

Heavy metal resistance: a new role for P-glycoproteins in *Leishmania*

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P-glycoproteins are responsible for multidrug resistance in tumor cell lines and are thought to have a physiologic role in exporting cellular metabolites. We now report that a P-glycoprotein gene in the H region of the trypanosomatid protozoan *Leishmania* confers resistance to heavy metals when present in multiple copies. The *Leishmania* H region is frequently amplified in drug-resistant lines and is associated with metal resistance. *Leishmania* expression vectors were used to introduce multiple copies of segments of the *Leishmania major* H region into wild-type *L. major* promastigotes. Only constructs bearing a segment of *L. major* DNA containing the P-glycoprotein *lmPGPA* conferred arsenite resistance. Deletional analysis of the arsenite-resistant construct mapped resistance to the *lmPGPA* protein coding region. Lines expressing *lmPGPA* showed resistance to arsenite and trivalent antimonials, but not to pentavalent antimonials, zinc, cadmium, or the typical multidrug-resistant P-glycoprotein substrates vinblastine and puromycin. Transfection of the *Leishmania tarentolae* P-glycoprotein homologue *ltPGPA* resulted in a similar resistance profile. Thus, these PGPA's represent a functionally distinct group of P-glycoproteins which exhibit a substrate specificity similar to prokaryotic heavy metal pumps. Additionally, several arguments suggest that PGPA's may play a role in the susceptibility of *Leishmania* to clinically utilized antimonials.