CERAMIDE AS THE CHIEF VILLAIN IN THE PERSPECTIVE OF VISCERAL LEISHMANIASIS: ITS ROLE AS THE PLATFORM FOR PATHOGENIC ESTABLISHMENT

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The progression of Leishmanial pathoegensis involves the immunosuppression of the infected macrophages, which is attributed to the increase in intracellular ceramide generation. Ceramide, a pleiotropic second messenger initiating an altered signaling cascade, is responsible for impaired PKC activity, the dephosphorylation of ERK through the activation of a Tyrosine phosphatase as well as parasite survival inside the macrophages. Thus, consequent to the dephosphorylation of PKC, ERK and JNK, ceramide led to the impairment of the nuclear translocation and DNA binding of NF-kB and AP-1 and also the suppression of macrophage microbicidal machinery, involving impairment of free radical generation, including superoxide anion and NO. On the other hand, the enhanced endogenous ceramide is responsible for the dephosphorylation of Protein kinase B (Akt) via two different pathways: primarily by the induction of atypical Ca independent PKC ζ which associates with Akt and deactivates it in the process; and secondly, the activation of protein phosphatase PP2A Ceramide also has been shown to modulate the entry and establishment of L. donovani *within macrophages by the activation of ASMase, resulting in the formation of ceramide-enriched 'lipid rafts', facilitating parasite entry; following which further increase in ceramide level from* de novo *synthesis displaces the cholesterol from the membrane and disrupts the lipid rafts, thereby inhibiting the antigen presenting capability in infected macrophages. Therefore, our compilation clearly suggests the principal role of ceramide in the establishment of Leishmanial pathogenesis thus hinting at the possibility of this molecule as a potent target for anti-leishmanial immunotherapy.*