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Designing vaccines against Visceral Leishmaniasis: Importance of liposomes

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Appropriate antigen delivery along with immunopotentiating adjuvants is required to stimulate broad humoral and T cell -mediated immunity to improve vaccine strategies against intracellular pathogens like *Leishmania*. Currently licensed adjuvants (for example, aluminium hydroxide and the oil-in-water emulsion MF59), primarily elicit humoral responses without stimulating cellular immunity. Hence, an unmet medical need exists for new adjuvants particularly that can induce a robust cellular immunity. Liposomes are membrane bound synthetic vesicles that can encapsulate antigens acting both as vaccine delivery system and adjuvant. Their efficacy, however, depends on particle size, charge and phospholipid composition and method of preparation. Our *in vivo* studies demonstrate that cationic multi-lamellar distearyol l-α-phosphatidyl choline (DSPC) liposomes are superior compared to both anionic and neutral liposomes in their ability to elicit humoral as well as cell-mediated immunity through MHC class II restricted $CD4^+$ Th1 cell responses, suggesting that they do not merely function as efficient delivery systems but also as immunomodulators towards the associated antigen. Cationic DSPC liposomes entrapping the 63-kDa glycoprotein (gp63) of *L. donovani* promastigotes induced significant protection and sustained immunity against progressive visceral leishmaniasis in susceptible BALB/c mice. However, the major obstacle to the clinical development of this vaccine is its success limited to the intraperitoneal (ip) route of immunization which is not feasible for human use. To address this problem, vaccine formulation combining cationic liposomes with MPL-TDM (monophosphoryl lipid-trehalose dicorynomycolate) as immunomodulator was used with soluble leishmanial antigen (SLA) and administered through clinically relevant subcutaneous (sc) route. Liposomal SLA+MPL-TDM immunized mice demonstrated the induction of IFN-γ and IgG2a antibody 4 months after the challenge infection with a down regulation of IL-4. Long-term protection corresponded to, in addition to the presence of antigen-specific Th1, $CD8^+$ T-cell responses. Similarly, liposomal formulations of recombinant gp63 (rGP63) and leishmanial cysteine proteases in association with MPL-TDM were also found to be protective in rodents via sc route. To this end, we found the innate involvement of dendritic cells and macrophages upon vaccination with liposomes and MPL-TDM adjuvant in the activation of effector mechanisms, which subsequently guided the leishmanicidal role of T cells through adaptive immunity. Taken together, our results validate the combined use of MPL-TDM and liposomes as a suitable adjuvant system for the induction of durable protection against *L. donovani* associated with $CD4^+$ and $CD8^+$ T cells.

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