FROM RESISTANCE TO RESURGENCE: HOW *LEISHMANIA INFANTUM* RECLAIMS ITS FITNESS AND METABOLIC EDGE AFTER ANTIMONY WITHDRAWAL

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Leishmaniasis, caused by the protozoan parasite *Leishmania*, continues to pose a major public health problem worldwide. Phenotypic shifts in this parasite related to genome plasticity contribute to resistance and complicate treatment. This study investigates the fitness cost of antimony resistance in *Leishmania infantum*. Ten SbIII-resistant clones were cultured under SbIII-free conditions for 18 passages, with most regaining sensitivity as indicated by their IC_{50} values. This resensitization was linked to decreased amplification of the *mrpA* gene, a key factor in resistance. Drug assays revealed the emergence of miltefosine resistance but not amphotericin B resistance after Sb^{III} removal. Resensitized clones exhibited significantly higher growth rates than resistant clones after eight drug-free passages, suggesting a fitness cost of resistance. Oxygen consumption assays showed increased O_2 consumption between passages P3 and P8, followed by a decrease after P8, indicating metabolic adaptations. Infection assays with bone marrow-derived macrophages showed reduced infectivity as the clones regained sensitivity, potentially linked to increased metacyclic differentiation, suggesting a trade-off between drug resistance and infectivity. Additionally, a significant decrease in MRP-A protein abundance was observed, with increases in AQP1, tryparedoxin, HSP70, PCNA, and tyrosine phosphatase at different time points. These changes indicate dynamic reprogramming of protein expression with the reversal of resistance. Our findings suggest that antimony resistance in *L. infantum* imposes a fitness cost, driven by genomic and proteomic adaptations that influence metabolism and infectivity. A comprehensive understanding of these mechanisms is essential for the development of effective strategies to manage drug-resistant *Leishmania* populations and improve relapse therapies.

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