

The Snf1-activating kinase Sak1 is a key regulator of metabolic adaptation and *in vivo* fitness of *Candida albicans*.

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Abstract

The metabolic flexibility of the opportunistic fungal pathogen *Candida albicans* is important for colonisation and infection of different host niches. Complex regulatory networks, in which protein kinases play central roles, link metabolism and other virulence-associated traits, such as filamentous growth and stress resistance, and thereby control commensalism and pathogenicity. By screening a protein kinase deletion mutant library that was generated in the present work using an improved SAT1 flipper cassette, we found that the previously uncharacterised kinase Sak1 is a key upstream activator of the protein kinase Snf1, a highly conserved regulator of nutrient stress responses that is essential for viability in *C. albicans*. The *sak1Δ* mutants failed to grow on many alternative carbon sources and were hypersensitive to cell wall/membrane stress. These phenotypes were mirrored in mutants lacking other subunits of the SNF1 complex and partially compensated by a hyperactive form of Snf1. Transcriptional profiling of *sak1Δ* mutants showed that Sak1 ensures basal expression of glyoxylate cycle and gluconeogenesis genes even in

glucose-rich media and thereby contributes to the metabolic plasticity of *C. albicans*. In a mouse model of gastrointestinal colonisation, *sak1Δ* mutants were rapidly outcompeted by wild-type cells, demonstrating that Sak1 is essential for the in vivo fitness of *C. albicans*.

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