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Markers found in macrophages using proteomics can function as targets for chemotherapeutic intervention of *Leishmania* infection

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Leishmaniasis has been treated by antimonial pentavalents for the last 70 years. However, the efficacy of leishmaniasis treatment is under scrutiny due to the rise of drug-resistant cases. To find in macrophages potential targets for alternative chemotherapeutic intervention against *Leishmania* infection, we employed a proteomic approach that allowed the identification of proteins whose expression changes in *Leishmania*-infected macrophages that might function as novel targets for leishmaniasis treatment. Using this proteomic approach, we found a total of 162 proteins modulated in macrophages upon *Leishmania* infection. Among them, a total of 15 proteins showed greater differences in expression in infected macrophages, and at least one of them, HIF-1α has the potentiality to be modulated by specific drugs. HIF-1α is one of the client proteins of the heat-shock protein (HSP)-90, a molecular chaperone that is highly abundant in mammalian cells and known to be induced during stress responses. This ATP-dependent chaperone is known to be involved in the stabilization, correct folding, and assembly of several client proteins including HIF-1α. Protozoan parasites also express HSP90, which is known to play a crucial role in the stabilization of heat-labile proteins within these cells. Herein we describe the modulation of *Leishmania* infection using in infected macrophages of 17-AAG, a benzoquinone ansamycin antibiotic that is a specific inhibitor of HSP90, treatment of infected macrophages with 17-AAG significantly reduced both the percentage of infected cells and parasite load in a dose- and time-dependent manner. Intracellular parasite death occurred independent of nitric oxide and superoxide production. Electron microscopy revealed morphological alterations suggestive of 17-AAG-induced parasite death results from an autophagic process. Further investigation using parasite mutants of the components of the autophagic pathway, such as GFP-ATG8 and ATG5-KO reinforces the notion that 17-AAG induced the formation of autophagic vacuoles in parasites. In addition, the 17-AAG induced autophagosomes showing reduced fusion between autophagosomes and lysosome/glycosome. These suggest that 17-AAG induced autophagic vacuoles that do not mature to autolysosomes that could be responsible for parasite death.

Biography

Patrícia Sampaio Tavares Veras graduated from the School of Medicine of the Federal University of Bahia and completed her PhD in the Department of Immuneparasitology of the Pasteur Institute in Paris. She currently works as a Researcher at the Gonçalo Moniz Research Center, a division of the Oswaldo Cruz Foundation (CPqGM/FIOCRUZ). She has experience in the fields of cellular and molecular biology, specifically in the area of cellular biology of host-pathogen interactions. She focused her research efforts on interactions between murine macrophages and *Leishmania* spp. Her group has developed studies concerning murine macrophages using large-scale approaches, aiming to identify molecules within macrophages that play crucial role on the course of *Leishmania* infection. Her group found promising molecules that proved to be useful as chemotherapeutic targets in therapeutic applications to fight against leishmaniasis.

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