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Opinion

Adipose Tissue: A Safe Haven for Parasites?

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Adipose tissue (AT) is no longer regarded as an inert lipid storage, but as an important central regulator in energy homeostasis and immunity. Three parasite species are uniquely associated with AT during part of their life cycle: *Trypanosoma cruzi*, the causative agent of Chagas disease; *Trypanosoma brucei*, the causative agent of African sleeping sickness; and *Plasmodium* spp., the causative agents of malaria. In AT, *T. cruzi* resides inside adipocytes, *T. brucei* is found in the interstitial spaces between adipocytes, while *Plasmodium* spp. infect red blood cells, which may adhere to the blood vessels supplying AT. Here, we discuss how each parasite species adapts to this tissue environment and what the implications are for pathogenesis, clinical manifestations, and therapy.

Parasites Find A Home in Adipose Tissue

Microbes show incredible diversity with respect to which environment they preferentially colonize or invade. Among microbes that infect mammals, some live inside host cells, while others are extracellular; some remain in the blood, while others penetrate and accumulate into tissues; and sometimes they accumulate in certain reservoirs for at least a period of time. The localization of microbes has major implications on the type and efficiency of the immune response, disease pathology, potential of transmission, and, ultimately, survival of the host.

AT (see Glossary), once regarded as a relatively inert and static organ specialized in lipid storage and release, is now appreciated as the largest endocrine organ that releases a vast number of bioactive peptides and larger proteins, critical metabolites, and signaling lipids [1]. The physiological roles of AT go beyond its role as a central player in systemic energy homeostasis. AT is involved in both innate and adaptive immune responses and is a critical player in stromal interactions with tumors [2]. Most importantly, its ability to store and neutralize lipotoxic lipids makes it essential to maintain normal cellular homeostasis in many other critical organs, such as the liver, kidney, and heart [3]. In mammals, most AT is white AT (WAT), which is functionally distinct from brown AT (BAT) and the more recently described beige AT [4]. Little is known about the specific involvement of BAT and beige AT that would set them apart from conventional WAT in the context of infection; therefore, we focus our discussion here predominantly on WAT.

The main constituent of AT is the **adipocyte**. In WAT, the adipocyte contains a large **lipid vacuole** that takes up most of the space in the cell and in which triglycerides are stored (Figure 1). The nucleus and other organelles are often 'squeezed' against the plasma membrane. However, AT is heterogeneous, containing many relevant cell types beyond the adipocyte. Endothelial cells, a vast array of immune cells, adipocyte precursor cells, as well as fibroblasts and myofibroblasts constitute the stromal vascular fraction of AT; each of these cell types has indispensable roles in the normal physiology of AT [5]. Therefore, dysfunctions in the AT that lead to impairment of the metabolic flexibility of this tissue (i.e., its ability to adapt effectively to feeding and fasting conditions) have widespread functional consequences [6,7]. Chronic overnutrition as

Trends

Several pathogens accumulate in AT.

Within the AT, pathogens occupy different niches, which means different access to nutrients and different exposure to the immune system.

Parasites adapt their gene expression to the tissue environment, which increases the phenotypic diversity of parasites within the host.

The exceptional longevity of adipocytes along with a nutrient-dense microenvironment offers an ideal long-term environment for parasites during the chronic stage of the infection.

Given that most drugs are designed to be hydrophilic, the persistence of parasites in AT may compromise the efficacy of drug treatment.

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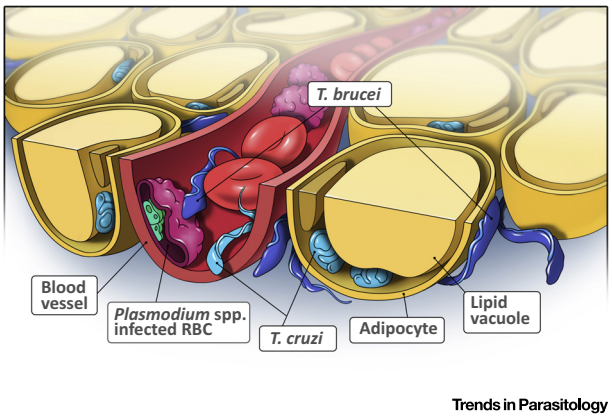

