Title: Transcriptional profiling of macrophage response to Cryptococcus neoformans and Cryptococcus gattii


Institutions: 1Centro de Biotecnologia, UFRGS, Porto Alegre, RS. 2Laboratório Nacional de Computação Científica, Petrópolis, RJ.

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 immune compromised 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