveen T, Gašparini D, Rahelić D, Wensveen FM. Type 2 diabetes and viral infection; cause and effect of disease. *Diabetes Res Clin Pract*. 2021;172:108637.
70. Singanayagam A, Glanville N, Cuthbertson L, et al. Inhaled corticosteroid suppression of cathelicidin drives dysbiosis and bacterial

infection in chronic obstructive pulmonary disease. *Sci Transl Med*. 2019;11(507):eaav3879.
71. Boman HG. Antibacterial peptides: basic facts and emerging concepts. *J Intern Med*. 2003;254(3):197-215.
72. Han SJ, Glatman Zaretsky A, Andrade-Oliveira V, et al. White adipose tissue is a reservoir for memory T cells and promotes protective memory responses to infection. *Immunity*. 2017;47(6):1154-1168.e6.
73. Reina-Campos M, Scharping NE, Goldrath AW. $CD8^+$ T cell metabolism in infection and cancer. *Nat Rev Immunol*. 2021;21(11):718-738.
74. O'Shea D, Corrigan M, Dunne MR, et al. Changes in human dendritic cell number and function in severe obesity may contribute to increased susceptibility to viral infection. *Int J Obes*. 2013;37(11):1510-1513.
75. Smith AG, Sheridan PA, Tseng RJ, Sheridan JF, Beck MA. Selective impairment in dendritic cell function and altered antigen-specific $CD8^+$ T-cell responses in diet-induced obese mice infected with influenza virus. *Immunology*. 2009;126(2):268-279.
76. Lynch L, Nowak M, Varghese B, et al. Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine production. *Immunity*. 2012;37(3):574-587.
77. Viel S, Besson L, Charrier E, et al. Alteration of natural killer cell phenotype and function in obese individuals. *Clin Immunol*. 2017;177:12-17.
78. Michelet X, Dyck L, Hogan A, et al. Metabolic reprogramming of natural killer cells in obesity limits antitumor responses. *Nat Immunol*. 2018;19(12):1330-1340.
79. O'Shea D, Hogan AE. Dysregulation of natural killer cells in obesity. *Cancer*. 2019;11(4):573.
80. Kanneganti TD, Dixit VD. Immunological complications of obesity. *Nat Immunol*. 2012;13(8):707-712.
81. Misumi I, Starmer J, Uchimura T, Beck MA, Magnuson T, Whitmire JK. Obesity expands a distinct population of T cells in adipose tissue and increases vulnerability to infection. *Cell Rep*. 2019;27(2):514-524.e5.
82. Dhurandhar NV. Infections and body weight: an emerging relationship? *Int J Obes*. 2002;26(6):745-746.
83. Pasarica M, Shin AC, Yu M, et al. Human adenovirus 36 induces adiposity, increases insulin sensitivity, and alters hypothalamic monoamines in rats. *Obesity*. 2006;14(11):1905-1913.
84. Dhurandhar NV, Whigham LD, Abbott DH, et al. Human adenovirus Ad-36 promotes weight gain in male rhesus and marmoset monkeys. *J Nutr*. 2002;132(10):3155-3160.
85. Rudrapatna S, Bhatt M, Wang KW, et al. Obesity and muscle-macrophage crosstalk in humans and mice: a systematic review. *Obes Rev*. 2019;20(11):1572-1596.
86. Bray GA, Kim KK, Wilding JPH, World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obes Rev*. 2017;18(7):715-723.
87. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006;444(7121):840-846.
88. Klingberg E, Bilberg A, Björkman S, et al. Weight loss improves disease activity in patients with psoriatic arthritis and obesity: an interventional study. *Arthritis Res Ther*. 2019;21(1):17.
89. Vlietstra L, Stebbings S, Meredith-Jones K, Abbott JH, Treharne GJ, Waters DL. Sarcopenia in osteoarthritis and rheumatoid arthritis: the association with self-reported fatigue, physical function and obesity. *PLoS One*. 2019;14(6):e0217462.
90. Vekic J, Zeljkovic A, Stefanovic A, Jelic-Ivanovic Z, Spasojevic-Kalimanovska V. Obesity and dyslipidemia. *Metabolism*. 2019;92:71-81.
