Trends in Parasitology

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Review

Dual faces of γδ T cells in trypanosomatid infections

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In this review, we tell the story of how two related parasites that belong to the same genus, *Trypanosoma brucei* and *Trypanosoma cruzi*, cause very distinct lethal diseases and how γδ T cells help shape these outcomes. It synthesizes current knowledge on γδ T-cell responses to *T. brucei* and *T. cruzi*, highlighting shared and parasite-specific features. Here we emphasize how γδ T-cell cytotoxic versus regulatory programs and tissue residency in blood, lymphoid organs, liver, gut, heart, and skin influence early parasite control, chronic persistence, and immunopathology. Finally, we discuss the gaps that need to be filled and how these insights may inform new interventions, including modulation of γδ function, γδ-targeted vaccine strategies, and γδ-based biomarkers for host-directed therapies in Chagas disease and human African trypanosomiasis.

Highlights

γδ T cells emerge as central regulators rather than bystanders in *T. cruzi* and *T. brucei* infection, integrating innate and adaptive signals.

Parasite glycolipids and CD1d are now recognized as key drivers of inflammatory double-negative ($CD4^{-}CD8^{-}$) γδ T cells in human Chagas cardiomyopathy.

In *T. brucei* infection, $Vγ6^{+}$ interleukin-17A-producing γδ T cells orchestrate skin–adipose crosstalk, adipose tissue wasting, and metabolic control of parasite burden.

Together, these advances establish trypanosomatid infections as powerful models to dissect γδ T-cell-driven trade-offs between parasite control and tissue damage.

γδ T cells at the host–parasite interface

Trypanosomatid parasites such as *Trypanosoma cruzi* and *Trypanosoma brucei* cause chronic, often fatal infections that remain major—and largely neglected—public health problems [1,2]. Current drugs are toxic, incompletely effective, and do little to control the chronic inflammation and tissue damage that drive cardiomyopathy in Chagas disease or neurological decline in sleeping sickness once they are established [3,4]. A fuller understanding of how the immune system senses and responds to these parasites is therefore critical to clarify disease-protective or pathogenic mechanisms and how this can be used to benefit infected individuals. γδ T cells are particularly interesting in this context, as they sit at the crossroads of innate and adaptive immunity, respond very rapidly to tissue stress, and are abundant at sites that trypanosomatids invade [5].

This topic is timely for several reasons. First, γδ T cells have come to the forefront of immunotherapy and vaccine research [6], revealing that they can be selectively expanded, reprogrammed, or targeted in humans. Second, advances in single-cell and spatial technologies [7] allow us to track γδ T-cell subsets and their interactions with other immune and stromal cells directly in infected tissues. Finally, there is growing evidence that γδ T cells can both protect against parasites and contribute to pathology, depending on their functional program and tissue context [8]. In this review, we explore what is known about γδ T cells in *T. cruzi* and *T. brucei* infections and how this emerging knowledge might be employed to refine vaccines, identify new host-directed therapies and biomarkers, and better explain the divergent clinical outcomes of these two emblematic trypanosomatid diseases.

Chagas disease and sleeping sickness: distinct diseases and related causative parasites

T. cruzi and *T. brucei* are kinetoplastid protozoa within the TriTryp group but represent deeply divergent lineages with distinct biogeographic histories. Phylogenetic and genomic analyses indicate that the ancestors of *T. cruzi* (a mainly American, stercorarian trypanosome transmitted by

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triatomine bugs) and *T. brucei* (an African, salivarian trypanosome transmitted by tsetse flies) separated roughly 100 million years ago, coinciding with Gondwanan fragmentation [9–11]. Since then, they have evolved different repertoires of surface gene families, antigenic-variation strategies, tissue tropism, and host–vector cycles, supporting their contrasting intracellular (*T. cruzi*) versus extracellular (*T. brucei*) lifestyles and the distinct diseases they cause in humans [9,10].

Chagas disease, caused by *T. cruzi*, is a leading vector-borne parasitosis in the Americas and an emerging global problem through migration. Around 6–10 million people are chronically infected, with substantial mortality and disability [1,12]. Most individuals remain in a clinical form named **indeterminate Chagas disease (IND)** (see Glossary), but 30–40% develop digestive megasyndromes and/or **chronic Chagas cardiomyopathy (CCC)**, which lead to severe gastrointestinal disease, heart failure, arrhythmias, thromboembolism, and often death [1]. **Human African trypanosomiasis (HAT)**, also known as sleeping sickness, caused by *T. b. gambiense* and *T. b. rhodesiense*, now causes fewer than 1000 reported cases annually but still affects highly exposed rural populations in sub-Saharan Africa [2,4] and is transmitted by the tsetse fly [13]. Importantly, this is a zoonotic disease that affects livestock, leading to extensive economic losses. Moreover, these infected livestock are reservoirs for the parasites, increasing the risk to human health. After an early febrile hemolymphatic stage, central nervous system invasion leads to sleep–wake disturbances, neuropsychiatric symptoms, and, if untreated, coma and death [2,4].

In addition to the severity of symptoms related to each disease, another common trait is that the pathology associated with these parasitoses, although quite distinct, is immune-mediated. Increasing evidence points to the participation of a particular subset of T cells, the γδ T cells, in the immune response in both infections. Understanding their functional characteristics and roles in Chagas disease and HAT will bring new perspectives to tackling these diseases.

