Macrophage-mediated Immune Cell Interaction Network and its Synergistic Immune Escape Mechanism in Leishmania Protozoa Infection

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***Abstract*—Leishmania infection is a highly prevalent cause of parasitic disease in tropical and subtropical regions of the world, causing severe clinical symptoms such as skin ulcers and internal organ damage, posing a long-term threat to public health. Macrophages, as the main host cells of Leishmania invasion, have long been a key blind spot in the study of anti-infection immunity because of their dynamic interactions with T cells, Dendritic Cells (DCs), natural Killer Cells (NKs), and other immune cells. In this paper, we systematically analyze the synergistic escape mechanism in the macrophage-mediated immune cell network through cytokine inhibition, antigen presentation blockade, and inflammatory modulation. The article demonstrates that infected macrophages inhibit T cell activation, dendritic cell maturation, and NK cell killing through the secretion of Transforming Growth Factor-*β* (TGF-*β*) and Interleukin-10 (IL-10). By down-regulating the expression of MHC molecules, infected macrophages form an "antigen presentation inhibition-immune cell inactivation" cascade. In addition, the study summarizes the reasons why the remodeling of the inflammatory microenvironment promotes parasite survival. This study provides new perspectives for therapeutic strategies targeting immune checkpoints.**

***Keywords*—Leishmania protozoa, macrophages, immune escape, cellular interaction networks, immunosuppressive cytokines**

I. Introduction

Leishmaniasis, which is endemic in tropical and subtropical regions of the world, currently affects approximately 12 million people, with 1.5–2 million new cases annually and a mortality rate of up to 25% for tropical cutaneous and visceral leishmaniasis. Leishmania parasites have evolved sophisticated immune escape strategies to hijack macrophages, a core cell of natural immunity, to achieve long-term parasitism and chronic infections in the human body [1]. Although macrophage-parasite interactions have been well-studied, recent studies have revealed that macrophages remodel the immune response at the systemic level by forming a synergistic network of interactions with T cells, Dendritic Cells (DCs), and Natural Killer cells (NKs) [2–4]. Therefore, by reviewing the literature, this paper systematically analyzes the immunosuppressive synergistic mechanism of the macrophage cytokine network, the cascade amplification effect of antigen presentation blockade, and the molecular switches involved in the remodeling of the inflammatory microenvironment, which will provide a theoretical basis for the development of immunotherapies targeting cytokine blockade or antigen presentation enhancement [4–6]. This study's analysis of the synergistic escape patterns of the "pathogen-host cell-immune network" has refined infection immunity theory and provides a new paradigm for the immunotherapy of chronic infectious diseases. It also helps to break through the limitations of drug resistance and offers new targets for the prevention and control of diseases in tropical and subtropical regions.

II. Macrophage-Driven Immune Cell Interactions

During Leishmania protozoan infection, macrophages become a central node by combining the dual roles of pathogen host cell and immune microenvironment regulatory hub. This duality makes it the hub of an interactive network that coordinates the functional state of T cells, DCs, and NKs through direct contact and indirect signaling. After pathogen invasion, macrophages activate the immunoregulatory program through a 2.3-fold upregulation of the expression of Programmed Death-Ligand 1 on their surface, remodeling the functional state of T cells, DCs, and NKs with the help of the dual pathway of soluble mediator secretion and direct cell contact [3, 7].

A. Macrophage-T Cells

Infected macrophages construct a regulatory network of T cell polarization through the co-secretion of Interleukin-10 (IL-10) and Transforming Growth Factor-*β* (TGF-*β*). IL-10 induces the differentiation of $CD4^+$ T cells toward a T helper 2 (Th2) phenotype and inhibits the Interferon-*γ* (IFN-*γ*) secretion required for protective T helper 1 (Th1) responses [8, 9]. TGF-*β* then further

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induces regulatory T cell expansion, creating a negative feedback inhibitory loop [7, 9]. Experimental evidence showed that IL-10 knockdown reduced parasite load by 89% and significantly elevated the proportion of IFN-γ^{+}CD4^{+} T cells in an L. major-infected mouse model, thus confirming the corepressor effect of IL-10 [1, 8]. This inhibitory effect is spatiotemporally specific. The number of T cells increases 3.5-fold in the later stages of infection compared to the early stages. This abnormal proliferation is positively correlated with chronic progression of the disease, suggesting that imbalances in the dynamics of the T-cell subpopulations are a key driver of chronic infections [5].

B. Macrophages—DC

Infected macrophages inhibit DC maturation by decreasing CD80/86 expression by 60%–70% [2, 4, 6]. This mechanism is associated with IL-10-mediated blockade of the TLR4 signaling pathway. Macrophage-derived IL-10 blocks the TLR4 signaling pathway within DCs, resulting in blocked NF-κB nuclear translocation [3]. This cascade effect further impairs the antigen cross-presentation capacity of DCs, reducing initial T cell activation efficiency by more than 40%. Notably, the bidirectional nature of this interaction is reflected in the fact that although DC-derived IL-12 would activate macrophage killing, in the infected microenvironment, overproduction of TGF-β neutralizes the pro-inflammatory effects of IL-12, creating an imbalance between immune activation and suppression [9].

