Abstract

Jenner and Pasteur used to take an old culture or crude source of pathogen and introduce into vaccinee even though not knowing the causative agent of the pathogen. This practice called variolation led to revolution because the person became resistant to the same pathogen or other pathogens that related to this original pathogen. The protection was associated with the poxvirus even though not knowing the mechanism related to protection. Later on, Leishmania, a protozoan parasite, was discovered, its structure was revealed and the genome was sequenced. Leishmaniasis is considered as neglected vector-borne diseases of the impoverished. The causative agent belongs to eukaryotic species of dimorphic, obligate, protozoan parasites of the genus *Leishmania*. Leishmania belongs to the order kinetoplastida and the family trypanosomatidae. Inside the host, these *Leishmania* parasites have a cellular niche known as macrophages wherein they survive and replicate. Being the primary host cells for the *Leishmania* parasite and an important cell type in the innate immune system, macrophages are responsible for killing the *Leishmania* parasite. Thus, the nature of interactions between the host and the parasite solely decides the outcome of *Leishmania* infection. However, the chemotherapeutic elimination of the parasite is challenged by the requirement of prolonged treatments or exorbitantly priced Ambisome, or highly toxic drugs such as miltefosine and resistance to the drug in prolonged use such as antimony. Therefore, an alternative is prophylactic immunization using a vaccine. Unfortunately, despite long trials, an effective anti-leishmanial vaccine remains elusive. MAPK10 (Mitogen-activated protein kinase10) a cytosolic signaling intermediate protein, having homology with mammalian host ERK-2 is therefore given a pre-clinical trial in a mouse model. As *L. major* derived MAPK10 gene shows host-protective effect in BALB/c mice, a susceptible host against experimental cutaneous leishmaniasis, we sought to determine whether priming with the same gene, i.e., MAPK10 would offer cross-protective efficacy against *L. donovani*

infection. We observed that priming with MAPK10 DNA in a mammalian expression vector significantly reduced the parasite burden, especially, in spleen and liver, associated with elevated NO production. The protection was associated with host-protective T-cell functions, T_H1-derived cytokines, and enhanced leishmanial antigen-specific IgG2a isotype response. The T-cell response against *L. donovani* infection was linked with an increase in IL-12 and IFN-γ, but reduced IL-10 and IL-4 production. These findings clearly support the cross-protective efficacy of LmjMAPK10 vaccination against *L. donovani* infection and the role of T-cells in the protection. A cytokine that regulates T-cell growth is IL-7. IL-7 is a non-hematopoietic stromal cell, not a T-cell, B-cell or NK cell-derived cytokine, secreted cytokine in thymic and bone marrow environment and is responsible for T-cell development and homeostasis. IL-7 works through its receptor that is comprised of two subunits- IL-7Rα (CD127) common with thymic stromal lymphopoietin (TSLP) and common γ chain (CD132). Binding of IL-7 with its receptor initiates signaling through JAK-STAT and PI3K/AKT pathway associated with survival and differentiation. As we previously reported that MAPK10 or M10 offers cross-protection against *L. donovani* infection. So, we sought to determine whether priming BALB/c mice (a susceptible model) with M10+rmIL-7 (recombinant murine IL-7) does regulate directly anti-leishmanial function. We found that immunized *L. donovani* infected mice significantly reduce the parasite burden in visceral organ spleen and liver as well as in Macrophage T-Cell co-culture in vitro. In addition, we noticed that CSA-stimulated splenocyte culture supernatant induced IL-12 and IFN-γ followed by a reduction in IL-10 and IL-4 production. As IL-12 promotes IFN-γ production that switches IgM to IgG2a and IL-10 facilitates IgG1 production, we collected sera from Immunized mice before and after infection.We found heightened IgG2a but suppressed IgG1 and IgM. The protection is also related to host protective T-cell function, T_H1 type cellular and humoral response. However, an increase in T_H1 cytokine IL-12 and suppressed T_H2, i.e.,

IL-4 and IL-10 production from macrophage T-cell co-culture supernatant accompanied by NO-mediated controlled parasite replication. These corroborative results suggest that M10+IL-7 regulated anti-leishmanial function against *L. donovani* infection in BALB/c susceptible mouse model.