THE YIP1 PROTEIN OF *LEISHMANIA MAJOR* AND ITS ROLE IN TERBINAFINE RESISTANCE

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The *HTBF* gene of *L. major* confers resistance to terbinafine, an inhibitor of Esqualene epoxidase. HTBF predicted aminoacid sequence revealed significant homology to the Yip1 protein of *Saccharomyces cerevisiae*. In the yeast, Yip1p participates in vesicle trafficking by interacting with Ypt, a rab/GTPase, allowing it to insert into vesicle membranes. Our hypothesis is that HTBF is involved in the formation and/or redirection of vesicles, improving mechanisms of drug extrusion or membrane repair. The rab/GTPase gene of *L. major*, *LmYPT,* was cloned and co-transfected into cell lines overexpressing *HTBF*. Expression of *LmYPT* led to the abolition of HTBF-mediated terbinafine resistance. The studied members of the YIP1 family localize in the Golgi complex and are widely conserved. A c-Myc::HTBF fusion was expressed in mammalian cell lines and localized in the Golgi complex, confirming its conservation. We further expressed a GFP::HTBF fusion in the parasite. Subcellular localization assays revealed that the fusion product was present in a region corresponding to the flagellar pocket and Golgi complex. Our results suggest not only that HTBF is the YIP1 of *L. major*, but also that the terbinafine resistance observed in HTBF overexpressors involves the vesicle trafficking machinery of the parasite.

Financial support: FAPESP, CNPq and CAPES