Processing of *Candida albicans* Ece1p is critical for Candidalysin maturation and fungal virulence.

Richardson JP, Mogavero S, Moyes DL, Blagojevic M, Krüger T, Verma AH, Coleman BM, De La Cruz Diaz J, Schulz D, Ponde NO, Carrano G, Kniemeyer O, Wilson D, Bader O, Enoiu SI, Ho J, Kichik N, Gaffen SL, Hube B, Naglik JR (2018) Processing of *Candida albicans* Ece1p is critical for Candidalysin maturation and fungal virulence. *mBio* 9(1), e02178-17.

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Abstract

Candida albicans is an opportunistic fungal pathogen responsible for superficial and life-threatening infections in humans. During mucosal infection, *C. albicans* undergoes a morphological transition from yeast to invasive filamentous hyphae that secrete candidalysin, a 31-amino-acid peptide toxin required for virulence. Candidalysin damages epithelial cell plasma membranes and stimulates the activating protein 1 (AP-1) transcription factor c-Fos (via p38-mitogen-activated protein kinase [MAPK]), and the MAPK phosphatase MKP1 (via extracellular signal-regulated kinases 1 and 2 [ERK1/2]-MAPK), which trigger and regulate proinflammatory cytokine responses, respectively. The candidalysin toxin resides as a discrete cryptic sequence within a larger 271-amino-acid parental preproprotein, Ece1p. Here, we

demonstrate that kexin-like proteinases, but not secreted aspartyl proteinases, initiate a two-step posttranslational processing of Ece1p to produce candidalysin. Kex2p-mediated proteolysis of Ece1p after Arg61 and Arg93, but not after other processing sites within Ece1p, is required to generate immature candidalysin from Ece1p, followed by Kex1p-mediated removal of a carboxyl arginine residue to generate mature candidalysin. *C. albicans* strains harboring mutations of Arg61 and/or Arg93 did not secrete candidalysin, were unable to induce epithelial damage and inflammatory responses in vitro, and showed attenuated virulence in vivo in a murine model of oropharyngeal candidiasis. These observations identify enzymatic processing of *C. albicans* Ece1p by kexin-like proteinases as crucial steps required for candidalysin production and fungal pathogenicity. IMPORTANCE *Candida albicans* is an opportunistic fungal pathogen that causes mucosal infection in millions of individuals worldwide. Successful infection requires the secretion of candidalysin, the first cytolytic peptide toxin identified in any human fungal pathogen. Candidalysin is derived from its parent protein Ece1p. Here, we identify two key amino acids within Ece1p vital for processing and production of candidalysin. Mutations of these residues render *C. albicans* incapable of causing epithelial damage and markedly reduce mucosal infection in vivo Importantly, candidalysin production requires two individual enzymatic events. The first involves processing of Ece1p by Kex2p, yielding immature candidalysin, which is then further processed by Kex1p to produce the mature toxin. These observations identify important steps for *C. albicans* pathogenicity at mucosal surfaces.

Involved units

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Bernhard Hube

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Olaf Kniemeyer

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Thomas Krüger

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Selene Mogavero

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Daniela Schulz

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Topics

Damage to the host

Identifier

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