CHARACTERIZATION OF INTERLEUKIN-1B PRODUCTION IN MYELOID CELLS IN RESPONSE TO THE FUNGAL PATHOGENS *CANDIDA ALBICANS* AND *CANDIDA PARAPSILOSIS*

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Introduction: *Candida albicans* and *C. parapsilosis* are clinically significant opportunistic fungal pathogens. Interleukin-1β (IL-1β), which is released from myeloid cells upon inflammasome activation, plays a crucial role in antifungal immunity. We have previously shown that *C. parapsilosis* induces lower T helper 17 (Th17) differentiation in comparison to *C. albicans.* In this study, we characterized the production of IL-1β in response to *Candida albicans* and *Candida parapsilosis.*

Methods: Freshly isolated human peripheral blood mononuclear cells (PBMCs; $5x10^5$) were stimulated with *C. albicans* or *C. parapsilosis* at an MOI of 0.02 for 24 h. PMA-induced (10 nM, 24 h) THP-1 monocytes ($5x10^5$) were stimulated with different amounts of *C. albicans* or *C. parapsilosis* for 24 h in the presence or absence of specific inhibitors. The concentration of cytokines (Il-1β, TNFα, IL-6) in cell culture supernatants was measured by ELISA. The amount of pro-IL-1β mRNA was determined by qRT-PCR. The concentration of pro-IL-1β protein was measured by ELISA following the lysis of THP-1 cells by repeated freeze-thaw cycles. Intracellular ROS was detected by DCFDA fluorescent assay.

Results: PBMCs stimulated with *C. parapsilosis* produced similar quantities of TNFα and IL-6, but much lower amounts of IL-1β, compared to *C. albicans*-stimulated cells. In PMA-induced THP-1 monocytes, *C. albicans* induced the release of IL-1β after 24 hours already at an MOI of 0.01, while a 100-times higher dose of *C. parapsilosis* cells (MOI of 1) was needed for the induction of IL-1β secretion. This marked difference in secreted IL-1β levels originated from the differential processing pro-IL-1β, as we found no difference in the level of IL-1ß mRNA and pro-IL-1ß. As it has been associated with inflammasome activation, we also measured the amount of intracellular ROS and found that *C. albicans* induced higher ROS production in THP-1 cells compared to *C. parapsilosis*. We also found that both *C. albicans* and *C. parapsilosis* induced pyroptosis in macrophages after 24 h, and the production of IL-1β in response to both species was dependent on Caspase-1, Caspase-8, Syk, NADPH oxidase and TLR4.

Conclusions: Our results strongly suggest that although *C. parapsilosis* is able to induce inflammasome activation when added in a high dose, it is very inefficient in inducing pro-IL-1β processing in comparison to *C. albicans*. These findings contribute to the better understanding of the pathogenesis of *Candida* infections, and highlight the importance of

studies focusing on different *Candida* species rather than *C. albicans* alone when investigating the immunity against these pathogens.

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