ROLE OF PD1/PDL1 IN THE INDUCTION OF REGULATORY T CELLS DURING LEISHMANIA AMAZONENSIS INFECTION

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\textit{Leishmania amazonensis} is the etiological agent of diffuse cutaneous leishmaniasis in South America. In murine models of this infection, dysregulated expansion of effector T cells is related to pathogenesis, while the induction of regulatory T cells (Treg) promotes lesion resolution. The most important co-stimulator/receptor pairs for Treg induction are PD1/PDL1, ICOS/ICOSL, OX40/OX40L and GITR/GITR. In this study, we examined the roles of these molecules in \textit{L. amazonensis}-infected C57BL/6 mice. We found that infected foot tissues had a 10- and 5-fold increase in PD1 and PDL1 expression levels, respectively, with minimal changes for other receptor/ligand pairs. In skin-draining lymph nodes of infected mice, there were an increase in the percentage of CD11c\textsuperscript{+}PDL1\textsuperscript{+} dendritic cells (DC) and PD1\textsuperscript{+}CD4\textsuperscript{+} T cells. To evaluate PDL1 expression on DC, we performed \textit{in vitro} infection with promastigotes and amastigotes. \textit{L. amazonensis} infection resulted in an increased PDL1, but decreased PD-L2, expression on DC surface. This induction-triggered PDL1 expression was dependent on STAT3, PI3K and mTOR, but not on STAT5, MAPK/ERK and MyD88. Infected DCs were more competent in inducing CD25\textsuperscript{+}FoxP3\textsuperscript{+} Treg in vitro than the control cells, and this Treg-promoting effect was dependent on PDL1 expression but not on TGF-beta production. Together, these data suggest a role for PD1/PDL1 in the regulation of local immune responses during \textit{L. amazonensis} infection. This study provides new insights on immune regulation of cutaneous leishmaniasis.