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Proteomics analysis of infected murine macrophages reveals modulation of proteins potentially involved in *Leishmania* intracellular survival

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CBA mice are resistant to *Leishmania major* yet susceptible to *Leishmania amazonensis*. In addition, CBA macrophages control infection by *L. major* and are permissive to *L. amazonensis*, which suggests that macrophages play an important role in the outcome of *Leishmania* infection. In order to evaluate the global macrophage response to *Leishmania* infection, proteomic studies were carried out. Protein expression was identified six and 24 hours after infection with *L. major* or *L. amazonensis*. Protein extracts were obtained from bone marrow-derived macrophage to identify peptides using LC-MS/MS with a MudPIT approach. The results from six independent experiments were analyzed and 382 proteins were found to be expressed differently, in accordance with infection by *L. amazonensis* or *L. major*. These proteins are involved in a variety of cell functions, including cell death, post-translational modification, lipid metabolism, molecular transport, amino acid metabolism, small molecule biochemistry, cell signaling, cell cycle and cell-mediated immune response. Using IPA software, ten protein networks were constructed. The proteins related to lipid metabolism and small molecule biochemistry were grouped into one network and exhibited higher expression levels in *L. amazonensis*-infected cells compared to *L. major*. Proteins related to cell signaling and cellular assembly, organization and movement formed another network exhibiting higher expression levels in *L. major*-infected cells compared to *L. amazonensis*. These results clearly demonstrate that *L. amazonensis* and *L. major* modulate macrophage functions in different ways. Macrophage response to *L. amazonensis* did not establish a definite activation profile. However, *L. major* activates cell-signaling networks, with respect to cell activation. One of the molecules with higher expression in *L. amazonensis*-when compared to, *L. major*-infected macrophages was the transferrin receptor (CD71) that participates in transferrin-iron complexes (HoloTf) uptake. Several studies have approached the involvement of iron in the course of infections by *Leishmania* but none compared the role iron plays in resistant and susceptible model of *Leishmania* infection, such as macrophages from CBA mice that respond differently to two *Leishmania* species. Thus, we validated the higher expression of CD71 in *L. amazonensis*-infected macrophages found in proteomic analysis. Using the CBA macrophages infected with *L. amazonensis* or *L. major*, we then evaluated the expression modulation of another essential enzyme in iron metabolism, heme oxygenase 1 (HO-1) that is involved in the degradation of the iron-containing cofactor heme, mediatingintracellular iron availability. Therefore, CD71 and HO-1 expression in CBA macrophages was evaluated six and 24 hours after infection with *L. amazonensis* or *L. major* by FACS and ELISA, respectively. As a result, we observed a higher expression in extracellular CD71 in *L. amazonensis*-infected macrophages.We also found a higher HoloTf binding and uptake in *L. amazonensis*-infected macrophages. In addition, a higher expression of HO-1 in macrophages infected with *L. amazonensis* compared to those infected with *L. major* was observed. These findings suggest that the difference in CD71 and HO-1 expression may lead to higher intracellular iron levels in *L. amazonensis*-infected cells and that this nutrient may favor in parasite survival inside macrophages. Further studies are underway to better evaluate the role iron plays in *Leishmania* infection outcome by determining the expression of other protein involved in iron metabolism, such as ferroportin 1, Nramp-1, and ferritin, as well as by quantifying intracellular free iron and by modulating, chelating or complementing, iron availability to *Leishmania*-infected cells.

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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