γδ T cells: a bridge between innate and adaptive responses

γδ T cells are unconventional T lymphocytes that bridge innate and adaptive immunity and are well-placed to sense tissue stress during infection. Unlike **innate lymphoid cells (ILCs)**, they express a **T-cell receptor (TCR)** composed of γ and δ chains, recognize antigens largely independently of the classical **major histocompatibility complex (MHC)**, and respond with rapid cytokine and cytotoxic programs [6]. In humans, circulating γδ T cells are predominantly $CD4^-$ $CD8^-$ (double negative), whereas tissue-associated γδ T-cell subsets can include $CD8^+$ and, more rarely, $CD4^+$ populations, reflecting site-specific differentiation and functional specialization [14]. Major γδ subsets are often grouped into **interferon gamma (IFN-γ)**- versus **interleukin (IL)**-17-skewed populations, with additional specialization into cytotoxic, antigen-presenting, follicular-helper-like, and regulatory functions [15,16]. IFN-γ-producing γδ T cells provide early type 1 help by licensing myeloid cells and supporting **T helper (Th)**1 and **CD**8^+ responses, whereas IL-17-producing γδ T cells secrete IL-17A/F and **granulocyte-macrophage colony-stimulating factor (GM-CSF)** to drive neutrophil recruitment and inflammatory monocyte activation. Regulatory γδ T cells instead release IL-10 and transforming growth factor beta (TGF-β) or express checkpoint molecules, limiting excessive inflammation but potentially favoring pathogen persistence [15,16]. These functional programs coexist with potent cytotoxic capacity, as activated γδ T cells kill infected or transformed targets through perforin, granzymes, and death-receptor pathways [6,17].

γδ T-cell biology is tightly linked to tissue residency and innate-like sensing. Murine γδ T cells are organized into developmentally programmed subsets defined by their TCR γ-chain usage and tissue localization, with $Vγ5^+$ cells forming dendritic epidermal T cells in the skin, $Vγ6^+$ cells enriched

Glossary

Amphiregulin (AREG): an EGFR ligand involved in tissue repair and stromal/adipose remodeling; can be produced by immune cells including γδ T cells.
Brown adipose tissue (BAT): mitochondria-rich fat specialized for nonshivering thermogenesis and energy expenditure.
Butyrophilin (BTN): Ig-like molecules (e.g., BTN2A1/BTN3A1) required for phosphoantigen sensing/activation of human Vγ9Vδ2 T cells.
Cardiotrophin-like cytokine factor 1 (CLCF1): IL-6-family cytokine signaling via gp130-containing receptor complexes; can reprogram adipose mitochondrial and thermogenic pathways.
Chronic Chagas cardiomyopathy (CCC): inflammatory/fibrotic heart disease in chronic Chagas disease, associated with arrhythmias, heart failure, and often death.
CD: standardized surface-marker nomenclature (e.g., CD4, CD8, and CD1d) used to define immune subsets.
DNAX accessory molecule-1 (DNAM-1): activating adhesion/co-stimulatory receptor binding CD112/CD155; promotes target killing and effector responses.
Glycolipid (GCL): membrane-bound lipids containing a covalently attached carbohydrate group. Glycolipid-rich *T. cruzi* components that activate immune cells, including γδ T cells, frequently via CD1-dependent presentation.
Granulocyte-macrophage colony-stimulating factor (GM-CSF): a cytokine that boosts myeloid cell production/activation and can intensify inflammation.
Human African trypanosomiasis (HAT): *T. brucei* infection transmitted by tsetse flies; can progress from hemolymphatic disease to neurological involvement and death if untreated.
Indeterminate Chagas disease (IND): a clinical form of chronic *T. cruzi* infection with no overt clinical symptoms.
Innate lymphoid cell (ILC): TCR-negative lymphocytes that rapidly produce cytokines in tissues.
Interferon gamma (IFN-γ): type 1 cytokine that activates macrophages and supports Th1/cytotoxic immunity.
Interleukin (IL): cytokine family prefix (e.g., IL-6, IL-10, IL-17) mediating

in lung, liver, and reproductive tissues, and Vγ1$^+$ and Vγ4$^+$ subsets predominating in secondary lymphoid organs and circulating pools, where they display greater functional plasticity [18]. In humans, Vγ9Vδ2 cells dominate the blood, whereas Vδ1 cells are enriched at mucosal, epithelial, hepatic, and other barrier sites as tissue-resident T cells [6,15,16]. Vγ9Vδ2 cells sense microbe- and host-derived phosphoantigens via butyrophilin 3A1/2A1 complexes, while Vδ1 cells can recognize CD1d-presented lipids and stress-induced self-ligands, including MHC class I-related molecules A and B (MICA/MICB) and UL16-binding proteins that are upregulated on infected, transformed, or stressed cells. In both cases, activation integrates TCR-dependent recognition with NK-receptor co-stimulation via the engagement of **natural killer group 2, member D (NKG2D)**, **DNAX accessory molecule-1 (DNAM-1)**, and **natural killer cell (NK)** cytotoxicity receptors (e.g., NKp30 and NKp44), which amplify effector responses [17,19]. Functionally, co-stimulatory NK receptors such as NKG2D and DNAM-1 can amplify γδ T-cell responses by synergizing with γδTCR signals, lowering the activation threshold and boosting degranulation/cytotoxicity and cytokine output when stress-induced ligands are expressed on target cells. Conversely, inhibitory NK receptors (e.g., CD94/NKG2A) impose a checkpoint that can dampen γδ T-cell effector function in ligand contexts that signal 'self' or low stress, helping to prevent excessive inflammation and collateral tissue damage [17,19]. γδ-derived IL-17, GM-CSF, and IFN-γ shape neutrophil, monocyte, and dendritic-cell responses, while IL-1β, IL-23, and IL-18 from myeloid cells reinforce γδ IL-17- or IFN-γ-producing programs [15,17,20]. Some γδ subsets acquire antigen-presenting-cell-like or follicular-helper-like properties, upregulating MHC class II and co-stimulatory molecules and producing IL-4 and IL-21 to support germinal-center B cells and antibody production [16]. Table 1 summarizes the characteristics and functions of γδ T cells. Through effector, regulatory, and helper functions, γδ T cells are poised to shape anti-trypanosomatid immunity from the earliest stages of infection onward. Given the variety of functions they can exert, diving into their interactions with *T. cruzi* and *T. brucei* will enlighten new strategies for disease control and management.

