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Perspective

Adipocytes: Hidden forces of the immune system?

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SUMMARY

While adipocytes are majorly recognized for their role in energy homeostasis, they recently emerged as regulators of immune functions and defenders against pathogens. This poses the question of whether these lipid-laden cells constitute a currently underappreciated but integral component of our immune defenses. Here, we discuss recent evidence that adipocytes may indeed exert classical immune functions, including pathogen recognition and elimination, production of antimicrobial peptides, metabolic adaptation during infection, and antigen presentation. Positioned near portals of pathogen entry, adipocytes dynamically contribute to barrier integrity and host defense, underscoring their role as an integral and active component of the immune system.

Bruce A. Beutler, recipient of the 2011 Nobel Prize in Physiology, once said, "If we think of the immune system as a machine, then we are far from even knowing all of its parts." We think that adipocytes represent one such underappreciated part of this machine.

This perspective will highlight that (1) it is evident from evolution that the functions of adipocytes and immune cells are closely intertwined, (2) the anatomical localization of adipose tissue predisposes the adipocytes therein to fulfill innate immune barrier functions, (3) adipocytes possess intrinsic antimicrobial activity, and (4) adipocytes are important for host defense at portals of pathogen entry. All these lines of evidence suggest that adipocytes may even represent an attractive future therapeutic target to support immunity at barrier sites.

BEYOND ENERGY STORAGE: ADIPOCYTES AT THE FRONT LINE OF HOST DEFENSE?

The first and immediate protection against pathogens is provided by local resident cells. This innate immune response comprises a collection of intricately regulated alarm and defense mechanisms that act rapidly and are a prerequisite of any subsequent adaptive immune response.[1,2] Almost all nucleated cells of the body have the ability to mount an innate immune response. However, certain cell types and tissues exhibit a stronger response to the presence of pathogens and engage multiple components of the innate immune system more robustly than others. These include not only classical immune-associated cells, such as macrophages, neutrophils, or dendritic cells, but also tissue-specific cells in the skin or gut, such as keratinocytes or intestinal epithelial cells.[3,4] We propose here that adipocytes within adipose tissue may be one of the currently underappreciated constituents of our innate immune defenses.

THE ADIPOSE TISSUE(S): WHITE, BROWN, AND BEIGE

White adipose tissue (WAT) stores excess energy as triglycerides and releases it in case of increased demand. It insulates and protects the body and internal organs and has significant endocrine activity.[5] Brown adipose tissue (BAT) is marked by the expression of uncoupling protein 1 (UCP1) and has the unique capability of dissipating energy in the form of heat, a process known as non-shivering thermogenesis.[6] It is most prevalent in newborns but also detectable in adults.[7] Under certain conditions, thermogenic capacity is induced in adipocytes in WAT, which are then referred to as beige adipocytes.[7]

All adipose tissues contain lipid-filled adipocytes, stem and progenitor cells, stromal and endothelial cells, and immune cells. Adipose-resident immune cells such as monocytes and macrophages, B and T cells, granulocytes, and natural killer (NK) cells not only regulate tissue homeostasis in the healthy state but also play a crucial role in disease pathogenesis, e.g., in obesity and related comorbidities.[8,9] Adipocytes have been acknowledged as "immune hubs" that orchestrate the functions of these immune cells (reviewed in Bradley et al.[8] and Sinton and Kajimura[10]). In light of recent evidence, we think it is time to revive and advance this previous concept. We therefore propose that not only the adipose tissue and its immune cells, but specifically the adipocytes therein, represent an integral part of our innate immune defenses.

ADIPOCYTES IN IMMUNITY—AN EVOLUTIONARY PERSPECTIVE

The storage of energy in the form of triglycerides in adipose tissue or related structures is evolutionarily highly conserved.[11] For example, in insects, the so-called fat body is a multipurpose organ that provides energy but is also responsible for detoxification of the insect's body.[12] Intriguingly, the fat body represents an essential part of the insect's immune system,[13,14] highlighting a close evolutionary relationship between metabolism and host defense. Upon pathogen recognition, fat body cells, i.e., the insect equivalent of adipocytes, also referred to as trophocytes, initiate the

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production of antimicrobial peptides (AMPs; also known as host defense peptides [HDPs]) such as diptericin, defensin, or drosomycin. These lytic AMPs are subsequently released into the hemolymph, the insect's circulatory fluid, thereby mediating a systemic humoral immune response.[15,16] In mosquitos, the fat body's trophocytes were recently identified to consist of different subpopulations, including one with a specialized role in immunity and host defense.[17] Effective immune responses require substantial energetic resources. Therefore, the integration of nutrient sensing, energy storage, and immune function is likely to have provided a strong evolutionary advantage.[18] Consistent with this concept, the insulin, tumor necrosis factor (TNF), and toll-like receptor (TLR) pathways are closely intertwined and remarkably conserved from insects to mammals. This highlights an evolutionarily conserved tight link between metabolism, inflammation, and host defense (reviewed in detail in Hotamisligil[18]). Thus, from an evolutionary perspective, it is well conceivable that the adipocyte retained or even further developed its immunological role in humans.