91. Koliaki C, Liatis S, Kokkinos A. Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism*. 2019;92:98-107.
92. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: emerging biological mechanisms and perspectives. *Metabolism*. 2019;92:121-135.
93. Stone TW, McPherson M, Gail DL. Obesity and cancer: existing and new hypotheses for a causal connection. *EBioMedicine*. 2018;30:14-28.
94. Boulet LP. Asthma and obesity. *Clin Exp Allergy*. 2013;43(1):8-21.
95. Stinkens R, Goossens GH, Jocken JW, Blaak EE. Targeting fatty acid metabolism to improve glucose metabolism. *Obes Rev*. 2015;16(9):715-757.
96. van der Kolk BW, Kalafati M, Adriaens M, et al. Subcutaneous adipose tissue and systemic inflammation are associated with peripheral but not hepatic insulin resistance in humans. *Diabetes*. 2019;68(12):2247-2258.
97. Keophiphath M, Achard V, Henegar C, Rouault C, Clément K, Lacasa D. Macrophage-secreted factors promote a profibrotic phenotype in human preadipocytes. *Mol Endocrinol*. 2009;23(1):11-24.
98. Tanaka M, Ikeda K, Suganami T, et al. Macrophage-inducible C-type lectin underlies obesity-induced adipose tissue fibrosis. *Nat Commun*. 2014;5(1):4982.
99. Wang H, Shen L, Sun X, et al. Adipose group 1 innate lymphoid cells promote adipose tissue fibrosis and diabetes in obesity. *Nat Commun*. 2019;10(1):3254.
100. Miethe S, Karsonova A, Karaulov A, Renz H. Obesity and asthma. *J Allergy Clin Immunol*. 2020;146(4):685-693.
101. Sideleva O, Suratt BT, Black KE, et al. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. *Am J Respir Crit Care Med*. 2012;186(7):598-605.
102. Periyalil HA, Wood LG, Wright TA, et al. Obese asthmatics are characterized by altered adipose tissue macrophage activation. *Clin Exp Allergy*. 2018;48(6):641-649.
103. Mraz M, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade inflammation. *J Endocrinol*. 2014;222(3):R113-R127.
104. Voss K, Hong HS, Bader JE, Sugiura A, Lyssiotis CA, Rathmell JC. A guide to interrogating immunometabolism. *Nat Rev Immunol*. 2021;21(10):637-652.
105. Makowski L, Chaib M, Rathmell JC. Immunometabolism: from basic mechanisms to translation. *Immunol Rev*. 2020;295(1):5-14.
106. Unamuno X, Gómez-Ambrosi J, Rodríguez A, Becerril S, Frühbeck G, Catalán V. Adipokine dysregulation and adipose tissue inflammation in human obesity. *Eur J Clin Investig*. 2018;48(9):e12997.
107. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int J Mol Sci*. 2014;15(4):6184-6223.
108. Wang Q, Wu H. T Cells in adipose tissue: critical players in immunometabolism. *Front Immunol*. 2018;9:2509.
109. Travers RL, Motta AC, Betts JA, Bouloumié A, Thompson D. The impact of adiposity on adipose tissue-resident lymphocyte activation in humans. *Int J Obes*. 2015;39(5):762-769.
110. Strissel KJ, DeFuria J, Shaul ME, Bennett G, Greenberg AS, Obin MS. T-cell recruitment and Th1 polarization in adipose tissue during diet-induced obesity in C57BL/6 mice. *Obesity*. 2010;18(10):1918-1925.
111. Kintscher U, Hartge M, Hess K, et al. T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. *Arterioscler Thromb Vasc Biol*. 2008;28(7):1304-1310.
112. Park CS, Shastri N. The role of T cells in obesity-associated inflammation and metabolic disease. *Immune Netw*. 2022;22(1):e13.
113. McDonnell WJ, Koethe JR, Mallal SA, et al. High CD8 T-cell receptor clonality and altered CDR3 properties are associated with elevated isolevuglandins in adipose tissue during diet-induced obesity. *Diabetes*. 2018;67(11):2361-2376.

114. Cho KW, Morris DL, DelProposto JL, et al. An MHC II-dependent activation loop between adipose tissue macrophages and CD4$^+$ T cells controls obesity-induced inflammation. *Cell Rep*. 2014;9(2):605-617.