Figure 1. Localization of Parasites in Adipose Tissue (AT). Adipocytes are the major constituent of AT, which contains a large lipid vacuole. *Trypanosoma cruzi* (light blue) can live in the blood as a trypomastigote or in the cytoplasm of cells (such as adipocytes) as an amastigote. *Trypanosoma brucei* (dark blue) can be found in the blood and in interstitial spaces of several tissues. In AT, they reside between adipocytes. *Plasmodium* species (green) live inside red blood cells (RBC), which adhere to the blood vessel when they are infected. Image generated by VisuallyMedical.com.

Glossary

Adipocyte: the main type of cell that comprises AT.
Adipose tissue (AT): also known as fat; comprises 10–50% of the body of a healthy human. It is a tissue that is essential for the maintenance of metabolism homeostasis.
Lipid vacuole: a storage structure found in adipocytes that contains neutral lipids (triglycerides).

well as infectious agents that target adipocytes specifically or constituents of the stromal vascular fraction can lead to both acute and chronic impairments to proper functionality.

Many organisms have been shown to persist in AT during infection, from viruses, to bacteria and parasites (Table 1). One of the best-studied examples is *Trypanosoma cruzi*, the causative agent of Chagas disease, an important cause of morbidity and some mortality in endemic areas of Mexico, Central and South America. Vectorial transmission has also been reported in the USA and is becoming increasingly an issue [8]. Due to immigration, chronic Chagas disease and mother-to-child vertical transmission have been described in nonendemic areas of the world. Before 2005, there were some scattered reports of *T. cruzi* being found in AT. In a mouse model, *T. cruzi* was seen in BAT [9] and Andrade and Silva published electron micrographs of amastigotes of *T. cruzi* within adipocytes [10]. Combs *et al*. eventually demonstrated that *T. cruzi* trypomastigotes readily infect AT and adipocytes [11]. Both BAT and WAT are targets of early infection [12] and a reservoir during the chronic phase in mice and humans [11,13].

Trypanosoma brucei is a unicellular and extracellular parasite that causes African trypanosomiasis, a neglected tropical disease restricted to Sub-Saharan Africa [14]. The human form of this disease, human African trypanosomiasis (HAT), also known as sleeping sickness, is believed to

Table 1. Examples of Pathogens that Persist in AT

Species	Type of pathogen	Disease	Host where persistence in AT was observed	Localization in AT	Refs
Trypanosoma cruzi	Parasite	Chagas disease	Mouse, humans	Cytoplasm of adipocytes	[9]
Trypanosoma brucei	Parasite	African trypanosomiasis	Mouse, humans	Interstitial spaces of visceral and subcutaneous AT	[17,18,20]
Plasmodium berghei	Parasite	Malaria	Mouse	Inside vessels	[29]
Rickettsia prowazekii	Bacteria	Epidemic typhus	Mouse	Cytoplasm of adipocytes	[59]
Coxiella burnetii	Bacteria	Q fever	Mouse	Intracellular: in adipocytes and macrophages	[60]
Mycobacterium tuberculosis	Bacteria	TB	Mouse, humans	Adipocytes and stromal vascular fraction	[61]
HIV and SIV	Virus	AIDS and SAIDS	Humans, macaques	Stromal vascular fraction (including immune cells)	[54]

be fatal in most cases. It is transmitted to mammalian hosts by the bite of a tsetse fly. *Trypanosoma brucei* lives in the blood and in interstitial spaces of many different tissues of the mammalian host [15]. When parasites penetrate the brain, they cause neuropsychiatric and sleep abnormalities [16–20].

