INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: Deciphering novel immunosuppressive mechanisms adopted by *Leishmania donovani* parasites in the pathogenesis of *kala-azar*

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SHORT ABSTRACT

Leishmaniasis *(*commonly termed as "*kala azar*" in Indian subcontinent*)* is one of the most neglected parasitic diseases in the world. Despite advances in chemotherapeutic inventions, high cost, toxicity, duration of treatment, route of administration and development of drug resistance are the major drawbacks of chemotherapy. Thus, there is a huge urge to develop novel strategy for long term treatment which can be addressed by the development of novel immuno-therapeutics. To do so, thorough knowledge of immunosuppressive mechanism during infection has to be evaluated. Numerous advances have been made in highlighting the regulation of inflammasomes and its involvement in innate immunity during any pathogenic infections. Inflammasome activation is a tightly regulated process in providing defense against pathogenic insults. Few studies on the involvement of nucleotide-binding domain and leucine-rich repeat containing (NLR) proteins, NLRP3 inflammasome have been reported in leishmanial infections with contradictory results and without much mechanistic insights. However, the role of NLRP3 inflammasome and its components has not been well deciphered in *Leishmania donovani* infection. Here we report for the first time a detailed mechanism and plausible impairment of caspase 1 activation during *L. donovani* infection leading to the survival of these parasites inside the host cells. We demonstrate the importance of caspase 1 in the host defense mechanism *in-vitro* via siRNA mediated knock-down of caspase 1 in macrophage cell lines resulting in significantly higher parasitic burden. In addition, we have also shown that parasite can exploit a host molecule BLIMP-1 to mediate impairment of NLRP3 inflammasome activation by its overexpression. This upregulation of BLIMP-1 has been found to inhibit various other molecules like NFκβ, NEK7, TAK1 and p53 leading to escape of parasite from host immune response. Cells deficient in BLIMP-1 expression were used to validate its role during infection and suggest these parasites are tweaking the tight regulation of NFκβ – NLRP3 signaling pathway by BLIMP-1 overexpression. Eventually, the parasites disrupt an inflammation-mediated pyroptosis cell death pathway in infected cells and evade the inflammatory response of the host cells. The detailed understanding of this novel mechanism can play a vital role in designing future immunotherapeutics to combat Leishmaniasis.