115. Zeng Q, Sun X, Xiao L, Xie Z, Bettini M, Deng T. A unique population: adipose-resident regulatory T cells. *Front Immunol*. 2018;9:2075.
116. Feuerer M, Herrero L, Cipolletta D, et al. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat Med*. 2009;15(8):930-939.
117. Mehta P, Nuotio-Antar AM, Smith CW. Gammadelta T cells promote inflammation and insulin resistance during high fat diet-induced obesity in mice. *J Leukoc Biol*. 2015;97(1):121-134.
118. Costanzo AE, Taylor KR, Dutt S, Han PP, Fujioka K, Jameson JM. Obesity impairs gammadelta T cell homeostasis and antiviral function in humans. *PLoS One*. 2015;10(3):e0120918.
119. Vitseva OI, Tanriverdi K, Tchkonia TT, et al. Inducible toll-like receptor and NF-kappaB regulatory pathway expression in human adipose tissue. *Obesity*. 2008;16(5):932-937.
120. Schäffler A, Schölmerich J. Innate immunity and adipose tissue biology. *Trends Immunol*. 2010;31(6):228-235.
121. Kopp A, Gross P, Falk W, et al. Fatty acids as metabolic mediators in innate immunity. *Eur J Clin Investig*. 2009;39(10):924-933.
122. Schaeffler A, Gross P, Buettner R, et al. Fatty acid-induced induction of toll-like receptor-4/nuclear factor-kappaB pathway in adipocytes links nutritional signalling with innate immunity. *Immunology*. 2009;126(2):233-245.
123. Cullberg KB, Larsen JØ, Pedersen SB, Richelsen B. Effects of LPS and dietary free fatty acids on MCP-1 in 3T3-L1 adipocytes and macrophages in vitro. *Nutr Diabetes*. 2014;4(3):e113.
124. Russo L, Lumeng CN. Properties and functions of adipose tissue macrophages in obesity. *Immunology*. 2018;155(4):407-417.
125. Sharma VM, Puri V. Mechanism of TNF-α-induced lipolysis in human adipocytes uncovered. *Obesity*. 2016;24(5):990.
126. Sethi JK, Hotamisligil GS. Metabolic messengers: tumour necrosis factor. *Nat Metab*. 2021;3(10):1302-1312.
127. Du X, Liu M, Tai W, et al. Tumor necrosis factor-α promotes lipolysis and reduces insulin sensitivity by activating nuclear factor kappa B and c-Jun N-terminal kinase in primary bovine adipocytes. *J Dairy Sci*. 2022;105(10):8426-8438.
128. Xia W, Veeragandham P, Cao Y, et al. Obesity causes mitochondrial fragmentation and dysfunction in white adipocytes due to RalA activation. *Nat Metab*. 2024;6(2):273-289.
129. Heinonen S, Buzkova J, Muniandy M, et al. Impaired mitochondrial biogenesis in adipose tissue in acquired obesity. *Diabetes*. 2015;64(9):3135-3145.
130. Chavakis T, Alexaki VI, Ferrante AW. Macrophage function in adipose tissue homeostasis and metabolic inflammation. *Nat Immunol*. 2023;24(5):757-766.
131. Becker M, Dirschl SM, Scherm MG, Serr I, Daniel C. Niche-specific control of tissue function by regulatory T cells—Current challenges and perspectives for targeting metabolic disease. *Cell Metab*. 2024;36(2):229-239.
132. Becker M, Levings MK, Daniel C. Adipose-tissue regulatory T cells: critical players in adipose-immune crosstalk. *Eur J Immunol*. 2017;47(11):1867-1874.
133. Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, et al. The role of adipokines in health and disease. *Biomedicine*. 2023;11(5):1290.
134. Zorena K, Jachimowicz-Duda O, Ślęzak D, Robakowska M, Mrugacz M. Adipokines and obesity. potential link to metabolic disorders and chronic complications. *Int J Mol Sci*. 2020;21(10):3570.
135. Barral DC, Brenner MB. CD1 antigen presentation: how it works. *Nat Rev Immunol*. 2007;7(12):929-941.
136. de Jong A, Peña-Cruz V, Cheng T-Y, Clark RA, Van Rhijn I, Moody DB. CD1a-autoreactive T cells are a normal component of the human αβ T cell repertoire. *Nat Immunol*. 2010;11(12):1102-1109.
