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Key Innate Immune Response in the Progress or Elimination of Infection by *Leishmania spp*.

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Editorial

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Abbreviations: PRR: Pattern Recognition Receptors; TLRs: Toll-like Receptors; PRR: Pattern Recognition Receptors; PAMP: Pathogen-Associated Molecular Patterns; APC: Antigen-Presenting Cells; MMR: Macrophage Mannose Receptors; ROS: Reactive Oxygen Species; NETs: Neutrophil Extracellular Traps.

Editorial

Leishmaniasis is a disease (with two clinical forms: integumentary [with three presentations: localized cutaneous, mucocutaneous and diffuse] and visceral) caused by protozoan of the genus *Leishmania spp*. transmitted by insects (*Phlebotomus spp*. in the Old World and *Lutzomya spp*. in the New World), 20 of these species cause disease and 15 are zoonotic. In humans, the disease is mainly caused by: *L. tropica*, *L. major*, *L. aethiopica*, *L. mexicana*, *L. amazonensis*, *L. panamensis*, *L. guyanensis*, *L. peruviana*, *L. braziliensis*, *L. infantum* and *L. donovani*. It is a tropical and subtropical disease considered neglected, the fourth most prevalent in this group of diseases (it affects 12 million people, with 350 million people at risk of infection, with 2 million new cases per year and endemic in 98 countries) and the second with the highest mortality rate, for some related to poverty [1].

When faced with an infection, such as that produced by parasites of the genus *Leishmania spp*., the host's immune system issues two types of responses, the rapid but non-specific ones (innate by macrophages, neutrophils, dendritic cells [these three are considered the most important functional cells of innate immunity, as they generate significant levels of cytokines such as: IFN-γ, IL-12 and TNF-α], mast cells, basophils, eosinophils and natural killer cells) and late ones, but as high specificity (adaptive in charge of T and B lymphocytes). The innate immune system focuses the initial recognition of *Leishmania spp*. in pattern recognition receptors (PRR), toll-like receptors (TLRs, are first receptors to recognize Leishmania-associated PAMPs), macrophage mannose receptors (MMR) and NOD-like receptors (NLR) expressed on antigen-presenting cells (APC) for initial recognition of parasites pathogen-associated molecular patterns (PAMP), which end with the activation of the complement cascade, induction of phagocytosis and production of inflammatory cytokines [1,2].

In the mammalian host, the progression of the infection is directly related to the intracellular proliferation capacity of the parasite (remodeling of the phagosomal compartment that interferes with the signaling that mediates the elimination of parasites and interfering with signaling pathways that mediate parasitic clearance) and with the type and strength of the immune response (which can enhance or limit the growth of *Leishmania spp*.), it is a paradoxical interaction. The early containment of the infection is carried out by neutrophils (modulated by TLRs, as it participates in the recruitment, activation and apoptosis of neutrophils), the first cells of the immune system that migrate to the site of penetration of *Leishmania spp.*, responsible for the absorption of promastigotes of *Leishmania spp*., and the production of neutrophil extracellular traps (NETs), lytic enzymes, reactive oxygen species (ROS) and differential cytokine production [1,3].

Neutrophils also act in the intermediate and late phase of infection by *Leishmania spp*., but, paradoxically, they also serve as Trojan horses in the spread of parasitic

forms to macrophages, since there is no activation of lethal antimicrobial factors (ROS), nor recruitment of apoptotic cells and even less premature sequestration of neutrophils for the recruitment of macrophages, but the induction of high expression of CD62L capable of inactivating the immune response of neutrophils [1,3].

Macrophages are considered the decisive cells for the elimination of *Leishmania spp*. infection. (Infectious intracellular forms of amastigotes are found in them), once the infected neutrophils (polymorphonuclear cells) have been phagocytosed, since they induce the secretion of proinflammatory cytokines (IL-1, IL-6, IL-12 and TNF) and nitric oxide , but the persistence of the infection can be favored by several receptors (TLR, complement receptors, kinases [the parasitic induction of IL-12 in macrophages generates the expression of monarch-1, a molecule that negatively regulates nuclear factor-kappaB, blocking p65/p50, and inducing the p50/p50 repressor causing the effective blockade of IFN-ɣ-mediated NO production by macrophages] and transcription factors [suppressing nuclear factor-kappaB] that regulates the expression of several essential antimicrobial molecules) that mediate the ingestion of promastigotes by the macrophage, but can also deactivate them [1,4].

The parasites of *Leishmania spp*. counteract the immune response of macrophages through the expression on their surface of lipophosphoglycan, a molecule that alters the cytoskeleton of macrophages by mediating the accumulation of periphagosomal F-actin, which attacks the phagosome membrane and alters the recruitment of synaptotagmin V an endosomal protein crucial for phagocytosis, therefore, it is seriously compromised. Macrophage TLRs can recognize lipophosphoglycans and induce nitric oxide production against the parasite [1,4].

Dendritic cells come into action, in relation to their activation and maturation (phenotypic transition from immature to mature cells characterized by the expression of CD40, CD80 and CD86, and production of proinflammatory cytokines [IL-12]), after the recognition of signals associated called pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRR) such as toll-like receptor on DC (TLRs) and C-type lectin, which drive the secretion of cytokines for the activation of T cells for the internalization of pathogens [1,5].

The species of the parasite, the morphological state of *Leishmania spp*., and the type of host determine the immune interaction between dendritic cells and the protozoan in dependence on the signaling cascade of the infectious stage, for example, it participates in the efficient phagocytosis of promastigotes. Dendritic cell receptor, DC-specific ICAM-3- grabbing nonintegrin (DC-SIGN), however, the parasite can alter the activation and maturation of dendritic cells by activating adenosine A2b with increased phosphorylation of extracellular signal-regulated protein kinases 1/2 (ERK1/2) and by modifying dendritic cell transcription factors especially the TLR/NF-kB/NLRP3 a axis [1,5].

It can be concluded that in the host-parasite interaction of *Leishmania spp*. There is differential modulation of the cells of the innate immune response that can induce or hinder the effectiveness of the host's protective response, which can explain the different clinical forms of presentation of the disease and that also depends on the mechanisms of evasion to the that the species of *Leishmania spp*. Hence the need to deepen research on such an important topic with the purpose of contributing to the control of *leishmaniasis*.

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