ADIPOSE TISSUE AS AN INNATE IMMUNE BARRIER

Similar to skin, which acts as a protective barrier against external threats, WAT is strategically localized subcutaneously and around internal organs such as the gut and also surrounds lymph nodes and blood vessels. This localization predisposes it to serve as an immune barrier. Recent advances in single-nucleus RNA sequencing (snRNA-seq) have revealed distinct adipocyte subsets in adipose tissue of human and mouse origin.[19–23] Interestingly, some of these adipocyte subsets display a gene expression signature related to immune function, e.g., immune-related (innate) adipocytes with positive regulation of phagocytosis and macrophage activation, as well as immune-related (adaptive) adipocytes mediating T cell activation and adaptive immune responses.[20] Notably, a recent meta-analysis reported inconsistencies in adipocyte heterogeneity,[24] and a follow-up study noted that previously proposed adipocyte subpopulation marker genes were not suitable for clear separation of described subsets.[25] Does this put the existence of "immune-competent adipocytes" into question? We argue that it does not, and a 2026 study provides further evidence for their existence[25]: Loft et al. performed archetype analysis,[25] a bioinformatic method that models transcriptional states as combinations of a small number of extreme reference states ("archetypes"), thereby uncovering underlying biological programs and continuous cell-state transitions. They identified three archetypical states of adipocytes, with one of them being linked to inflammatory signaling.[25] It is important to note that a universally accepted definition of adipocyte subtypes is currently lacking, and ongoing advances in single-cell and spatial technologies will likely refine our current understanding of adipocyte heterogeneity. A key limitation of snRNA-seq studies is that their conclusions are largely based on transcriptomic signatures only, and formal proof of the functional relevance of specific adipocyte subtypes is often lacking. Nevertheless, they point toward the existence of specialized adipocyte populations, including putative immune-competent adipocytes[19–23,25] supporting our concept of adipocyte immunity at pathogen entry sites.

INTRINSIC IMMUNITY: PHAGOCYTOSIS AND AUTOPHAGY IN ADIPOCYTES

Innate immunity includes a collection of ancient cell-intrinsic, non-cytokine-mediated defense mechanisms, among them phagocytosis and autophagy.[26–28] Phagocytosis is an important host defense strategy and promotes detection of pathogens (reviewed in Moretti and Blander[29]). The multi-step process of phagocytosis begins with recognition and binding of the target followed by engulfment and eventually the formation of phagosomes.[30] The phagosome then matures and fuses with lysosomes, forming a phagolysosome where enzymatic degradation of the ingested material occurs.[30] Finally, digested components are either recycled or expelled from the cell.

Professional phagocytes include macrophages, neutrophils, and dendritic cells, which engulf and digest pathogens and cellular debris, helping to clear infections and maintain tissue integrity.[30] Interestingly, there are also non-professional phagocytes such as fibroblasts or epithelial or endothelial cells.[31,32] It has been described years ago that mammalian adipocyte precursor cells possess phagocytic activity *in vitro* and *in vivo*.[33,34] Activation of PPARγ, a bona fide marker of adipogenesis, inhibited phagocytic activity in murine 3T3-L1 cells,[35] suggesting that phagocytic capacity decreases during adipogenic differentiation. Interestingly, a recent study in *Drosophila* showed that fat body cells, the insect's adipocytes, migrated to sites of tissue injury and removed debris by phagocytosis,[36] indicating that mature adipocytes can, in principle, perform phagocytosis. Convincing functional evidence of phagocytosis by mature mammalian adipocytes, however, is still lacking. Thus, future studies are needed to determine whether adipocyte phagocytosis is conserved across species.

Whereas phagocytosis ensures host defense by engulfing and destroying extracellular microbes, macroautophagy (hereafter autophagy) complements phagocytosis in innate immunity by targeting intracellular pathogens or their components for lysosomal degradation.[27,37] Peptides generated from microbial components during autophagy are additionally presented to adaptive immune cells as microbial antigens. During autophagy, cytoplasmic cargoes, i.e., the cellular materials marked for degradation, are engulfed by double-membraned vesicles, termed "autophagosomes."[38] In selective autophagy, cargoes are recognized by dedicated autophagy receptors such as the ubiquitin-binding protein SQSTM1/p62 or Optineurin (OPTN).[39] Finally, the autophagosome fuses with a lysosome, leading to degradation of the cargo by lysosomal proteases and hydrolases and release of the degraded material as recycled nutrients back into the cytoplasm. That autophagy plays a crucial role as host defense mechanism is further illustrated by the fact that many pathogens have evolved ways to block autophagy, escape autophagosomes, and hijack autophagy mechanisms to ensure their own replication.[37,40–43]

Autophagy is essential for adipogenesis as demonstrated in mouse models with adipocyte-specific deletion of the autophagy core machinery gene *Atg7*.[44,45] Furthermore, autophagy has been identified as protective factor in WAT remodeling in mice with inducible adipocyte-specific knockout of *Atg7* under diet-induced obesity.[46] Here, loss of adipocyte

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autophagy substantially exacerbated fibrosis in visceral WAT.[46] Autophagy is upregulated during obesity in murine and human WAT, where it might function to limit inflammation as demonstrated in human Simpson-Golabi-Behmel syndrome (SGBS) adipocytes and adipose tissue explants.[47] Adipocyte autophagy also plays a role in regulating inflammation in adjacent organs. For example, intestinal inflammation caused increased autophagy in neighboring adipocytes, which, in turn, produced anti-inflammatory interleukin (IL)-10.[48] In line, adipocyte-specific loss of the autophagy gene *Atg7* resulted in increased gut inflammation in mice *in vivo*.[48] Thus, adipocytes are equipped with the autophagic machinery and use it to control inflammation in their vicinity. While the role of autophagy in innate immunity and pathogen defenses is very well established in various cell types and models,[37,40] it is currently unknown whether adipocytes specifically use autophagy to combat microbial infections. Comprehensive future functional studies are needed to close this gap.