137. Frasca D, Diaz A, Romero M, et al. Identification and characterization of adipose tissue-derived human antibodies with "anti-self" specificity. *Front Immunol*. 2020;11:392.
138. Cotton RN, Wegrecki M, Cheng T-Y, et al. CD1a selectively captures endogenous cellular lipids that broadly block T cell response. *J Exp Med*. 2021;218(7):e20202699.
139. Gapin L. CD1a autoreactivity: when size does matter. *J Exp Med*. 2021;218(7):e20210531.
140. Guo Z, Yang Y, Liao Y, Shi Y, Zhang LJ. Emerging roles of adipose tissue in the pathogenesis of psoriasis and atopic dermatitis in obesity. *JID Innov*. 2022;2(1):100064.
141. Hossler E, Wood G, Still C, Mowad C, Maroon M. The effect of weight loss surgery on the severity of psoriasis. *Br J Dermatol*. 2013;168(3):660-661.
142. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. *Am J Clin Nutr*. 2008;88(5):1242-1247.
143. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. *J Immunol*. 2005;174(9):5789-5795.
144. Shibata S, Saeki H, Tada Y, Karakawa M, Komine M, Tamaki K. Serum high molecular weight adiponectin levels are decreased in psoriasis patients. *J Dermatol Sci*. 2009;55(1):62-63.
145. Nakamizo S, Honda T, Adachi A, et al. High fat diet exacerbates murine psoriatic dermatitis by increasing the number of IL-17-producing γδ T cells. *Sci Rep*. 2017;7(1):1-13.
146. Zhang Y, Li Q, Rao E, et al. Epidermal fatty acid binding protein promotes skin inflammation induced by high-fat diet. *Immunity*. 2015;42(5):953-964.
147. Varga J, Marangoni RG. Dermal white adipose tissue implicated in SSc pathogenesis. *Nat Rev Rheumatol*. 2017;13(2):71-72.
148. Varga J, Marangoni RG. Systemic sclerosis in 2016: dermal white adipose tissue implicated in SSc pathogenesis. *Nat Rev Rheumatol*. 2017;13(2):71-72.
149. Vossen ARJV, van der Zee HH, Prens EP. Hidradenitis suppurativa: a systematic review integrating inflammatory pathways into a cohesive pathogenic model. *Front Immunol*. 2018;9:2965.
150. Sabat R, Jemec GBE, Matusiak Ł, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. *Nat Rev Dis Primers*. 2020;6(1):18.
151. Segura S, Requena L. Anatomy and histology of normal subcutaneous fat, necrosis of adipocytes, and classification of the panniculitides. *Dermatol Clin*. 2008;26(4):419-424.
152. Requena L, Sánchez YE. Panniculitis. Part II. Mostly lobular panniculitis. *J Am Acad Dermatol*. 2001;45(3):325-361.
153. Diaz Cascajo C, Borghi S, Weyers W. Panniculitis: definition of terms and diagnostic strategy. *Am J Dermatopathol*. 2000;22(6):530-549.
154. Blake T, Manahan M, Rodins K. Erythema nodosum—A review of an uncommon panniculitis. *Dermatol Online J*. 2014;20(4):22376.
155. Mokhtari F, Abtahi-Naeini B, Pourazizi M. Erythema nodosum migrans successfully treated with indomethacin: a rare entity. *Adv Biomed Res*. 2014;3:264.
156. Anzengruber F, Mergenthaler C, Murer C, Dummer R. Potassium iodide for cutaneous inflammatory disorders: a monocentric, retrospective study. *Dermatology*. 2019;235(2):137-143.
157. Lehman CW. Control of chronic erythema nodosum with naproxen. *Cutis*. 1980;26(1):66-67.
158. Hayashi S, Ishikawa S, Ishii E, et al. Anti-inflammatory effects of potassium iodide on SDS-induced murine skin inflammation. *J Invest Dermatol*. 2020;140(10):2001-2008.
159. Costa RO, Macedo PM, Carvalhal A, Bernardes-Engemann AR. Use of potassium iodide in dermatology: updates on an old drug. *An Bras Dermatol*. 2013;88(3):396-402.
