VIEWPOINT

# From fat storage to immune hubs: the emerging role of adipocytes in coordinating the immune response to infection

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Adipose tissue is a rich source of diverse cell populations, including immune cells, adipocytes and stromal cells. Interactions between these different cell types are now appreciated to be critical for maintaining tissue structure and function, by governing processes such as adipogenesis, lipolysis and differentiation of white to beige adipocytes. Interactions between these cells also drive inflammation in obesity, leading to an expansion of adipose tissue immune cells, and the secretion of proinflammatory cytokines from immune cells and from adipocytes themselves. However, in evolutionary terms, obesity is a recent phenomenon, raising the question of why adipocytes evolved to express factors that influence the immune response. Studies of various pathogens indicate that adipocytes are highly responsive to infection, altering their metabolic profiles in a way that can be used to release nutrients and fuel the immune response. In the case of infection with the extracellular parasite *Trypanosoma brucei*, attenuating the ability of adipocytes to sense the cytokine IL-17 results in a loss of control of the local immune response and an increased pathogen load. Intriguingly, comparisons of the adipocyte response to infection suggest that the immune responses of these cells occur in a pathogen-dependent manner, further confirming their complexity. Here, with a focus on murine adipose tissue, we discuss the emerging concept that, in addition to their canonical function, adipocytes are immune signalling hubs that integrate

**Abbreviations**

AdipoR1, adiponectin receptor 1; ATGL, adipose triglyceride lipase; BAT, brown adipose tissue; Breg, B regulatory cell; C3, complement component 3; CCL12, chemokine (C-C motif) ligand 12; Ccl6, chemokine (C-C motif) ligand 6; Ccl8, chemokine (C-C motif) ligand 8; Ccl9, chemokine (C-C motif) ligand 9; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; cDC1, conventional dendritic cell type 1; cDC2, conventional dendritic cell type 2; CXCL10, C-X-C motif chemokine 10; Cxcl12, C-X-C motif chemokine 12; FFA, free fatty acid; GDF15, growth/differentiation factor 15; gWAT, gonadal white adipose tissue; HIV, human immunodeficiency virus; HSL, hormone-sensitive lipase; IAV, influenza A virus; IFNγ, interferon gamma; IL-10, interleukin 10; IL-12, interleukin 12; IL-13, interleukin 13; IL-17A, interleukin 17A; IL-17F, interleukin 17F; IL-17RA, interleukin 17 receptor A; IL-17RC, interleukin 17 receptor C; IL-1β, interleukin 1B; IL-22, interleukin 22; IL-23, interleukin 23; IL-33, interleukin 33; IL-35, interleukin 35; IL-4, interleukin 4; IL-5, interleukin 5; IL-6, interleukin 6; IL-8, interleukin 8; ILC, innate lymphoid cell; ILC2, group 2 innate lymphoid cell; iNKT, invariant natural killer cell; LPS, lipopolysaccharide; SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2; scWAT, subcutaneous white adipose tissue; TGF-β, transforming growth factor beta; TGF-β1, transforming growth factor beta 1; T$_H$17, T helper 17 cell; T$_H$2, T helper 2 cell; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; TLR9, toll-like receptor 9; TNFα, tumour necrosis factor alpha; Treg, T regulatory cell; Ucp1, uncoupling protein 1; WAT, white adipose tissue.

and disseminate signals from the immune system to generate a local environment conducive to pathogen clearance.

## Introduction

The adipose tissue, which was once thought of as an inert energy storage facility, is now understood to exert profound effects on energy balance, through both endocrine signalling and regulation of organismal behaviour. Whilst it is made up of a number of cell types, including stromal (e.g. fibroblasts and preadipocytes) and immune cells (e.g. macrophages), the major cell of the adipose tissue is the adipocyte, which, under physiological conditions, stores fuel, mainly in the form of triglycerides, which can be hydrolyzed through lipolysis and then released to fuel distal tissues. Advances in single-cell transcriptomic studies have also revealed that there is heterogeneity within the adipocyte populations, with variation in these cell types across different white adipose tissue (WAT) depots [1–3]. Spatial transcriptomic analyses of human subcutaneous WAT (scWAT) also demonstrated that only a subset of adipocytes respond to insulin stimulation, and that there is a correlation between the size of this subset and whole-body insulin sensitivity. Moreover, this study used neighbourhood analyses to reveal homotypic clustering of a separate adipocyte subset, with putative pro-inflammatory properties [4]. These studies clearly highlight the previously unappreciated complexity and organisation of this tissue, and the need to understand the function of different subpopulations of adipocytes.
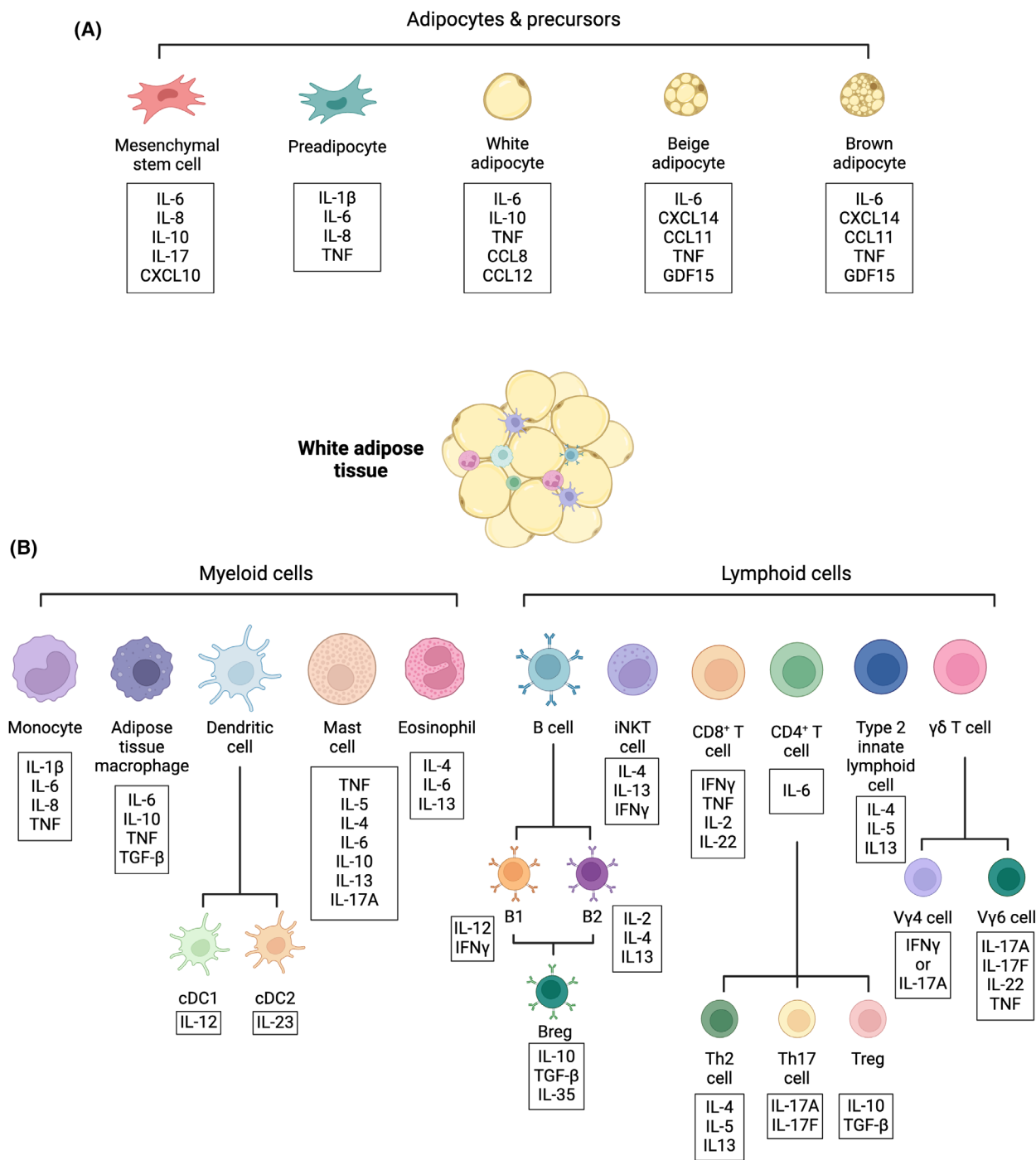
Beyond their energy storage function, adipocytes also secrete bioactive proteins called adipokines, which regulate a range of physiological functions, including food intake [5], fat distribution [6,7], energy expenditure [8] and body temperature [9]. In addition to their physiological roles, adipokines such as leptin play a role in the immune response, by stimulating immune cell activation and promoting inflammation [10]. The term adipokine also encompasses molecules that are canonical players within the immune system, including cytokines like interleukin (IL)-6 and tumour necrosis factor alpha (TNFα), which are elevated during obesity, and contribute to inflammation [11]. In addition to these pro-inflammatory cytokines, white adipocytes also express anti-inflammatory IL-10 [12,13] suggesting that they can contribute to playing a role in regulating the immune response, as well as activating it (Fig. 1A). Based on emerging evidence discussed throughout this Viewpoint, we propose that adipocytes are immune hubs that integrate innate immune signals, using them to coordinate local and systemic responses to infection.

