

3rd International Conference and Exhibition on Clinical & Cellular Immunology

September 29-October 01, 2014 DoubleTree by Hilton Baltimore-BWI Airport, USA

Leishmania donovani negatively regulates TLR4 mediated host response by preventing ubiquitination dependent degradation of TRAF3

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Leishmania donovani, causative agent of fatal visceral leishmaniasis, is an intramacrophage pathogen. It escapes host Limmune response by subverting Toll like receptor (TLR) signaling, which is critically regulated by protein ubiquitination. Our work identified tumour necrosis associated factor (TRAF) 3 as a target used by Leishmania to deactivate LPS-mediated TLR4 signaling. TRAF3 is an E3 ubiquitin ligase of the membrane associated signaling complex that regulates TLR pathway through distinct protein ubiquitination at specific residues. We observed that TRAF3 which is ubiquitinated at lys 48 position and subsequently degraded following LPS treatment, persisted in *L. donovani* as well as *L. donovani* + LPS co-stimulated cells due to defective lys 48 ubiquitination. Unlike lys 48, lys 63-linked ubiquitinated proteins has been implicated in the signaling mediated activation of the molecules. Our results revealed lys 63-linked ubiquitination and subsequent degradation was significantly reduced during infection. The reason may be reduced association between ubiquitin conjugating enzyme Ubc13 and TRAF6 during infection. Persistence of TRAF3 resulted in stabilization of signalosome complex at the membrane resulting in inhibition of TAK-1 mediated pro-inflammatory responses. Inhibition of TRAF3 prior to infection by small hairpin RNA in Balb/c mice also showed enhanced production of IL-12 and TNF- α and significantly decreased spleen and liver parasite burden. Our findings identified TRAF3 as a novel molecular regulator exploited by Leishmania for successful infection.

Biography

Purnima Gupta is pursuing her PhD in Biochemistry from Calcutta University. She has received the prestigious CSIR-fellowship for Doctoral studies. Her research interest includes understanding how intramacrophage pathogens evade host cell defenses utilizing host signaling molecules to aid their survival within macrophage hostile environment.

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