160. Khalilzadeh M, Shayan M, Jourian S, Rahimi M, Sheibani M, Dehpour AR. A comprehensive insight into the anti-inflammatory

properties of dapsone. *Naunyn Schmiedeberg's Arch Pharmacol*. 2022;395(12):1509-1523.
161. Shippey EA, Wagler VD, Collamer AN. Hydroxychloroquine: an old drug with new relevance. *Cleve Clin J Med*. 2018;85(6):459-467.
162. Szczęch J, Matławska M, Rutka M, Reich A. Clinical presentation of erythema nodosum. *Post N Med*. 2018;31(1A):25-28.
163. Pérez-Garza DM, Chavez-Alvarez S, Ocampo-Candiani J, Gomez-Flores M. Erythema nodosum: a practical approach and diagnostic algorithm. *Am J Clin Dermatol*. 2021;22(3):367-378.
164. Requena L, Sánchez YE. Erythema nodosum. *Semin Cutan Med Surg*. 2007;26(2):114-125.
165. Jones JV, Cumming RH, Asplin CM. Evidence for circulating immune complexes in erythema nodosum and early sarcoidosis. *Ann N Y Acad Sci*. 1976;278:212-219.
166. Maliniemi P, Hahtola S, Ovaska K, et al. Molecular characterization of subcutaneous panniculitis-like T-cell lymphoma reveals up-regulation of immunosuppression- and autoimmunity-associated genes. *Orphanet J Rare Dis*. 2014;9:160.
167. Kunz M, Beutel S, Bröcker E. Leucocyte activation in erythema nodosum. *Clin Exp Dermatol*. 1999;24(5):396-401.
168. De Simone C, Caldarola G, Scaldaferri F, et al. Clinical, histopathological, and immunological evaluation of a series of patients with erythema nodosum. *Int J Dermatol*. 2016;55(5):e289-e294.
169. Schneider JW, Jordaan HF. The histopathologic spectrum of erythema induratum of Bazin. *Am J Dermatopathol*. 1997;19(4):323-333.
170. Mascaró JM, Baselga E. Erythema induratum of Bazin. *Dermatol Clin*. 2008;26(4):439-445.
171. Wu X, Subtil A, Craiglow B, Watsky K, Marks A, Ko C. The coexistence of lupus erythematosus panniculitis and subcutaneous panniculitis-like T-cell lymphoma in the same patient. *JAAD Case Rep*. 2018;4(2):179-184.
172. Burrows NP, Walport MJ, Hammond AH, Davey N, Jones RR. Lupus erythematosus profundus with partial C4 deficiency responding to thalidomide. *Br J Dermatol*. 1991;125(1):62-67.
173. Bolognia JL. Panniculitis. *Dermatology*. In: Bolognia JL et al., eds. 3rd ed. Elsevier Saunders; 2012.
174. Lee ATJ, Thway K, Huang PH, Jones RL. Clinical and molecular spectrum of liposarcoma. *J Clin Oncol*. 2018;36(2):151-159.
175. Mentzel T. Cutaneous lipomatous neoplasms. *Semin Diagn Pathol*. 2001;18(4):250-257.
176. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019;133(16):1703-1714.
177. Parveen Z, Thompson K. Subcutaneous panniculitis-like T-cell lymphoma: redefinition of diagnostic criteria in the recent World Health Organization-European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas. *Arch Pathol Lab Med*. 2009;133(2):303-308.
178. Fink-Puches R, Zenahlik P, Bäck B, Smolle J, Kerl H, Cerroni L. Primary cutaneous lymphomas: applicability of current classification schemes (European Organization for Research and Treatment of Cancer, World Health Organization) based on clinicopathologic features observed in a large group of patients. *Blood*. 2002;99(3):800-805.
179. Bauer WM, Aichelburg MC, Griss J, et al. Molecular classification of tumour cells in a patient with intravascular large B-cell lymphoma. *Br J Dermatol*. 2018;178(1):215-221.
180. Gonzalez CL, Medeiros LJ, Braziel RM, Jaffe ES. T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. *Am J Surg Pathol*. 1991;15(1):17-27.
