Cutaneous Leishmaniasis Patients in The Pre-Ulcerative Phase: High Inflammatory Response and Unresponsiviness to IL-10 at Lesion Site

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Introduction: Cutaneous leishmaniasis (CL) is an infectious disease caused by parasites of the Lesihmania genus, characterized by the presence of ulcerated lesions with raised borders. Pentavalent antimony is the main drug used to treat leishmanisis in Brazil and high therapeutic failure rate is observed in L. braziliensis transmission areas. Regarding immune response, the lesion infiltrate is composed, predominantly, by lymphocytes and macrophages, and few parasites are observed. During CL strong inflammatory response, with high levels of TNF and IL-1β, is observed. Also, an important role for CD8+ T lymphocytes and NK in the pathogenesis of CL has been documented. These cells produce granzyme B, a protease that induces pro-inflammatory responses. Before the ulcer develops, CL individuals present a large regional lymphadenopathy, followed by an exoulcerative papule or lesion, and area characterized by early cutaneous leishmaniasis patients (ECL). ECL lesions exhibit higher parasitic load and lower numbers of T CD4+ and T CD8+ lymphocytes when compared to CL. Recently, it has been demonstrated in the lesions of ECL an intense cytotoxic activity with high frequency of granzyme B+ cells. Our aim was to investigate the presence of inflammatory markers in ECL and the ability of IL-10 to modulate the production of these factors in the lesion of ECL patients. Methods and Results: Skin lesion fragments from 10 patients with ECL and 11 with CL were obtained and maintained in cultures in the presence or absence of rIL-10 for 72 hours. Levels of granzyme B, IL-1β, IL-10, CCL2, CXCL9 and CXCL10 were determined in supernatant cultures, by ELISA. We observed that cells from lesion from ECL patients produce IL-1β, IL-10 and CCL2 in similar levels to those from CL, but they exhibit higher levels of granzyme B, CXCL9 and CXCL10 than CL. Addition of exogenous IL-10 did not decrease the production of granzyme B, IL-1β, CXCL9 and CXCL10 in ECL or in CL individuals. We also found that ECL patients had higher ratios granzyme B:IL-10; CXCL9:IL10 and CXCL10:IL-10. Conclusion: Our results suggest that increased production granzyme B, CXCL9 and CXCL10 are associated with ulcer development and therapeutic failure in ECL patients, and show that cells infiltrating the lesion are unresponsive to IL-10.