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Topic: Role of G-Protein Coupled Receptors (GPCRs) in Regulation of Macrophage functions by *Leishmania donovani*

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Abstract

G-Protein Coupled Receptors (GPCRs) signaling is a crucial regulator of cellular processes, such as apoptosis, cell proliferation, migration, and differentiation. Recent studies have shown that this signaling is generally found altered during infectious diseases. In the present study, we have checked the expression of GPCRs in infected and uninfected macrophages. In our study, we found a decrease in the expression of these S1PR 1-3 post infections. However, the expression of S1PR2 and S1PR3 at mRNA were significantly decreased. To further confirm the role of these receptors mediated signaling in *Leishmania* infection. Using specific inhibitors of S1PR2-3 we found a significant increase in parasite load and increased IL-10 and ERK1/2 phosphorylation which confirm the role of these receptors. In addition, there was an increase in IL-12 expression in presence of S1PR2 and S1PR3 inhibitor.

Furthermore, we demonstrated that sphingosine kinase 1, a key enzyme for S1P biosynthesis, found to be down-regulated in infected macrophages which suggested that *Leishmania* parasite infection may dampen S1P production as well as S1P mediated signaling during infection. Pharmacological inhibition of the sphingosine kinase by N-N dimethyl sphingosine (DMS) resulted in a profound increase in parasite load and increased IL-10 expression. In addition, IL-

12 has decreased in DMS treated macrophages. In contrast, exogenous addition of S1P leads to decreased parasite load and ERK1/2 phosphorylation. We also observed that S1P treatment leads to increase in p38 phosphorylation. Thus, this study showed a novel signaling mechanism through which *L. donovani* invades host cell for successful parasitism.