

HOST RESPONSE TO *CANDIDA PARAPSILOSIS* INFECTION

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Despite the increasing clinical importance, little is known about the host response upon *C. parapsilosis* infection. Thus, we have analyzed the transcriptional responses of murine macrophage-like cell line J774.2 cells to infection with *C. parapsilosis* at 3h and 8h. The complex response of murine macrophages to infection with *C. parapsilosis* was investigated at the level of gene expression using an Agilent mouse microarray. The comparison of the gene expression profiles of *C. parapsilosis* stimulated and non-stimulated J774.2 cells revealed 158 and 527 genes differentially expressed by at least 2.0 fold at 3 h and 8 h post infection, respectively. Of particular interest was the upregulation of proinflammatory cytokines, typical of the classically activated macrophages such as TNF, IL-1 and IL-15. To validate our microarray platform, we performed quantitative Real-Time PCR analysis. The 6 selected genes (IL1b, IL12b, TNF alfa, PTGS2, CD83, IL15) showed a significant correlation between the qPCR and microarray data. Interestingly, the most upregulated gene (14.01 fold by 3h and 74.3 fold by 8h) identified by microarray was TNFRSF9, the gene of tumor necrosis factor receptor superfamily, member 9 (4-1BB). To further characterize the up-regulation characteristics of this receptor molecule we compared the regulation of the TNFRSF9 gene following infection with 8 different pathogen *Candida* species (*C. albicans*, *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. metapsilosis*, *C. orthopsilosis*, *C. parapsilosis*, *C. tropicalis*) we found a significant upregulation of TNFRSF9 at mRNA level by all cases. Notably, the highest induction (108 fold) was detected by infection with *C. parapsilosis* at 12 hours. To confirm our findings as relevant in human infections we analyzed the regulation of the human TNFRSF9 gene during *C. parapsilosis* infection. We found a significant upregulation by the TNFRSF9 mRNA level after 6 hour infection (3.5 fold) and the highest induction was detected at 12 hour post infection (6.7 fold). The molecule 4-1BB was initially described in mice as a protein upregulated during T cell activation. Murine CD4⁺ T cells can be directly and effectively co-stimulated by 4-1BB, and has been implied in promotion of Th1 T-helper cell responses. Understanding how macrophages respond to *C. parapsilosis* at the molecular level may facilitate the development of new therapeutic paradigms. Additionally,

the microarray data revealed significant differences

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