Tropism has recently been described to the skin and testis, which is important for transmission both by tsetse and sexually, respectively [17–19,21]. *Trypanosoma brucei* was also found in the skin of 0.5% of patients screened for *Onchocerca* microfilaria in the Democratic Republic of Congo, suggesting that undiagnosed individuals can act as a previously unknown source of transmission [17]. In an independent study in mice, Trindade *et al*. recently showed, by quantitative PCR, that the AT harbors around tenfold more parasites than are found in the blood during chronic stages of the disease [20]. Interestingly, in the two studies describing tropism of the skin, many parasites were found in the vicinity of subcutaneous adipocytes [17,18]. Although the relative number of parasites in skin, visceral AT, and testes from the same mouse awaits comparison, there is no doubt that the AT is a major parasite reservoir. The implications of these extravascular parasite reservoirs in terms of pathogenesis, transmission, treatment, and diagnosis are only now beginning to be investigated.

Plasmodium spp. are obligate intracellular parasites and the causative agents of malaria. Although five species can cause malaria in humans, *Plasmodium falciparum* is responsible for the majority of malaria deaths globally and is the most prevalent species in Sub-Saharan Africa. The remaining species are not typically as life threatening as *P. falciparum*. Erythrocytes infected with *P. falciparum* are known to cytoadhere to endothelial cells lining blood vessels of different organs, and this feature has been associated, in part, with the severity of the malaria pathology. Examination of postmortem tissue from individuals who died of malaria revealed that *P. falciparum*-infected red blood cells (iRBCs) sequester in differing amounts in tissues of a variety of organs. While the lung and spleen are recognized as the main sites for accumulation of *P. falciparum*, AT has also been identified as a site of *P. falciparum* iRBC sequestration [22,23].

In this review, we discuss how and why these three different parasites (*T. cruzi, T. brucei*, and *Plasmodium species)* have found a home in AT. Most of the knowledge was obtained using well-established mouse models of the relevant infections, although we also mention clinical studies where appropriate. Data are still scarce when it comes to *Plasmodium*, but we include it in the discussion where relevant.

Within the Adipose Tissue, Where Do Parasites Live?

Trypanosoma brucei is an extracellular parasite and, in AT, can be found in the interstitial spaces between adipocytes. Replicating parasites have been found both in AT and in the skin, suggesting that these tissue environments provide enough nutrients to support parasite growth [17,18,20]. A large number of nondividing transmissible forms have also been found in these tissues [15], suggesting that transmission may occur from extravascular sites [17,20].

Trypanosoma brucei displays waveforms that appear to be adapted to moving in confined viscous environments [17,20], such as tissue spaces [24]. Live imaging revealed that some slender *T. brucei* parasites demonstrate fast, persistent movement, while others are less mobile [17]. Conversely, based on scanning electron microscopy, parasites appear to tightly interact with subcutaneous adipocytes, with entanglement by reticular fibers and embedment between collagen bundles [17,18,20]. It is not known whether the parasites interact with adipocytes to propel themselves forward, or as a means of slowing themselves down, at least temporarily. We also do not know whether slender and stumpy forms show any different behavior in terms of their physical interaction with host cells.

Trypanosoma cruzi trypomastigotes infect almost any cell in the body including preadipocytes and adipocytes [25,26]. Trypomastigotes transform into intracellular amastigotes, which escape the parasitophorous vacuole and live free in the cytoplasm. Here, they multiply by binary fission and convert back to trypomastigotes, which escape the host cells and invade adjacent uninfected cells. Alternatively, they enter the blood and lymphatic vessels and begin another infection cycle.

The adherence of *Plasmodium* iRBCs to host tissue, also known as sequestration, occurs in small capillaries and postcapillary venules of many organs, and this is no different in AT. *Plasmodium* iRBCs remain in blood vessels. Through the use of *in vitro* binding assays, several host molecules that are expressed on the surface of endothelial cells have been identified as having a role in *P. falciparum* iRBC adherence. However, CD36 and chondroitin sulfate A (CSA) are the only two receptors that maintain stable stationary adherence to iRBCs [27,28]. The application of *in vivo* imaging techniques in laboratory animals that either express or lack CD36 revealed that CD36 has a major role in sequestration of the rodent malaria parasite *Plasmodium berghei*, specifically in AT and lungs [29]. In animals deficient in CD36, the sequestration of iRBCs in both the lungs and AT was significantly reduced [29].

How Do Parasites Enter and/or Invade the Adipose Tissue?

