T cell-dependent upregulation of arginase 1 in monocyte-derived cells accounts for chronic cutaneous leishmaniasis caused by Leishmania mexicana

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Control of intracellular Leishmania (L.) parasites requires IFNγ-dependent induction of type 2 nitric oxide (NO) synthase (NOS2) converting L-arginine into citrulline and leishmanicidal NO. NOS2 activity may be counteracted by host cell arginase (Arg) 1, which is induced by Th2 cytokines, and by mitochondrial Arg2. Both enzymes cleave L-arginine into urea and ornithine. The latter is a precursor of polyamines that are essential for immune cell and parasite proliferation. Recently, we observed that Arg1 and Arg2 were upregulated in L. mexicana-infected BALB/c and C57BL/6 mice during disease progression. Here, we tested the hypothesis that arginases promote inflammation and prevent resolution of chronic cutaneous leishmaniasis caused by L. mexicana. Mice lacking Arg1 in hematopoietic and endothelial cells (Tie2Cre+Arg1fl/fl), Arg2-/-, Tie2Cre+Arg1fl/flArg2-/- double knockout and the respective wildtype (WT) controls were infected with L. mexicana. WT mice developed chronic progressive disease, in Arg2-deficient mice onset of disease was delayed, whereas Arg1- and Arg1/2- deficient mice showed an ameliorated infection with strongly reduced pathology, which was ultimately clinically resolved despite persisting parasites. As the course of infection was comparable in Cx3cr1Cre+Arg1fl/fl and Tie2Cre+Arg1fl/fl mice, Arg1 expression by monocyte-derived myeloid cells appears to account for disease pathology. Analysis of CD4Cre+IL-10fl/fl revealed that CD4+ T cell-derived IL-10 was responsible for the induction of Arg1 and the non-resolving phenotype. Whether IL-10 directly induces Arg1 or whether it acts in an indirect manner is currently investigated. Interestingly, deletion of Arg1 did not alter NOS2 activity, as the NO levels in the tissue were similar in WT controls and Cx3cr1Cre+Arg1fl/fl or Tie2Cre+Arg1fl/fl mice.
Together, we conclude that upregulation of Arg1 in myeloid cells by T cell-derived IL-10 is crucial for pathology in chronic cutaneous leishmaniasis and prevents resolution of L. mexicana infections. Ongoing research focuses on the apparently NOS2-independent mechanism by which Arg1 causes chronic leishmaniasis.

Keywords : Leishmaniasis, Arginase, Chronicity, Resolution
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