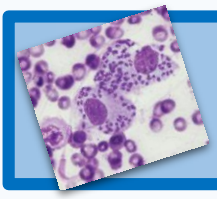

Leishmania: Evasion Mechanisms

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Introduction

Parasites of the genus *Leishmania* are the causative agents of cutaneous, mucocutaneous or visceral leishmaniasis. This disease is considered endemic in over 90 countries and about 2 million new cases occur every year. More than 12 million people are believed to be infected, 310 million people are at risk and around 20 to 50 thousand deaths annually are due to the disease. [1]

Immunology

Macrophages are indispensable for parasite survival, replication and differentiation. Appropriate activation of macrophages is crucial for eliminating the pathogen. The activation is divided into classical and alternative activation. [2]

Promastigotes

TLR2 → recognizes LPG and amastigote-specific antigens.
TLR4 → recognizes GSLP and P8GLC

Gp63 → binds to fibronectin receptors.

MyD88

TNF-α, IL-12, IFN-γ, NO, ROS [3]

Amastigotes

IgG-coated parasites bind to FcγR

Parasite adhesion and internalization [4, 5]

Life cycle

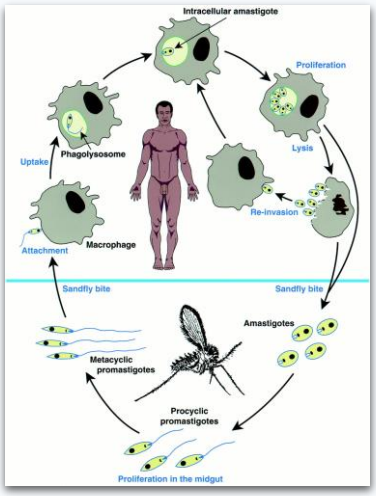

Figure 1: Life cycle of *Leishmania*.
Handman, E. (2001). Leishmaniasis: Current Status of Vaccine Development. *Clin. Microbiol. Rev.* 14(2), 229-243

Evasion mechanisms [6]

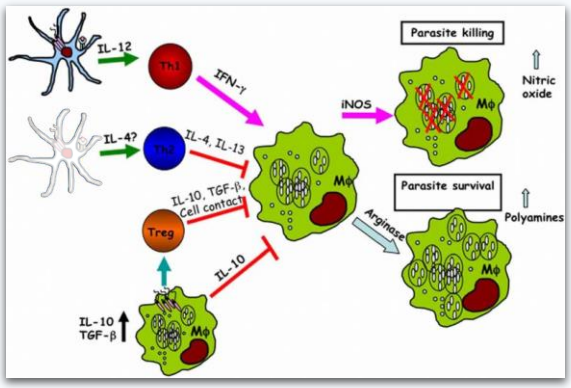

Figure 2: Dendritic cells and macrophages regulate the outcome of *Leishmania* infection.
Uzonna, Jude E., and Dong Liu. (2012). The early interaction of *Leishmania* with macrophages and dendritic cells and its influence on the host immune response. *Frontiers in Cellular and Infection Microbiology*. 2(83).

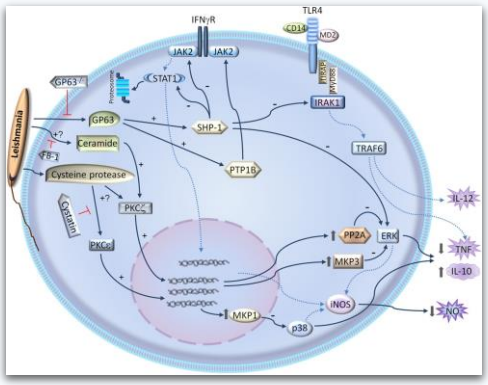

Figure 3: *Leishmania*-induced host phosphatase activation.
Tiemi Shio, M., Olivier, M. (2010). *Leishmania* survival mechanisms: the role of host phosphatases. *Journal of Leukocyte Biology*. 88(1), 1-2.

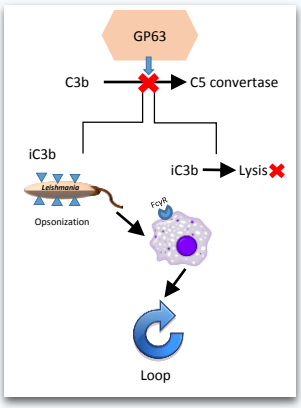

Figure 4: Modification of the Complement System by GP63.

Alteration of Toll-Like Receptor Pathways	Consequence
Suppressors of SOCS-1 and SOCS-3	Negatively regulates TLR2 induced cytokine induction
Activation of host ubiquitinating editing enzyme A20	Impairment of TLR2-mediated release of IL-12 and TNF-α
Activation of SHP-1	Inhibits interaction with TRAF6 and further induction of NO, IL-12 and TNF-α
Inhibitors of serine protease (ISP)	Prevent TLR4 activation
Surviving in the Phagosome	**Consequence**
Acid phosphatases	Inhibits the attack of superoxide and hydroxyl radicals
Proton pump	Resist attack of acidic enzymes, maintaining pH close to neutral
LPG	Inhibits lysosomal enzymes. Inhibits respiratory burst
Iron transporters LIT1 and LIT2	Counteracts Nramp1 functions. Compete with the host's iron sequestering mechanism.
Arginase	Attenuates iNOS, facilitates growth (polyamine pathway)

Treatments

Treatment	Function
Classical drugs	
Pentavalent antimonials [7]	Induction of ROS and NO production. Upregulation of IFN-γ receptors. IL-12 production
Miltefosine [8]	Enhance IFN-γ receptors. Induce IL-12-dependent Th1 response and reverse Th2 to Th1 response.
Immunotherapy	
Cytokine immunotherapy [9]	Treatment with IL-12 or neutralizing antibody to IL-4 → reverses nonhealing disease phenotype

Conclusions

1. Macrophages and DCs play a critical role in leishmaniasis disease.
2. Cytokine patterns lead with different disease outcomes.
3. The effective mechanisms for parasite killing are the production of NO, ROS and lysosomal proteases.
4. *Leishmania* uses a variety of evasion mechanisms to favor its survival and replication in macrophages.
5. Current treatments to leishmaniasis include the use of drugs, but their side effects are high.
6. Immunotherapy is a promising alternative to conventional drugs, but its use is controversial and further study is needed.

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