Trypomastigotes of both *T. cruzi* and *T. brucei* reside extracellularly. Therefore, they must cross the capillary wall to reach inside a tissue. We can envision several nonexclusive possibilities for how parasites enter the parenchyma of the AT. First, these parasites may cross the vessels into and out of all tissues, but only AT provides the conditions for them to replicate or avoid being eliminated by the immune system. Second, the entry may be specific: it could involve the recognition of, and binding to, a specific receptor that is enriched in capillaries of AT. How this process exactly occurs has not been extensively examined. However, AT endothelium can be targeted specifically [30], and it is possible that the trypomastigotes gain entry through one of these uniquely enriched markers. Indeed, this has been shown for the entry of *T. brucei* across the blood–brain barrier, which occurs only in vessels where the endothelial basement membrane contains the laminin α4 chain [31]. A third possibility is that the vasculature in AT is constantly undergoing remodeling, more so than any other tissue in the system. This is based on the observation that AT is most susceptible to the effects of angiogenesis inhibitors in the absence of a tumor mass [32] and easily becomes leaky with small changes in vascular endothelial growth factor (VEGF), even within the physiological range [7,33], although there is no direct evidence for this process. This high level of constant remodeling with intermittent stages of vascular leakage may also enable parasites to gain easy access to adipocytes. A fourth possibility is that entry is favored by the immune response mounted against these parasites when they are in the blood. The passage of *T. brucei* into the brain is facilitated by the presence of several components of the immune system [such as interferon γ IFN-γ] [31,34]. IFN-γ is abundantly expressed during *T. brucei* infection and promotes parasite growth [35]. However, there are currently no experimental data showing that parasite entry into the brain and other tissues share similar features.

Once in the interstitial space, *T. cruzi* continues its journey into the adipocyte. Here, another set of receptors, including the low-density lipoprotein receptor (LDLr), serve as the primary target for the parasites to gain access to the intracellular milieu [25]. *Trypanosoma cruzi* invasion via the LDLr may exert important effects on intracellular cholesterol homeostasis [26].

Do Parasites Adapt to Living in the Adipose Tissue?

The bloodstream is populated by two forms of *T. brucei* that correspond to the two life-cycle stages: the replicative slender form and the cell cycle-arrested transmissible stumpy form. These two stages are functionally different, as demonstrated by their different gene expression

signatures, including the upregulation in stumpy forms of mitochondrial components [36,37]. Are slender and stumpy forms in AT phenotypically identical to these forms in the blood? Trindade *et al*. used RNA-Seq as a proxy to test this hypothesis. The authors demonstrated that parasites in AT have a gene expression signature that is different from that of parasites in the blood [20], suggesting that the phenotypic diversity of parasites in the host is greater than previously anticipated [20]. Many of the differentially expressed genes are related to metabolism, which suggests that parasites adapt to the tissue environment. A biochemical assay confirmed the activation of fatty acid beta-oxidation, a pathway in which fatty acids are used as a carbon source. Although we do not know the source of these lipids and/or fatty acids, it is possible that they are either imported from the AT interstitial space, where there are high levels of lipid trafficking between feeding and fasting periods.

How Are Adipocytes Affected by Infection?

When mice were infected by *T. cruzi*, during the early stage of infection (15 days post infection - dpi), AT displayed widespread macrophage invasion and a reduction in lipid accumulation and adipocyte size [12]. Of interest, there was a reduction in fat mass associated with increased expression of lipolytic enzymes. Many of the increases in proinflammatory mediators described at 30 and 90 dpi were already present during the very early stages of infection. Both BAT and WAT obtained from *T. cruzi*-infected mice display increased markers of oxidative stress, findings consistent with the persistent inflammatory state observed [38]. *Trypanosoma cruzi* infection of AT alters the expression and function of the connexin-43 gap junction protein, which may have widespread implications for intercellular communication in AT [39]. Caradonna and colleagues demonstrated that the prereplication phase of the *T. cruzi* infection cycle is predominantly affected by host cell signaling pathways and cytoskeletal regulators. By contrast, factors in the host that foster *T. cruzi* amastigote growth are highly enriched for metabolic functions [40].

