TITLE: FUNCTIONAL CHARACTERIZATION OF *CRYPTOCOCCUS GATTII ZIP3* GENE.

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Cryptococcus neoformans and *Cryptococcus gattii* are the etiologic agents of cryptococcosis, a fungal disease that affects humans and animals. This disease is characterized by a primary lung infection that may disseminate to the whole organism, leading to meningoencephalitis. *C. gattii* is mainly recognized by its capability to infect immune compromised patients, as well as healthy individuals. The intricate interplay played by both host and pathogens cells is far for complete understanding. The control of nutrients bioavailability is essential for elimination of many pathogens, a process named nutritional immunity. Among such nutrients, zinc and manganese are important cofactors for many proteins in the cells. Several organisms mobilize zinc and other metals from internal storage or extracellular space to cytoplasm by the activity of proteins from the ZIP family. We previously described that proper uptake of zinc in *C. gattii* is mediated by Zip1, while Zip2 appears to play a marginal role. However, the function of the remaining two other ZIP proteins coded by *C. gattii* genome remain unknown. The aim of this work was to characterize to role of the *ZIP3* product. The *C. gattii* ZIP3 gene is ortholog of *Saccharomyces cerevisiae ATX2*, a manganese intracellular transporter located in the Golgi apparatus. Null mutants of *ZIP3* were constructed and evaluated for zinc and manganese associated phenotypes. Tolerance to high concentrations of zinc and manganese was observed to *zip3*Δ strain compared to WT strain. A possible compensatory effect of divalent cation intracellular transporters was also observed in *zip3*Δ cells cultured in presence of manganese excess, including the manganese Golgi transporter Pmr1 and the vacuolar transporters Vcx1 and Pmc1. In line with these results, *zip3*Δ cells displayed hypersensitivity to the calccineurin inhibitor FK506. In addition, we could detect a higher concentration of polyphosphate in *zip3*Δ cells, which would aid in the manganese buffering. Together, our results suggest that Zip3 is involved in manganese homeostasis in cryptococcal cells.

Keywords: Cryptococcus, metal transporter, ZIP3 gene

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