γδ T cells in *T. cruzi* infection: from experimental models to human cardiomyopathy

γδ T cells are best known for tissue immunosurveillance and antitumor activity, but increasing evidence shows they also shape outcomes in parasitic disease. In Chagas disease, γδ T cells meet multiple criteria for causal involvement in both parasite control and immunopathology, particularly in the heart, where γδ responses contribute to the early containment of parasitism while, when sustained, they can amplify tissue injury.

Experimental evidence for a dual role

γδ T-cell function can be interrogated using complementary approaches. Transient antibody-mediated depletion (commonly with anti-TCRγδ clone GL3) enables loss-of-function experiments in otherwise immunocompetent animals [21]. Expansion/activation strategies include cytokine-driven growth (notably IL-15, often with IL-2) and, for human Vγ9Vδ2 cells, phosphoantigen/aminobisphosphonate plus IL-2 protocols (e.g., zoledronate + IL-2), widely used for *ex vivo* expansion [22]. Adoptive transfer of purified or *ex vivo*-expanded γδ T cells permits subset-specific tracking and direct testing of protection versus pathology in infection models [23]. Genetic ablation of γδ T cells (*TCRδ*$^{-/-}$) is another strategy, which has been used in *T. cruzi*-infected mice. Studies using mice without γδ T cells (*TCRδ*$^{-/-}$) infected with *T. cruzi* showed that genetic ablation attenuated disease severity and improved survival relative to δ$^{+/-}$ controls despite comparable parasitemia, linking these cells with pathology [24]. Histopathology at late time points reinforced this dissociation between parasite load and tissue damage: *TCRδ*$^{-/-}$ hearts displayed fewer myocytolytic foci and less interstitial injury with reduced mononuclear infiltration; skeletal muscle showed the same pattern. Notably, no visible parasite nests were detected in high-pathology mice, whereas nests persisted in lower-pathology animals, stressing that immunopathology, rather than residual parasite burden, dominated late injury

immune-cell communication and tissue inflammation/repair and orchestrating several aspects of the immune response.
Major histocompatibility complex (MHC): antigen-presenting molecules (class I/II) central to T-cell selection and activation; many γδ responses are relatively MHC-independent.
Mechanistic target of rapamycin (mTOR): nutrient-sensing kinase controlling growth/metabolism (including glycolysis), influencing immune and adipocyte programs.
Myeloid differentiation primary response 88 (MyD88): adaptor for many Toll-like/IL-1 family receptors, triggering NF-κB-dependent inflammatory programs.
Natural killer cell (NK): an innate cytotoxic lymphocyte that kills stressed/infected cells and produces cytokines (notably IFN-γ).
Natural killer group 2, member D (NKG2D): activating receptor on NK, γδ, and CD8$^+$ T cells recognizing stress-induced ligands to amplify cytotoxicity/cytokines.
Peripheral blood mononuclear cells (PBMC): mixed blood immune-cell fraction (lymphocytes + monocytes).
Subcutaneous white adipose tissue: fat depot beneath skin that can act as an immunometabolic niche and parasite reservoir during infection.
T-cell receptor (TCR): antigen-sensing receptor on T cells (αβ or γδ) that initiates activation and effector programs; γδ TCRs often recognize stress/microbial ligands.
T helper cell (Th): CD4$^+$ T-cell lineages (e.g., Th1/Th2/Th17) that coordinate immune responses via cytokines and help other leukocytes.
White adipose tissue (WAT): primary energy-storage endocrine organ producing adipokines and inflammatory mediators.

Table 1. Overall characteristics and functions of γδ T-cell subsets

Subset/feature	Antigen/ligand recognition	Key cytokines/molecules	Main functions	Typical localization
All γδ T cells	TCR composed of γ and δ chains; recognizes antigens largely independently of classical MHC	IFN-γ, IL-17, GM-CSF, IL-10, and TGF-β; cytotoxic, death-receptor ligands	Bridge innate and adaptive immunity; rapid response to tissue stress; cytokine production and cytotoxicity	Widely distributed; enriched at barrier and vascularized sites
Vγ9Vδ2 (human)	Microbe- and host-derived phosphoantigens presented via butyrophilin 3A1/2A1 complexes; co-stimulation via NKG2D, DNAM-1, NKp30, NKp44	IFN-γ, TNF, and cytotoxic mediators	Early sensing of infection, anti-microbial and antitumor cytotoxicity, shaping myeloid and αβ T-cell responses	Dominant γδ subset in blood
Vδ1 (human)	CD1d-presented lipids and stress-induced self-ligands; co-stimulation via NK receptors (e.g., NKG2D, NKp44)	IFN-γ, IL-17, and regulatory cytokines; cytotoxic mediators	Surveillance of stressed/infected cells at barrier sites; tissue repair or damage depending on program	Enriched in mucosal, epithelial, hepatic, and other tissue-resident niches
IFN-γ-producing	TCR plus inflammatory cytokines (e.g., IL-18); NK receptor co-stimulation	IFN-γ and TNF	Provide early type 1 help; support Th1 and $CD8^+$ T-cell responses; enhance pathogen control	Blood and inflamed tissues
IL-17-producing	TCR plus IL-1β, IL-23, and other innate cues	IL-17A/F and GM-CSF	Drive neutrophil recruitment; activate inflammatory monocytes; amplify innate responses and tissue inflammation	Often tissue-resident/barrier-associated
Regulatory	Similar sensing as other γδ, but biased by tolerogenic cues	IL-10 and TGF-β; checkpoint molecules	Limit excessive inflammation; restrain tissue damage but may allow pathogen persistence	Inflamed or chronically stimulated tissues
Cytotoxic	Recognition of stressed, infected, or transformed cells via TCR and NK receptors	Perforin, granzymes, and FasL/TRAIL	Direct killing of targets; complement cytokine-mediated control	Blood and tissues during acute/chronic inflammation
APC-like/Tfh-like	Antigen uptake and processing; interactions with B cells and DCs	IL-4 and IL-21; upregulated MHC II and co-stimulatory molecules	Support germinal center B cells and antibody production; shape quality of humoral responses	Lymphoid organs and tertiary lymphoid structures

APC: antigen-presenting cell; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand.

