Title: Trancriptional profiling of macrophage response to *Cryptococcus neoformans* and *Cryptococcus gattii*

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Abstract:

The basidiomycetous yeasts *Cryptococcus neoformans* and *Cryptococcus gattii* are the etiological causes of cryptococcosis, a life-threatening disease characterized by meningoencephalitis. While *C. neoformans* infects primarily immunecompromised patients, *C. gattii* can infect healthy individuals. The infectious process for both species starts with the deposition of yeast cells in lung alveoli, where an intricate and complex interaction of cryptococcal cells with macrophages takes place. This interaction normally results in the inhibition of macrophage function or even apoptosis. To evaluate whether other macrophage pathways and genes could be affected by cryptococcal infection, a genome-scale comparative analysis of transcriptional changes in macrophages exposed to *C. neoformans* and *C. gattii* was conducted. Infection of J774.1 macrophages with *C. neoformans* H99 strain and *C. gattii* R265 strains were allowed to progress during 6 hours. Poly(A) RNA was purified from macrophage cells and submitted to sequencing in a Ion PGM System. Reads were aligned to *Mus musculus* genome using TMAP, the reads associated with each gene counted by HTSeq and differential expression analysis were performed using the package EdgeR. Functional enrichment was performed using the DAVID platform. Using 1.5 fold change as cutoff, the expression of near 1.000 genes was shown to be altered positively either by *C. neoformans* or *C. gattii*. Correlation analysis showed that the transcriptional response of macrophages to *C. neoformans* was different for the response to *C. gattii.* The functional enrichment analysis of differentially expressed genes led to the conclusion that several pathways were altered in response to cryptococcal infection. Of note, alternative splicing is enriched in macrophage *C. neoformans*-induced genes, whilst such process is enriched in macrophage *C. gattii*-repressed genes. Our results indicate that *C. neoformans* and *C. gattii* can exploit the modulation of different pathways in macrophages, suggesting that different strategies were used by these species to reduce macrophage antifungal activities.

Keywords: macrophage, RNA Seq, *Cryptococcus neoformans*, *Cryptococcus gattii.*

Financial support: CAPES, CNPq, FAPERGS