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Immunotherapeutic targets in parasitic infections: Unlocking new frontiers in host-directed therapy.

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Introduction

In schistosomiasis, immune responses contribute to both parasite control and pathology. Immunotherapeutic strategies aim to modulate granuloma formation and fibrosis by targeting Tregs, IL-13, and TGF-β pathways. Vaccines incorporating TLR agonists and cytokine adjuvants are also under development. Chagas disease, caused by *Trypanosoma cruzi*, involves chronic inflammation and cardiac damage. Immunotherapy targeting TNF-α and IL-17 has shown potential in reducing tissue pathology. Additionally, checkpoint inhibitors and macrophage modulators are being explored to enhance parasite clearance. Parasitic infections continue to pose a significant global health burden, particularly in low- and middle-income countries. Diseases such as malaria, leishmaniasis, schistosomiasis, and Chagas disease affect hundreds of millions annually, leading to chronic illness, disability, and death. Traditional antiparasitic drugs often face limitations including toxicity, resistance, and incomplete efficacy. In recent years, immunotherapy—modulating the host immune response—has emerged as a promising strategy to complement or replace conventional treatments. By targeting immune pathways and cellular mechanisms, immunotherapeutics offer a novel approach to controlling parasitic infections and improving patient outcomes [1].

Malaria remains a leading cause of morbidity and mortality. Immunotherapeutic approaches include monoclonal antibodies targeting the circumsporozoite protein (CSP), checkpoint blockade to reverse T cell exhaustion, and cytokine modulation to enhance Th1 responses. Passive immunization with anti-CSP antibodies has shown protection in clinical trials, and host-directed therapies may complement antimalarial drugs. Leishmaniasis is characterized by immune suppression and chronic inflammation. Immunotherapy targeting IL-10, PD-1, and TLRs has shown efficacy in restoring immune function and reducing parasite burden. Combination therapies with antimonials and immune modulators are being investigated to improve cure rates and reduce relapse. Parasites are adept at evading host immunity through complex life cycles, antigenic variation, and immune modulation. Many parasitic infections persist chronically due to the parasite's ability to suppress or misdirect host immune responses. Immunotherapy aims to restore or enhance protective immunity, either by boosting host defenses or by counteracting parasite-induced immunosuppression [2].

Future research should focus on identifying biomarkers for patient stratification, optimizing combination therapies, and developing affordable immunotherapeutic platforms. Integration with vaccine development and public health strategies will be key to maximizing impact. Unlike direct antiparasitic agents, immunotherapeutics can offer long-term protection, reduce relapse rates, and potentially contribute to vaccine development. Moreover, host-directed therapies may circumvent the problem of drug resistance by targeting conserved immune pathways rather than parasite-specific molecules. Immune checkpoint molecules such as PD-1 and CTLA-4 regulate T cell activation and prevent excessive immune responses. In chronic parasitic infections like visceral leishmaniasis and malaria, overexpression

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of PD-1 leads to T cell exhaustion and impaired parasite clearance. Blocking PD-1/PD-L1 interactions has shown promise in restoring T cell function and enhancing parasite control in preclinical models [3].

Cytokines are central to orchestrating immune responses. Therapeutic modulation of cytokines—either through recombinant proteins or monoclonal antibodies—can shift the immune balance toward parasite elimination. For example, IL-12 promotes Th1 responses critical for intracellular parasite control, while IL-10 suppresses inflammation and is often exploited by parasites to evade immunity. Targeting IL-10 or enhancing IL-12 signaling has shown efficacy in experimental models of leishmaniasis and toxoplasmosis. TLRs are pattern recognition receptors that detect pathogen-associated molecular patterns and initiate innate immune responses. Agonists of TLRs, such as TLR4 and TLR9, have been used to boost immune activation against parasites. For instance, CpG oligodeoxynucleotides (TLR9 agonists) have demonstrated adjuvant effects in malaria and leishmaniasis vaccine studies [4].

TLR-based immunotherapy may enhance antigen presentation and cytokine production, improving parasite clearance. Tregs play a crucial role in maintaining immune homeostasis but can also suppress protective responses during parasitic infections. Elevated Treg activity has been observed in schistosomiasis, filariasis, and leishmaniasis, contributing to chronic infection and immune tolerance. Therapeutic depletion or functional inhibition of Tregs may restore effective immunity and facilitate parasite elimination, although care must be taken to avoid autoimmunity. Macrophages can adopt pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes. Many parasites, including *Leishmania* and *Trypanosoma*, manipulate macrophage polarization to favor M2 responses, which support parasite survival. Immunotherapeutic strategies that reprogram macrophages toward an M1 phenotype can enhance parasite killing and improve disease outcomes. Agents such as IFN-γ and GM-CSF have been explored to modulate macrophage function in parasitic infections [5].

Conclusion

Immunotherapeutic targets in parasitic infections represent a transformative frontier in infectious disease management. By harnessing and modulating the host immune system, these strategies offer new hope for controlling persistent and drug-resistant parasitic diseases. Continued research, innovation, and global collaboration are essential to translate these advances into accessible and effective treatments for the populations most in need.

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