Secreted aspartic protease cleavage of *Candida albicans* Msb2 activates Cek1 MAPK signaling affecting biofilm formation and oropharyngeal candidiasis.

Puri S, Kumar R, Chadha S, Tati S, Conti HR, Hube B, Cullen PJ, Edgerton M (2012) Secreted aspartic protease cleavage of *Candida albicans* Msb2 activates Cek1 MAPK signaling affecting biofilm formation and oropharyngeal candidiasis. *PLOS One* 7(11), e46020-e46020.

Details

Abstract

Perception of external stimuli and generation of an appropriate response are crucial for host colonization by pathogens. In pathogenic fungi, mitogen activated protein kinase (MAPK) pathways regulate dimorphism, biofilm/mat formation, and virulence. Signaling mucins, characterized by a heavily glycosylated extracellular domain, a transmembrane domain, and a small cytoplasmic domain, are known to regulate various signaling pathways. In Candida albicans, the mucin Msb2 regulates the Cek1 MAPK pathway. We show here that Msb2 is localized to the yeast cell wall and is further enriched on hyphal surfaces. A msb2Δ/Δ strain formed normal hyphae but had biofilm defects. Cek1 (but not Mkc1) phosphorylation was absent in the msb2Δ/Δ mutant. The extracellular domain of Msb2 was shed in cells exposed to elevated temperature and carbon source limitation, concomitant with germination and Cek1 phosphorylation. Msb2 shedding occurred differentially in cells grown planktonically or on solid surfaces in the presence of cell wall and osmotic stressors. We further show that Msb2 shedding and Cek1 phosphorylation were

inhibited by addition of Pepstatin A (PA), a selective inhibitor of aspartic proteases (Saps). Analysis of combinations of Sap protease mutants identified a sap8Δ/Δ mutant with reduced MAPK signaling along with defects in biofilm formation, thereby suggesting that Sap8 potentially serves as a major regulator of Msb2 processing. We further show that loss of either Msb2 (msb2Δ/Δ) or Sap8 (sap8Δ/Δ) resulted in higher C. albicans surface β-glucan exposure and msb2Δ/Δ showed attenuated virulence in a murine model of oral candidiasis. Thus, Sap-mediated proteolytic cleavage of Msb2 is required for activation of the Cek1 MAPK pathway in response to environmental cues including those that induce germination. Inhibition of Msb2 processing at the level of Saps may provide a means of attenuating MAPK signaling and reducing C. albicans virulence.

Involved units

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