INNATE IMMUNITY: INDUCTION OF CYTOKINE-MEDIATED DEFENSES IN ADIPOCYTES

One core function of innate immunity is the recognition of non-self moieties, usually pathogens, leading to the secretion of cytokines, which alarm adjacent cells or tissues to initiate the immune response.[1,49] A number of different microbes can infect adipocytes. Among them are bacteria, such as *Mycobacterium tuberculosis*,[50,51] *Mycobacterium abscessus*,[52] *Staphylococcus aureus* (*S. aureus*),[53] *Listeria monocytogenes* (*L. monocytogenes*),[54] and *Chlamydia pneumoniae*[55]; viruses like SARS-CoV-2[56–60] or influenza A virus (IAV)[59]; and parasites, such as *Leishmania infantum*[61] or *Trypanosoma cruzi*.[62] During infection with bacteria, viruses, and parasites, pathogen recognition occurs via specialized pattern-recognition receptors (PRRs).[63] PRRs include TLRs, NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs).[64–66] PRRs are activated by pathogen-associated molecular patterns (PAMPs), which represent microbe-specific structural motifs. Sensing of these patterns allows innate immunity to recognize even previously unknown pathogens. Recognition of pathogens by PRRs eventually activates diverse transcription factors, including interferon-regulatory factors (IRFs), nuclear factor kappa B (NF-κB), and activator protein-1 (AP-1), leading to the production of alarming pro-inflammatory cytokines, among them prominently interferons (IFNs). Binding of these cytokines to the releasing cell (autocrine) or to neighboring cells (paracrine) elicits a transcriptional program that sets the cells effectively in an antimicrobial/antiviral state, and recruits cells of the adaptive immune system.

Activation of PRRs like NLRs or absent in melanoma 2 (AIM2)-like receptors (ALRs) causes the formation of a multiprotein complex in the cytoplasm termed inflammasome.[63] Inflammasomes are activated by diverse signals, including potassium efflux, reactive oxygen species (ROS), and lysosomal damage. Within the ALR family, AIM2 is a DNA sensor that detects cytoplasmic double-stranded DNA derived from viruses or intracellular bacteria.[63] Inflammasome assemblies eventually result in the activation of pro-caspase-1 that processes IL-1β and IL-18, which are then secreted.[63,67] Furthermore, the inflammasome also drives pyroptosis, a lytic and highly inflammatory form of programmed cell death, aimed at eliminating infected or damaged cells to limit pathogen spread.[68]

The knowledge on the role of PRRs in pathogen sensing in adipocytes is incomplete. Lipopolysaccharide (LPS) and Pam3CSK4 stimulation induced an inflammatory program in adipose tissue explants and primary *in vitro*-differentiated human adipocytes,[69,70] arguing for the presence of active TLRs. Indeed, TLRs, which tend to be expressed on more specialized innate immune cells like macrophages or dendritic cells, have been detected in 3T3-L1 and primary adipocytes.[71–74] Caputa et al. found that the expression of nuclear-binding oligomerization domain 1 (NOD1), an intracellular PRR of the NLR family, was induced by IFN-γ and served as a sensor for *L. monocytogenes* in perinodal adipocytes *ex vivo* and in 3T3-L1 adipocytes *in vitro*.[54] NOD1 synergized with IFN-γ to promote the expression of inducible nitric oxide synthase (iNOS), an enzyme responsible for the production of nitric oxide (NO), a free radical with potent antimicrobial activity.[54] These findings support the concept that adipocytes not only contribute to systemic defense mechanisms mediated by the immune system but also actively fight microbes by, e.g., NO production.[54]

While sensing of microbes by adipocytes has often been neglected in the past, the role of PRRs in metabolic disturbances is well documented.[75] The expression of several PRRs was found upregulated in WAT in obesity.[75] TLR4, for example, plays a causal role in obesity-induced adipose inflammation and insulin resistance.[76] This suggests that innate immune and metabolic functions are closely intertwined. Acute insulin resistance and hyperglycemia are part of the acute phase reaction during sepsis[77]: instead of storing energy substrates in WAT, they stay in the circulation and are rerouted toward usage by immune cells.

In summary, these hints suggest that adipocytes express functional PRRs, including TLRs, which are often restricted to specialized innate immune cells. This is an important prerequisite to raising a cytokine/secretome-mediated innate immune alarm during host defense.

THE ADIPOCYTE'S SECRETOME IN HOST DEFENSE

The secretome plays a crucial role in innate defense by raising an alarm both locally and systemically, thereby regulating inflammation and coordinating the host's defense mechanisms against pathogens. Adipocytes are highly secretory cells producing and secreting many different factors, including cytokines, chemokines, IFNs, growth factors, hormones, lipids, and other metabolites such as free fatty acids (FFAs).[5,78] In primary murine mature adipocytes, for example, LPS stimulation induced secretion of IFN-β and activation of the IFN/IFN-α receptor (IFNAR) axis, uncovering a dormant gene expression profile similar to inflammatory myeloid cells.[79] The production of AMPs is an efficient host defense mechanism to restrict local pathogen growth.[80] Adipocytes were shown to produce AMPs such as, for example, cathelicidin in response to infection with *S. aureus* *in vivo* and in 3T3-L1 cells during adipogenesis *in vitro*.[81] In addition, adipocytes represent a huge source of extracellular vesicles (EVs).[5] Their cargo not only includes proteins, nucleic acids, and metabolites but also microRNAs (miRNAs), which are

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an integral part of the host immune response to infection,[82] or mitochondria.[83] Different cell-derived factors enhancing the phagocytosis of pathogens, such as complement proteins, extracellular matrix proteins, sphingosine-1-phosphate (S1P), and fractalkine (also known as CX3CL1),[84] are well-known secretion products of adipocytes.[5,85] This further suggests that adipocytes—via their secretion products—may enhance the phagocytic activity of neighboring (immune) cells.

