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Immunomodulation by protozoan parasites: A tug of war.

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Introduction

Leishmania resides within macrophages, subverting their killing mechanisms. It inhibits nitric oxide production and promotes anti-inflammatory cytokines. The balance between Th1 and Th2 responses determines disease severity—Th1 promotes parasite clearance, while Th2 facilitates persistence. *T. gondii* is a master manipulator of host immunity. It alters dendritic cell migration, modulates NF-κB signaling, and induces IL-10 to suppress inflammation. Despite robust IFN-γ responses, the parasite establishes lifelong latency in neural and muscular tissues. *T. cruzi* evades immunity through antigenic variation and immune suppression. It induces T-cell apoptosis and promotes Treg expansion. Chronic infection leads to immune-mediated tissue damage, particularly in the heart. Protozoan parasites are among the most cunning pathogens in the microbial world. Responsible for diseases such as malaria, leishmaniasis, toxoplasmosis, and Chagas disease, these single-celled organisms have evolved sophisticated strategies to manipulate host immunity. Their survival depends not only on evading immune detection but also on modulating immune responses to create a favorable niche for replication and transmission. This dynamic interplay between host defenses and parasite countermeasures represents a biological tug of war—one that shapes disease outcomes and challenges vaccine and therapeutic development [1].

Immunomodulation allows parasites to persist for years, often asymptomatically. Continuous antigen exposure leads to dysfunctional T cells and impaired memory responses. Skewed immune responses can cause tissue damage, as seen in cerebral malaria or Chagas cardiomyopathy. Antigenic variation and immune suppression hinder the development of effective vaccines. Understanding these dynamics is crucial for designing interventions that restore immune balance without exacerbating pathology. Checkpoint inhibitors may rejuvenate exhausted T cells in chronic protozoan infections. Advances in single-cell sequencing, systems immunology, and imaging are shedding light on the complex host-parasite interface. Upon infection, protozoan parasites encounter a multi-layered immune system. The innate immune response is the first line of defense, involving: Pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) that detect parasite-associated molecular patterns. Phagocytic cells like macrophages and dendritic cells that engulf and present antigens. Inflammatory cytokines including IL-1β, TNF-α, and IFN-γ that activate immune cells and promote pathogen clearance [2].

T-cell activation, particularly CD4+ Th1 cells that produce IFN-γ to control intracellular parasites. B-cell responses, generating antibodies that neutralize extracellular stages. Despite this arsenal, protozoan parasites often persist, thanks to their immunomodulatory tactics. Protozoan parasites deploy a wide range of strategies to subvert host immunity: Parasites like *Trypanosoma brucei* and *Plasmodium falciparum* frequently change their surface antigens, evading antibody recognition. *T. brucei* expresses variant surface glycoproteins (VSGs), switching them periodically to stay ahead of the immune system [3].

Toxoplasma gondii interferes with MHC class II expression and antigen processing in dendritic cells, impairing T-cell activation. Similarly, *Leishmania* inhibits phagosome maturation, preventing effective antigen presentation. Many protozoa skew cytokine responses to suppress protective immunity. *Leishmania major* promotes IL-10 production, dampening Th1 responses. *Plasmodium* species induce regulatory cytokines

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like TGF-β to limit inflammation and facilitate chronic infection. Tregs suppress effector T-cell responses and promote immune tolerance. *T. cruzi* and *T. gondii* infections are associated with increased Treg populations, contributing to parasite persistence [4].

Some parasites inhibit apoptosis of infected cells to prolong their intracellular niche. Others, like *Entamoeba histolytica*, induce host cell death to disrupt tissue barriers and facilitate invasion. Malaria parasites manipulate both innate and adaptive immunity. They suppress dendritic cell function, impairing T-cell priming. Chronic exposure leads to immune exhaustion, with reduced cytokine production and memory T-cell formation. The parasite's ability to hide in hepatocytes and erythrocytes further complicates immune clearance [5].

Conclusion

Protozoan parasites are not passive invaders—they are active architects of the immune landscape. Through a sophisticated arsenal of evasion and modulation strategies, they engage in a relentless tug of war with host defenses. While this interplay ensures their survival, it also drives chronic disease and complicates treatment. By unraveling the mechanisms of immunomodulation, we can tip the balance in favor of the host—transforming these ancient adversaries into manageable threats.

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