[24]. The mechanisms by which these cells fueled pathology independent of parasitemia were, at the time, unknown.

Later, another study suggested that the production of IFN-γ, mostly derived from γδ T cells, was critical for parasite control in the liver. While uncommon in chronically infected patients, liver involvement leading to hepatomegaly and hepatosplenomegaly may occur in the human acute phase due to oral infection [25] and in experimental *T. cruzi* infection. Sardinha *et al*. showed that during acute *T. cruzi* infection, NK cells provided a precocious burst of IFN-γ, which later shifted to $CD4^+$, $CD8^+$, and double-negative ($CD4^-CD8^-$) T cells, with γδ cells showing the most pronounced expansion among liver lymphocytes [26]. Despite high blood parasitemia, amastigote nests were rarely seen in the liver unless IFN-γ was absent, suggesting that a local type-1 response, fed in great part by γδ T cells, efficiently restrained replication. This supports a timing-dependent model in which γδ programs contribute beneficially to early IFN-γ-mediated control in visceral tissues, even as sustained activation in the heart and skin aligns with tissue damage.

A mechanistic link for this early, tissue-resident, γδ response was later provided by work showing that IL-18R–**myeloid differentiation primary response 88 (MyD88)** signaling is indispensable

for γδ T-cell expansion and function during experimental *T. cruzi* infection. In wild-type mice, there was a rapid γδ T-cell infiltration of the heart, but in Il18r1$^{-/-}$ and Myd88$^{-/-}$ animals, these cells were markedly reduced and showed impaired proliferation, as well as defective generation of granzyme B and IFN-γ [27]. These knockout mice also generated fewer Vγ1.1^{+} effector γδ T cells and became more susceptible, with higher cardiac parasite loads. Importantly, adoptive transfer of IL-18R-sufficient γδ T cells into Il18r1$^{-/-}$ hosts rescued parasitemia and mortality, indicating that IL-18 is a cell-intrinsic licensing signal for immunoprotective γδ T-cell responses in acute *T. cruzi* experimental infection. Depletion studies further refined this by pointing Vγ1^{+} cells as a subset that 'helps' Th1 responses, since their absence led to higher parasitemia and early mortality, together with a drop in IFN-γ^{+} by both CD4^{+} and CD8^{+} T cells [28].

A persistent challenge in studying *T. cruzi* and Chagas disease is that the parasite is not a single, fixed entity but rather a genetically heterogeneous complex of discrete typing units with distinct virulence, immunogenicity, and geographic distribution [29–31]. This heterogeneity can influence T-cell responses. In adult rats, the highly virulent CL-Brener strain triggered a 20-fold expansion of CD4^{-}CD8^{-} T cells and systemic IFN-γ/tumor necrosis factor α (TNF-α) production, whereas the less virulent JG strain induced only an eightfold CD4^{-}CD8^{-} increase and preserved a higher IL-10/IFN-γ ratio [32]. While this study did not define the TCR expressed by the CD4^{-}CD8^{-} T cells, it is known that these cells predominantly express the γδ TCR. Thus, by extrapolation, it is possible to hypothesize that different parasite isolates can induce expansion of γδ/CD4^{-}CD8^{-} axis toward a highly inflammatory setting or toward a more modulated one.

Experimental *T. cruzi* infection has also shown that γδ T cells are capable of active regulation. T cells from infected young adult BALB/c mice exhibit suppressor activity when added to fully allogeneic mixed lymphocyte cultures, which could not be reverted after the addition of IL-2 [33]. Interestingly, this suppression was not dependent on IL-4, IL-10, or TGF-β, cytokines normally associated with this profile. In fact, splenic γδ T cells from these young acutely infected mice were responsible for this suppressive activity either *in vitro* or *in vivo*, since the removal of γδ but not αβ T cells abolished the suppressor activity and enhanced IFN-γ expression [33]. However, in aged mice, γδ T-cell-dependent suppressor activity is not detectable during acute *T. cruzi* infection, and these animals go on to develop early, severe autoimmune myocarditis [33]. This contrast with young mice supports the idea that a γδ-mediated regulatory circuit helps maintain cardiac self-tolerance in the acute phase; when that brake fails, autoimmune pathology emerges.

Human γδ T cells in chronic Chagas disease

While no studies have, to date, been performed in the acute phase of human Chagas disease regarding γδ T cells, several studies have evaluated their role during the chronic phase of the disease. Villani and colleagues showed that when **peripheral blood mononuclear cells (PBMC)** from chronically infected individuals are exposed to live *T. cruzi* trypomastigotes *in vitro*, CD4^{-}CD8^{-} T cells of both αβ and γδ lineages expand. This expansion is observed in patients of both polar forms: IND and CCC [34]. However, only IND patients displayed a γδ CD4^{-}CD8^{-} subset that produces high, antigen-specific IL-10 and correlates with better ventricular function. In contrast, CCC patients expand CD4^{-}CD8^{-} T cells, particularly those TCRγδ^{+}, with a predominantly inflammatory profile determined by a high frequency of cells expressing IFN-γ and TNF-α and by the ratio of cells expressing these inflammatory cytokines in relation to IL-10, linking the loss of γδ-IL-10 with pathology. Subsequent analyses refined these observations by examining the memory composition of CD4^{-}CD8^{-} T cells in chronic Chagas disease. The CD4^{-}CD8^{-} subpopulation from IND was enriched for central-memory γδ CD4^{-}CD8^{-} T cells that co-expressed IFN-γ and IL-10 and displayed a lower activation profile, consistent with a regulatory or

damage-limiting role. By contrast, CCC accumulated effector-memory and terminal-effector γδ $CD4^{-}CD8^{-}$ T cells with a predominantly inflammatory signature [35].

