Title: GENDER INFLUENCE ON THE MACROPHAGES INTERACTION WITH *Cryptococcus gattii*

Authors Costa, M.C. [1], Fernandes, H.B. [2], Silveira, R.R. [1], Freitas, G.J.C. [1], Oliveira, L.V.N. [1], Silva, A.M. [2], Santos, D.A. [1]

Institute [1] Departamento de Microbiologia - Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brasil (Av. Antônio Carlos, 6627, Pampulha - Belo Horizonte - MG - CEP 31270-901), [2] Departamento de Biologia Celular - Instituto de Ciências Biológicas - Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brasil (Av. Antônio Carlos, 6627, Pampulha - Belo Horizonte - MG - CEP 31270-901)

Abstract:

Cryptococcus gattii is one of the agents of cryptococcosis, a systemic mycosis that occurs in humans and animals. *C. gattii* is an emerging primary pathogen that mainly infects healthy individuals. Clinical studies have shown that patients infected with this fungus exhibit severely compromised lungs. There is speculation that females are more resistant to infection by this fungus. Epidemiological studies have demonstrated gender influence in the pathogenesis of *Cryptococcus neoformans* in a ratio of 2-3 men: 1 woman. However, it is still unclear the influence of sex hormones in cryptococcosis and in host responses. Phagocytic cells represent the first line of nonspecific host defense against this pathogen and the interaction of macrophages with this yeast plays a central role in cryptococcosis. Therefore, this study aims to evaluate the influence of gender and β-estradiol hormone in the infection of macrophages. For this purpose, primary macrophages derived from bone marrow cells of male and female mice were infected with *C. gattii*, in the presence or absence of 200 nM β-estradiol. After 3 and 24 hours, phagocytosis, intracellular proliferation and reactive oxygen species rates were quantified. In both times there was a higher capacity of the derived macrophages of female in contain the infection, since these were shown to be more efficient to internalize the fungus, produce more reactive oxygen species, resulting in reduced proliferation rate of this fungus inside the cells. In the estradiol presence, the ability of these cells was enhanced. Although estradiol presence has positively influenced the macrophages obtained from females in the ability to contain infection, it was not observed in macrophages derived from male mice. Another study showed that treatment of *C. neoformans* with testosterone, the principal male sex hormone, induces increase in content of polysaccharide glucoroxilomanana (GXM) in laboratory and clinical isolates, therefore enhancing its virulence and reducing the rate of phagocytosis by alveolar macrophages. On the other hand, in the presence of β-estradiol, macrophages phagocytize and eliminate the fungus, since this hormone induces no increased content GXM. Thus, our study reinforces data indicating gender difference in susceptibility to cryptococcosis and contributes to better understanding of *Cryptococcus*-host interaction.

Keywords: Cryptococcosis, *Cryptococcus gattii*, macrophages, gender

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