

TITLE: OXIDATIVE STRESS ALTERS PHAGOCYTOSIS OF *Candida tropicalis* MORPHOTYPES BY HEMOCYTES AND MACROPHAGES

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ABSTRACT:

Innate immunity is highly conserved on the evolutionary scale. Mammals and invertebrates share mechanisms of phagocytic response and production of reactive oxygen species (ROS). On the other hand, pathogens present escape mechanisms from phagocytosis and manifestation of virulence factors. The aim of this study was to analyze the effect of exposure to hydrogen peroxide (H₂O₂) on phagocytosis of *Candida tropicalis* morphotypes by hemocytes (*Galleria mellonella*) and macrophages (*Mus musculus*). To this end, we analyzed clinical isolates 49.07 and 100.10 (Parental strains) of *C. tropicalis* and their switch variants (Crepe) before and after exposure to H₂O₂. The filamentation percentage during the interaction between fungal and phagocytic cells and the expression of genes (*EFG1*, *WOR1* and *HOG1* - qPCR) under these conditions was also analyzed. All morphotypes were phagocytosed at similar rates by macrophages and hemocytes, except for the crepe variant that was more phagocytosed by hemocytes (p<0.001). Differently, after exposure to H₂O₂, crepe variants from the two clinical isolates were less phagocytosed (<20%, p<0.001). One of the escape mechanisms to phagocytosis is bud-hyphae transition. The crepe variant (100.10 counterpart) showed high true hyphae percentage in co-culture with both phagocytic cells (6%), while Crepe (49.07) showed the same profile to hemocytes (15%). The filamentation profile was maintained for all morphotypes after exposure to H₂O₂. During co-culture with hemocytes there was overexpression of the *HOG1*, *WOR1* and *EFG1* by all morphotypes of isolate 49.07. Crepe showed more expression than Parental. For isolate 100.10 there was *HOG1* overexpression of Parental. Exposition to H₂O₂ upregulated expression of all genes tested in 49.07 morphotypes (except *WOR1*-Parental); Crepe morphotype showed higher expression than Parental. *EFG1* for Parental and Crepe 100.10 morphotypes showed upregulation after stress exposition. The overexpression of genes related to morphogenesis (*EFG1*, *WOR1*), switch forms (*EFG1*) and stress response (*HOG1*) may be associated to the phenotypic plasticity of morphotypes analyzed against the interaction with phagocytes and the oxidative stress. The present work could observe the phenotypic switching in *C. tropicalis* promote emergence of strains more responsive to oxidative stress by H₂O₂ what can be related to scape from phagocytic cells.

Keywords: *Candida tropicalis*, phagocytosis, hemocyte, macrophage, phenotypic switching.

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