## The immune system and adipose tissue physiology

Under homeostasis, the adipose tissue is enriched with a multitude of immune cells, including monocytes, macrophages, dendritic cells, mast cells, eosinophils, B cells, CD4$^+$ T cells, regulatory T cells (Tregs), CD8$^+$ T cells, innate lymphoid cells (ILCs) and gamma delta (γδ) T cells [14–21] (Fig. 1B). It is likely that under homeostasis and varying nutritional states, inflammatory and immunoregulatory signals from adipose tissue immune populations form a critical role in WAT remodelling. Beyond the adipose tissue, these resident immune populations can influence systemic metabolism. For example, IL-33 signalling through adipose-resident Tregs improves systemic glucose tolerance during obesity [22]. Further to this, IL-17A$^+$ γδ T cells drive IL-33 expression from adipose stromal cells (including preadipocytes), which is critical for the maintenance of body temperature [23]. IL-17A was defined as a key factor for maintaining body temperature, promoting thermogenic responses and driving adipose tissue expression of adipocyte genes associated with thermogenesis, including *Ucp1*. Indeed, the effect of IL-17A on body temperature was profound, with cold exposure proving lethal for IL-17A knockout mice. An independent study confirmed that IL-17-expressing γδ T cells are critical for thermogenesis and also identified that the effects are mediated through the adipocyte IL-17 receptor C (IL-17RC) [24]. IL-17F signalling through IL-17RC upregulated transforming growth factor β1 (TGF-β1), which in turn supported adipose tissue innervation and thermogenesis. Numerous studies have explored the effects of other immune factors on adipose tissue thermogenesis, revealing that a range of different immune cells, including anti-inflammatory macrophages [25] and type 2 innate lymphoid cells (ILC2s) [26,27], contribute to this process.

The WAT has also been extensively studied in the context of obesity, where it has been shown that pro-

**(A)** Adipocytes & precursors



| Mesenchymal stem cell | Preadipocyte | White adipocyte | Beige adipocyte | Brown adipocyte |
|---|---|---|---|---|
| IL-6<br>IL-8<br>IL-10<br>IL-17<br>CXCL10 | IL-1β<br>IL-6<br>IL-8<br>TNF | IL-6<br>IL-10<br>TNF<br>CCL8<br>CCL12 | IL-6<br>CXCL14<br>CCL11<br>TNF<br>GDF15 | IL-6<br>CXCL14<br>CCL11<br>TNF<br>GDF15 |

**White adipose tissue**

**(B)**

Myeloid cells / Lymphoid cells

| Monocyte | Adipose tissue macrophage | Dendritic cell | Mast cell | Eosinophil | B cell | iNKT cell | CD8+ T cell | CD4+ T cell | Type 2 innate lymphoid cell | γδ T cell |
|---|---|---|---|---|---|---|---|---|---|---|
| IL-1β<br>IL-6<br>IL-8<br>TNF | IL-6<br>IL-10<br>TNF<br>TGF-β | | TNF<br>IL-5<br>IL-4<br>IL-6<br>IL-10<br>IL-13<br>IL-17A | IL-4<br>IL-6<br>IL-13 | | IL-4<br>IL-13<br>IFNγ | IFNγ<br>TNF<br>IL-2<br>IL-22 | IL-6 | IL-4<br>IL-5<br>IL13 | |

cDC1 — IL-12
cDC2 — IL-23

B1 — IL-12 IFNγ
B2 — IL-2 IL-4 IL13

Breg — IL-10 TGF-β IL-35

Vγ4 cell — IFNγ or IL-17A
Vγ6 cell — IL-17A IL-17F IL-22 TNF

Th2 cell — IL-4 IL-5 IL13
Th17 cell — IL-17A IL-17F
Treg — IL-10 TGF-β

**Fig. 1.** Immune composition of adipose tissue. (A) Schematic view of adipocyte subsets and precursors, and common cytokines that they express. (B) Schematic view of the multitude of immune cells within the white adipose tissue, and common cytokines that they express. The adipose tissue comprises ~ 30% adipocytes, with the remaining cells composed of stromal and immune cells. The adipocytes and their precursors (mesenchymal stem cells and preadipocytes) secrete cytokines under homeostatic conditions, which can play a role in controlling adipose tissue structure and function. There is also a classical view that the majority of immune cells within the adipose tissue are macrophages, but we now understand that the diversity of immune cells within this tissue is vast, and complex, as illustrated here.

inflammatory cytokines such as TNFα signal directly to adipocytes, leading to adipocyte insulin resistance [28,29]. This, in turn, elevates adipocyte lipolysis and export of free fatty acids (FFAs) into the circulation [30] and contributes to ectopic lipid deposition. TNFα was also found to be expressed by adipocytes themselves, acting in both an autocrine and paracrine manner [31,32]. Numerous other cytokines (e.g. IL-1β, IL-6, IL-17) have also been demonstrated to drive lipolysis in cultured adipocytes [33–36], which is puzzling, as these cytokines are all elevated during obesity. In response to obesity, adipocytes also alter their transcriptional program to express immune-related factors, including the chemokines *Ccl6*, *Ccl8*, *Ccl9* and *Cxcl12* [2,37]. In the context of obesity in both humans and mice, the expression of adipocyte chemotactic networks promotes the recruitment of inflammatory myeloid cells, such as macrophages, further contributing to adipose tissue inflammation [38,39]. Altogether, these studies demonstrate that the WAT is a rich immunological niche, and that adipocytes themselves are capable of producing factors that contribute to the maintenance of tissue homeostasis.

## Adipocyte lipolysis: responses to infection

Many studies of the adipose tissue have focused on understanding how it functions under homeostasis or how it is affected by obesity. These studies have provided essential insights into how adipocytes function and also respond/contribute to inflammation, but there is increasing interest in the response of the WAT to infection, and how it contributes to the ensuing immune response (Table 1). This is important from the point of view of understanding how the host fuels its immune response, but also for understanding whether adipocytes themselves contribute to that response.

Ayari *et al.* [40] identified that during influenza A infection (IAV), the WAT downregulates genes associated with lipolysis and lipogenesis, which appears to be counterintuitive, since lipolysis could potentially liberate nutrients that immune cells can use to function. For example, the induction of lipolysis and release of FFAs through pharmacological intervention or overnight fasting leads to an increase in adipose tissue macrophages [41,42]. Additionally, cells such as T cells [43], germinal centre B cells [44] and anti-inflammatory macrophages [45] all utilise free fatty acids to function. Despite this dichotomy, many studies have reported downregulation of lipolysis in the adipose tissue during different infection models, including during viral (SARS-CoV-2 [46]) and parasitic (*Trypanosoma brucei*

[47]) infections, which was coupled with downregulation of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), two enzymes that are critical for lipolysis (Table 1). Furthermore, whilst sepsis and endotoxemia are typically associated with elevation of lipolysis, in aged mice this effect is reversed, with B cell accumulation inhibiting lipolysis in the adipose tissue [48]. On the one hand, it is possible that the release of FFAs could be beneficial for resolving infection by promoting a more robust immune response. Conversely, it is possible to have too much of a good thing, and the release of FFAs may be lowered during infection to prevent inappropriate levels of immune cell activation and exacerbation of inflammation. In the case of SARS-CoV-2, it was demonstrated that stimulating lipolysis increased viral replication, leading to the hypothesis that anti-lipolytic responses to infection represent part of an anti-viral immune response. This is supported from studies of both IAV and SARS-CoV-2, where pharmacological inhibition of lipid droplet-associated lipases conferred protection from severe infection and mortality [49]. The lipolytic response to *T. brucei* infection is interesting as lipolysis increases during the early stages of infection but decreases as the infection progresses to the chronic phase. Early activation of lipolysis may be important for supporting the innate immune response, including the recruitment of cells such as neutrophils [50,51]. Moreover, lipolysis is also important for the function of adaptive immune cells, such as B cells, which use FFAs to support the production of cytokines such as IL-10 [52], which is highly upregulated during *T. brucei* infection [53,54]. Decreases in lipolysis that occur during chronic *T. brucei* infection may also represent a mechanism to slow replication of the parasite, as it has been shown that this parasite can take advantage of the lipid-rich WAT environment, and upon colonisation of the tissue upregulates fatty acid oxidation to utilise the products of host lipolysis [55]. However, the impact of decreased lipolysis on the immune response to chronic infection remains unexplored.

Conversely, several studies have demonstrated the opposite effect, whereby infections can increase rates of adipocyte lipolysis, including viral (e.g. HIV [56]), bacterial (e.g. sepsis [57]) and parasitic (e.g. Chagas disease [58]) (Table 1). In the case of sepsis, early studies described that adipocytes sense bacterial endotoxins (LPS) via toll-like receptor 4 (TLR4), which in turn stimulates lipolysis [59]. This raises the possibility that bacteria are able to stimulate lipolysis, driving the release of nutrients that they can use for their own survival and proliferation. However, more recent studies suggest that TLR4 is involved in mediating

