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Discovering drug targets and virulence factors by mapping the lipid metabolism of the pathogenic fungus Histoplasma capsulatum

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Abstract

Lipids are major components of biological membrane, energy storage molecules and cell signaling transducers. Therefore, not surprisingly, lipids play major function in host-pathogen interactions and are frequently targeted for drug development. Seeking to better understand the function of lipids in fungal pathogenesis and identify potential drug targets, we performed a comprehensive analysis of the Histoplasma capsulatum lipid metabolic pathway by integrating proteomic and lipidomic analyses. This analysis resulted in mapping of 5 major lipid metabolic pathways, 19 lipid subclasses and 371 individual lipid species. We demonstrate that the H. capsulatum fatty acid desaturation and sphingolipid metabolism diverge from Saccharomyces cerevisiae and human, being promising targets for drug development. Thiocarlide (inhibitor of fatty acid desaturases) and myriocin (inhibitor of the first step of sphingolipid biosynthesis) have minimum inhibitory concentrations of 12 μM and 30 nM, respectively. The analysis also showed that H. capsulatum produces analogs of platelet-activating factor (PAF), a potent regulator of the human immune response. The structural information of the H. capsulatum PAF analogs was further validated by tandem mass spectrometry, ion mobility and liquid chromatographic analyses. We also demonstrated that the H. capsulatum PAF analogs induces platelet aggregation and the production of the cytokines interleukin-10 and tumor necrosis factor alpha. Overall, our approach led to the discovery of chemotherapy targets and the identification of an immunoregulatory bioactive lipid from H. capsulatum.