THESIS ABSTRACT

Dynamicity and evolution of immune responses during progressive experimental visceral leishmaniasis

Visceral leishmaniasis (VL) or kala-azar, a deadly and disseminated infection of the lymphoreticular system, is caused by the protozoan parasites of Leishmania donovani complex. Active VL is characterized by suppression of cell-mediated immunity. Unfortunately, the mechanism of downregulation of host immune response during the disease is not well understood. Moreover, the role played by regulatory T cells and their cytokines in VL progression is still not clear. In the present study, we have investigated the profile of various immune cells and their cytokines during progressive murine VL. We found CD4⁺CD25⁺FOXP3⁺ and CD8⁺CD25⁺FOXP3⁺ T cells were the most significant sources of immuno-suppressive cytokines, IL-10, TGF-β and IL-35. Among these IL-35 and TGF-β may act synergistically for creating an immuno-suppressive environment, resulting into exacerbation of the disease. Further, a combined neutralization of IL-35 and TGF-β led to induction of protective response resulting in arrest of the infection.

Our work on Th17 cell and cytokines indicate that Th17 cell may act as an additive to the Th1 response against progressive murine VL. We observed that even in the absence of a Th1 response, Th17 showed protection against the disease. Moreover, we found that Treg mediated IL-35 along with TGF-β effectively suppresses the Th17 response, and neutralisation of suppressive cytokines results into upregulation of Th17 response.

In the absence of a successful vaccine, chemotherapy is the mainstay to combat VL. Amphotericin B is an excellent anti-leishmanial drug but it is associated with toxicity. Therefore, liposomal formulations of AmB have been introduced which are, however, very costly. Thus, we evaluated a new ergosterol-rich liposomal amphotericin B formulation, KALSOME™10 for its toxicity, efficacy and immunomodulatory role. We found that treatment of L. donovani infected mice with KALSOME™10 resulted in almost complete parasite clearance from both liver and spleen without inflicting any liver or kidney toxicity. The cure was well supported by significant fall in disease promoting cytokines, IL-10 and TGF-β with subsequent increase in protective cytokines (IL-12 and IFN-γ). This drug is expected to reduce the treatment cost and chances for relapse with improved safety.

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