That adipocytes modulate immunity via the secretion of pro- and anti-inflammatory cytokines and chemokines, which are also secreted from other cells, is well documented and reviewed elsewhere.[10] Here, we will focus on adipocyte-specific proteins and secretion products with immune-modulating or direct antimicrobial activity.

Adipocyte-specific immune modulators

Besides secreting well-known antimicrobial cytokines, chemokines, and peptides, adipocytes may be capable of more adipocyte-specific immune responses. It has been known since the late 1990s that the adipokine leptin regulates T cell proliferation and cytokine production and can counteract starvation-induced immunosuppression, connecting its crucial role in the regulation of metabolism with immune function.[86] Therefore, it is not surprising that leptin plays an important role in host protection against gram-negative bacteria, as underlined by leptin-deficient *ob*/*ob* mice[87] being prone to LPS-induced lethality.[88] C57BL/6J mice homozygous for the diabetes spontaneous mutation in the leptin receptor gene (Lep^{db}; *db*/*db* mice) are prone to chronic infection with *S. aureus*.[89] *In vitro*, neutrophils from *db*/*db* mice showed a diminished respiratory burst upon stimulation with *S. aureus*.[89] Mechanistically, leptin was shown to modulate production of anti-inflammatory IL-1 receptor antagonist (IL-1Ra) in RAW 264.7 murine macrophages *in vitro*.[88] In addition, leptin was reported to enhance phagocytosis of THP-1 cells and peripheral blood mononuclear cells infected with *Leishmania donovani*.[90] Leptin reverses starvation-induced compromised host defense against *Streptococcus pneumoniae*,[91] is essential to fight lung infections with *Klebsiella pneumoniae*, and alveolar macrophages from leptin-deficient *ob*/*ob* mice exhibited impaired phagocytosis of opsonized *Klebsiella pneumonia in vitro*.[92] Furthermore, leptin enhanced IL-1β-induced production of the AMP human beta-defensin-2 (hBD-2) in keratinocytes,[93] suggesting that leptin secretion by adipocytes supports local control of infection by neighboring cells.

Leptin is also important for viral host defense. Leptin-deficient (*ob*/*ob*) mice, but not mice with diet-induced obesity, had a higher mortality rate after severe influenza infection, which was fully reversed by exogenous leptin supplementation leading to an improved Th1 antiviral systemic response.[94] Both *ob*/*ob* mice with and without exogenous leptin supplementation showed equal viral clearance, suggesting that the antiviral immunity in *ob*/*ob* mice was not severely compromised.[94] Instead, the authors suggested that leptin may be essential for maintenance of heart rate and body temperature upon severe viral infection.[94]

Although crucial for host defense against bacteria and viruses,[89,91,92,94] leptin seems to have detrimental effects in malaria. Mice deficient in leptin or its receptor showed a survival advantage in experimental cerebral malaria.[95] Furthermore, leptin production in subcutaneous WAT was higher in patients with cerebral malaria than in patients without during infection with *Plasmodium falciparum*.[96]

Adiponectin, an adipokine that circulates at high levels in healthy, lean subjects and is downregulated in the obese state, is well known for its anti-inflammatory properties.[5] Adiponectin-deficient mice showed attenuated clearance of *L. monocytogenes*, and adiponectin treatment restored emergency granulopoiesis and bacterial clearance in adiponectin-deficient mice.[97] Increased mortality and fungal load were observed after lung infection with *Aspergillus fumigatus* in adiponectin-deficient mice in a neutropenic model of invasive aspergillosis with upregulation of TNF in alveolar macrophages,[98] further demonstrating a crucial role of adiponectin in host defense. Mechanistically, adiponectin stimulates fungal killing in alveolar macrophages by LC3-associated phagocytosis.[99] In contrast to beneficial effects in bacterial or fungal infections, adiponectin might have a detrimental role in the defense against viruses. Adiponectin-deficient mice displayed stronger immune responses upon infection with Coxsackievirus B3 (CVB3), and reconstitution with adiponectin suppressed innate antiviral immunity, promoting CVB3-myocarditis.[100] In line, elevated adiponectin levels predicted the severity of hepatitis B virus-induced liver disease.[101] By contrast, low adiponectin levels were linked to severe disease outcome in patients with SARS-CoV-2 infection.[102]

Taken together, adipocytes, like other cells, secrete inflammatory cytokines, AMPs, and cytotoxic molecules. In addition, however, they release adipocyte-specific leptin and adiponectin, which not only shape the function of immune cells but also integrate important metabolic information about the body's energy stores and insulin sensitivity.[5]

FEED A COLD, STARVE A FEVER? METABOLIC IMMUNITY MEDIATED BY ADIPOCYTES

Energy and nutrient availability are needed to sustain effective immune responses. However, increased energy availability does not uniformly enhance host defense. A prototype example here is patients with obesity who present with an energy surplus but still remain more vulnerable to a broad range of infections.[103–106] In line, interference with infection-induced anorexia[107] through energy supplementation can worsen clinical outcomes of certain infections in mice.[108,109] Starvation was shown to induce antimicrobial autophagy *in vitro*,[110] prompting the notion that systemic autophagy-mediated defenses may be activated, e.g., by dieting. However, caloric restriction may have both beneficial and adverse effects.[111] Accumulating evidence indicates that the impact of energy availability on host defense is context-dependent, varying with both the pathogen and the dominant metabolic substrate. In mice, fasting metabolism was protective during infection with the bacterium *L. monocytogenes* but harmful during influenza virus infection.[112] In this study, glucose prevented damage to the brain during viral infection, whereas glucose absence limited ROS-induced brain damage during bacterial