Although infections caused by *T. brucei* and *P. berghei* are typically associated with weight loss and cachexia [41,42], the consequences of these infections on adipocytes have not been characterized.

What Is the Immune Response in AT and Is It Weaker than in Blood?

There is no accepted literature that argues that AT is immune depleted. In fact, the more we learn about immunometabolism, the more complex the situation appears to be in AT. *Trypanosoma cruzi* hides inside adipocytes [43]. By definition, intracellular residency in a long-living cell is one of the most effective ways to escape the immune response, Nevertheless, infection of adipocytes by *T. cruzi* results in increased expression of proinflammatory cytokines and chemokines, and prompts a migration of $F4/80^{+}$ macrophages into AT as early as 15 dpi [12]. These events are accompanied by a reduction in adiponectin serum levels and adiponectin expression in AT (adiponectin is an important insulin-sensitizing adipokine) [11]. Adiponectin is also a potent negative regulator of inflammation and a critical secretory adipokine required to maintain normal AT function during dietary challenges [44]. The increased expression of proinflammatory cytokines in AT was still evident well into the chronic stage in surviving mice [11].

AT is highly enriched in a vast number of immune cells. With respect to macrophage populations, there is a balance between proinflammatory M1 macrophages, and macrophages expressing a gene expression profile more consistent with a role in remodeling (M2 macrophages) [45]. During a *T. cruzi* mouse infection, a shift towards M2 macrophages was described, which could help maintain tissue homeostasis or promote parasite survival [46]. However, it remains unknown whether the M1 response is muted. Further studies are necessary to clarify the role of inflammatory mechanisms in AT during *T. cruzi* infection.

The local immune response against *T. brucei* and *P. berghei* has not yet been studied and it is unknown whether there is an immune suppressive environment in AT that could explain the persistence of the parasites in that tissue.

Is the Adipose Tissue A Nutrient-Rich Environment?

Why would *T. cruzi* opt to reside in adipocytes during the chronic stage of the infection? We can only speculate about the answer, since specific data are missing. One possible explanation is the extreme longevity of adipocytes, both in humans [47] and mice [48]. Adipocytes have a half-life on average of approximately 10 years; thus, this may allow parasites to remain in a quiescent state for prolonged periods of time without the need to go through another infectious cycle. A second possibility is that the adipocyte offers intracellularly a constant source of nutrients, in particular fatty acids, which can be mobilized easily from the lipid droplet through recruitment of specific intracellular lipases, such as adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacyl glycerol lipase (MGL) [49]. Indeed, *T. cruzi* amastigotes are in close proximity to the lipid vacuole, which ensures a continuous supply of fatty acids from the adipocyte to the parasite [11]. Furthermore, postprandial surges of insulin ensure an influx of glucose on a regular basis. Thus, both the carbohydrate and lipid needs of the parasite during its quiescent state are readily met by the adipocyte.

It is not so obvious how *T. brucei* and *P. berghei* could benefit from the nutrients available inside the adipocytes. It is possible that the parasites directly or indirectly induce adipocytes to release stored nutrients (such as free fatty acids and glycerol), which could be subsequently taken up by the parasites external to the these organelles.

Clinical Relevance and Drug Treatment

The possible clinical importance of AT in Chagas disease or sleeping sickness remains unclear. Recent studies demonstrated that *T. cruzi*-infected mice fed a high-fat diet displayed a reduction in parasitemia and myocardial pathology, associated with an increase in parasite load in WAT, suggesting that WAT acts as a 'sponge' for the parasite and perhaps protects the heart from an increased parasite load [50,51]. By contrast, *T. cruzi* infection of obese and diabetic leptin receptor-deficient (*db/db*) mice led to increased mortality compared with lean genetically modified *db/db* mice [52]. Another study showed that, in infected mice, there was an impairment of insulin release from the pancreas [53], but there are no definitive data showing whether there is an increase in the incidence of diabetes in humans infected with *T. cruzi*. Thus, there are currently no reliable data that suggest that *T. cruzi* infection causes obesity or that obese individuals are more likely to become infected or that the parasite load is greater in patients who are obese [11–13]. As far as we know, no epidemiological study has been undertaken in patients with HAT to assess whether the number or severity of HAT cases is correlated with body mass index before infection. In mice, a *T. brucei* infection in obese and diabetic *db/db* mice resulted in decreased mortality compared with wildtype, suggesting a protective role of AT [51]. Other mouse mutants, drugs, and diets need to be tested in infection mouse models to understand whether there is a causal relation between AT mass and infectivity.