**Table 1.** Pathogens that influence adipocyte function.

| Pathogen | Disease | Host/model | Tissue type or cell line | Effect on adipocytes | Reference |
|---|---|---|---|---|---|
| **Viral** | | | | | |
| HIV | HIV and AIDS | Human | Serum | Decreased lipolysis and fatty acid oxidation | [56] |
| | | In vitro—mouse | 3T3-L1-derived adipocytes | Impaired adipogenesis Downregulation of PPARγ expression | [114] |
| | | In vitro—mouse | SGBS adipocytes | Downregulation of adiponectin and glucose transporters Upregulation of IL-6, IL-8 and MCP-1 | [115] |
| Influenza A | Flu | Mouse | Inguinal and gonadal adipose tissue | Beiging of white adipose tissue (upregulation of *Ucp1*) | [40] |
| | | In vitro—mouse | 3T3-L1-derived adipocytes | Induction of a brown-like phenotype in adipocytes | [116] |
| | | In vitro—human | Adipocytes differentiated from primary human preadipocytes (depot not described) | Upregulation of MCP-1, CXCL10 and IFNγ | |
| SARS-CoV-2 | COVID | In vitro—human | Adipocytes derived from primary human subcutaneous preadipocytes | Decreased lipolysis | [46] |
| | | In vitro—human | Adipocytes derived from primary human subcutaneous, visceral, pericardial or epicardial preadipocytes | Upregulation of inflammatory genes IFNA1, IFNB1, IER3, ISG15 and IFI27 | [117] |
| | | Human | Serum | Upregulation of adiponectin, leptin and resistin in humans with acute respiratory distress syndrome | [118] |
| | | Syrian hamsters | Inguinal and gonadal adipose tissue | Downregulation of adiponectin and leptin | |
| | | Mouse | 3T3-L1-derived adipocytes | | |
| | | Human | Serum | Elevated circulating adiponectin, leptin, resistin and visfatin | [119] |
| **Bacterial** | | | | | |
| *Mycobacterium tuberculosis* | Tuberculosis | In vitro—mouse | Mature adipocytes from inguinal adipose tissue | Upregulation of TNFα, IL-6 and MCP-1 | [120] |
| | | Mouse | Gonadal adipose tissue | Decreased adipocyte lipid droplet volume Downregulation of adiponectin and PPARγ Increased phosphorylation of hormone-sensitive lipase | [121] |
| | | In vitro—mouse | 3T3-L1 cells | Elevated production of nitric oxide, TNFα, IL-12p40, IL-6, IL-17 and IL-4 | [122] |
| *Listeria monocytogenes* | Listeriosis | Mouse | Brown adipose tissue | Increased lipid droplet volume (whitening effect) | [123] |
| | | Mouse | Perinodal adipose tissue | Transient increase in adipose tissue mass | [124] |
| | | | Isolated adipocytes from perinodal adipose tissue | Upregulation of adipocyte inflammatory cytokines (including *Il6*, *Cd86*, *Cd80*) and cytokine receptors (including *Ifnar1* and *Ifnar2*) | |
| | | In vitro—mouse | 3T3-L1 cells and adipocytes derived from primary murine inguinal preadipocytes | Upregulation of *Nos2* driven by IFNγ | |
| | | | | Adipocytes engage the argininosuccinate shunt to generate nitric oxide and clear intracellular bacterial | |
| *Coxiella burnetii* | Q fever | In vitro—mouse | 3T3-L1 cells | Upregulation of inflammatory cytokines (e.g. *Il6*), chemokines (e.g. *Cxcl5*) and toll-like receptors (e.g. *Tlr2*) | [125] |

**Table 1.** (Continued).

| Pathogen | Disease | Effect on adipocytes | Host/model | Tissue type or cell line | Reference |
|---|---|---|---|---|---|
| *Staphylococcus aureus* | Sepsis, skin infections, pneumonia | Upregulation of IL-6, MCP-1 and visfatin | *In vitro*—mouse | 3T3-L1 cells | [126] |
| | | Downregulation of resistin and adiponectin | | | |
| | | Inhibition of lipolysis | | | |
| | | Upregulation of visfatin and leptin | Rat | Serum | [127] |
| | | Downregulation of adiponectin | | Serum | |
| | | Upregulation of resistin and downregulation of AdipoR1 | | Gonadal adipose tissue | |
| | | Downregulation of resistin and leptin | Mouse | Gonadal adipose tissue | |
| | | Upregulation of visfatin | | Serum | |
| *Chlamydia pneumoniae* | Pneumonia | Decreased adipose tissue mass | Mouse | Gonadal adipose tissue | [128] |
| | | Decreased adipocyte lipid droplet volume | | | |
| | | Elevated phosphorylation of hormone-sensitive lipase | | | |
| | | Elevated lipolysis and FABP4 secretion | *In vitro*—mouse | 3T3-L1 cells | [128,129] |
| | | Induces endoplasmic reticulum stress, activation of the unfolding protein response and reactive oxygen species production | *In vitro*—mouse | 3T3-L1 cells | [129] |
| **Parasitic** | | | | | |
| *Trypanosoma brucei* | Human African trypanosomiasis and African Animal trypanosomiasis | Decreased adipose tissue mass | Mouse | Gonadal, inguinal and brown adipose tissue | [47,55] |
| | | Decreased adipocyte lipid droplet volume | Mouse | Inguinal adipose tissue | [13,47] |
| | | Increased lipolysis during acute infection | Mouse | Gonadal and inguinal adipose tissue explants | [130,131] |
| | | Decreased lipolysis during chronic infection | Mouse, Human | Serum | [47] |
| | | Promotes expression of pro- and anti-inflammatory cytokines by adipocytes (*Tnf* and *Il10*, respectively) | Mouse | Subcutaneous adipocytes | [13] |
| | | IL-17 signalling through adipocytes partially controls local parasite numbers | Mouse | Inguinal adipose tissue | [47] |
| *Trypanosoma cruzi* | Chagas disease | Decreased adipose tissue mass and adipocyte lipid droplet volume | Mouse | White adipose (depot not described) | [62] |
| | | Decreased circulating leptin and transient decrease in circulating adiponectin during chronic infection | Mouse | Gonadal white adipose tissue | [132] |
| | | | | Serum | [132,133] |
| | | Downregulation of adiponectin, ATGL, HSL, pHSL, PPARγ, leptin, HSL, ATGL, FAS, LPL, DGAT1 and DGAT2 | Mouse | Gonadal adipose tissue | [134] |
| | | | | Mature adipocytes purified from gonadal adipose tissue | [132] |
| | | Upregulation of PPARγ and downregulation of adiponectin | | White adipose (depot not described) and brown adipose tissue | [58] |
| | | Upregulation of cytokines (IL-1β, IL-4, IL-10 and IFNγ and TNFα), chemokines (CCL2, CCL3, CCL5 and CXCL10), and toll-like receptors (TLR2 and TLR9) | *In vitro*—mouse | 3T3-L1 cells | [62] |
| | | Downregulation of PPARγ and adiponectin | *In vitro*—mouse | 3T3-L1 cells | [62,135] |

**Table 1.** (Continued).

| Pathogen | Disease | Effect on adipocytes | Host/model | Tissue type or cell line | Reference |
|---|---|---|---|---|---|
| *Toxoplasma gondii* | Toxoplasmosis | Decreased adipose tissue mass | Mouse | Gonadal and inguinal adipose tissue | [136] |
| | | Development of adipose tissue fibrosis | Mouse | Gonadal adipose tissue | [137] |
| *Plasmodium falciparum* | Malaria | Upregulation of leptin triggered by mTORC1 activity | Mouse | Serum and perigonadal adipose tissue | [93] |
| | | Adipocyte leptin production correlates with development of cerebral malaria and mortality | Human | Subcutaneous adipose tissue | [83] |
| *Leishmania major* | Leishmaniasis | Elevated circulating leptin | Mouse | Serum | [138] |
| **Polymicrobial** | | | | | |
| Caecal-ligation and puncture model of sepsis | Sepsis | Decreased adipocyte lipid droplet volume Increased number of mitochondria in adipocytes Beiging of white adipose tissue (upregulation of Ucp1) | Mouse | Inguinal and gonadal adipose tissue | [139] |
| | | Increased nitric oxide and reactive oxygen species production | Mouse | Perivascular adipose tissue | [140] |

adipocyte-immune crosstalk during bacterial infection, but that it does not necessarily drive lipolysis directly [60]. This may indicate that increased lipolysis during sepsis is driven by the immune response rather than the pathogen and supports the work from Wang *et al.* [61], demonstrating that fasting, which elevates lipolysis and release of FFAs, is protective during sepsis. During Chagas disease, which is caused by the intracellular *Trypanosoma cruzi* parasite, there is evidence that lipolysis also increases, and this is associated with upregulation of TLR2, TLR4 and TLR9 [58,62]. However, *T. cruzi*-derived molecules that could stimulate adipocyte TLR signalling have yet to be described, meaning that it remains unclear how infection with this intracellular parasite drives lipolysis. As with sepsis, it is possible that lipolysis is driven primarily by the immune response to the infection. If the modulation of lipolysis observed in different infections is driven by the immune response, then the question remains of why some immune responses induce lipolysis and others suppress it, and how does the host decide whether more or fewer resulting FFAs are required. Since FFAs are used by a number of immune cell types to fuel their activation, the answer to this question is likely to lie in understanding the precise nature of the immune response to the infection that the host is experiencing, in terms of the cell types that are recruited and the immune factors, such as cytokines and antibodies, that they make.

## Adipocytes as immune hubs: integration and dissemination of instructions

Both innate and adaptive immune responses to infection stimulate the release of an extensive range of cytokines and chemokines, the composition of which depends on the pathogen, the location of the infection, infection intensity and whether the infection is acute or chronic. There is a growing appreciation that adipocytes are not only capable of sensing these molecules but also responding to them and releasing a range of different factors that can contribute to the immune response. Probably, the most well-described immune-adipocyte interaction is between immune cell-derived TNFα and adipocytes, which has long been known to drive lipolysis [63–66]. However, it is now known that TNFα signalling also upregulates expression of a number of different cytokines and chemokines in adipocytes, including IL-1β [67,68], which is a key player in the antiviral response and is a pyrogen, acting on the brain to induce fever [69]. Moreover, white adipocytes secrete prostaglandin E2, a

pyrogenic mediator that acts on the preoptic area of the brain and stimulates sympathetic nerve activity and brown adipose tissue (BAT) thermogenesis [70,71], further supporting the role of WAT in mediating the response to infection.

Intriguingly, IAV drives beiging of scWAT, through upregulation of the mitochondrial biogenesis program, conferring a thermogenic phenotype during infection [40], which is remarkable considering that this infection is localised to the lungs but drives profound effects in the distal adipose tissue. This suggests that WAT beiging and downstream induction of thermogenesis form components of the antiviral response to infection, contributing to fever and disease resolution. TNFα was also found to stimulate leptin expression in the gonadal WAT (gWAT) of mice [72], an adipokine that suppresses hunger over time by signalling through the leptin receptor in neurons of the lateral hypothalamus [73]. In contrast, studies of the scWAT found that exposure of adipocytes to TNFα in this depot reduced tissue expression of leptin [74,75], suggesting that there is heterogeneity in how adipocytes sense and respond to immune signals. Food intake is commonly suppressed (sickness-induced anorexia) during infection and forms part of a behavioural program that is conserved across vertebrates and invertebrates [47,76,77], termed 'sickness behaviour'. Therefore, it is likely that during infection, TNFα contributes to sickness-induced anorexia by signalling through adipocytes to modulate adipokine expression and alter feeding behaviour. However, recent evidence from experimental *Toxoplasma gondii* infections suggests that this process may, in some scenarios, be driven independently of TNFα, via growth/differentiation factor 15 (GDF15) [78]. GDF15 is secreted by a range of tissues, including the liver, inguinal WAT and BAT [79], and can contribute to sickness-induced anorexia independently of TNFα, via direct signalling in the hindbrain [80]. In *T. gondii* infection, GDF15 expression is driven by IFNγ and is critical for the sickness-induced anorexia and weight loss associated with this disease [78]. Although much research has focused on the role TNFα as a driver of sickness behaviour and subsequent weight loss, it is becoming increasingly clear that a range of cytokines and adipokines, including IL-1b, IL-17, IL-6 and leptin, contribute to these processes [47,81–83], likely acting in tandem.