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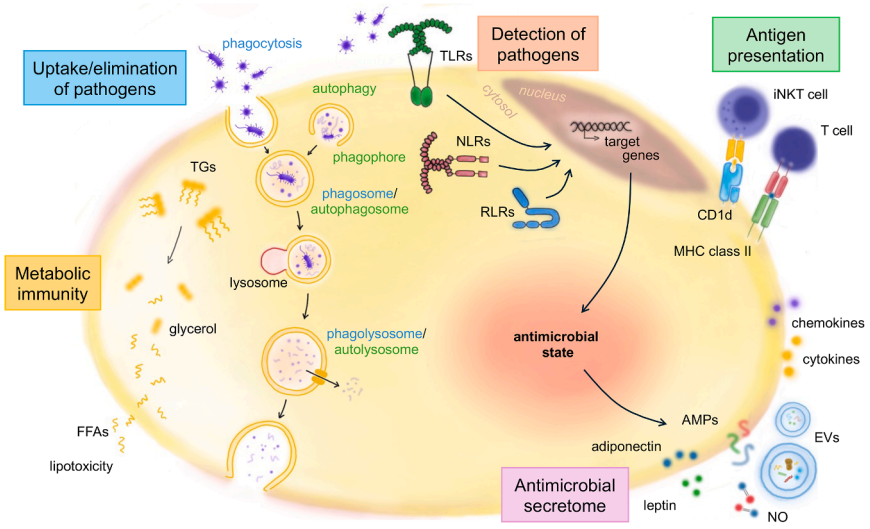

Figure 1. Immune functions of adipocytes

Adipocytes detect pathogens via pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs); may take up and eliminate pathogens by phagocytosis/autophagy; provide metabolic immunity by, e.g., breakdown of triglycerides (TGs) into glycerol and free fatty acids (FFAs); or fight infections with their antimicrobial secretome containing cytokines, chemokines, antimicrobial peptides (AMPs), nitric oxide (NO), adipocyte-specific immune modulators such as leptin and adiponectin, and extracellular vesicles (EVs). The adaptive immune system is activated by adipocytes presenting antigens via cluster of differentiation (CD)1d or major histocompatibility complex (MHC) class II molecules.

infection,[112] suggesting that specific metabolites can differentially shape antimicrobial immunity.

Metabolism is tightly coupled to innate immunity, as effective host defense requires metabolic adaptation.[113] Whereas an effective metabolic response is required for host defense, microbes also benefit from active host metabolism.[114] Adipocytes are central to the regulation of whole-body metabolism and rich in building blocks such as lipids, which they release upon increased energy demand. Thus, these cells may represent an integral component of metabolic immunity, i.e., the reprograming of the host metabolism to restrict metabolic building blocks for pathogen growth.[115] But can lipolysis, i.e., the breakdown of triglycerides into FFAs and glycerol, be regarded as a host defense mechanism of adipocytes? FFAs are described as highly active antimicrobial agents in human skin, produced by sebaceous glands via lipolysis.[116] They exert their function on bacterial metabolism via inhibition of metabolic enzymes or nutrient uptake, by disrupting the electron transport chain, or by (auto)lysis of bacteria (summary in Desbois and Smith[116]). The contribution of adipocytes to antimicrobial defense by FFAs is not well studied. Adipocyte lipolysis protected against infection with Trypanosoma brucei, a parasite causing sleeping sickness in humans, as demonstrated in a mouse model with adipocyte-specific deletion of adipose triglyceride lipase (ATGL).[117] Of note, *Trypanosoma brucei* can adapt to the lipid-rich environment in WAT and change its metabolism to fatty acid β-oxidation.[118] Other reports suggest that host fatty acids are hijacked by microbes to fuel their survival and replication.[119,120] Proliferation of *Chlamydia pneumoniae* within 3T3-L1 adipocytes *in vitro*, for example, is dependent on fatty acid binding protein (FABP) 4 and hormone sensitive lipase (HSL)-mediated lipolysis.[55] Lipid droplets are increasingly recognized as important compartments required for efficient flavi virus infection, suggesting that these viruses hijack lipid metabolism.[121] The synthesis of fatty acids via fatty acid synthase (FASN) propagates infection with SARS-CoV-2, and orlistat, an inhibitor of FASN, resulted in lower SARS-CoV-2 virus concentrations in the lungs, reduced lung pathology, and increased survival rates of infected mice.[122] In line, lipase inhibitors protected mice from lethal IAV infection and mitigated severe lung lesions in SARS-CoV-2-infected hamsters, underlining the importance of lipolysis for viral propagation.[123]

Thus, lipolysis and the release of FFAs may represent one additional mechanism of how adipocytes modulate immunity against microbial infection (Figure 1).

ANTIGEN PRESENTATION BY ADIPOCYTES—LINKING INNATE AND ADAPTIVE IMMUNITY

Most specialized innate immune cells present antigens, e.g., microbial peptides, to adaptive immune cells to activate adaptive defenses. Whereas the antigen-presenting major histocompatibility complex (MHC) class I molecules are expressed on the surface of all nucleated cells,[124] MHC class II molecules are typically expressed by professional antigen-presenting cells (APCs) such as dendritic cells, macrophages, or B cells.[124] In addition, so-called non-professional APCs such as endothelial or epithelial cells as well as fibroblasts also express MHC class II molecules.[125] Interestingly, adipocytes of mice on high-fat diet (HFD) start to express MHC class II and the co-stimulatory molecules cluster of differentiation (CD) 80 and 86.[126] Upregulation of MHC class II and CD86 especially occurs in large adipocytes from mice on HFD, suggesting that hypertrophic adipocytes activate T cells, thereby aggravating WAT inflammation during obesity.[127]

