

Transcriptome profile of the human endothelial cell response to high- and low-density infections of *Candida albicans*.

ABSTRACT

Background: *Candida albicans* morphology switching and quorum-sensing are important factors for pathogenicity and virulence in persons with a compromised or deficient immune system. This study investigates the in vitro response of human umbilical vein endothelial cells (HUVECs) to infections with low and high densities of *C. albicans*. We hypothesize that higher cell densities of *C. albicans* yeast-form cells (blastospores), are more detrimental to HUVECs than lower cell densities of hyphal forms. **Methods:** Three biological replicates of confluent HUVECs in 6-well plates were challenged with 10^6 *C. albicans* blastospores (low-density infection) and 5×10^7 blastospores (highdensity infection) for 8 hours. The low-density infection generated true hyphae, but in the high-density infection, *C. albicans* remained as blastospores. RNA from these samples were subjected to DNA microarray transcript profiling. For MTT and XTT cell proliferation assays, conditioned media from the co-cultures for microarray experiments were incubated with HUVECs in 96-well plates for 24 hours. **Results:** The high-density blastospore-HUVEC co-cultures elicited significantly higher differential expression of genes involved in functional pathways of apoptosis, immune response, cell-cell signaling and cancer development, such as *ZC3HAV1*, *HES1*, *CSF2*, *CXCL2* and *PIM1*, compared to the low-density true hyphae-HUVEC co-cultures. Cell proliferation assays also show that HUVECs incubated with conditioned media from the highdensity infection caused a higher percentage of cell death compared to incubation with conditioned media from the low-density infection. These results suggest that high densities of unattenuated, innate *C. albicans* blastospore cells can cause significant cellular toxicity, even though the cells are in the yeast form, not filamentous. **Conclusion:** Transcript profiling of this in vitro endothelial cell model may provide new insights into how *C. albicans* cell densities affect the host during the colonization and invasion through the bloodstream to the deep organs. We also suggest that quorum-sensing molecules and other unknown secretions from high-density *C. albicans* infections are strong inducers of cellular injury leading to cell death in systemic candidiasis.