THE FIBROBLAST GROWTH FACTOR SIGNALING PATHWAY AND THE STAT-6 SIGNALING PATHWAY CONVERGE TO INCREASE ARGINASE IN VISCERAL LEISHMANIASIS

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Host arginase 1 (Arg-1) expression is associated with the pathogenesis of cutaneous and visceral leishmaniasis (VL) in animal models of the disease. We showed previously in a hamster model of progressive VL that *Leishmania donovani*-induced Arg-1 expression was dependent on STAT-6 activation, but did not require the presence of interleukin (IL)-4. To investigate the mechanisms involved in the parasite induced STAT-6 activation and Arg1 regulation, we screened a chemical library of kinase inhibitors and evaluated the inhibition of Arg1 expression. We found that several inhibitors targeting tyrosine kinase receptors (RTKs) inhibited Arg1 transcription. The addition of recombinant ligands of RTKs (epidermal growth factor, fibroblast growth factor [FGF]) to bone marrow macrophages (BMMs) and fibroblasts increased the activation of STAT6 and transcription of Arg-1 suggesting a role of the RTK pathway in the regulation of Arg-1. We investigated the activation status of the RTK signaling cascade in VL by western blot of infected spleen tissue and found evidence of increased activation of the FGF receptor (FGFR)-1 signaling pathway. Chemical inhibitors of FGFR-1 and knockdown of STAT-6 in BMMs, inhibited parasite and FGF-induced Arg1 expression, suggesting a connection between the pathways. Additionally, we found the transcription factors CREB, STAT-3 and SRE, which are known to be activated through FGFR signaling, were activated in vitro by *L. donovani* in U-937 human monocytic cells. The results suggest that the FGFR signaling pathway and STAT-6 signaling pathway interact to regulate the transcription of host arginase, and that fibroblast growth factor signaling may contribute to the pathogenesis of VL.