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Short Communication

Molecular Mechanisms of Virulence by *Histoplasma capsulatum*

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DESCRIPTION

The morphological and behavioural changes required for virulence are reflected in the dimorphism of *Histoplasma*. The thermally induced change to the pathogenic yeast-phase programme is mediated by the dimorphism regulating kinase DRK1 and the *Histoplasma* WOR1 homolog RYP1. This regulon's expressed genes have an impact on how the host and pathogen interact, favouring *Histoplasma* virulence. In contrast to yeast-glucan polysaccharides, which mask immunostimulatory cell wall -glucans from detection by macrophage receptors, surface localized HSP60 promotes yeast attachment to host macrophages. CBP, a secreted, protease-resistant calcium-binding protein designed to operate within the phagolysosomal environment, promotes the growth of yeast cells inside macrophages. YPS3 encourages the spread of yeast from pulmonary infection sites in some *Histoplasma* strains. Additional cell surface and extracellular components in the *Histoplasma* yeast-phase program may play a role in additional virulence-related functions [1].

One such intracellular fungal infection that can parasitize phagocytic immune cells is *Histoplasma capsulatum*. This fungus is widespread throughout the world, but it is particularly prevalent in the Ohio and Mississippi River valleys in the United States. 80% of the people in this endemic region are thought to have come into contact with *Histoplasma*. The inhalation of mycelium-produced conidia into a mammalian lung results in the acquisition of *Histoplasma,* which is transformed into pathogenic yeast cells at 37 °C [2]. Neutrophils and alveolar macrophages both come into contact with yeast cells. However, *Histoplasma* infections cannot be managed by the innate immune system alone. After being ingested by phagocytes, yeasts multiply inside phagosomes until the host cell bursts, releasing the yeasts, which are then ingested by nearby phagocytes. Immunocompetent hosts are typically able to control yeast growth upon activation of the adaptive immune response, which strengthens the antifungal response of phagocytes. Immunocompromised hosts are susceptible to infection just like immunocompetent hosts are, but immunocompetent hosts are more likely to do so [3].

Since *Histoplasma* yeasts and host phagocytes interact heavily, *Histoplasma's* capacity to prevent or neutralize ROS is a crucial aspect of its pathogenesis. Although *Histoplasma* yeasts do not cause an oxidative burst in resting macrophages, activation of macrophages or opsonization of yeasts does. On the other hand, when PMNs come into contact with *Histoplasma*, they quickly create ROS. *Histoplasma* yeasts may endure the ROS challenge regardless of the cell type or reaction. The molecular processes underlying this resistance to ROS are still largely unclear. Recently, we showed that yeasts produce extracellular Superoxide Dismutase (Sod3), which is necessary for full virulence in a mouse infection paradigm and protects *Histoplasma* against superoxide produced by macrophages and PMNs [4].

Surface-localized components of *H. capsulatum* yeasts are possible PAMPs that may be identified or may affect the yeast-macrophage interaction since the cell wall is the major surface that interacts with the macrophage. Due to their function as vaccine substrates or immunologically dominant epitopes, cell wall-localized factors have been the subject of several studies. These include the extracellular catalase CatB/M-antigen, histone 2B, the previously mentioned Hsp60 protein, and Hsp70. Some lineages of *H. capsulatum* express the yeast phase-specific protein Yps3, which connects with the yeast cell surface through interactions with chitin. Purified recombinant Yps3 was demonstrated to bind to and activate TLR2 in microglial cells, which resulted in TLR2-dependent NF-B stimulation and chemokine production. However, no interaction of Yps3 in the typical context of a yeast cell was determined, and the effects of TLR2-dependent yeast interaction with macrophages were not determined either. Although Yps3 does not affect lung infection by *H. capsulatum* yeasts, Yps3-deficient strains of the yeast exhibit less dispersion. Based on these findings, a speculative model proposes that interactions between Yps3 and TLR2 promote chemokine production, enhancing the recruitment of phagocytes that act as host cells for the yeast and carriers of extra-pulmonary dissemination [5].

The pathogenic mechanisms underlying *Histoplasma* virulence thanks to the completion of genome sequences from various phylogenetic groupings as well as the ongoing development and

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use of molecular genetic tools. For two of the most researched strains, G186A and G217B, the pathogenesis that results is shaped by both conserved elements (such as Cbp1, Sid1) and unique factors (such as-glucan, Yps3). The examples of AGS1 and YPS3 demonstrate how variance between strains with remarkably identical genomic sequences can be influenced by different transcriptional regulation.

It is challenging to extrapolate experimental results from one *Histoplasma* strain to the others because surprisingly few mechanistic studies have been conducted with many strains. Additional characteristics that set differentiating *Histoplasma* strains apart are anticipated based on the variation in the few virulence variables investigated so far. It will be necessary to acknowledge the differences between strains and conduct comparative studies using the currently available molecular genetic tools in order to determine the relevance of such mechanistic differences to the pathogenesis of *Histoplasma*.

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