The role of TREM-1 in the severity of human Cutaneous Leishmanaisis (CL) through a translational study.

Mariana Ampuero[1,2], Sara Nunes[1,2], Daniel Feijó[2], Ricardo Khouri; Claudia Brodskyn[1,2] and Natalia Tavares[1,2]

1. Universidade Federal da Bahia (UFBA), Salvador/BA – Brazil.
2. Centro de Pesquisas Gonçalo Moniz – Fundação Oswaldo Cruz (CPqGM-Fiocruz), Salvador/BA - Brazil

Keywords: TREM; TLR; *Leishmania braziliensis*.

Abstract:

Leishmaniasis is a neglected disease caused by the intracellular parasite from *Leishmania* genus. The host immune response against *Leishmania* is critical for parasite killing, but it also accounts for inflammation and disease severity. In this context, the Triggering Receptors Expressed on Myeloid Cells (TREM) was recently identified as an amplifier of the innate immune response, which synergize with Toll-like receptors (TLRs) in the production of proinflammatory cytokines. TREM-1 is expressed in cells of myeloid lineage, manly neutrophils. Its signaling pathway depends on the adapter protein DAP12, which results in cell degranulation, production of reactive oxigen species (ROS) and activation of NFkB, leading to the expression of inflammatory genes. Our group has investigated the role of TREM-1 during Leishmania infection through a translational approach. We used bioinformatics tolls to analyze public transcriptome data of lesions from patients infected with *Leishmania braziliensis*. We observed an increase in the expression of all signaling factors involved in TREM-1 pathway. After, we obtained fresh samples of blood and biopsy from patients with active lesion of CL to validate these findings through Real-Time PCR. The expression of DAP12 and TLR4 messenger RNA (mRNA), but not of TREM-1 and TLR2, is significantly increased in biopsies. On the other hand, the expression of these mRNA is not altered in peripheral blood mononuclear cells (PMBC). Finally, we observed a down regulation in TREM-1, DAP12, TLR2 and TLR4 expression in resting neutrophils from these patients. Moreover, TREM-2, the soluble form that act as counterregulatory molecule, attenuating inflammation, was not detected in any of these samples. In conclusion, TREM-1 is differentially regulated between different compartments and its modulation depends on the presence of inflammatory stimulus. Undergoing *in vitro* assays

are important to define the role of TREM-1 in the balance between inflammation and parasite killing during *L. braziliensis* infection.