Beyond sickness-induced anorexia, modulating leptin levels is critical for the immune response to numerous infections, as this adipokine signals through multiple different immune cell types to modulate their function, including macrophages [84], NK cells [85], neutrophils [86] and CD4$^+$ T cells (specifically IL-17$^+$ T$_H$17 cells [87]). However, the role of leptin in the immune response to infection is not straightforward, and it can either be beneficial or harmful depending upon the nature of the infection. For example, during *Leishmania donovani* [88], *T. cruzi* [89], *Mycobacterium tuberculosis* [90,91] and *Pneumococcal pneumonia* [92] infections, elevated leptin is beneficial for improving the immune response, clearing pathogens and resolving infection. Conversely, in the context of infections like malaria, sequestration of infected red blood cells in the WAT drives leptin expression, which drives the development of cerebral malaria, increasing the risk of death [83,93].

As discussed throughout this Viewpoint, many other cytokines act upon adipocytes and stimulate lipolysis, or the release of cytokines and adipokines that have effects on the immune system during infection. In recent studies, we identified that IL-17 signalling through adipocytes during infection with *T. brucei* limited the characteristic adipocyte atrophy associated with this disease, which occurred in a sex-dependent manner [13,47]. During *T. brucei* infection, in addition to increased secretion of IL-17A by CD4$^+$ and γδ T cells, adipocytes upregulate the cognate receptor, IL-17 receptor A (IL-17RA) [13] and IL-17 receptor C (IL-17RC) [47]. Whilst IL-17 signalling is known to play a role in modulating adipose tissue structure and function during obesity [94], as well as modulating functions such as thermogenesis [23,24], it remains unclear whether this is due to upregulation of the cognate IL-17 receptors, or increased signalling through them. Strikingly, when we deleted adipocyte IL-17RA, limiting the ability of adipocytes to sense IL-17A and IL-17F, there was a significant increase in the number of parasites in the scWAT [47] (Fig. 2). This unexpected observation suggests that IL-17 signalling through adipocyte IL-17RA primes the adipocytes to either directly control local parasite burden, perhaps through the release of antimicrobial peptides, such as cathelicidin [95]. In mouse models of *T. brucei* infection, cathelicidins were found to decrease parasite viability and delay infection-induced mortality [96], but it has not yet been demonstrated whether adipocytes express these trypanolytic compounds during infection. However, as adipocytes secrete cathelicidins, alongside other antimicrobial compounds, such as lipocalins [97], this could potentially represent a direct way in which adipocytes are able to control local pathogen numbers. It is also possible that IL-17 signalling, by driving adipose tissue wasting and adipocyte atrophy, induces the release of specific lipid species, such as sphingolipids, which have antimicrobial properties [98], or can act as
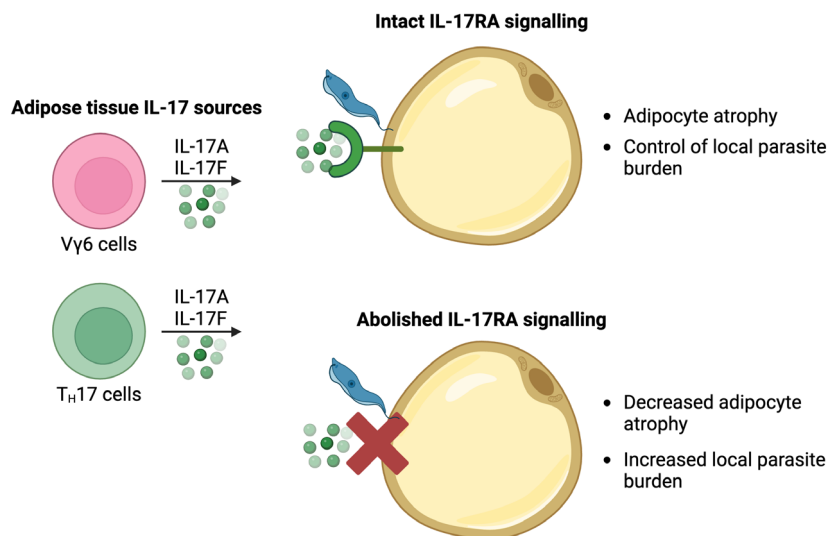
**Fig. 2.** Effects of IL-17 receptor A signalling during infection. In the inguinal white adipose tissue (iWAT), there are multiple sources of IL-17A and IL-17F, including Vγ6 and T$_H$17 cells. We previously identified that these cytokines signal through the adipocytes during *Trypanosoma brucei* infection to drive adipocyte atrophy. When IL-17 receptor A was deleted from adipocytes, they experienced less atrophy during infection, demonstrating that IL-17 acts directly on the adipocytes to drive this process. Moreover, we found a higher number of parasites in the iWAT when adipocytes were unable to sense IL-17, indicating that the adipocytes are able to integrate local immune signals and either directly affect *T. brucei* or disseminate these signals to the local immune system, and contributing to an environment that is more conducive for mounting an effective immune response.

signalling molecules to modulate the local immune response [99]. In this regard, lipids such as fatty acids have been demonstrated to influence both differentiation and activation of immune cells, including CD8$^+$ T cells [100], and macrophages [101]. Alternatively, these findings may suggest that IL-17 signalling in adipocytes promotes the expression of different cytokines and chemokines, to orchestrate the local immune response and control the pathogen numbers in the WAT. Adipocytes are also a major source of complement proteins, including C3, which is capable of killing African trypanosomes prior to them engaging mechanisms to evade immune attacks, namely antigenic variation [102]. As IL-17 can promote expression of C3 in fibroblasts, it is possible that IL-17 signalling through adipocytes helps to control parasite numbers by modulating the complement system. Whilst the exact mechanism underpinning this effect remains unknown, and whether this is a direct or indirect effect, it demonstrates that the adipocytes of the scWAT are able to sense immune signals, integrate them and then exert a profound effect on the outcome of infection. Furthermore, it will be important to understand whether sex plays a role in mediating the effects of IL-17 on adipocytes and their downstream immune effector function. We observed that IL-17 drives weight loss during *T. brucei* infection in males but not in females, and previous studies of urinary tract infection found that

IL-17 was critical for resolving infection in females but not males [103]. Together, this demonstrates that there are many factors influencing the role that IL-17 plays during infection, and there is still much to be uncovered.

## Conclusions and future perspectives

Whilst there are many questions left to answer about the response of adipose tissue to infection, there are also technological challenges that need to be addressed. Adipose tissue is notoriously challenging to work with for multiple reasons, including the loose structure of the tissue, the fragility of the adipocytes themselves and the abundance of lipids within the tissue. Single-nucleus RNA sequencing (snRNAseq) is increasingly being used to interrogate the response of the adipose tissue to different challenges. An issue facing snRNAseq is that it does not capture cytosolic mRNA molecules, but recent advances have been made to enable the capture of the endoplasmic reticulum in addition to the nucleus, maximising mRNA capture [3,104]. Another issue is that adipocytes are rich in RNAseq, leading to extensive degradation of mRNA. So *et al.* [105] have now demonstrated that using protease inhibitors, as well as RNAseq inhibitors, overcomes this obstacle and preserves mRNA integrity during nuclei isolation. In tandem spatial

transcriptomics [4,13,106] and emerging single-cell proteomics [107], snRNAseq will undoubtedly advance our understanding of how adipose tissue functions and responds to challenges. These technologies will also benefit from the range of genetic deletion models that are now available to the adipocyte biology field, including mice with constitutive or inducible deletions of genes in white (*Adipoq*-Cre, *Adipoq*-CreERT2 [108,109]) and brown (*Ucp1*-Cre, *Ucp1*-CreERT2 [110,111]) adipose tissue. Although these markers are useful for studying mature adipocytes, a major challenge in the field is identifying genes that are specific to adipocyte precursor cells, and overcoming this will enable deeper studies of adipocyte development and plasticity. Recent studies have used lineage tracing to overcome the lack of deletion models, elegantly demonstrating the trajectory of preadipocytes to a white [112] or beige adipocyte lineage [113]. These technological advances have already improved our understanding of adipocyte biology in mice and humans, and as they continue to develop will allow the field to develop deeper insights into how adipocytes respond to challenges such as obesity and infection, and how they contribute to the immune response.

We have learned a lot about the immune responses of adipocytes from studies of obesity, but obesity is a relatively modern disease, and it is likely that adipocytes evolved to express immune factors under different evolutionary pressures, such as exposure to injury and infection. Under these conditions, it is emerging that adipocytes are key contributors to the immune response, but we still know little about adipose depot-specific responses to infection, and whether these responses are impaired when there is an excess of adipose tissue, such as during obesity. Furthermore, we do not yet understand how local infections, such as in the lung, are able to trigger distal responses in the adipose tissue, or what the benefit of this is to the host. One possibility is that an infection in the lung could prompt the adipose tissue to release FFAs and adipokines into circulation, which can then be used to mount an appropriate immune response. Understanding these interactions may be important for a clinical point of view, where a patient is underweight or obese and has an impaired adipose tissue response.