Studying the *T. cruzi*-derived component that activated these cells, it was found that the main trigger was not protein but **glycolipid (GCL)-enriched** components. When PBMCs from IND and CCC patients were stimulated, GCLs induced the highest CD69 expression on γδ $CD4^{-}CD8^{-}$ T cells [36]. Strikingly, the pattern of cytokine response diverged in the same way as mentioned earlier: GCL stimulation increased the frequency of IL-10^{+} γδ $CD4^{-}CD8^{-}$ T cells in IND, while in CCC it skewed toward IFN-γ production, increasing the IFN-γ/IL-10 ratio and thereby favoring inflammation. These experiments identified *T. cruzi* GCLs as the major parasite component licensing γδ $CD4^{-}CD8^{-}$ T cells toward the pathogenic profile in CCC.

In parallel, a study analyzing antigen-presentation pathways in chronic Chagas disease patients found that parasite stimulation of PBMC led to the upregulation of CD1a, CD1b, CD1c, and CD1d expression on $CD14^{+}$ monocytes, but only CD1d expression was associated with both $CD4^{-}CD8^{-}$ T-cell activation and poorer ventricular function [37]. Interestingly, CD1d is one of the key receptors responsible for mediating γδ T-cell responses to GCLs [38,39]. Blocking CD1d-mediated presentation led to a clear reduction in γδ $CD4^{-}CD8^{-}$ T-cell activation and to lower IFN-γ production, whereas conventional $CD4^{+}$ and $CD8^{+}$ T cells were minimally affected [37]. Decreasing CD1d-mediated activation of γδ $CD4^{-}CD8^{-}$ T cells also leads to an increase in IL-10 expression by effector memory γδ $CD4^{-}CD8^{-}$ T cells from CCC, restoring a balanced profile like that observed in the protective central memory γδ $CD4^{-}CD8^{-}$ T cells from IND [35].

More recent analyses demonstrate that $CD4^{-}CD8^{-}$ γδ T cells from CCC display a highly cytotoxic and migratory profile [40]. They express high levels of granzyme A, perforin, and inflammatory chemokine receptors, such as CCR5, and transcripts encoding these molecules are correspondingly increased in CCC myocardial tissue, supporting their capacity to home to and injure the heart. Importantly, blockade of CD1d-dependent activation *in vitro* reduced both the cytotoxic profile and the expression of chemotactic receptors, suggesting that interference with this pathway can concomitantly limit recruitment, inflammation, and target-cell killing.

Taken together, experimental and clinical observations support a unifying framework for γδ T cells in Chagas disease, in which their activity must be finely balanced to promote parasite control without exacerbating pathology. Early, IL-18-dependent, Vγ1-skewed γδ responses occupy a narrow window in which effector output is sufficient to activate innate and conventional T-cell immunity and to limit *T. cruzi* dissemination. By contrast, parasite genetic background, host aging, and, critically, sustained CD1d presentation of parasite glycolipids can shift the same compartment, generating chronically activated, IFN-γ- and granzyme-rich, heart-homing γδ T cells that are enriched in CCC. Because these inflammatory γδ T cells and CD1d upregulation on monocytes associate with worse ventricular function, their frequency, memory phenotype, and IFN-γ/IL-10 balance after glycolipid stimulation are attractive biomarkers to distinguish individuals who will remain as IND from those at risk of progression to CCC. The finding that CD1d blockade restores IL-10 and de-arms γδ $CD4^{-}CD8^{-}$ T cells highlights the CD1d–glycolipid axis as a mechanistically and therapeutically approachable if IL-10-competent central-memory γδ $CD4^{-}CD8^{-}$ T cells are preserved. Figure 1 summarizes the role of γδ T cells in Chagas disease.

γδ T cells in *T. brucei* infection

An increasing body of work has revealed that γδ T cells have a critical role in the response to *T. brucei*. Once it has been transmitted, the parasite disseminates to practically every tissue in the body [41] but forms persistent reservoirs in the adipose tissue [42,43] and the skin [44].

