

Analysis of the regulation, expression, and localisation of the isocitrate lyase from *Aspergillus fumigatus*, a potential target for antifungal drug development.

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Abstract

Invasive aspergillosis, caused by *Aspergillus fumigatus*, is a severe systemic infection in immunocompromised patients. New drug targets are required, since therapeutic treatment often fails and is hampered by severe side effects of antifungals. Enzymes of the glyoxylate bypass are potential targets, since they are absent in humans, but required for growth of *Aspergillus* on C2-generating carbon sources. The key enzyme isocitrate lyase (ICL) can be inhibited by 3-nitropropionate, both as a purified enzyme and within intact cells, whereas the latter inhibition upregulates ICL promoter activity. ICL was found in distinct subcellular structures within growing hyphae, but only under conditions requiring ICL activity. In contrast, ICL was constitutively found in conidia, suggesting a specific role during germination. Lipids, as potential substrates, were detected in conidia and macrophages. Additionally, germinating conidia within macrophages contain ICL, suggesting that the glyoxylate shunt might be a relevant target for development of antifungals.

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