Since the AT is a lipid-rich environment and most drugs are hydrophilic, it may pose some limitations to the efficacy of drug treatments. Indeed, this has been observed for HIV treatment: AT acts as an HIV reservoir that prevents full treatment [54]. Recently, it was demonstrated that the failure of posaconazole to cure *T. cruzi* in a mouse model was due to the failure to eliminate the parasite from its protected environment in AT during the acute phase [55]. Trindade *et al.* have shown, using transplantation experiments, that parasites can egress from AT and repopulate the blood [20]. Thus, it is possible that AT contributes to the relapses also observed in the treatment of African trypanosomiasis, which are typically less than 5–10% after treatment [56,57].

Importantly, the gene expression adaptation of parasites to tissues means that there is a greater phenotypic diversity of parasites within the host than previously anticipated. A specific drug target may be expressed at different levels in each tissue type (i.e., AT and brain), which would result in different susceptibilities to drug treatment depending on the tissue in which the parasites reside. Such a scenario could also contribute to the inefficacy of drug treatment and to relapses.

Concluding Remarks

Tissues and blood differ in many aspects, including: (i) biochemically (such as the concentration of nutrients and oxygen); (ii) biomechanically (tissues are more viscous and crowded environments); (iii) immunogenically (different types of immune response are triggered in tissues); and (iv) their interface with the exterior environment and possible transmission vectors. In recent years, there has been an increased appreciation in the role of AT in the pathogenesis of infectious agents [58], but we still have a limited understanding of this topic. Many questions need to be addressed before we can ultimately understand the selective advantage of parasite tropism to AT (see Outstanding Questions). Parasites may have access to different nutrients, benefit from a weaker immune response, or AT may act as a reservoir of replicative forms. When parasites are in the skin, they may also benefit from some of these advantages due to the presence of subcutaneous AT. However, in the skin, the most obvious selective advantage is an increased chance of transmission by the tsetse vector.

Conversely, it is also possible that AT is the 'lesser of two evils'; that is, perhaps infection of AT causes less damage to the host than infection of other organs, such as liver or brain. Given that the survival of the host is important for pathogens to ensure their replication and transmission, there may have been a selective pressure for pathogens that were best adapted to live in this tissue.

Another interesting question is how to integrate the accumulation of parasites in different tissues. *Plasmodium* species accumulate not only in AT, but also in lung. *Trypanosoma brucei* also infects testis, skin, and brain. Is the tropism for one tissue independent from that of the others? Is there a common mechanism for entry and adaptation? Can the presence of parasites in one tissue have repercussions for parasites in another, because the metabolism of the host is systemically affected, for example?

Trypanosoma brucei is capable of sensing and adapting to the tissue environment. What is the nature of the factors that trigger this adaption? It could be a nutrient or perhaps a mechanical signal. It will be interesting to study whether these adaptations change with the stage of infection and/or between tissues or organs. For example, given that the brain is a lipid-rich environment, does *T. brucei* undergo an adaptation similar to when it is in AT? It will also be interesting to study whether other parasites also adapt to their surrounding tissue. For example, are *Plasmodium*-infected erythrocytes phenotypically identical when they are sequestered in lungs and AT? We hope this article may spur others to investigate other roles of AT in the setting of infection, immunity, and metabolism.

Outstanding Questions

Do all parasites adapt to every tissue they occupy?

What is the selective advantage to persisting in AT?

Is the elimination of parasites in AT less efficient?

How do parasites sense when they are in AT?

Do parasites manipulate adipocytes to redirect nutrients for their own benefit?

Is there a causal relation between persistence in AT and pathogenesis?

Does the chronic presence of parasites in AT lead to a higher chance of pathological sequelae, such as diabetes and chronic kidney disease?

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