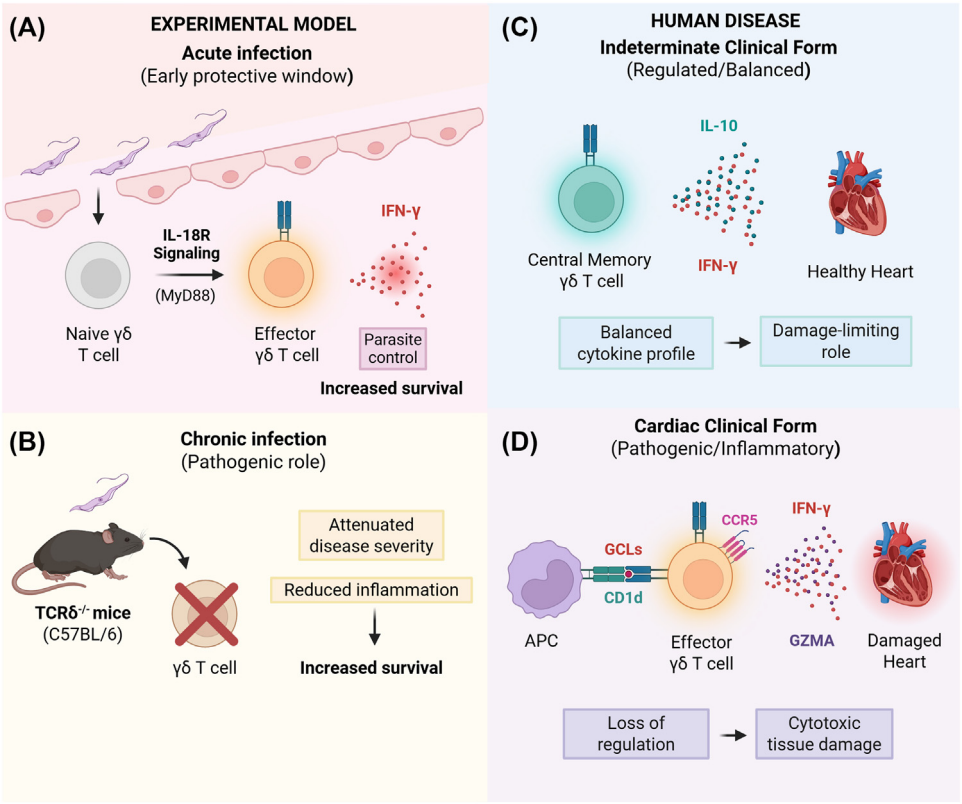

Figure 1. γδ T cells in experimental infection with *T. cruzi* and chronic human disease. (A) During murine early infection, IL-18R–MyD88 signaling drives γδ T-cell expansion and effector differentiation, enabling robust type-1 output (e.g., IFN-γ; cytotoxic programs) that contributes to parasite control and improved survival. (B) In murine chronic infection, genetic ablation of γδ T cells (TCRδ$^{-/-}$) attenuates tissue inflammation and disease severity and improves survival, despite broadly comparable parasitemia, supporting a dominant contribution of γδ-driven immunopathology at late stages. (C) In indeterminate Chagas disease (IND) patients, γδ compartments, especially the CD4^{-}CD8^{-} (DN) T cells, are enriched for central-memory phenotypes with a balanced IL-10/IFN-γ program, consistent with damage-limiting regulation and preserved cardiac function. (D) In patients with chronic Chagas cardiomyopathy (CCC), sustained activation through the CD1d–parasite glycolipid axis (GCLs) skews DN γδ T cells toward a higher IFN-γ/IL-10 ratio and acquisition of heart-homing/cytotoxic features (e.g., CCR5 and granzymes), promoting myocardial injury; CD1d blockade can de-arm these programs and partially restore IL-10. APC: antigen-presenting cell; CCR5: C-C chemokine receptor type 5; DN: double-negative (CD4^{-}CD8^{-}); GZMA: granzyme A; IFN: interferon; IL-18R: interleukin-18 receptor; MyD88: myeloid differentiation primary response 88; TCR: T-cell receptor

Indeed, these parasites have been observed in the skin and the adipose tissue of both mice [42,45] and naturally infected humans [44], demonstrating that this is a conserved feature of the infection. Another strongly conserved feature of chronic infection in humans and animals is severe weight loss and adipose tissue wasting, similar to cachexia [46]. Here we will discuss the interplay of the immune system between the skin and the adipose tissue and the role that γδ T cells play during *T. brucei* infection.

The skin as a site of interplay between *T. brucei* and γδ T cells

The skin, in particular, is an important niche for onward transmission, as the parasite must reside in a location where it can be transmitted back to the vector [44]. However, this brings the challenge of facing a sustained local immune response within this reservoir. Although our knowledge of the immune responses of the skin to infection with *T. brucei* is still developing, it is becoming

increasingly evident that γδ T cells are an important contributor to that response. A major outstanding question within this field is how Vγ6$^+$ cells and, more broadly, γδ T cells sense *T. brucei* in the skin and initiate their interactions with the stroma. How γδ T cells sense antigen remains somewhat unclear, but subsets such as Vγ9Vδ2$^+$ can sense microbial phosphoantigens via the cell surface immunoglobulins butyrophilin 2A1 (BTN2A1) and BTN3A1 [47]. However, it has not been demonstrated whether *T. brucei* parasites express factors that could be detected by **butyrophilin (BTN)** molecules or whether γδ T cells could be activated by factors within the saliva of the vector tsetse fly.

We previously observed that during chronic *T. brucei* infection, there is an increased number of myeloid cells within the skin, including monocytes, macrophages, and mast cells [48]. Concurrently, there was an increase in T-cell subsets, including ILC2s and CD4$^+$ T cells. Within the T-cell subsets, there was also an increase in the activation of dermal Vγ6$^+$ γδ T cells, which are known to secrete IL-17A [49]. To test the role of Vγ6$^+$ cells in controlling *T. brucei*, Vγ4/6$^{-/-}$ mice were infected, which increased skin inflammation relative to control animals. However, there was no effect on local or systemic parasite burden, suggesting that Vγ4$^+$ and Vγ6$^+$ cells are dispensable for clearing the parasite. This does not rule out the possibility that Vγ4$^+$ and Vγ6$^+$ cells play a role in controlling pathogen burden, but there may be mechanisms that are able to compensate for their loss.

Adipose tissue as an active site of inflammation and metabolic reprogramming of γδ T cells

Intriguingly, using a spatial sequencing approach, we observed that Vγ6$^+$ cells were dominant in the epidermal and dermal layers of the skin under homeostasis but migrated to the **subcutaneous white adipose tissue** layer during *T. brucei* infection. This is likely due to the upregulation of the chemokines *Cxcl1*, *Cxcl9*, and *Cxcl10* by adipocyte precursors (preadipocytes) during infection. *In silico* interaction analyses further suggested that the expression of *Areg* and *Clcf1* by Vγ6 cells may directly impact adipocytes, which upregulate the cognate receptors for these factors, which, in turn, may impact the metabolism and immunoregulatory phenotype of the adipocytes [50,51]. Indeed, during *Staphylococcus aureus* infection, macrophage-derived **amphiregulin (AREG)** drives the transition of preadipocytes to myofibroblasts in the bone marrow via the **mechanistic target of rapamycin (mTOR)** signalling, a pathway that has also been demonstrated to increase aerobic glycolysis [52,53]. As AREG has been demonstrated to regulate glycolysis via mTOR in several different tissues, it is plausible to hypothesize that it also drives this pathway in mature adipocytes. In addition, **cardiotrophin-like cytokine factor 1 (CLCF1)** has a profound effect on adipose tissue. In the **brown adipose tissue (BAT)**, CLCF1 inhibits mitochondrial biogenesis and drives the BAT to a **white adipose tissue (WAT)**-like phenotype, diminishing its capacity to induce nonshivering thermogenesis and decreasing energy expenditure [54]. Notably, CLCF1 has the opposite effect on WAT and increases mitochondrial biogenesis, demonstrating that the effects of this factor are likely context and tissue specific.