We propose that during infection the adipocyte forms a cellular hub that integrates incoming immune signals and uses them to coordinate the local and systemic immune response, in turn making the adipose tissue a key, but underappreciated, player in the immune system.

## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

MCS and SK conceptualised the manuscript. MCS wrote the manuscript.

## References

1 Rajbhandari P, Arneson D, Hart SK, Ahn IS, Diamante G, Santos LC, Zaghari N, Feng A-C, Thomas BJ, Vergnes L *et al.* (2019) Single cell analysis reveals immune cell–adipocyte crosstalk regulating the transcription of thermogenic adipocytes. *Elife* **8**, e49501.

2 Sárvári AK, Van Hauwaert EL, Markussen LK, Gammelmark E, Marcher A-B, Ebbesen MF, Nielsen R, Brewer JR, Madsen JGS & Mandrup S (2021) Plasticity of epididymal adipose tissue in response to diet-induced obesity at single-nucleus resolution. *Cell Metab* **33**, 437–453.e5.

3 Emont MP, Jacobs C, Essene AL, Pant D, Tenen D, Colleluori G, Di Vincenzo A, Jørgensen AM, Dashti H, Stefek A *et al.* (2022) A single-cell atlas of human and mouse white adipose tissue. *Nature* **603**, 926–933.

4 Bäckdahl J, Franzén L, Massier L, Li Q, Jalkanen J, Gao H, Andersson A, Bhalla N, Thorell A, Rydén M *et al.* (2021) Spatial mapping reveals human adipocyte subpopulations with distinct sensitivities to insulin. *Cell Metab* **33**, 1869–1882.e6.

5 Klok MD, Jakobsdottir S & Drent ML (2007) The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obes Rev* **8**, 21–34.

6 Staiger H, Tschritter O, Machann J, Thamer C, Fritsche A, Maerker E, Schick F, Häring H-U & Stumvoll M (2003) Relationship of serum adiponectin and leptin concentrations with body fat distribution in humans. *Obes Res* **11**, 368–376.

7 Park K-G, Park KS, Kim M-J, Kim H-S, Suh Y-S, Ahn JD, Park K-K, Chang Y-C & Lee I-K (2004) Relationship between serum adiponectin and leptin

concentrations and body fat distribution. *Diabetes Res Clin Pract* **63**, 135–142.

8 Ahima RS & Lazar MA (2008) Adipokines and the peripheral and neural control of energy balance. *Mol Endocrinol* **22**, 1023–1031.

9 Chen Q, Huang L, Pan D, Hu K, Li R, Friedline RH, Kim JK, Zhu LJ, Guertin DA & Wang Y-X (2022) A brown fat-enriched adipokine Adissp controls adipose thermogenesis and glucose homeostasis. *Nat Commun* **13**, 7633.

10 Fernández-Riejos P, Najib S, Santos-Alvarez J, Martín-Romero C, Pérez-Pérez A, González-Yanes C & Sánchez-Margalet V (2010) Role of leptin in the activation of immune cells. *Mediators Inflamm* **2010**, 568343.

11 Han MS, White A, Perry RJ, Camporez J-P, Hidalgo J, Shulman GI & Davis RJ (2020) Regulation of adipose tissue inflammation by interleukin 6. *Proc Natl Acad Sci USA* **117**, 2751–2760.

12 Juge-Aubry CE, Somm E, Pernin A, Alizadeh N, Giusti V, Dayer J-M & Meier CA (2005) Adipose tissue is a regulated source of interleukin-10. *Cytokine* **29**, 270–274.

13 Quintana JF, Sinton MC, Chandrasegaran P, Lestari AN, Heslop R, Cheaib B, Ogunsola J, Ngoyi DM, Kuispond Swar N-R, Cooper A *et al.* (2023) γδ T cells control murine skin inflammation and subcutaneous adipose wasting during chronic *Trypanosoma brucei* infection. *Nat Commun* **14**, 5279.

14 Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S *et al.* (2009) Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat Med* **15**, 930–939.

15 Molofsky AB, Nussbaum JC, Liang H-E, Van Dyken SJ, Cheng LE, Mohapatra A, Chawla A & Locksley RM (2013) Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *J Exp Med* **210**, 535–549.

16 Mathis D (2013) Immunological goings-on in visceral adipose tissue. *Cell Metab* **17**, 851–859.

17 Caspar-Bauguil S, Cousin B, Galinier A, Segafredo C, Nibbelink M, André M, Casteilla L & Pénicaud L (2005) Adipose tissues as an ancestral immune organ: site-specific change in obesity. *FEBS Lett* **579**, 3487–3492.

18 Hernández-García E, Cueto FJ, Cook ECL, Redondo-Urzainqui A, Charro-Zanca S, Robles-Vera I, Conde-Garrosa R, Nikolić I, Sabio G, Sancho D *et al.* (2022) Conventional type 1 dendritic cells protect against age-related adipose tissue dysfunction and obesity. *Cell Mol Immunol* **19**, 260–275.

19 Masuda A, Yoshikai Y, Aiba K & Matsuguchi T (2002) Th2 cytokine production from mast cells is directly induced by lipopolysaccharide and distinctly regulated by c-Jun N-terminal kinase and p38 pathways. *J Immunol* **169**, 3801–3810.

20 Lin AM, Rubin CJ, Khandpur R, Wang JY, Riblett M, Yalavarthi S, Villanueva EC, Shah P, Kaplan MJ & Bruce AT (2011) Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J Immunol* **187**, 490–500.

21 Massier L, Jalkanen J, Elmastas M, Zhong J, Wang T, Nono Nankam PA, Frendo-Cumbo S, Bäckdahl J, Subramanian N, Sekine T *et al.* (2023) An integrated single cell and spatial transcriptomic map of human white adipose tissue. *Nat Commun* **14**, 1438.

22 Vasanthakumar A, Moro K, Xin A, Liao Y, Gloury R, Kawamoto S, Fagarasan S, Mielke LA, Afshar-Sterle S, Masters SL *et al.* (2015) The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue–resident regulatory T cells. *Nat Immunol* **16**, 276–285.

23 Kohlgruber AC, Gal-Oz ST, LaMarche NM, Shimazaki M, Duquette D, Koay H-F, Nguyen HN, Mina AI, Paras T, Tavakkoli A *et al.* (2018) γδ T cells producing interleukin-17A regulate adipose regulatory T cell homeostasis and thermogenesis. *Nat Immunol* **19**, 464–474.

24 Hu B, Jin C, Zeng X, Resch JM, Jedrychowski MP, Yang Z, Desai BN, Banks AS, Lowell BB, Mathis D *et al.* (2020) γδ T cells and adipocyte IL-17RC control fat innervation and thermogenesis. *Nature* **578**, 610–614.

25 Nguyen KD, Qiu Y, Cui X, Goh YPS, Mwangi J, David T, Mukundan L, Brombacher F, Locksley RM & Chawla A (2011) Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis. *Nature* **480**, 104–108.

26 Brestoff JR, Kim BS, Saenz SA, Stine RR, Monticelli LA, Sonnenberg GF, Thome JJ, Farber DL, Lutfy K, Seale P *et al.* (2015) Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. *Nature* **519**, 242–246.

27 Lee M-W, Odegaard JI, Mukundan L, Qiu Y, Molofsky AB, Nussbaum JC, Yun K, Locksley RM & Chawla A (2015) Activated type 2 innate lymphoid cells regulate beige fat biogenesis. *Cell* **160**, 74–87.

28 Szalkowski D, White-Carrington S, Berger J & Zhang B (1995) Antidiabetic thiazolidinediones block the inhibitory effect of tumor necrosis factor-alpha on differentiation, insulin-stimulated glucose uptake, and gene expression in 3T3-L1 cells. *Endocrinology* **136**, 1474–1481.

29 Liu LS, Spelleken M, Röhrig K, Hauner H & Eckel J (1998) Tumor necrosis factor-alpha acutely inhibits insulin signaling in human adipocytes: implication of the p80 tumor necrosis factor receptor. *Diabetes* **47**, 515–522.

30 Curry TB, Roberts SK, Basu R, Basu A, Schroeder D, Joyner MJ & Miles JM (2011) Gastric bypass surgery is associated with near-normal insulin suppression of lipolysis in nondiabetic individuals. *Am J Physiol Endocrinol Metab* **300**, E746–E751.

31 Hotamisligil GS, Shargill NS & Spiegelman BM (1993) Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. *Science* **259**, 87–91.

32 Xu H, Uysal KT, Becherer JD, Arner P & Hotamisligil GS (2002) Altered tumor necrosis factor-alpha (TNF-alpha) processing in adipocytes and increased expression of transmembrane TNF-alpha in obesity. *Diabetes* **51**, 1876–1883.

33 Price SR, Mizel SB & Pekala PH (1986) Regulation of lipoprotein lipase synthesis and 3T3-L1 adipocyte metabolism by recombinant interleukin 1. *Biochim Biophys Acta Mol Cell Res* **889**, 374–381.

34 Ji C, Chen X, Gao C, Jiao L, Wang J, Xu G, Fu H, Guo X & Zhao Y (2011) IL-6 induces lipolysis and mitochondrial dysfunction, but does not affect insulin-mediated glucose transport in 3T3-L1 adipocytes. *J Bioenerg Biomembr* **43**, 367–375.

35 Petersen EW, Carey AL, Sacchetti M, Steinberg GR, Macaulay SL, Febbraio MA & Pedersen BK (2005) Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro. *Am J Physiol Endocrinol Metab* **288**, E155–E162.

36 Shin JH, Shin DW & Noh M (2009) Interleukin-17A inhibits adipocyte differentiation in human mesenchymal stem cells and regulates pro-inflammatory responses in adipocytes. *Biochem Pharmacol* **77**, 1835–1844.

37 Jiao P, Chen Q, Shah S, Du J, Tao B, Tzameli I, Yan W & Xu H (2009) Obesity-related upregulation of monocyte chemotactic factors in adipocytes: involvement of nuclear factor-kappaB and c-Jun NH2-terminal kinase pathways. *Diabetes* **58**, 104–115.

