TITLE: MODULATION OF MACROPHAGE MICROBICIDE RESPONSE DURING THE INFECTION WITH DRUG RESISTANT *LEISHMANIA INFANTUM* ISOLATES.

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ABSTRACT

Visceral Leishmaniasis is an infectious disease of neglected people and caused by protozoa *Leishmania*. The control of infection and parasite dissemination is essentially executed by phagocytes like macrophages, the main cell of parasite tropism. However, when the disease is stablished the chemotherapy is the main form of control of the leishmaniasis. But in the last years have been shown increasing cases of treatment relapse patients and *Leishmania* parasites resistant to drug. Thereby, we collected mononuclear cell of peripheral blood of healthy donors (n = 7) and differentiate into macrophages. After this, we infected the macrophages with different strains of *Leishmania infantum*: two from relapse patients and naturally *in vitro* drug resistant and one isolated from responsive patient and *in vitro* drug sensitive. Moreover, we treated the infected macrophages with different immune modulators: activators of microbicide response, IFNγ + LPS; macrophage co-activation with recombinant sCD40L; blocking of Interleukin-10 action; inhibition of Nitric Oxide (NO) production by Aminoguanidine. Also, we used pentavalent antimonial treatment. The percentage of infected macrophages and the number of parasites inside of the macrophages was determined by counting of 100 cells into coverslips. From this, our results show the inability of macrophages in control the parasite dissemination only to the resistant isolates at 24h when compared to initial infection (02h). In addition, the use of pentavalent antimonial is unable to control this situation. Interestingly, we observed a significative reduction at 24h in the number of infected macrophages when we treated the macrophages with immune activators or make the co-activation, with IFN + LPS or recombinant sCD40L. Besides, the IL-10 blockade makes the macrophages able to control the parasite dissemination at the 24h time. Moreover, when we inhibited the NO production the number of infected macrophages in 24h was similar the 02h, but we observed an increased number of amastigotes parasitizing the cells. In conclusion, the phenotype of drug resistance in *L. infantum* isolates is related to different pattern in macrophage infection and the modulation of immune response of infected macrophages can control the parasites dissemination. These results, open new perspectives to alternative control of treatment relapses cases of visceral leishmaniasis.

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Keywords: leishmaniasis; drug resistance; immune response.