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Host immune evasion strategies of *Trypanosoma cruzi* during chronic chagas disease

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Abstract

One observation that has puzzled parasitologists for decades is how *Trypanosoma cruzi* persists in human hosts for a lifetime despite generating strong humoral and cellular immune responses. This research characterized the immune evasion mechanisms employed by *T. cruzi* during experimental chronic Chagas disease in BALB/c mice (n = 48) infected with the Y strain and monitored for 24 weeks. Blood parasitemia, tissue parasite burden, complement evasion capacity, surface antigen diversity, T cell exhaustion markers, and regulatory T cell (Treg) frequencies were tracked at biweekly intervals. Complement resistance was the dominant evasion mechanism during acute infection (contributing an estimated 24.3% of overall immune escape), while T cell exhaustion (PD-1+/Tim-3+ CD8+ T cells rising from 8.4% to 43.7%) and Treg induction (CD4+FoxP3+ cells doubling from 6.2% to 12.8%) became the main strategies sustaining chronic persistence. Parasite surface trans-sialidase diversity peaked during the acute-to-chronic transition (weeks 6-10) with 14 distinct variants detected by sequencing. These temporal shifts suggest that *T. cruzi* deploys an ordered succession of evasion mechanisms rather than relying on a single strategy throughout infection.

Keywords: Immune evasion, *Trypanosoma cruzi*, chagas disease, chronic infection, parasite-host interaction, complement resistance, t cell exhaustion, trans-sialidase, regulatory t cells, immune subversion

Introduction

An observation worth pausing over: *Trypanosoma cruzi* can live inside a human host for 30 or 40 years, sitting quietly in cardiac and gastrointestinal muscle cells while the immune system tries and fails to clear it. Unlike malaria parasites, which cycle through blood-stage crises, or helminths, which physically wall themselves off, *T. cruzi* maintains a low-grade intracellular presence that slowly damages tissues without triggering the kind of acute immune response that might eliminate it ^[1].

The parasite's evasion toolkit includes at least six known strategies: complement resistance through surface glycoproteins, antigenic variation of surface trans-sialidases, induction of T cell exhaustion via checkpoint receptor engagement, expansion of host regulatory T cells that suppress effector responses, subversion of macrophage killing mechanisms, and apoptosis mimicry through phosphatidylserine exposure ^[2, 3]. But the relative importance of each strategy changes as infection progresses from acute to chronic phases, and the temporal sequence of these shifts hasn't been mapped in a single experimental system.

This research tracked all six evasion mechanisms longitudinally in BALB/c mice infected with *T. cruzi* Y strain over 24 weeks at the Kamchatka College of Marine Biology, Petropavlovsk-Kamchatsky, from January to August 2023, aiming to build a timeline of immune evasion during the establishment of chronic Chagas disease.

Material and Methods

Material

Forty-eight female BALB/c mice (6-8 weeks, 18-22 g) were obtained from the Institute of Experimental Animals, Moscow. *T. cruzi* Y strain trypomastigotes were maintained by passage in Vero cells. Mice were infected intraperitoneally with 1,000 blood-form trypomastigotes. Control mice (n = 8) received sterile saline. Anti-PD-1, anti-Tim-3, anti-FoxP3, and anti-CD4/CD8 antibodies were from BioLegend.

Complement components C3 and C5b-9 antibodies were from Abcam. Research was approved by the Kamchatka College Animal Ethics Committee (Protocol KCMB-AEC-2022-019, December 2022).

Methods

Parasitemia was monitored by microscopic counting of Giemsa-stained tail blood smears every two weeks. Tissue parasite burden in heart and skeletal muscle was quantified at sacrifice time points (weeks 4, 8, 12, 18, 24; n = 8 per time point) by quantitative PCR targeting the *T. cruzi* satellite DNA repeat. Complement resistance was measured by incubating blood-form trypomastigotes with 50% normal mouse serum for 60 minutes and counting surviving parasites. T cell phenotyping used multicolor flow cytometry on splenic lymphocytes, gating on CD8+PD-1+Tim-3+ (exhausted) and CD4+FoxP3+ (Treg) populations. Trans-sialidase gene diversity was assessed by amplifying the N-terminal variable region from parasite DNA isolated at each time point and sequencing 50 clones per sample on an Illumina MiSeq. Macrophage killing capacity was tested by infecting bone marrow-derived

macrophages with trypomastigotes at 5:1 ratio and counting intracellular amastigotes at 48 hours. Data were analyzed by two-way ANOVA with time and infection as factors.

Results

Table 1: Temporal profile of immune evasion parameters during 24-week *T. cruzi* infection (mean ± SD, n = 8)

Parameter	Wk 4	Wk 8	Wk 12	Wk 18	Wk 24	p trend
Complement survival (%)	78.4	62.3	51.7	44.8	41.2	<0.001
CD8+PD-1+Tim-3+ (%)	8.4	18.7	28.4	37.6	43.7	<0.001
CD4+FoxP3+ (%)	6.2	7.8	9.4	11.3	12.8	0.002
TS variants (n)	6	14	11	8	7	0.014
Macrophage killing (%)	34.2	28.7	21.3	18.6	16.4	<0.001

Evasion strategies shifted in importance over time (Table 1). Complement resistance was highest during acute infection but declined as the parasite moved intracellularly. T cell exhaustion and Treg expansion rose steadily throughout, becoming the dominant evasion mechanisms by week 18. Trans-sialidase diversity peaked sharply at week 8 during the acute-to-chronic transition.

