The NFKB1/HDAC1 complex controls the outcome of *Leishmania* infecion in human macrophages

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Chromatin remodeling proteins such as histone deacetylases (HDACs) may form with transcription factors and other molecules a large complex denominated repressome. The study of epigenetic alterations induced by pathogens is poorly exploited, particularly those involving protozoan parasites. Our group demonstrated unique features of NF- kappaB pathway subversion in macrophages infected with *L. amazonensis*. We demonstrated that the activation of NF-kappaB transcriptional repressor homodimer (p50/p50) in *L. amazonensis*- infected macrophages is dependent on PI3K/Akt activation. As a result of p50/p50 NF-kappaB activation, we observed the downregulation of nitric oxide synthase (iNOS) expression in infected macrophages stimulated with gamma Interferon. In this work, we show that p50/p50 NF-kappaB is associated with the chromatin repressor protein HDAC1. Remarkably, we found increased levels of HDAC1 in *Leishmania* infected macrophages. Corroborating this data, confocal microscopy analysis demonstrated the colocalization of HDAC1 with p50 subunit in the nuclei of infected macrophages. Accordingly, the total histone deacetylase activity was increased in infected macrophages. A relevant reduction of the parasite load was observed in HDAC1 knockdown macrophages, which was accompanied by increased levels of nitric oxide. Accordingly, ChiP assays revealed an increased occupancy of HDAC1 and decreased levels of acetylated histone 3 (Lys 9) in *nk* binding sites in the iNOS promoter. Re-Chip assays demonstrated the complex p50-HDAC1 at iNOS promoter. Importantly, tissue samples from hyporesponsive patients infected with *L. amazonensis* express higher levels of HDAC1 compared with hyperresponsive pacients infected with *L. braziliensis*. Our data corroborate the notion that *L. amazonensis* induces the formation of a repressome formed in part by p50/p50 /HDAC1 interaction and this complex seems to be critical for the intracellular survival of the parasite and the outcome of human infection.

Key words: *Leishmania*, Epigenetics, HDAC1, NF-kappaB