181. Herbst KL. Rare adipose disorders (RADs) masquerading as obesity. *Acta Pharmacol Sin*. 2012;33(2):155-172.
182. Szolnoky G, Ifeoluwa A, Tuczai M, et al. Measurement of capillary fragility: a useful tool to differentiate lipedema from obesity? *Lymphology*. 2017;50(4):203-209.
183. Al-Ghadban SL, Herbst KA, Bunnell B. Adipose Tissue–An Update. *Lipedema: A Painful Adipose Tissue Disorder*; Intech Open. 2019.
184. Torre YS, Wadeea R, Rosas V, Herbst KL. Lipedema: friend and foe. *Horm Mol Biol Clin Invest*. 2018;33(1). doi: 10.1515/hmbci-2017-0076
185. Kruppa P, Georgiou I, Biermann N, Prantl L, Klein-Weigel P, Ghods M. Lipedema—Pathogenesis, diagnosis, and treatment Options. *Dtsch Arztebl Int*. 2020;117(22-23):396-403.
186. Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome—Systematic review. *Clin Obes*. 2012;2(3-4):86-95.
187. Felmerer G, Stylianaki A, Hollmén M, et al. Increased levels of VEGF-C and macrophage infiltration in lipedema patients without changes in lymphatic vascular morphology. *Sci Rep*. 2020;10(1):10947.
188. Suga H, Araki J, Aoi N, Kato H, Higashino T, Yoshimura K. Adipose tissue remodeling in lipedema: adipocyte death and concurrent regeneration. *J Cutan Pathol*. 2009;36(12):1293-1298.
189. Al-Ghadban S, Diaz ZT, Singer HJ, Mert KB, Bunnell BA. Increase in leptin and PPAR-γ gene expression in lipedema adipocytes differentiated in vitro from adipose-derived stem cells. *Cells*. 2020;9(2):430.
190. Al-Ghadban S, Pursell IA, Diaz ZT, Herbst KL, Bunnell BA. 3D spheroids derived from human lipedema ASCs demonstrated similar adipogenic differentiation potential and ECM remodeling to non-lipedema ASCs in vitro. *Int J Mol Sci*. 2020;21(21):8350.
191. Mann JP, Savage DB. What lipodystrophies teach us about the metabolic syndrome. *J Clin Invest*. 2019;129(10):4009-4021.
192. Melvin A, Stears A, Savage DB. Recent developments in lipodystrophy. *Curr Opin Lipidol*. 2019;30(4):284-290.
193. Majka SM, Miller HL, Helm KM, et al. Analysis and isolation of adipocytes by flow cytometry. *Methods Enzymol*. 2014;537:281-296.
194. Shi J, Kandror KV. Study of glucose uptake in adipose cells. *Methods Mol Biol*. 2008;456:307-315.
195. Zhu GZ, Zhang M, Kou CZ, et al. Effects of Lyrm1 knockdown on mitochondrial function in 3 T3-L1 murine adipocytes. *J Bioenerg Biomembr*. 2012;44(1):225-232.
196. Crewe C. The challenges of interrogating adipose tissue extracellular vesicle functions in physiology. *Commun Biol*. 2022;5(1):581.
197. Gomez-Serrano M, Ponath V, Preusser C, Pogge von Strandmann E. Beyond the extracellular vesicles: technical hurdles, achieved goals and current challenges when working on adipose cells. *Int J Mol Sci*. 2021;22(7):3362.
198. Blaszczak AM, Wright VP, Anandani K, et al. Loss of antigen presentation in adipose tissue macrophages or in adipocytes, but not both, improves glucose metabolism. *J Immunol*. 2019;202(8):2451-2459.
199. Weyer C, Foley J, Bogardus C, Tataranni P, Pratley R. Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. *Diabetologia*. 2000;43(12):1498-1506.
200. Xiao L, Yang X, Lin Y, et al. Large adipocytes function as antigen-presenting cells to activate $CD4^+$ T cells via upregulating MHCII in obesity. *Int J Obes*. 2016;40(1):112-120.
201. Deng T, Lyon CJ, Minze LJ, et al. Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. *Cell Metab*. 2013;17(3):411-422.
202. Lengyel E, Makowski L, DiGiovanni J, Kolonin MG. Cancer as a matter of fat: the crosstalk between adipose tissue and tumors. *Trends Cancer*. 2018;4(5):374-384.