In addition to AREG and CLCF1, Vγ6$^+$ cells are major sources of IL-17A and IL-17F, both of which are increased during human and murine *T. brucei* infections. This is noteworthy, as recent studies have demonstrated the importance of γδ T cells and IL-17 signaling for controlling adipose tissue function and homeostasis [55–57]. For example, deletion of γδ T cells or the adipocyte IL-17 receptor C (IL-17RC) leads to elevated mitochondrial biogenesis in the WAT [56]. It has also been demonstrated that T cells [58] and, in particular, IL-17A producers [45] are major drivers of the weight loss and adipose tissue wasting associated with *T. brucei* infection. This occurs via adipocyte IL-17 signaling through adipocyte IL-17 receptor A (IL-17RA). When mice with a deletion of IL-17RA on adipocytes are infected with *T. brucei*, similar to global *Il17a/f*$^{-/-}$, they are protected from adipose tissue wasting [45]. Although this signaling pathway has been

identified as a driver of adipose tissue wasting, how it controls this effect has not yet been resolved. Recent work from Douglas *et al.* provides some intriguing hints as to how this may occur [59]. When studying the BAT, they found that mice with a global deletion of IL-17A and IL-17F (*Il17af*$^{-/-}$) expressed lower levels of *Atgl*, the rate-limiting enzyme for adipocyte lipolysis, which supports the observation that IL-17-expressing cells drive adipose tissue wasting during *T. brucei* infection. If this also occurs in the WAT, then this may provide evidence for how IL-17 signaling drives wasting. The wasting associated with *T. brucei* infection also has consequences for the immune response to the parasite, as the parasite burden increases when the IL-17 receptor A (IL-17RA) is deleted from adipocytes [48]. Machado *et al.* provide a possible explanation for this by demonstrating that free fatty acids released by lipolysis are lipotoxic for the parasite [60] and, therefore, γδ T-cell-derived IL-17 may control parasite burden by driving lipolysis during infection. However, this does not negate the possibility that adipose tissue lipolysis and subsequent wasting may alter the immune response to infection. For example, uptake of oxidized lipids and long-chain acylcarnitine species can impair CD8^{+} T-cell and NK cell function, respectively [61,62]. If adipose tissue wasting during *T. brucei* infection leads to the release of oxidized lipids and long-chain acylcarnitine species, then this may be permissive for expansion of the parasite. These intriguing findings suggest that interplay between γδ T cells and stromal/parenchymal cells is critical for the immune response to *T. brucei* infection. This complex interplay is depicted in Figure 2.

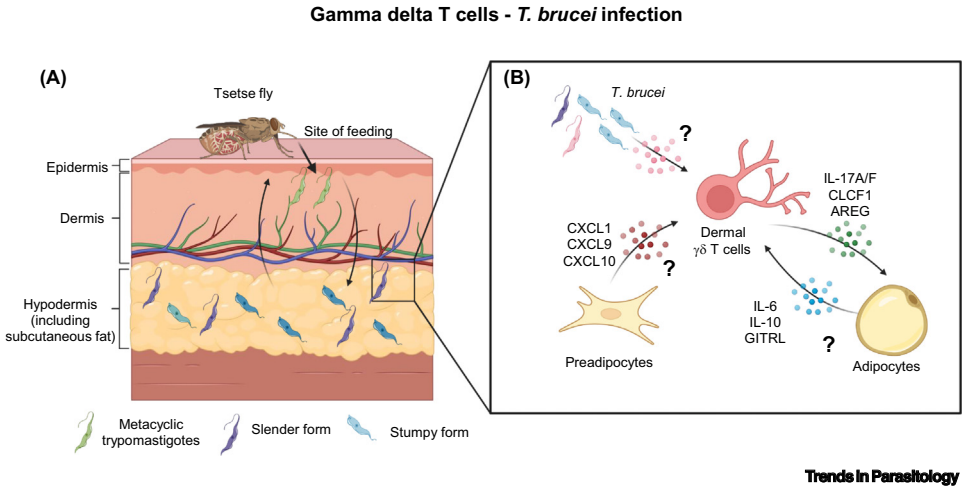

Figure 2. γδ T cells as coordinators of dermal immune responses at the host–vector–pathogen interface in experimental human African trypanosomiasis (HAT). (A) During a blood meal, tsetse flies transmit *T. brucei* metacyclic trypomastigotes that establish infective niches throughout the body, including in the subcutaneous white adipose tissue (sWAT). In the process, the flies also take up stumpy and slender forms able to establish further infections in vectors. (B) We previously demonstrated the importance of Vγ6^{+} γδ T cells acting concertedly with stromal cells, including preadipocytes and mature adipocytes, shaping dermal responses to *T. brucei* infection. We propose that γδ T cells migrate from the dermis into the hypodermis and sWAT in a process orchestrated by chemokines such as CXCL1, CXCL9, and CXCL10 expressed by preadipocytes. Once in the sWAT, γδ T cells establish an intricate interaction with mature adipocytes mediated, at least in part, by IL-17 signaling to sustain adipose tissue homeostasis and resilience during infection. Additional factors such as cardiotrophin-like cytokine factor 1 (CLCF1) and amphiregulin (AREG) also play a role in this process. Similarly, adipose tissue-derived adipokines such as IL-6, IL-10, and glucocorticoid-induced TNFR-related protein ligand (GITRL) also modulate the effector function of dermal γδ T cells, although this remains to be tested. Whether parasite-derived factors (e.g., extracellular vesicles and secreted virulence factors) affect γδ T cells also remains unclear. Genetic ablation of these signaling pathways between γδ T cells and stromal cells in the skin results in uncontrolled parasite burden in the skin, demonstrating the physiological relevance of these novel interactions in shaping dermal *T. brucei* population. Whether this increases fly infectivity and disease transmission remains to be studied. CXCL1: C-X-C motif chemokine ligand 1; CXCL9: C-X-C motif chemokine ligand 9; CXCL10: C-X-C motif chemokine ligand 10; IL: interleukin; TNFR: tumor necrosis factor receptor.