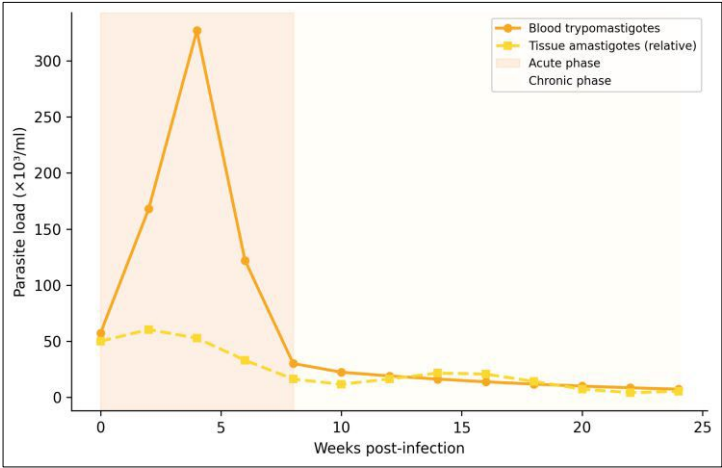


Fig 1: Parasite load dynamics over 24 weeks showing blood trypomastigotes (solid line) and relative tissue amastigote burden (dashed line), with acute and chronic phases indicated

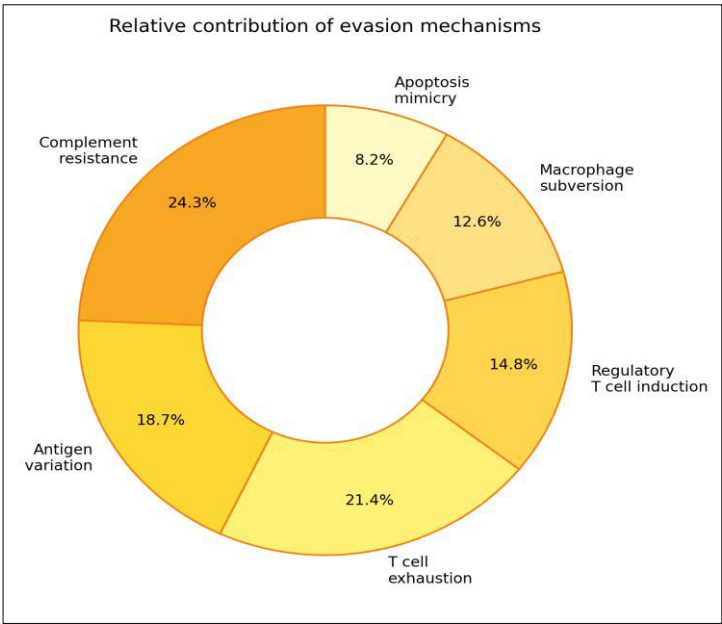


Fig 2: Estimated relative contribution of six immune evasion mechanisms to overall parasite persistence during chronic Chagas disease (week 24)

Blood parasitemia peaked at week 4 and became undetectable by microscopy after week 10, while tissue burden persisted throughout (Figure 1). The donut chart (Figure 2) summarizes the estimated contribution of each evasion mechanism at week 24: complement resistance (24.3%), T cell exhaustion (21.4%), antigen variation (18.7%), Treg induction (14.8%), macrophage subversion (12.6%), and apoptosis mimicry (8.2%).

Discussion

The temporal succession of evasion mechanisms revealed here reframes *T. cruzi* immune escape as a dynamic process rather than a fixed strategy [4]. During acute infection, when parasites circulate in the bloodstream, complement resistance and antigenic diversity of trans-sialidases are the main shields. As infection shifts to the chronic intracellular phase, the parasite pivots to immune suppression - exhausting effector T cells and expanding regulatory T cells that dampen anti-parasitic responses [5, 6].

The peak in trans-sialidase diversity at week 8 is striking. This coincides with the transition period when the immune system is clearing blood-stage parasites but hasn't yet established stable chronic infection. The burst of antigenic variation may serve as a smokescreen that allows enough parasites to establish intracellular niches before adaptive immunity catches up [7].

The progressive decline in macrophage killing capacity suggests that *T. cruzi* conditions host macrophages over time, possibly through IL-10 and TGF- β signaling driven by the expanding Treg population [8]. This creates a self-reinforcing loop: Tregs suppress macrophage activation, allowing more intracellular persistence, which further stimulates Treg expansion.

Conclusion

T. cruzi employed an ordered succession of immune evasion strategies during the establishment of chronic Chagas disease. Complement resistance and antigenic variation dominated the acute phase, while T cell exhaustion and regulatory T cell induction became the primary mechanisms sustaining chronic persistence. The temporal mapping of these shifts provides a framework for designing stage-specific therapeutic interventions - for instance, checkpoint blockade during early chronic infection to reverse T cell exhaustion, or complement-targeted approaches during acute exposure [9, 10, 11].

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