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Ex vivo studies for pre-clinical evaluation of genetically modified live attenuated Leishmania parasites as potential vaccine candidate against visceral leishmaniasis in human blood PBMCs

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Visceral leishmaniasis (VL) is one of the world's most neglected and deadliest parasitic diseases, second only to malaria, endemic in 88 countries worldwide. Currently no effective vaccine is available for the potentially fatal disease, visceral leishmaniasis (VL) caused by protozoan parasites of *Leishmania donovani* complex. We have developed two genetically defined live attenuated *Leishmania donovani* parasites, one lacking centrin1, a growth regulating gene (*Ldcen1-/-*) and another lacking p27 gene (*Ldp27-/-*), an essential component of cytochrome c oxidase complex, involved in oxidative phosphorylation. Both vaccine candidates have been demonstrated as safe, immunogenic and protective in animal models. Here, we studied the immune responses generated by these mutant parasites in human PBMCs obtained from healed VL (HVL, n=15), post kala-azar dermal leishmaniasis (PKDL, n=15), VL (n=7) and healthy individuals (n=15). The infectivity of mutant parasites to human macrophages was similar to the wild type parasite. Further, *Ldcen1-/-* and *Ldp27-/-* strongly stimulated production of pro-inflammatory cytokines including, IL-12, IFN-γ, TNF-α, IL-2, IL-6 and IL-17 in the PBMCs obtained from individuals with a prior exposure to Leishmania (HVL and PKDL); however, no significant stimulation was found in anti-inflammatory cytokines (IL-4 and IL-10). This Th1 biased response was further supported by a remarkable increase in IFN-γ secreting $CD4^+$ and $CD8^+$ T cells and IL-17 secreting $CD4^+$ cells while there was no increase in IL-10 secreting $CD4^+$ and $CD8^+$ T cells in PBMCs from HVL blood. These results suggest that *Ldcen1-/-* and *Ldp27-/-* are both promising vaccine candidates against VL since they elicit strong protective immune response in human PBMCs from HVL, similar to the wild type parasite infection, mimicking a naturally acquired protection following cure.

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