38 Kim D, Kim J, Yoon JH, Ghim J, Yea K, Song P, Park S, Lee A, Hong C-P, Jang MS *et al.* (2014) CXCL12 secreted from adipose tissue recruits macrophages and induces insulin resistance in mice. *Diabetologia* **57**, 1456–1465.

39 Tourniaire F, Romier-Crouzet B, Lee JH, Marcotorchino J, Gouranton E, Salles J, Malezet C, Astier J, Darmon P, Blouin E *et al.* (2013) Chemokine expression in inflamed adipose tissue is mainly mediated by NF-κB. *PLoS One* **8**, e66515.

40 Ayari A, Rosa-Calatrava M, Lancel S, Barthelemy J, Pizzorno A, Mayeuf-Louchart A, Baron M, Hot D, Deruyter L, Soulard D *et al.* (2020) Influenza infection rewires energy metabolism and induces browning features in adipose cells and tissues. *Commun Biol* **3**, 1–15.

41 Capel F, Klimcáková E, Viguerie N, Roussel B, Vítková M, Kovácikivá M, Polák J, Kovácová Z, Galitzky J, Maoret J-J *et al.* (2009) Macrophages and adipocytes in human obesity: adipose tissue gene expression and insulin sensitivity during calorie restriction and weight stabilization. *Diabetes* **58**, 1558–1567.

42 Kosteli A, Sugaru E, Haemmerle G, Martin JF, Lei J, Zechner R & Ferrante AW (2010) Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. *J Clin Invest* **120**, 3466–3479.

43 Patsoukis N, Bardhan K, Chatterjee P, Sari D, Liu B, Bell LN, Karoly ED, Freeman GJ, Petkova V, Seth P *et al.* (2015) PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. *Nat Commun* **6**, 6692.

44 Weisel FJ, Mullett SJ, Elsner RA, Menk AV, Trivedi N, Luo W, Wikenheiser D, Hawse WF, Chikina M, Smita S *et al.* (2020) Germinal center B cells selectively oxidize fatty acids for energy while conducting minimal glycolysis. *Nat Immunol* **21**, 331–342.

45 Huang SC-C, Everts B, Ivanova Y, O'Sullivan D, Nascimento M, Smith AM, Beatty W, Love-Gregory L, Lam WY, O'Neill CM *et al.* (2014) Cell-intrinsic lysosomal lipolysis is essential for alternative activation of macrophages. *Nat Immunol* **15**, 846–855.

46 Saccon TD, Mousovich-Neto F, Ludwig RG, Carregari VC, dos Anjos Souza AB, dos Passos ASC, Martini MC, Barbosa PP, de Souza GF, Muraro SP *et al.* (2022) SARS-CoV-2 infects adipose tissue in a fat depot- and viral lineage-dependent manner. *Nat Commun* **13**, 5722.

47 Sinton MC, Chandrasegaran P, Capewell P, Cooper A, Girard A, Ogunsola J, Perona-Wright G, Ngoyi DM, Kuispond N, Bucheton B *et al.* (2023) IL-17 signalling is critical for controlling subcutaneous adipose tissue dynamics and parasite burden during chronic *Trypanosoma brucei* infection. *bioRxiv*. doi: 10.1101/2022.09.23.509158

48 Carey A, Nguyen K, Kandikonda P, Kruglov V, Bradley C, Dahlquist KJV, Cholensky S, Swanson W, Badovinac VP, Griffith TS *et al.* (2024) Age-associated accumulation of B cells promotes macrophage inflammation and inhibits lipolysis in adipose tissue during sepsis. *Cell Rep* **43**, 113967.

49 Baek Y-B, Kwon H-J, Sharif M, Lim J, Lee I-C, Ryu YB, Lee J-I, Kim J-S, Lee Y-S, Kim D-H *et al.* (2022) Therapeutic strategy targeting host lipolysis limits infection by SARS-CoV-2 and influenza A virus. *Signal Transduct Target Ther* **7**, 1–12.

50 Watanabe Y, Nagai Y, Honda H, Okamoto N, Yanagibashi T, Ogasawara M, Yamamoto S, Imamura R, Takasaki I, Hara H *et al.* (2019) Bidirectional crosstalk between neutrophils and adipocytes promotes

adipose tissue inflammation. *FASEB J* **33**, 11821–11835.

51 Caljon G, Mabille D, Stijlemans B, De Trez C, Mazzone M, Tacchini-Cottier F, Malissen M, Van Ginderachter JA, Magez S, De Baetselier P *et al.* (2018) Neutrophils enhance early *Trypanosoma brucei* infection onset. *Sci Rep* **8**, 11203.

52 Fu Y, Wang L, Yu B, Xu D & Chu Y (2022) Immunometabolism shapes B cell fate and functions. *Immunology* **166**, 444–457.

53 Quintana JF, Chandrasegaran P, Sinton MC, Briggs EM, Otto TD, Heslop R, Bentley-Abbot C, Loney C, de Lecea L, Mabbott NA *et al.* (2022) Single cell and spatial transcriptomic analyses reveal microglia-plasma cell crosstalk in the brain during *Trypanosoma brucei* infection. *Nat Commun* **13**, 5752.

54 Ngotho M, Kagira JM, Jensen HE, Karanja SM, Farah IO & Hau J (2009) Immunospecific immunoglobulins and IL-10 as markers for *Trypanosoma brucei rhodesiense* late stage disease in experimentally infected vervet monkeys. *Trop Med Int Health* **14**, 736–747.

55 Trindade S, Rijo-Ferreira F, Carvalho T, Pinto-Neves D, Guegan F, Aresta-Branco F, Bento F, Young SA, Pinto A, Van Den Abbeele J *et al.* (2016) *Trypanosoma brucei* parasites occupy and functionally adapt to the adipose tissue in mice. *Cell Host Microbe* **19**, 837–848.

56 Cade WT, Reeds DN, Mittendorfer B, Patterson BW, Powderly WG, Klein S & Yarasheski KE (2007) Blunted lipolysis and fatty acid oxidation during moderate exercise in HIV-infected subjects taking HAART. *Am J Physiol Endocrinol Metab* **292**, E812–E819.

57 Wellhoener P, Vietheer A, Sayk F, Schaaf B, Lehnert H & Dodt C (2011) Metabolic alterations in adipose tissue during the early phase of experimental endotoxemia in humans. *Horm Metab Res* **43**, 754–759.

58 Nagajyothi F, Desruisseaux MS, Machado FS, Upadhya R, Zhao D, Schwartz GJ, Teixeira MM, Albanese C, Lisanti MP, Chua SC *et al.* (2012) Response of adipose tissue to early infection with *Trypanosoma cruzi* (Brazil strain). *J Infect Dis* **205**, 830–840.

59 Zu L, He J, Jiang H, Xu C, Pu S & Xu G (2009) Bacterial endotoxin stimulates adipose lipolysis via toll-like receptor 4 and extracellular signal-regulated kinase pathway. *J Biol Chem* **284**, 5915–5926.

60 McKernan K, Varghese M, Patel R & Singer K (2020) Role of TLR4 in the induction of inflammatory changes in adipocytes and macrophages. *Adipocyte* **9**, 212.

61 Wang A, Huen SC, Luan HH, Yu S, Zhang C, Gallezot J-D, Booth CJ & Medzhitov R (2016) Opposing effects of fasting metabolism on tissue tolerance in bacterial and viral inflammation. *Cell* **166**, 1512–1525.e12.

62 Nagajyothi F, Desruisseaux MS, Thiruvur N, Weiss LM, Braunstein VL, Albanese C, Teixeira MM, de Almeida CJ, Lisanti MP, Scherer PE *et al.* (2008) *Trypanosoma cruzi* infection of cultured adipocytes results in an inflammatory phenotype. *Obesity (Silver Spring)* **16**, 1992–1997.

63 Plomgaard P, Fischer CP, Ibfelt T, Pedersen BK & van Hall G (2008) Tumor necrosis factor-alpha modulates human in vivo lipolysis. *J Clin Endocrinol Metab* **93**, 543–549.

64 Yang X, Zhang X, Heckmann BL, Lu X & Liu J (2011) Relative contribution of adipose triglyceride lipase and hormone-sensitive lipase to tumor necrosis factor-α (TNF-α)-induced lipolysis in adipocytes. *J Biol Chem* **286**, 40477–40485.

65 Zhang HH, Halbleib M, Ahmad F, Manganiello VC & Greenberg AS (2002) Tumor necrosis factor-α stimulates lipolysis in differentiated human adipocytes through activation of extracellular signal-related kinase and elevation of intracellular cAMP. *Diabetes* **51**, 2929–2935.

66 Du X, Liu M, Tai W, Yu H, Hao X, Loor JJ, Jiang Q, Fang Z, Gao X, Fan M *et al.* (2022) 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* **105**, 8426–8438.

67 Zhang HH, Kumar S, Barnett AH & Eggo MC (2001) Dexamethasone inhibits tumor necrosis factor-alpha-induced apoptosis and interleukin-1 beta release in human subcutaneous adipocytes and preadipocytes. *J Clin Endocrinol Metab* **86**, 2817–2825.

68 Nov O, Kohl A, Lewis EC, Bashan N, Dvir I, Ben-Shlomo S, Fishman S, Wueest S, Konrad D & Rudich A (2010) Interleukin-1β may mediate insulin resistance in liver-derived cells in response to adipocyte inflammation. *Endocrinology* **151**, 4247–4256.

69 Cartmell T, Luheshi GN & Rothwell NJ (1999) Brain sites of action of endogenous interleukin-1 in the febrile response to localized inflammation in the rat. *J Physiol* **518**, 585–594.

70 Nakamura K & Morrison SF (2011) Central efferent pathways for cold-defensive and febrile shivering. *J Physiol* **589**, 3641–3658.

