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EXPLORING HYPOTHETICAL PROTEINS TO UNVEIL NOVEL TARGETS ASSOCIATED WITH Sb^V-RESISTANCE IN *Leishmania* PARASITES

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Abstract

In many countries, the first-line drugs to treat leishamniasis rely on antimony (Sb^V)-based medicines. However, factors such as high cost, difficulties in administration, severe toxicity, and the emergence of resistant strains highlight the need for new therapeutic strategies. *Leishmania* parasites exhibit high genome plasticity that favors the selection of Sb^V-resistant strains (SbR). Studies revealed that *Leishmania* spp. genomes code for approximately 60% of hypothetical proteins, which includes those differentially expressed in SbR mutants. In this sense, it is crucial to understand the role of these protein-encoding genes in the context of Sb resistance. Elucidating the role of these proteins may reveal new therapeutic targets for leishmaniasis treatment. This study aimed to identify differentially expressed genes (DEGs) encoding hypothetical proteins in *Leishmania* resistant to Sb and to perform computational function prediction based on their structure. To achieve this, we evaluate publicly available data on DEGs in SbR *Leishmania*. 204 out of 603 DEGs were classified as hypothetical or functionally unknown proteins and were present in at least two independent studies. Among these genes, 28 exhibited a *cutoff* greater than 1.5, providing further strong evidence of their potential role in resistance. Some known markers harbored in chromosome 23 were found to be upregulated in half of the analyzed studies, reinforcing its established role in Sb resistance phenotype. These 204 targets are being analyzed to predict their structure using AlfaFold and compare it on PDB through the FoldSeek tool to propose and validate their functions. Our findings highlight the importance of these proteins in Sb resistance and suggest potential new therapeutic targets. The functional characterization of these proteins is essential for developing effective alternatives for leishmaniasis treatment.

Keywords: Leishmaniasis, antimony resistance, hypothetical proteins, structural prediction
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