Candida albicans utilizes a modified β-oxidation pathway for the degradation of toxic propionyl-CoA.

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Details

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Abstract

Propionyl-CoA arises as a metabolic intermediate from the degradation of propionate, odd-chain fatty acids, and some amino acids. Thus, pathways for catabolism of this intermediate have evolved in all kingdoms of life, preventing the accumulation of toxic propionyl-CoA concentrations. Previous studies have shown that fungi generally use the methyl citrate cycle for propionyl-CoA degradation. Here, we show that this is not the case for the pathogenic fungus Candida albicans despite its ability to use propionate and valerate as carbon sources. Comparative proteome analyses suggested the presence of a modified β-oxidation pathway with the key intermediate 3-hydroxypropionate. Gene deletion analyses confirmed that the enoyl-CoA hydratase/dehydrogenase Fox2p, the putative 3-hydroxypropionyl-CoA hydrolase Ehd3p, the 3-hydroxypropionate dehydrogenase Hpd1p, and the putative malonate semialdehyde dehydrogenase Ald6p essentially contribute to propionyl-CoA degradation and its conversion to acetyl-CoA. The function of Hpd1p was further supported by the detection of accumulating 3-hydroxypropionate in the hpd1 mutant on propionyl-CoA-generating nutrients. Substrate specificity of Hpd1p was determined from recombinant purified enzyme, which revealed a

preference for 3-hydroxypropionate, although serine and 3-hydroxyisobutyrate could also serve as substrates. Finally, virulence studies in a murine sepsis model revealed attenuated virulence of the hpd1 mutant, which indicates generation of propionyl-CoA from host-provided nutrients during infection.

Beteiligte Forschungseinheiten

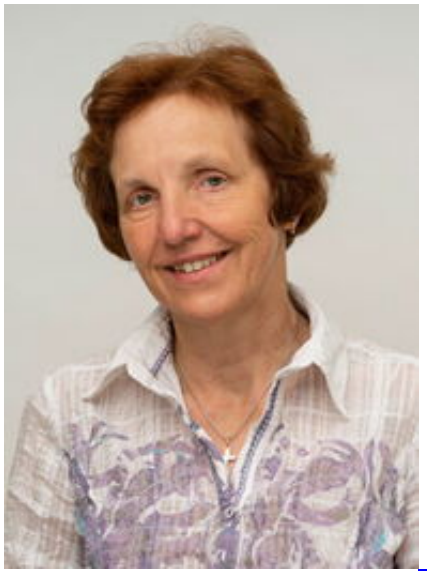
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Leibniz-HKI-Autor*innen



Bettina Bardl

Details



Matthias Brock

Details



Ilse Denise Jacobsen

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