Identification of hypoxia-inducible target genes of *Aspergillus fumigatus* by transcriptome analysis reveals cellular respiration as important contributor to hypoxic survival.

Kroll K, Pähtz V, Hillmann F, Vaknin Y, Schmidt-Heck W, Roth M, Jacobsen ID, Osherov N, Brakhage AA, Kniemeyer O (2014) Identification of hypoxia-inducible target genes of *Aspergillus fumigatus* by transcriptome analysis reveals cellular respiration as important contributor to hypoxic survival. *Eukaryot Cell* 13(9), 1241-1253.

Abstract

Aspergillus fumigatus is an opportunistic, airborne pathogen causing invasive aspergillosis in immunocompromised patients. During the infection process A. fumigatus is challenged by hypoxic microenvironments occurring in inflammatory, necrotic tissue. To gain further insights into the adaptation mechanism, A. fumigatus was cultivated in an oxygen-controlled chemostat under hypoxic and normoxic conditions. Transcriptome analysis revealed a significant increase of transcripts associated with cell wall polysaccharide metabolism, amino acid and metal ion transport, nitrogen metabolism and glycolysis. A concomitant reduction in transcript levels was observed with cellular trafficking and G-protein coupled signaling. To learn more about the functional roles of hypoxia-induced transcripts we deleted A. fumigatus genes putatively involved

in reactive nitrogen species detoxification (fhpA), NAD(+) regeneration (frdA, osmA) nitrogen metabolism (niaD, niiA) and respiration (rcfB). We show that the NO-detoxifying flavohemoprotein gene fhpA is strongly induced by hypoxia independent of the nitrogen source, but is dispensable for hypoxic survival. By deleting the nitrate reductase gene niaD, the nitrite reductase gene niiA and the two fumarate reductase genes frdA and osmA, we found that alternative electron acceptors such as nitrate and fumarate do not have a significant impact on growth of A. fumigatus during hypoxia, but that functional mitochondrial respiratory chain complexes are essential under these conditions. Inhibition studies indicated that primarily complex III and IV play a crucial role in the hypoxic growth of A. fumigatus.

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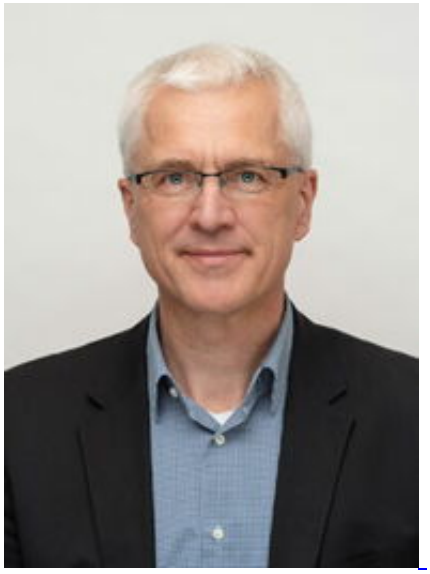

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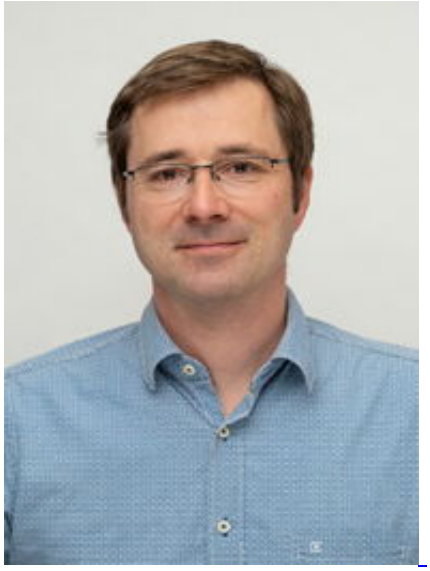

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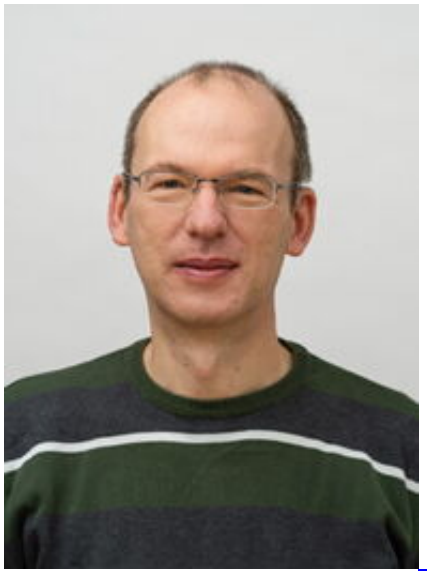

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doi: EC.00084-14

PMID: 25084861