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Title: Role of G-proteins in *Leishmania* infection

Abstract

Keywords: Signaling, *Leishmania,* Macrophages, Ras, MAP kinases, cytokines, THP-1.

Leishmania donovani is a parasite that resides and replicates in macrophages and causes Leishmaniasis. The disease is transmitted by the bite of female sandflies. *Leishmania* parasite can go in the host macrophages securely and replicates inside. The parasite modifies the signaling pathways of macrophages, which accelerate its infection and proliferates inside the cell. G-proteins are a group of enzymes called GTPases which are classified into two forms namely heterotrimeric and monomeric GTPases. Small G-proteins become activated when they bound with guanosine triphosphate (GTP) and inactivated when the guanosine diphosphate (GDP) attached with them. Small GTPases are divided into five families; Ras, Rho/Rac, Rab, Arf and Ran family. Ras family is the largest amongst them and has mainly three isoforms; K-Ras, H-Ras, and N-Ras. The interaction of ligand bound receptor molecules to the adaptor molecules activates Ras proteins and the activated Ras proteins further regulate downstream signaling pathways such as PI3K, Akt, RAF, MEK, ERK pathway which further control cell explosion, cell existence, apoptosis and cellular death. We deliberated whether Ras isoforms had differential roles in *Leishmania donovani* infection. We observed that *Leishmania donovani* enhanced N-Ras expression, whereas it inhibited K-Ras and H-Ras and also increased N-Ras activity in THP-1

differentiated human macrophages. We inhibited Ras with its inhibitor (Farnesyl Thiosalicylic Acid, FTS) and checked whether it had a role in *Leishmania* infection. We found that Ras inhibition suppressed the Leishmania induced IL-10 expression but enhanced IL-12 expression. We also observed, Ras inhibitor treatment macrophages decreased the phosphorylation of ERK1/2and increased p38MAPK phosphorylation. This study suggests a novel immune evasion strategy of *Leishmania donovani* and has potential to develop an effective anti-leishmanial therapy.