Of note, in contrast to MHC molecules, CD1 molecules present lipid antigens. CD1 molecules present endogenous as well as microbial lipids to CD1-restricted T cells, which play a crucial role at the interface of innate and adaptive immunity.[128] Among the CD1 family, CD1d is expressed by primary murine adipocytes *ex vivo* and in 3T3-L1 adipocytes *in vitro* and activates invariant NK T (iNKT) cells, a specialized subset of CD1-restricted T cells.[129] Lipid antigen presentation by adipocytes via CD1d is causative for WAT inflammation and insulin resistance, as demonstrated in mouse models with adipocyte-specific deletion of CD1d.[130] More recently, a landmark study by Caputa and colleagues revealed that CD1d-mediated lipid antigen presentation also occurs during perinodal adipocyte infection with *L. monocytogenes*, underlining the immunological

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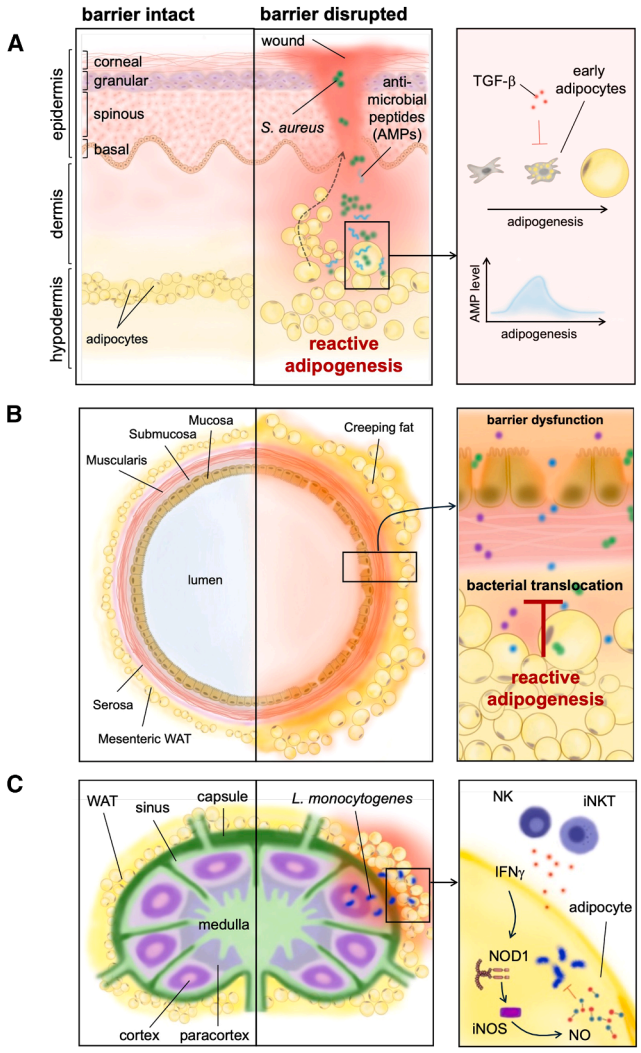

Figure 2. Adipocytes in host defense at barrier sites

(A) In healthy skin, adipocytes form part of the hypodermis. Wounded skin predisposes to infection with, e.g., *S. aureus*, leading to inflammation and reactive adipogenesis. Adipocytes enter the wound bed to support granulation and barrier integrity. Furthermore, adipocytes secrete antimicrobial peptides (AMPs) to contain and fight the infection. During reactive adipogenesis, which is inhibited by transforming growth factor (TGF)-β, AMP levels are highest in early adipocytes.

(B) Barrier dysfunction during Crohn's disease (CD) leads to bacterial translocation. Reactive adipogenesis, also known as creeping fat in CD, occurs to prevent systemic spread of the infection.

(C) Adipocytes surrounding lymph nodes contribute to host defense against *L. monocytogenes* (*Lm*). IFN-γ secreted by natural killer (NK) and invariant NK T (iNKT) cells induces expression of nuclear-binding oligomerization domain 1 (NOD1) following infection with *Lm.* Activation of NOD1, in turn, leads to production of nitric oxide (NO) via inducible nitric oxide synthase (iNOS) to fight the infection.

relevance of lipid antigen presentation by adipocytes via CD1d in the context of infection.[54] Together, these findings demonstrate that adipocytes can function as APCs during WAT inflammation and infection.

In summary, adipocytes possess the essential machinery for microbial uptake, sensing, and elimination, supported by a unique secretome that enables them to initiate immune responses, directly eliminate pathogens, and regulate metabolic immunity. Furthermore, in certain contexts, adipocytes function as APCs (Figure 1).

ADIPOCYTE IMMUNITY AT BARRIER SITES

Adipocytes in skin immunity

As a barrier tissue, the skin protects the body against external threats, including thermal or mechanical trauma, UV light damage, and microbial infection.[131] Human skin is composed of different layers (Figure 2A). The epidermis—from top to bottom—comprises the corneal, granular, spinous, and basal layers.[131] Keratinocytes originate from the basal layer and constitute the most numerous cell type in the epidermis. The dermis, localized underneath the epidermis, is a layer of dense connective tissue and the home of the sweat glands, hair follicles, sensory neurons, and blood vessels.[131] The deepest skin layer is called hypodermis and comprises the subcutaneous adipose tissue (SAT).