C. Macrophage-NK Cells

Macrophages exert direct and indirect inhibition of NK cells through the secretion of TGF-β with IL-10, which reduces NKG2D receptor expression on the surface of NK cells by 55% and directly inhibits their cytotoxicity [1, 7]. In a chronic infection model, the rate at which NKs kill infected macrophages was reduced from normal values of 70% to 15%, which was significantly correlated with parasite persistence [7]. In addition, IL-10 indirectly impairs NKs' capacity to secrete IFN-γ by inhibiting IL-12 production by macrophages [8]. In chronic infection models, this dual inhibitory mechanism is significantly associated with parasite persistence, revealing that inhibition of NK cell function is an important strategy for pathogens to escape innate immune clearance.

III. Macrophage-Dependent Immune Escape Mechanisms in Leishmania Protozoa

By hijacking macrophage function, pathogens construct a multilayered escape system containing cytokine network inhibition, antigen presentation blockade, and microenvironment remodeling.

A. Cytokine Inhibitory Network

TGF-β and IL-10 constitute the core immunosuppressive axis, reinforcing the inhibitory effect through a positive feedback loop. IL-10 directly impairs intracellular parasite clearance by decreasing nitric oxide production by 80% through the reduction of macrophage Inducible Nitric Oxide Synthase (iNOS) activity [7, 9]. TGF-β, on the other hand, blocks IFN-γ signaling in T/NK cells through the inhibition of Signal Transducer and Activator of Transcription 1 (STAT1) phosphorylation, which blocks IFN-γ signaling in T/NK cells, leading to a 3.2-fold down-regulation of IFN-γ responsive gene expression [7, 9]. The synergistic effect of the two is manifested by IL-10 promoting TGF-β secretion, while TGF-β enhances macrophage IL-10 receptor expression, resulting in a sustained inhibitory microenvironment [1, 3].

B. Antigen Presentation Dual Pathway Blockade

Infected macrophages directly affect CD4^{+} T cell recognition by decreasing Major Histocompatibility Complex class II (MHC-II) expression by over 50% [1]. At the same time, IL-10-mediated reduction of MHC-I molecules on the DC surface by 40% hinders CD8^{+} T cell activation. This culminates in Antigen-Presenting Cell (APC)-T cell dual pathway blockade. This mechanism leads to a 67% decrease in antigen-specific T-cell proliferation and hinders memory T-cell formation, impairing host clearance of reinfection [5, 8]. At the molecular level, the parasite-derived protease Cathepsin B-like Protease (CPB) participates in this process by degrading the MHC molecular transcription factors, thus revealing active disruption of the host antigen-presentation mechanism by the pathogen [3].

C. Inflammatory Microenvironment Remodeling

Macrophage-secreted IL-10 dominates the cytokine profile, shifting pro-inflammatory (e.g., TNF-α, IL-12) to anti-inflammatory (e.g., IL-10, TGF-β), and provides an immunosuppressive environment for the parasite to survive by remodeling the local metabolic microenvironment (e.g., the arginine metabolism pathway by favoring polyamine synthesis rather than nitric oxide production) [3, 10]. This phenotypic shift is initiated early in the course of infection and is closely associated with macrophage polarization to the M2 type, which constitutes a key pathological basis for chronic infection.

IV. Discussion

Current research faces two core problems: model limitations and cell type omission. In terms of modeling, more than 80% of mechanism insights are based on in vitro experiments or mouse models, and the cellular heterogeneity and signaling complexity of human tissue microenvironments (e.g., splenic/cutaneous granulomatous structures) have not been adequately modeled. In addition, the role of emerging immune cell subpopulations in the reciprocal network, whose secretion of IL-13 may reinforce Th2 bias, has not been quantified [1].

In response to the aforementioned issues, future research could break through the development bottleneck

through both technological innovation and therapeutic translation. In terms of technology, applying in vivo two-photon microscopy to track the dynamic contact between macrophages and DCs at the site of infection (e.g., the length of intercellular signaling), combined with single-cell transcriptome sequencing to resolve the signaling crosstalk between ILC subpopulations and macrophages, could precisely locate the key regulatory nodes [4, 9]. In terms of therapeutic translation, the development of bispecific antibodies targeting the immunosuppressive axis (simultaneously blocking TGF-β and IL-10 signaling) and DC-targeted nanovaccines (loaded with antigens and designed to enhance MHC-I cross-presentation) is expected to break the immunosuppressive network established by the pathogen and provide a new strategy for anti-Leishmania immunotherapy [6, 7]. These research directions will not only deepen the systematic understanding of pathogen-host interactions, but also have practical significance for clinical translation.

V. Conclusion

By integrating the evidence from the cutting-edge literature, the present study reveals that Leishmania donovani achieves immune escape through a triple synergistic mechanism of cytokine inhibition, antigen presentation blockade, and inflammation regulation via interactions between macrophages, T cells, DCs, and NKs. It is clear from the study that Leishmania parasites can interfere with the host immune response in multiple dimensions by means of the immune interaction network built by macrophages, which provides a new molecular framework for analyzing the immune escape mechanisms of pathogens.

However, the current article still has some limitations in experimental evidence and literature coverage, including the fact that the causality of key molecular nodes has not yet been experimentally verified, and the cross-regulatory mechanisms of immune metabolic reprogramming (e.g., remodeling of arginine/glutamine metabolism) and cellular interactions are not sufficiently explored due to the limited quantity and scope of existing literature.

Future studies will be conducted through integrated 3D organoid infection models combined with mass cytometry to quantify the intensity of cellular interactions. We will also re-evaluate the potential of "metabolic checkpoint inhibitors" in reversing immune escape following a systematic investigation of immune metabolism.

Conflict of Interest

The author declares no conflict of interest.

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