71 Yoneshiro T, Kataoka N, Walejko JM, Ikeda K, Brown Z, Yoneshiro M, Crown SB, Osawa T, Sakai J, McGarrah RW *et al.* (2021) Metabolic flexibility via mitochondrial BCAA carrier SLC25A44 is required for optimal fever. *Elife* **10**, e66865.

72 Kirchgessner TG, Uysal KT, Wiesbrock SM, Marino MW & Hotamisligil GS (1997) Tumor necrosis factor-alpha contributes to obesity-related hyperleptinemia by

regulating leptin release from adipocytes. *J Clin Invest* **100**, 2777–2782.

73 Lee YH, Kim Y-B, Kim KS, Jang M, Song HY, Jung S-H, Ha D-S, Park JS, Lee J, Kim KM *et al.* (2023) Lateral hypothalamic leptin receptor neurons drive hunger-gated food-seeking and consummatory behaviours in male mice. *Nat Commun* **14**, 1486.

74 Medina EA, Stanhope KL, Mizuno TM, Mobbs CV, Gregoire F, Hubbard NE, Erickson KL & Havel PJ (1999) Effects of tumor necrosis factor alpha on leptin secretion and gene expression: relationship to changes of glucose metabolism in isolated rat adipocytes. *Int J Obes Relat Metab Disord* **23**, 896–903.

75 Fawcett RL, Waechter AS, Williams LB, Zhang P, Louie R, Jones R, Inman M, Huse J & Considine RV (2000) Tumor necrosis factor-α inhibits leptin production in subcutaneous and omental adipocytes from morbidly obese humans. *J Clin Endocrinol Metabol* **85**, 530–535.

76 Ayres JS & Schneider DS (2009) The role of anorexia in resistance and tolerance to infections in Drosophila. *PLoS Biol* **7**, e1000150.

77 Zaragoza WJ, Krediet CJ, Meyer JL, Canas G, Ritchie KB & Teplitski M (2014) Outcomes of infections of sea anemone *Aiptasia pallida* with *Vibrio* spp. pathogenic to corals. *Microb Ecol* **68**, 388–396.

78 Reyes J, Zhao Y, Pandya K & Yap GS (2024) Growth differentiation factor-15 is an IFN-γ regulated mediator of infection-induced weight loss and the hepatic FGF21 response. *Brain Behav Immun* **116**, 24–33.

79 Campderrós L, Moure R, Cairó M, Gavaldà-Navarro A, Quesada-López T, Cereijo R, Giralt M, Villarroya J & Villarroya F (2019) Brown adipocytes secrete GDF15 in response to thermogenic activation. *Obesity* **27**, 1606–1616.

80 Tsai VW-W, Zhang HP, Manandhar R, Schofield P, Christ D, Lee-Ng KKM, Lebhar H, Marquis CP, Husaini Y, Brown DA *et al.* (2019) GDF15 mediates adiposity resistance through actions on GFRAL neurons in the hindbrain AP/NTS. *Int J Obes (Lond)* **43**, 2370–2380.

81 Chaskiel L, Bristow AD, Bluthé R-M, Dantzer R, Blomqvist A & Konsman JP (2019) Interleukin-1 reduces food intake and body weight in rat by acting in the arcuate hypothalamus. *Brain Behav Immun* **81**, 560–573.

82 Kozak W, Poli V, Soszynski D, Conn CA, Leon LR & Kluger MJ (1997) Sickness behavior in mice deficient in interleukin-6 during turpentine abscess and influenza pneumonitis. *Am J Physiol* **272**, R621–R630.

83 Mejia P, Treviño-Villarreal JH, De Niz M, Meibalan E, Longchamp A, Reynolds JS, Turnbull LB, Opoka RO, Roussilhon C, Spielmann T *et al.* (2021) Adipose tissue parasite sequestration drives leptin production in

mice and correlates with human cerebral malaria. *Sci Adv* **7**, eabe2484.

84 Monteiro LB, Prodonoff JS, Favero de Aguiar C, Correa-da-Silva F, Castoldi A, Bakker NT, Davanzo GG, Castelucci B, Pereira JAS, Curtis J *et al.* (2022) Leptin signaling suppression in macrophages improves immunometabolic outcomes in obesity. *Diabetes* **71**, 1546–1561.

85 Lamas B, Goncalves-Mendes N, Nachat-Kappes R, Rossary A, Caldefie-Chezet F, Vasson M-P & Farges M-C (2013) Leptin modulates dose-dependently the metabolic and cytolytic activities of NK-92 cells. *J Cell Physiol* **228**, 1202–1209.

86 Bruno A, Conus S, Schmid I & Simon H-U (2005) Apoptotic pathways are inhibited by leptin receptor activation in neutrophils. *J Immunol* **174**, 8090–8096.

87 Reis BS, Lee K, Fanok MH, Mascaraque C, Amoury M, Cohn L, Rogoz A, Dallner OS, Moraes-Vieira PM, Domingos AI *et al.* (2015) Leptin receptor signaling in T cells is required for Th17 differentiation. *J Immunol* **194**, 5253–5260.

88 Dayakar A, Chandrasekaran S, Veronica J, Bharadwaja V & Maurya R (2017) Leptin regulates granzyme-a, PD-1 and CTLA-4 expression in T cell to control visceral leishmaniasis in BALB/c mice. *Sci Rep* **7**, 14664.

89 Nagajyothi F, Zhao D, Machado FS, Weiss LM, Schwartz GJ, Desruisseaux MS, Zhao Y, Factor SM, Huang H, Albanese C *et al.* (2010) Crucial role of the central leptin receptor in murine *Trypanosoma cruzi* infection. *J Infect Dis* **202**, 1104–1113.

90 van Crevel R, Karyadi E, Netea MG, Verhoef H, Nelwan RHH, West CE & van der Meer JWM (2002) Decreased plasma leptin concentrations in tuberculosis patients are associated with wasting and inflammation. *J Clin Endocrinol Metab* **87**, 758–763.

91 Ye M & Bian L-F (2018) Association of serum leptin levels and pulmonary tuberculosis: a meta-analysis. *J Thorac Dis* **10**, 1027–1036.

92 Hsu A, Aronoff DM, Phipps J, Goel D & Mancuso P (2007) Leptin improves pulmonary bacterial clearance and survival in ob/ob mice during *Pneumococcal pneumonia*. *Clin Exp Immunol* **150**, 332–339.

93 Mejia P, Treviño-Villarreal JH, Hine C, Harputlugil E, Lang S, Calay E, Rogers R, Wirth D, Duraisingh MT & Mitchell JR (2015) Dietary restriction protects against experimental cerebral malaria via leptin modulation and T-cell mTORC1 suppression. *Nat Commun* **6**, 6050.

94 Teijeiro A, Garrido A, Ferre A, Perna C & Djouder N (2021) Inhibition of the IL-17A axis in adipocytes suppresses diet-induced obesity and metabolic disorders in mice. *Nat Metab* **3**, 496–512.

95 Hochberg A, Patz M, Karrasch T, Schäffler A & Schmid A (2021) Serum levels and adipose tissue gene

expression of cathelicidin antimicrobial peptide (CAMP) in obesity and during weight loss. *Horm Metab Res* **53**, 169–177.

96 McGwire BS, Olson CL, Tack BF & Engman DM (2003) Killing of African trypanosomes by antimicrobial peptides. *J Infect Dis* **188**, 146–152.

97 Lemecha M, Chalise JP, Takamuku Y, Zhang G, Yamakawa T, Larson G & Itakura K (2022) Lcn2 mediates adipocyte-muscle-tumor communication and hypothermia in pancreatic cancer cachexia. *Mol Metab* **66**, 101612.

98 Wu Y, Liu Y, Gulbins E & Grassmé H (2021) The anti-infectious role of sphingosine in microbial diseases. *Cells* **10**, 1105.

99 Lee M, Lee SY & Bae Y-S (2023) Functional roles of sphingolipids in immunity and their implication in disease. *Exp Mol Med* **55**, 1110–1130.

100 Zhang S, Lv K, Liu Z, Zhao R & Li F (2024) Fatty acid metabolism of immune cells: a new target of tumour immunotherapy. *Cell Death Discov* **10**, 1–12.

101 Batista-Gonzalez A, Vidal R, Criollo A & Carreño LJ (2020) New insights on the role of lipid metabolism in the metabolic reprogramming of macrophages. *Front Immunol* **10**, 2993.

102 Macleod OJS, Cook AD, Webb H, Crow M, Burns R, Redpath M, Seisenberger S, Trevor CE, Peacock L, Schwede A *et al.* (2022) Invariant surface glycoprotein 65 of *Trypanosoma brucei* is a complement C3 receptor. *Nat Commun* **13**, 5085.

103 Scharff AZ, Rousseau M, Mariano LL, Canton T, Consiglio CR, Albert ML, Fontes M, Duffy D & Ingersoll MA (2019) Sex differences in IL-17 contribute to chronicity in male versus female urinary tract infection. *JCI Insight* **4**, e122998.

104 Gulko A, Essene A, Belmont-Rausch DM, Veregge M, Pant D, Tenen D, Kapel BS, Emont MP, Pers TH, Rosen ED *et al.* (2024) Protocol for flow cytometry-assisted single-nucleus RNA sequencing of human and mouse adipose tissue with sample multiplexing. *STAR Protoc* **5**, 102893.

105 So J, Strobel O, Wann J, Kim K, Paul A, Acri DJ, Dabin LC, Kim J & Roh HC (2024) Robust single nucleus RNA sequencing reveals depot-specific cell population dynamics in adipose tissue remodeling during obesity. *Elife* **13**, doi: 10.7554/eLife.97981.1

106 Stansbury CM, Dotson GA, Pugh H, Rehemtulla A, Rajapakse I & Muir LA (2023) A lipid-associated macrophage lineage rewires the spatial landscape of adipose tissue in early obesity. *JCI Insight* **8**, e171701.

