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Lysine biosynthesis in *Aspergillus fumigatus*

Lysine is an essential amino acid for humans and must be obtained from the diet. In contrast, fungi, such as *Aspergillus fumigatus*, are able to synthesise lysine de novo via the alpha-aminoadipate pathway. Deletion of *A. fumigatus* homoaconitase, a key enzyme of lysine biosynthesis, leads to a strongly attenuated virulence in a murine infection model for bronchopulmonary invasive aspergillosis, making these enzymes interesting targets for new antifungal drugs. However, biochemistry of alpha-aminoadipate pathway enzymes is not well studied and an important catalytic step has not been investigated yet.

Therefore, the following main issues are addressed:
1) Re-evaluation of lysine biosynthesis as antifungal drug target. Deletion of the first key enzyme of lysine biosynthesis, the homocitrate synthase, showed a strongly attenuated virulence in murine infection model for bronchopulmonary invasive aspergillosis. However, this attenuation is less pronounced under lysine supplementation and not observed in a model for disseminated aspergillosis. In agreement, in vitro growth experiments on protein containing media showed a requirement of free lysine for conidia germination, whereas hyphae secrete proteases, which release sufficient lysine from proteins to enable growth. These results indicate that drugs directed against lysine biosynthetic enzymes might only be useful for preventing conidia germination but not for therapy of an already manifested infection.

2) Conversion of homocitrate to homoisocitrate: A reaction solely carried out by the homoaconitase? To elucidate this question the homoaconitase was purified as recombinant enzyme. Interestingly, homoaconitase displayed no activity with homocitrate as substrate, suggesting the involvement of additional, yet unknown, enzymes in this conversion. one candidate is the citric acid cycle Aconitase, but further studies are required to confirm this assumption.

Publications

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