Comparative analysis of Sb-resistant *Leishmania major* and *L. braziliensis* cell lines isolated in vitro

Wilton C. Z. Lopes; André L. Fernandes and Luiz R. O. Tosi
Departamento de Biologia Celular e Molecular e Bioagentes Patogênicos.
Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo.

Resistance to antimonials is a major problem in treating leishmaniasis in India and has already been described for New World parasites. Clinical response to meglumine antimoniate in infection with parasites of the *Viannia* subgenus can be variable suggesting the presence of mechanisms of drug resistance. In this work we compared *L. major* and *L. braziliensis* mutants selected in different drugs. Using stepwise selection we isolated cell lines resistant to both antimonial forms (SbIII and SbV). Northern analysis revealed that these mutants presented a lower level of transcripts for genes involved in thiol biosynthesis (?-Glutamylcysteine synthetase); activation of the prodrug (Arsenate reductase) and the uptake of SbIII (Aquaglyceroporin 1). These results are in agreement with the data obtained from *L. donovani* strains isolated from patients in eastern Nepal. Also, preliminary analysis suggested a lower level of intracellular thiols in these mutants.. The cross-resistance profiles of some cell lines were comparable to that of mutants bearing H locus amplicons. However, amplified episomal molecules were exclusively detected in *L. major* mutants. The absence of amplicons in *L. braziliensis* suggests that this species may not favour extra-chromosomal gene amplification as a source of phenotypic heterogeneity and fitness maintenance in changing environments.

Supported by FAPESP, CNPq and CAPES.