

Molecular and Biochemical characterization of resistant *Leishmania donovani* isolates.

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Quest for a definite molecular tool for identification of cross resistant *Leishmania* strains and their difference with the sensitive ones led to the study of fluidity of *Leishmania* membrane, and the abundance of a particular sugar moiety on their surface. Extent of resistivity to a particular drug among the field isolates has been assigned by the degree of clearance of amastigotes from infected macrophages representative of their EC50 values of the four drugs SSG, Miltefosine, Amphotericin B and Paromomycin. Out of the 18 isolates studied, 5.55% were sensitive to all the drugs, 11.11%, 16.67%, 38.89% and 27.78% were resistant to either one, two, three or four drugs respectively. Flow cytometry studies with FITC labeled lectins suggested higher level of expression of N-acetyl- α -D-galactosaminyl residue in resistant isolates as compared to the sensitive ones. A more fluidic nature of membrane has been revealed by the anisotropy experiments using membrane incorporative fluorescent probes DPH and TMA-DPH. This altered fluidity may be a consequence of modified metabolomic profile for SSG resistant LD isolates. There is a notable difference in the sphingolipid and phospholipid metabolism for SSG sensitive and resistant species. The SSG resistant strains possess higher levels of PC with low fatty acyl unsaturation, while the sensitive were enriched in PC (Phosphatidyl choline) with high fatty acyl unsaturation. Association of some thiol metabolizing enzymes like Thiol dependent reductase, Trypanothione reductase and Mercaptopyruvate sulfur transferase, is likely to be present if the resistant field isolates exhibit cross resistance to all the foresaid drugs. Adaptation of SSG resistant field isolates in infected macrophages during host parasite interaction elevates level of cytokine production like IL10 for sustainable infection and stimulation of ABC Transporters like MRP1 and PGP efflux pumps has been ascertained in accordance to SSG resistivity.