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EPIGENETIC MODIFICATIONS IN *LEISHMANIA AMAZONENSIS*-INFECTED MACROPHAGES: THE ROLE OF THE ENZYME ENHANCER OF ZESTE HOMOLOG 2

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Abstract

Parasites of the Leishmania genus possess an arsenal of molecules that modulate the epigenetic state of the host, and the release of these molecules through Extracellular Vesicles (EVs) may be a strategy to ensure the survival of the parasite. Previous studies have shown that histone deacetylase 1 (HDAC1) plays a crucial role in the epigenetic regulation of macrophages during *Leishmania amazonensis* infection. In addition, the enzyme EZH2, responsible for the repressive epigenetic marker H3K27me3, regulates essential biological processes; however, its role during *L. amazonensis* infection, its relationship with HDAC1 and its impact on pathogenesis remain unknown. Thus, we propose to test the hypothesis that *L. amazonensis* infection induces repressive epigenetic modifications in macrophages, evaluating the role of EZH2 and the contribution of EVs. For this purpose, EVs were purified from *L. amazonensis* promastigotes at 35°C and, by microscopy, we observed the budding of these EVs. The predominant size was around 100 nm, and the concentration of 2.6x10e7 particles/mL was determined by NTA. Using the Western blotting technique, an increase in H3K27me3 was observed in *L. amazonensis* infection and also by treatment with EVs for 5 hours. In a period of 18 hours, it was possible to observe the decrease of this mark. Notably, the expression of EZH2 increased during infection and after treatment with EVs. Inhibition of EZH2 by GSK-343 for 24 hours in THP1 macrophages led to a decrease in the parasite load and the H3K27me3 even after infection. Significantly, that EVs were able to neutralize the inhibitory effect and recover the parasite load. HDAC1 and DNMT1 levels increased upon infection and after EV treatment. It is possible that EZH2 recruits DNA methyltransferases and histone deacetylases to silence genes that allow subversion of the macrophage response. Therefore, our data may provide new insights into the epigenetic modifications that occur after infection.

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