107 Bennett HM, Stephenson W, Rose CM & Darmanis S (2023) Single-cell proteomics enabled by next-generation sequencing or mass spectrometry. *Nat Methods* **20**, 363–374.

108 Eguchi J, Wang X, Yu S, Kershaw EE, Chiu PC, Dushay J, Estall JL, Klein U, Maratos-Flier E & Rosen ED (2011) Transcriptional control of adipose lipid handling by IRF4. *Cell Metab* **13**, 249–259.

109 Sassmann A, Offermanns S & Wettschureck N (2010) Tamoxifen-inducible Cre-mediated recombination in adipocytes. *Genesis* **48**, 618–625.

110 Kong X, Banks A, Liu T, Kazak L, Rao RR, Cohen P, Wang X, Yu S, Lo JC, Tseng Y-H *et al.* (2014) IRF4 is a key thermogenic transcriptional partner of PGC-1α. *Cell* **158**, 69–83.

111 Rosenwald M, Perdikari A, Rülicke T & Wolfrum C (2013) Bi-directional interconversion of brite and white adipocytes. *Nat Cell Biol* **15**, 659–667.

112 Stefkovich M, Traynor S, Cheng L, Merrick D & Seale P (2021) Dpp4+ interstitial progenitor cells contribute to basal and high fat diet-induced adipogenesis. *Mol Metab* **54**, 101357.

113 Oguri Y, Shinoda K, Kim H, Alba DL, Bolus WR, Wang Q, Brown Z, Pradhan RN, Tajima K, Yoneshiro T *et al.* (2020) CD81 controls beige fat progenitor cell growth and energy balance via FAK signaling. *Cell* **182**, 563–577.e20.

114 Shrivastav S, Kino T, Cunningham T, Ichijo T, Schubert U, Heinklein P, Chrousos GP & Kopp JB (2008) Human immunodeficiency virus (HIV)-1 viral protein R suppresses transcriptional activity of peroxisome proliferator-activated receptor {gamma} and inhibits adipocyte differentiation: implications for HIV-associated lipodystrophy. *Mol Endocrinol* **22**, 234–247.

115 Díaz-Delfín J, Domingo P, Wabitsch M, Giralt M & Villarroya F (2012) HIV-1 tat protein impairs adipogenesis and induces the expression and secretion of proinflammatory cytokines in human SGBS adipocytes. *Antivir Ther* **17**, 529–540.

116 Hornung F, Schulz L, Köse-Vogel N, Häder A, Grießhammer J, Wittschieber D, Autsch A, Ehrhardt C, Mall G, Löffler B *et al.* (2023) Thoracic adipose tissue contributes to severe virus infection of the lung. *Int J Obes (Lond)* **47**, 1088–1099.

117 Martínez-Colón GJ, Ratnasiri K, Chen H, Jiang S, Zanley E, Rustagi A, Verma R, Chen H, Andrews JR, Mertz KD *et al.* (2022) SARS-CoV-2 infection drives an inflammatory response in human adipose tissue through infection of adipocytes and macrophages. *Sci Transl Med* **14**, eabm9151.

118 Reiterer M, Rajan M, Gómez-Banoy N, Lau JD, Gomez-Escobar LG, Ma L, Gilani A, Alvarez-Mulett S, Sholle ET, Chandar V *et al.* (2021) Hyperglycemia in acute COVID-19 is characterized by insulin resistance and adipose tissue infectivity by SARS-CoV-2. *Cell Metab* **33**, 2174–2188.e5.

119 Flikweert AW, Kobold ACM, van der Sar-van der Brugge S, Heeringa P, Rodenhuis-Zybert IA, Bijzet J, Tami A, van der Gun BTF, Wold KI, Huckriede A *et al.* (2023) Circulating adipokine levels and COVID-19 severity in hospitalized patients. *Int J Obes (Lond)* **47**, 126–137.

120 Agarwal P, Khan SR, Verma SC, Beg M, Singh K, Mitra K, Gaikwad AN, Akhtar MS & Krishnan MY (2014) *Mycobacterium tuberculosis* persistence in various adipose depots of infected mice and the effect of anti-tubercular therapy. *Microbes Infect* **16**, 571–580.

121 Ayyappan JP, Ganapathi U, Lizardo K, Vinnard C, Subbian S, Perlin DS & Nagajyothi JF (2019) Adipose tissue regulates pulmonary pathology during TB infection. *mBio* **10**, e02771-18.

122 Kim J-S, Ryu M-J, Byun E-H, Kim WS, Whang J, Min K-N, Shong M, Kim H-J & Shin SJ (2011) Differential immune response of adipocytes to virulent and attenuated *Mycobacterium tuberculosis*. *Microbes Infect* **13**, 1242–1251.

123 Martinez N, Cheng CY, Ketheesan N, Cullen A, Tang Y, Lum J, West K, Poidinger M, Guertin DA, Singhal A *et al.* (2019) mTORC2/Akt activation in adipocytes is required for adipose tissue inflammation in tuberculosis. *EBioMedicine* **45**, 314–327.

124 Caputa G, Matsushita M, Sanin DE, Kabat AM, Edwards-Hicks J, Grzes KM, Pohlmeyer R, Stanczak MA, Castoldi A, Cupovic J *et al.* (2022) Intracellular infection and immune system cues rewire adipocytes to acquire immune function. *Cell Metab* **34**, 747–760.e6.

125 Bechah Y, Verneau J, Ben Amara A, Barry AO, Lépolard C, Achard V, Panicot-Dubois L, Textoris J, Capo C, Ghigo E *et al.* (2014) Persistence of *Coxiella burnetii*, the agent of Q fever, in murine adipose tissue. *PLoS One* **9**, e97503.

126 Hanses F, Kopp A, Bala M, Buechler C, Falk W, Salzberger B & Schäffler A (2011) Intracellular survival of *Staphylococcus aureus* in adipocyte-like differentiated 3T3-L1 cells is glucose dependent and alters cytokine, chemokine, and adipokine secretion. *Endocrinology* **152**, 4148–4157.

127 Schmid A, Karrasch T, Thomalla M, Schlegel J, Salzberger B, Schäffler A & Hanses F (2017) Innate immunity of adipose tissue in rodent models of local and systemic *Staphylococcus aureus* infection. *Mediators Inflamm* **2017**, 5315602.

128 Kurihara Y, Walenna NF, Ishii K, Soejima T, Chou B, Yoshimura M, Ozuru R, Shimizu A, Itoh R, Furuhashi M *et al.* (2023) *Chlamydia pneumoniae* lung infection in mice induces fatty acid-binding protein 4-dependent White adipose tissue pathology. *J Immunol* **210**, 1086–1097.

129 Walenna NF, Kurihara Y, Chou B, Ishii K, Soejima T & Hiromatsu K (2020) *Chlamydia pneumoniae* infection-induced endoplasmic reticulum stress causes fatty acid-binding protein 4 secretion in murine adipocytes. *J Biol Chem* **295**, 2713–2723.

130 Machado H, Hofer P, Zechner R, Smith TK & Figueiredo LM (2023) Adipocyte lipolysis protects mice against *Trypanosoma brucei* infection. *Nat Microbiol* **8**, 2020–2032.

131 Redford SE, Varanasi SK, Sanchez KK, Thorup NR & Ayres JS (2023) CD4+ T cells regulate sickness-induced anorexia and fat wasting during a chronic parasitic infection. *Cell Rep* **42**, 112814.

132 González FB, Villar SR, Toneatto J, Pacini MF, Márquez J, D'Attilio L, Bottasso OA, Piwien-Pilipuk G & Pérez AR (2019) Immune response triggered by *Trypanosoma cruzi* infection strikes adipose tissue homeostasis altering lipid storage, enzyme profile and adipokine expression. *Med Microbiol Immunol* **208**, 651–666.

133 Combs TP, Nagajyothi, Mukherjee S, de Almeida CJG, Jelicks LA, Schubert W, Lin Y, Jayabalan DS, Zhao D, Braunstein VL *et al.* (2005) The adipocyte as an important target cell for *Trypanosoma cruzi* infection. *J Biol Chem* **280**, 24085–24094.

134 Lizardo K, Ayyappan JP, Oswal N, Weiss LM, Scherer PE & Nagajyothi JF (2021) Fat tissue regulates the pathogenesis and severity of cardiomyopathy in murine chagas disease. *PLoS Negl Trop Dis* **15**, e0008964.

135 Santamaría MH, Ríos LD & Corral RS (2021) *Trypanosoma cruzi* down-regulates adiponectin expression in mouse adipocytes via the NFAT signaling pathway. *Microbes Infect* **23**, 104757.

136 Hatter JA, Kouche YM, Melchor SJ, Ng K, Bouley DM, Boothroyd JC & Ewald SE (2018) *Toxoplasma gondii* infection triggers chronic cachexia and sustained commensal dysbiosis in mice. *PLoS One* **13**, e0204895.

137 Melchor SJ, Hatter JA, Castillo ÉAL, Saunders CM, Byrnes KA, Sanders I, Abebayehu D, Barker TH & Ewald SE (2020) *T. gondii* infection induces IL-1R dependent chronic cachexia and perivascular fibrosis in the liver and skeletal muscle. *Sci Rep* **10**, 15724.

138 Martins VD, Silva FC, Caixeta F, Carneiro MB, Goes GR, Torres L, Barbosa SC, Vaz L, Paiva NC, Carneiro CM *et al.* (2020) Obesity impairs resistance to *Leishmania major* infection in C57BL/6 mice. *PLoS Negl Trop Dis* **14**, e0006596.

139 Ayalon I, Shen H, Williamson L, Stringer K, Zingarelli B & Kaplan JM (2018) Sepsis induces adipose tissue Browning in nonobese mice but not in obese mice. *Shock* **50**, 557–564.

140 Barp CG, Benedet PO & Assreuy J (2020) Perivascular adipose tissue phenotype and sepsis vascular dysfunction: differential contribution of NO, ROS and beta 3-adrenergic receptor. *Life Sci* **254**, 117819.