

Small but crucial: the novel small heat shock protein Hsp21 mediates stress adaptation and virulence in *Candida albicans*.

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Abstract

Small heat shock proteins (sHsps) have multiple cellular functions. However, the biological function of sHsps in pathogenic microorganisms is largely unknown. In the present study we identified and characterized the novel sHsp Hsp21 of the human fungal pathogen *Candida albicans*. Using a reverse genetics approach we demonstrate the importance of Hsp21 for resistance of *C. albicans* to specific stresses, including thermal and oxidative stress. Furthermore, a *hsp21Δ/Δ* mutant was defective in invasive growth and formed significantly shorter filaments compared to the wild type under various filament-inducing conditions. Although adhesion to and invasion into human-derived endothelial and oral epithelial cells was unaltered, the *hsp21Δ/Δ* mutant exhibited a strongly reduced capacity to damage both cell lines. Furthermore, Hsp21 was required for resisting killing by human neutrophils. Measurements of intracellular levels of stress protective molecules demonstrated that Hsp21 is involved in both glycerol and glycogen regulation and plays a major role in trehalose homeostasis in response to elevated temperatures. Mutants

defective in trehalose and, to a lesser extent, glycerol synthesis phenocopied HSP21 deletion in terms of increased susceptibility to environmental stress, strongly impaired capacity to damage epithelial cells and increased sensitivity to the killing activities of human primary neutrophils. Via systematic analysis of the three main *C. albicans* stress-responsive kinases (Mkc1, Cek1, Hog1) under a range of stressors, we demonstrate Hsp21-dependent phosphorylation of Cek1 in response to elevated temperatures. Finally, the *hsp21* Δ/Δ mutant displayed strongly attenuated virulence in two in vivo infection models. Taken together, Hsp21 mediates adaptation to specific stresses via fine-tuning homeostasis of compatible solutes and activation of the Cek1 pathway, and is crucial for multiple stages of *C. albicans* pathogenicity. Hsp21 therefore represents the first reported example of a small heat shock protein functioning as a virulence factor in a eukaryotic pathogen.

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Leibniz-HKI-Autor*innen



Bernhard Hube

[Details](#)



Ilse Denise Jacobsen

[Details](#)



François Mayer

[Details](#)



Pedro Miramón

[Details](#)



Silvia Slesiona

[Details](#)



Duncan Wilson

[Details](#)

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