Molecular targets of the antifungal prototypes thiosemicarbazide and thiosemicarbazide camphene

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Abstract

Paracoccidioidomycosis (PCM) is a neglected human systemic disease caused by *Paracoccidioides* spp. The disease commits the host's lungs and can disseminate to many other organs. It affects mostly men who work with soil in endemic areas at Latin America. The disease treatment is usually done with amphotericin B, sulfadiazine, trimethoprim-sulfamethoxazole, itraconazole, ketoconazole or fluconazole The treatment duration is usually long, during from six months to two years. In this way, many adverse effects are related to the treatment and the patients can have many co-morbidities and difficulties in treatment adhesion. For those reasons, the search for more effective and less toxic drugs is needed. Thiosemicarbazide (TSC) and thiosemicarbazide camphene (TSC-C) were able to inhibit *Paracoccidioides lutzii* growth in a low dosage and were not toxic to fibroblast cells. In order to investigate the mode of action of those compounds we performed a chemoproteomic approach and unveiled which fungal proteins bound to each of these compounds. We also performed activity assays in order to confirm if those proteins really bound to the compounds and we were able to see that they could inhibit some of protein's enzymatic activities. Some proteins that bound to the compounds are related to mycelium to yeast differentiation and when comparing the transition of treated cells to control cells, we could see that TSC inhibited 38,28% and TSC-C inhibited 66,67% of mycelium to yeast transition. In comparison with transcriptome and proteome data previously obtained by our group, we could relate the mode of action of TSC and TSC-C to a bioenergetic collapse, by inhibiting the electron transport chain and low energy production.