203. Cozzo AJ, Fuller AM, Makowski L. Contribution of adipose tissue to development of cancer. *Compr Physiol*. 2017;8(1):237-282.
204. López-Lerma I, Peñate Y, Gallardo F, et al. Subcutaneous panniculitis-like T-cell lymphoma: clinical features, therapeutic approach, and outcome in a case series of 16 patients. *J Am Acad Dermatol*. 2018;79(5):892-898.

205. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;21(11):739-751.
206. Ter Poorten MC, Thiers BH. Panniculitis. *Dermatol Clin*. 2002;20(3):421-433.
207. Johnson EF, Tolkachjov SN, Gibson LE. Alpha-1 antitrypsin deficiency panniculitis: clinical and pathologic characteristics of 10 cases. *Int J Dermatol*. 2018;57(8):952-958.
208. Morgan AJ, Schwartz RA. Cutaneous polyarteritis nodosa: a comprehensive review. *Int J Dermatol*. 2010;49(7):750-756.
209. Bhat RM, Vaidya TP. What is new in the pathogenesis and management of erythema nodosum leprosum. *Indian Dermatol Online J*. 2020;11(4):482-492.
210. Crowson AN, Mihm MC Jr, Magro CM. Cutaneous vasculitis: a review. *J Cutan Pathol*. 2003;30(3):161-173.
211. Lee JT, Kalani MA. Treating superficial venous thrombophlebitis. *J Natl Compr Cancer Netw*. 2008;6(8):760-765.
212. LeBlanc RE, Tavallaee M, Kim YH, Kim J. Useful parameters for distinguishing subcutaneous panniculitis-like T-cell lymphoma from lupus erythematosus panniculitis. *Am J Surg Pathol*. 2016;40(6):745-754.
213. Requena C, Sanmartín O, Requena L. Sclerosing panniculitis. *Dermatol Clin*. 2008;26(4):501-504.
214. Greenberg AS, Hasan A, Montalvo BM, Falabella A, Falanga V. Acute lipodermatosclerosis is associated with venous insufficiency. *J Am Acad Dermatol*. 1996;35(4):566-568.
215. Polcari IC, Stein SL. Panniculitis in childhood. *Dermatol Ther*. 2010;23(4):356-367.
216. Burden AD, Krafchik BR. Subcutaneous fat necrosis of the newborn: a review of 11 cases. *Pediatr Dermatol*. 1999;16(5):384-387.
217. Dahl PR, Su WP, Cullimore KC, Dicken CH. Pancreatic panniculitis. *J Am Acad Dermatol*. 1995;33(3):413-417.
218. Delgado-Jimenez Y, Fraga J, García-Díez A. Infective panniculitis. *Dermatol Clin*. 2008;26(4):471-480.
219. Moreno A, Marcoval J, Peyri J. Traumatic panniculitis. *Dermatol Clin*. 2008;26(4):481-483.
220. Quesada-Cortés A, Campos-Muñoz L, Díaz-Díaz RM, Casado-Jiménez M. Cold panniculitis. *Dermatol Clin*. 2008;26(4):485-489.
221. Pielasinski Ú, Machan S, Camacho D, et al. Postirradiation pseudoscleroderma tous panniculitis: three new cases with additional histopathologic features supporting the radiotherapy etiology. *Am J Dermatopathol*. 2013;35(1):129-134.
222. Yanes AF, Owen JL, Colavincenzo ML. Factitial panniculitis as a manifestation of self-imposed factitious disorder. *Dermatol Online J*. 2019;25(5):1-4.
223. Marcoval J, Moreno A, Mañá J, Peyri J. Subcutaneous sarcoidosis. *Dermatol Clin*. 2008;26(4):553-556.
224. Kwon EJ, Emanuel PO, Gribetz CH, Mudgil AV, Phelps RG. Poststeroid panniculitis. *J Cutan Pathol*. 2007;34(1):64-67.
225. Tran TA, DuPree M, Carlson JA. Neutrophilic lobular (pustular) panniculitis associated with rheumatoid arthritis: a case report and review of the literature. *Am J Dermatopathol*. 1999;21(3):247-252.
226. Sutra-Loubet C, Carlotti A, Guillemette J, Wallach D. Neutrophilic panniculitis. *J Am Acad Dermatol*. 2004;50(2):280-285.

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