The skin is colonized by different microorganisms, which constitute the skin microbiome, including not only harmless or even beneficial commensal bacteria but also harmful pathogenic microorganisms.[132] That adipocytes actively participate in host defense against invading bacteria is illustrated by a number of studies. Fat body cells, the insect's adipocytes, for example, actively migrate to injuries, where they seal the wound. They help hemocytes, the insect's macrophages, to clear the wound of debris and release AMPs directly at the site of injury to fight microbial infection.[36]

During wound healing in mice, adipocytes were shown to enter large wound beds and form granulation tissue,[133,134] suggesting that adipocytes actively participate in the maintenance of skin barrier integrity. Furthermore, following skin injury in mice, adipocyte lipolysis initiated macrophage recruitment and inflammation necessary for subsequent repair, as shown in a mouse model with adipocyte-specific deletion of ATGL.[135] This shows that adipocytes regulate wound healing via lipolysis.

If the barrier function of the skin is compromised, *S. aureus* can turn from a commensal into a pathogen causing not only severe skin and soft tissue infections but also organ abscesses, pneumonia, and sepsis.[136] Differentiating dermal adipocytes were shown to possess direct antimicrobial activity against *S. aureus*.[81] This was illustrated in a landmark study in mice, in which skin infection with *S. aureus* resulted in rapid proliferation of preadipocytes and expansion of the dermal fat layer.[81] The differentiating adipocytes within produced the AMP cathelicidin, thereby inhibiting bacterial growth.[81] When adipogenesis was impaired by genetic or pharmacological inhibition, cathelicidin expression was diminished and bacterial infection enhanced.[81] Thus, the production of AMPs by local resident cells such as adipocytes is an important mechanism to restrict the pathogen. The same group showed that this defense mechanism called reactive adipogenesis might be compromised in people with obesity, as adipocyte precursors were lost from the dermis of mice on HFD, resulting in decreased AMP production and enhanced susceptibility to *S. aureus* infection.[137] Interestingly, the antimicrobial defense function of adipocytes seems to be restricted to early stages of adipogenesis and lost in mature hypertrophic adipocytes.[137] Reactive adipogenesis and the production of cathelicidin following skin infection with *S. aureus* were further identified to be highest in the neonatal skin

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of mice and humans and are gradually lost during aging.[138] Since transforming growth factor (TGF)-β inhibited reactive adipogenesis during obesity and aging, inhibitors of TGF-β were proposed as a potential future therapeutic option to restore adipocyte immunity in the skin.[137,138]

Adipocytes in gut immunity

The visceral adipose tissue in close proximity to the intestines is represented by the mesenteric and omental depots and the appendices epiploicae attached to the outside of the colon.[139] The epiploic WAT is enriched in a subtype of adipocytes expressing serum amyloid A1 and 2 (*SAA1* and *SAA2*), referred to as adipo^{SAA}.[140] SAA proteins are produced in response to inflammation or infection.[141] Of note, LPS upregulated *SAA1* and *SAA2* expression in adipocytes but not in other cell types.[140] SAA1, in turn, promoted immune responses in tissue-resident myeloid cells.[140] This suggests that adipocytes act as danger sensors at the gut barrier, initiating an immune alarm in response to tissue damage or infection. The omentum, a cushion-like fold of the peritoneum descending from the stomach and covering the abdominal organs, contains the omental adipose tissue. The mesenteric adipose tissue is located within the mesentery, a fold of the peritoneum that anchors the intestines and contains the supplying blood and lymphatic vessels, as well as nerves. The intestinal barrier allows the absorption of nutrients and immune sensing while restricting the entry of pathogens.[142] Intestinal barrier defects are causative for a broad range of gastrointestinal diseases, including celiac disease and inflammatory bowel disease (IBD).[142]

Mesenteric WAT has been suggested to form part of the intestinal barrier.[143] The ability of adipocytes to respond to inflammatory stimuli was shown to be essential for mesenteric adipose tissue expansion and the prevention of microbial translocation in mice *in vivo*.[143] Reactive adipogenesis as observed during bacterial skin infection[81,137,138] also occurred in mesenteric adipose tissue and the intestinal submucosal layer in a mouse model of DSS-induced colitis.[144] This suggests that reactive adipogenesis is a common innate immune defense mechanism in barrier tissues. An extreme manifestation of reactive adipogenesis is the formation of creeping fat (CrF) in patients with Crohn's disease (CD). CrF refers to the expansion of mesenteric WAT that wraps around inflamed segments of the intestine, primarily in the ileum.[145] CrF has long been recognized as a hallmark yet enigmatic feature of CD.[146] In 2020, a seminal study demonstrated that CrF represents a protective response, whereby mesenteric WAT expands toward sites of intestinal barrier dysfunction to limit the systemic dissemination of potentially harmful microbes translocating from the gut lumen[145] (Figure 2B). While bacterial translocation to mesenteric WAT was shown to occur frequently, the bacterial specimens within CrF in patients with CD are dominated by *Clostridium innocuum*, which has been implicated in driving CrF formation as a mechanism to contain infection and prevent its systemic spread.[145]

Adipocyte-mediated host defense around lymph nodes

Lymph nodes belong to the body's lymphoid organs, such as the thymus, the spleen, and the tonsils.[147] Throughout our body, lymphatic vessels and lymph nodes are surrounded by adipose tissue. The emerging bidirectional relationship between lymphatics and adipose tissue (dys)function has just recently been summarized in the context of obesity.[148] The lymph contains tissue fluid, immune cells, antigens, proteins, and lipids. Lymph nodes have the shape of a kidney and comprise—from inside to outside—the medulla, the cortex divided into paracortex and outer cortex comprising the T cells and B cells, respectively, the subscapular sinus, and the capsule[147] (Figure 2C). The lymph nodes' primary function is filtering the lymph, whereby the antigens contained in it are presented via APCs to the B and T cells within the lymph node, leading to their activation and proliferation to initiate an adaptive immune response.[147] Owing to their filtering function, lymph nodes are frequently exposed to microbial pathogens, which can lead to infection and subsequent swelling, a condition referred to as lymphadenitis.

