

An interspecies regulatory network inferred from simultaneous RNA-seq of *Candida albicans* invading innate immune cells.

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Abstract

The ability to adapt to diverse micro-environmental challenges encountered within a host is of pivotal importance to the opportunistic fungal pathogen *Candida albicans*. We have quantified *C. albicans* and *M. musculus* gene expression dynamics during phagocytosis by dendritic cells in a genome-wide, time-resolved analysis using simultaneous RNA-seq. A robust network inference map was generated from this dataset using NetGenerator, predicting novel interactions between the host and the pathogen. We experimentally verified predicted interdependent sub-networks comprising Hap3 in *C. albicans*, and Ptx3 and Mta2 in *M. musculus*. Remarkably, binding of recombinant Ptx3 to the *C. albicans* cell wall was found to regulate the expression of fungal Hap3 target genes as predicted by the network inference model. Pre-incubation of *C. albicans* with recombinant Ptx3 significantly altered the expression of Mta2 target cytokines such as IL-2 and IL-4 in a Hap3-dependent manner, further suggesting a role for Mta2 in host-pathogen interplay as predicted in the network inference model. We propose an integrated model for the functionality of

these sub-networks during fungal invasion of immune cells, according to which binding of Ptx3 to the *C. albicans* cell wall induces remodeling via fungal Hap3 target genes, thereby altering the immune response to the pathogen. We show the applicability of network inference to predict interactions between host-pathogen pairs, demonstrating the usefulness of this systems biology approach to decipher mechanisms of microbial pathogenesis.

Beteiligte Forschungseinheiten

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