

The monothiol glutaredoxin GrxD is essential for sensing iron starvation in *Aspergillus fumigatus*.

Misslinger M†, Scheven MT†, Hortschansky P, Sanchez Lopez-Berges M, Heiss K, Beckmann N, Heigl T, Hermann M, Krüger T, Kniemeyer O, Brakhage AA*, Haas H* †shared first authors, *corresponding authors (2019) The monothiol glutaredoxin GrxD is essential for sensing iron starvation in *Aspergillus fumigatus*. *PLOS Genetics* 15(9), e1008379.

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Abstract

Efficient adaptation to iron starvation is an essential virulence determinant of the most common human mold pathogen, *Aspergillus fumigatus*. Here, we demonstrate that the cytosolic monothiol glutaredoxin GrxD plays an essential role in iron sensing in this fungus. Our studies revealed that (i) GrxD is essential for growth; (ii) expression of the encoding gene, *grxD*, is repressed by the transcription factor SreA in iron replete conditions and upregulated during iron starvation; (iii) during iron starvation but not iron sufficiency, GrxD displays predominant nuclear localization; (iv)

downregulation of grxD expression results in de-repression of genes involved in iron-dependent pathways and repression of genes involved in iron acquisition during iron starvation, but did not significantly affect these genes during iron sufficiency; (v) GrxD displays protein-protein interaction with components of the cytosolic iron-sulfur cluster biosynthetic machinery, indicating a role in this process, and with the transcription factors SreA and HapX, which mediate iron regulation of iron acquisition and iron-dependent pathways; (vi) UV-Vis spectra of recombinant HapX or the complex of HapX and GrxD indicate coordination of iron-sulfur clusters; (vii) the cysteine required for iron-sulfur cluster coordination in GrxD is in vitro dispensable for interaction with HapX; and (viii) there is a GrxD-independent mechanism for sensing iron sufficiency by HapX; (ix) inactivation of SreA suppresses the lethal effect caused by GrxD inactivation. Taken together, this study demonstrates that GrxD is crucial for iron homeostasis in *A. fumigatus*.

Involved units

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