Adipocytes surrounding lymph nodes, also known as perinodal adipose tissue (PAT), undergo lipolysis during infection and are an important energy source for immune cells during host defense.[149,150] Recent work extended the function of adipocytes within PAT from sole energy supply to active host defense during infection with *L. monocytogenes in vivo*[54] (Figure 2C). Here, the activation of NOD1 by *L. monocytogenes*, together with IFN-γ secretion of infiltrating NK and iNKT cells, led to metabolic reprogramming of infected adipocytes.[54] This, in turn, resulted in NO production by adipocytes via iNOS to support local control of the infection as shown in 3T3-L1 and primary *in vitro*-differentiated murine adipocytes.[54] Similar findings were observed when mice were infected with *S. aureus*,[54] suggesting NO production to be a general defense mechanism of adipocytes.

Lipomatosis of the lymph node, i.e., the replacement of lymph node parenchyma by adipocytes, is commonly observed during aging. It is suggested that this fat accumulation contributes to the decreased immune function in the elderly.[151] Given that perinodal adipocytes actively contribute to host defense,[54] we raise the question of whether adipose tissue accumulation represents not a cause but rather a consequence of declining immunity, potentially serving as a compensation mechanism of the body—analogous to CD, where CrF is thought to limit microbial spread.[145]

In summary, the skin, gut, and lymph nodes represent critical portals of potential pathogen entry. Adipocytes strategically located near these sentinel tissues have emerged as dynamic contributors in sustaining barrier integrity and host defense, uncovering their integral role in immune protection.

CONCLUDING REMARKS, OPEN QUESTIONS, AND FUTURE DIRECTIONS

Recent literature supports the existence of specialized subsets of adipocytes with immune function.[19–23] Here, we presented accumulating evidence that adipocytes have a surprisingly large arsenal of defense strategies against pathogens at their disposal. In addition, these cells are strategically localized underneath the skin and around the lymph nodes and inner organs to provide an additional layer of barrier immunity. It will be important to determine if specialized immune-competent adipocytes are enriched in certain adipose tissue depots, and whether spatial transcriptomics can localize them near sites of direct microbial contact within barrier tissues as shown in Jalkanen et al.[140] The respiratory epithelium of the lungs is another critical barrier that protects the body from airborne pathogens. Initial

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evidence indicates that adipose tissue regulates viral[59] and bacterial[152] lung infections, and that adipocytes are present in the outer wall of large airways, particularly in individuals with obesity[153] or idiopathic pulmonary fibrosis.[154] While these findings indicate a potential role for adipocytes in lung immunity, the underlying molecular mechanisms regulating the adipose tissue increase in close proximity to the airways remain unclear.

Lipodystrophy, which is characterized by the absence or loss of adipose tissue, is associated with an increased risk of serious infections resulting in hospitalization.[155] On the other hand, obesity with its excessive accumulation of WAT is also a risk factor for infection and infection-related mortality across diverse types of pathogens.[156] This may seem contradictory; however, obesity causes a dysfunction of WAT.[157] Thus, it is not the sheer mass of WAT that matters for appropriate host defense but rather the presence of healthy and fully functional adipocytes. However, there are many parameters which remain unknown. Future studies are direly needed to learn not only how age, sex, body weight, WAT distribution, and weight loss but also diets, lifestyles, medications, or diseases impact the immune function of adipocytes.

Despite the emerging evidence that adipocytes may play an underappreciated role in host defense, many questions remain open. Does infection-induced WAT remodeling lead to an increase specifically in immune-competent adipocytes? Are specific subtypes of adipocytes responsible for reactive adipogenesis? Or can all adipocytes develop into immune-competent adipocytes under certain conditions? Do adipocytes shape host defense by the release of certain metabolites, such as FFAs, lactate, etc.?[158] "Cellular memory" has emerged across diverse cell types as the ability of cells to intrinsically retain information about a transient stimulus, thereby influencing their subsequent state or response.[159,160] Infections and other environmental challenges, for example, can induce long-lasting reprogramming in immune but also non-immune cells.[161–163] This raises the question of whether microbial infection may likewise leave a persistent molecular imprint on adipocytes that shapes their response to subsequent encounters. This possibility is particularly intriguing given recent evidence that adipocytes preserve an epigenetic memory of obesity even after substantial weight loss.[164]

The most burning question, though, is if and how the immune competence of adipocytes could be exploited therapeutically. It seems very intuitive to target local adipocytes and enhance their antimicrobial activity in, e.g., difficult-to-treat skin infection. Different strategies are conceivable, among them activation of preexisting immune-competent adipocytes, stimulation of *de novo* formation or increase of immune-competent adipocytes, or local delivery of adipocytes. Of note, adipose-derived stromal cells are already tested in clinical studies.[165] Depending on the clinical condition, both delivery and selective elimination of (over)reactive immune-competent adipocytes may be useful. Beyond reacting to microbial threats such as bacteria and viruses, the immune competence of adipocytes might also be exploited against internal dangers such as cancer.

We can't wait to see the next developments in this exciting field!

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AUTHOR CONTRIBUTIONS

Conceptualization, J.Z. and P.F.-P.; visualization, J.Z.; writing – original draft: all authors; writing – review & editing: all authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (GPT-5, Open AI) for literature research and wording suggestions during the writing process. The authors reviewed and edited the output as needed and take full responsibility for the content of the published article.

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