

Nitrogen catabolite repression in *Trichophyton rubrum* during the adaptive process to host molecules

Maíra Pompeu Martins, Pablo R. Sanches, Nilce M. Martinez-Rossi, Antonio Rossi

Abstract

The environmental challenges imposed to fungal pathogens require a dynamic metabolic modulation, resulting in the activation or repression of critical factors, enabling the establishment and perpetuation of the infection in their host. Wherefore, to conquer the different host microenvironments, pathogens not only depend on virulence factors but also on metabolic flexibility, dynamically responding to stressing conditions in the host. The dermatophyte *Trichophyton rubrum* is a pathogenic fungus adapted to degrade keratinized tissues as the skin and nails, utilizing the resulting amino acids and peptides as the final carbon sources. During infection, the proteolytic activity is associated with deamination reactions, resulting in the accumulation of nitrogen mainly as ammonium ions, actively secreted by the fungus through intensive ammonia production. The secreted ammonia raises the extracellular pH, resulting in an alkalinized ambient, acting as a supporting factor to pathogenicity. We evaluated *T. rubrum* interaction with keratin, in a metabolic perspective, providing information about gene modulation of the dermatophyte during early infection stage after shifting from glucose- to keratin-containing culture media, in comparison to glucose as the carbon source. Analyzing *T. rubrum* transcriptome using high-throughput RNA-sequencing (RNA-seq) technology, we identified the repression of essential genes related to nitrogen metabolism, as the ammonium transporter MepA, a glutamate synthase, a proline-specific permease, and a urease. These results suggest the activation of an alternative pathway for nitrogen assimilation in the tested conditions, necessary for the fungus survival in the host. The gene expression profiling of the host-pathogen interaction highlights candidate genes involved in fungal adaptation and survival, elucidating the machinery required to the establishment of the initial stages of the infection.

Funding: FAPESP, CNPq, CAPES, and FAEPA