Evaluation of lysine biosynthesis as an antifungal drug target: biochemical characterization of *Aspergillus fumigatus* homocitrate synthase and virulence studies.

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Abstract

Aspergillus fumigatus is the main cause of severe invasive aspergillosis. To combat this life-threatening infection, only limited numbers of antifungals are available. The fungal alpha-aminoadipate pathway, which is essential for lysine biosynthesis, has been suggested as a potential antifungal drug target. Here we reanalyzed the role of this pathway for establishment of invasive aspergillosis in murine models. We selected the first pathway-specific enzyme, homocitrate synthase (HcsA), for biochemical characterization and for study of its role in virulence. A. fumigatus HcsA was specific for the substrates acetyl-coenzyme A (acetyl-CoA) and alpha-ketoglutarate, and its activity was independent of any metal ions. In contrast to the case for other homocitrate synthases, enzymatic activity was hardly affected by lysine and gene expression increased under conditions of lysine supplementation. An hcsA deletion mutant was lysine auxotrophic and unable to germinate on unhydrolyzed proteins given as a sole nutrient source. However, the addition of partially purified A. fumigatus proteases restored growth, confirming the

importance of free lysine to complement auxotrophy. In contrast to lysine-auxotrophic mutants from other fungal species, the mutant grew on blood and serum, indicating the existence of high-affinity lysine uptake systems. In agreement, although the virulence of the mutant was strongly attenuated in murine models of bronchopulmonary aspergillosis, virulence was partially restored by lysine supplementation via the drinking water. Additionally, in contrast to the case for attenuated pulmonary infections, the mutant retained full virulence when injected intravenously. Therefore, we concluded that inhibition of fungal lysine biosynthesis, at least for disseminating invasive aspergillosis, does not appear to provide a suitable target for new antifungals.

Beteiligte Forschungseinheiten

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