Concluding remarks and future perspectives

γδ T cells have emerged as key orchestrators of immunity across many conditions, including cancer, bacterial sepsis, tuberculosis, viral infection, and parasitic diseases, such as malaria and leishmaniasis [5,63–68]. In these settings, γδ T cells provide rapid cytokine bursts, cytotoxicity, and tissue surveillance but can also acquire regulatory or tissue-repair functions, making them powerful shapers of whether inflammation resolves or spirals into pathology [5,63–68]. Our synthesis of data from *T. cruzi* and *T. brucei* infection reinforces this duality: the same γδ compartment that constrains early parasite growth, when chronically activated or skewed, drives destructive myocarditis, adipose wasting, and possibly neuroinflammation. In sleeping sickness, neuroinflammation is a defining feature of the meningoencephalitic stage and reflects parasite invasion of the central nervous system combined with sustained immune activation; although direct evidence is limited, γδ T cells could respond to inflammatory cues at the blood–brain barrier and shape leukocyte recruitment and glial activation, thereby influencing the balance between parasite control and immunopathology. Alternatively, γδ T cells located in the dura mater [69] could also represent important immunological coordinators of the responses observed at the brain borders, which is especially relevant in the context of the chronic and pathological meningitis observed in sleeping sickness. Whether the cytokines derived from meningeal γδ T cells, reported to regulate anxiety [69] and short-term memory [70], are also involved in the sleep and circadian disturbances observed during sleeping sickness also merits further investigation.

How the intracellular versus extracellular lifestyles of these parasites shape γδ T-cell responses remains an open question. The predominantly intracellular amastigote stage of *T. cruzi* likely promotes γδ T-cell activation via host cell stress signals and uses intracellular pathways of antigen presentation. In contrast, the exclusively extracellular trypomastigote stages of *T. brucei* may favor activation through direct sensing of parasite-derived molecules, leading to more systemic inflammatory cues. One potential route of activation might involve the release of virulence factors and extracellular vesicles, as reported for *T. brucei* [71] and *T. cruzi* [72]. Whether the lipid composition of the internal content of these vesicles is able to trigger γδ T-cell activation remains an open question.

The central take-home message is that γδ T cells are not bystanders but conditional 'decision makers' in trypanosomatid infection: their balance of IFN-γ versus IL-17, cytotoxic versus regulatory programs, and stromal crosstalk strongly influences whether hosts control parasites with limited damage or progress to severe disease. Moving forward, three knowledge gaps stand out. First, we still have a fragmentary view of antigen recognition, especially for tissue-resident γδ subsets. Thus, defining parasite, vector, and damage-associated ligands for γδ TCRs, CD1 molecules, and BTNs is, therefore, essential. Second, most mechanistic insight comes from mice and *ex vivo* human blood; single-cell and spatial approaches in target tissues are needed to link γδ T cells to disease outcomes. Third, interventional studies are lacking: selectively amplifying protective γδ circuits (e.g., via targeted adjuvants or metabolic modulation) while dampening pathogenic axes will be crucial to test γδ T cells as therapeutic targets, vaccine adjuvant platforms, and prognostic biomarkers in Chagas disease and sleeping sickness.

T. cruzi and *T. brucei* infections provide complementary, clinically relevant models in which γδ T cells can be studied across intracellular versus extracellular organisms and in acute versus chronic disease trajectories, offering a powerful framework to dissect how these cells integrate pathogen control with immune-mediated pathology in many diseases.

Ultimately, tackling the major issues highlighted in this review (see Outstanding questions) will require bringing γδ T cells from the periphery of trypanosomatid research to its center.

Outstanding questions

Which parasite, vector, and damage-associated ligands are recognized by γδ T-cell receptors during *T. cruzi* and *T. brucei* infection *in vivo*?

How do distinct γδ T-cell subsets traffic to and persist within the heart, adipose tissue, skin, liver, and nervous system over the course of infection, and what signals drive their switching between interferon gamma, interleukin-17, cytotoxic, and regulatory programs?

To what extent do γδ T-cell phenotypes defined in murine models mirror those in humans with asymptomatic infection, Chagas cardiomyopathy or megasyndromes, and different clinical forms of human African trypanosomiasis?

Can γδ T-cell responses be therapeutically tuned, for example, via CD1d ligands, butyrophilin-targeting agents, or cytokine or metabolic cues, to enhance parasite control without worsening tissue damage or immune exhaustion?

How can γδ T-cell-related transcriptional, cytokine, or metabolic signatures in blood or tissues be developed into biomarkers of disease progression, therapeutic response, or risk of relapse?

What roles do γδ T cells play in long-term sequelae such as chronic cardiomyopathy, neurocognitive impairment, and metabolic remodeling after apparent parasite control or cure, and are these processes reversible?

How do coinfections, microbiota, nutritional status, and host genetics shape γδ T-cell networks in trypanosomatid infections, and could targeting these modifiers improve outcomes in endemic populations?

Mechanistically, pairing single-cell and spatial profiling of human tissues with refined experimental models can define which γδ programs are truly protective versus pathogenic and when they operate during infection. Translationally, this knowledge can guide the rational design of γδ-targeted adjuvants for vaccines, host-directed therapies, and γδ-based biomarkers to stratify risk and monitor treatment response. If embedded in collaborative networks that include endemic-area clinics and laboratories, such efforts could ultimately lead to the discovery of much-needed prognostic markers, safer and more effective new therapeutic strategies, and clinical management.

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Declaration of interests

The authors declare no competing interests.

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