Lipid signaling via Pkh1/2 regulates fungal CO2 sensing through the kinase Sch9.

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Details

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Abstract

Adaptation to alternating CO_2 concentrations is crucial for all organisms. Carbonic anhydrases-metalloenzymes that have been found in all domains of life-enable fixation of scarce CO_2 by accelerating its conversion to bicarbonate and ensure maintenance of cellular metabolism. In fungi and other eukaryotes, the carbonic anhydrase Nce103 has been shown to be essential for growth in air (~0.04% CO_2). Expression of NCE103 is regulated in response to CO_2 availability. In Saccharomyces cerevisiae, NCE103 is activated by the transcription factor ScCst6, and in Candida albicans and Candida glabrata, it is activated by its homologues CaRca1 and CgRca1, respectively. To identify the kinase controlling Cst6/Rca1, we screened an S. cerevisiae kinase/phosphatase mutant library for the ability to regulate NCE103 in a CO_2-dependent manner. We identified ScSch9 as a potential ScCst6-specific kinase, as the sch9Δ mutant strain showed deregulated NCE103 expression on the RNA and protein levels. Immunoprecipitation revealed the binding capabilities of both proteins, and detection of ScCst6 phosphorylation by ScSch9 in vitro confirmed Sch9 as the Cst6 kinase. We could show that CO_2-dependent activation of Sch9, which

is part of a kinase cascade, is mediated by lipid/Pkh1/2 signaling but not TORC1. Finally, we tested conservation of the identified regulatory cascade in the pathogenic yeast species C. albicans and C. glabrata Deletion of SCH9 homologues of both species impaired CO_2-dependent regulation of NCE103 expression, which indicates a conservation of the CO_2 adaptation mechanism among yeasts. Thus, Sch9 is a Cst6/Rca1 kinase that links CO_2 adaptation to lipidsignalingviaPkh1/2 in fungi.

IMPORTANCE:

All living organisms have to cope with alternating CO_2 concentrations as CO_2 levels range from very low in the atmosphere (0.04%) to high (5% and more) in other niches, including the human body. In fungi, CO_2 is sensed via two pathways. The first regulates virulence in pathogenic yeast by direct activation of adenylyl cyclase. The second pathway, although playing a fundamental role in fungal metabolism, is much less understood. Here the transcription factor Cst6/Rca1 controls carbon homeostasis by regulating carbonic anhydrase expression. Upstream signaling in this pathway remains elusive. We identify Sch9 as the kinase controlling Cst6/Rca1 activity in yeast and demonstrate that this pathway is conserved in pathogenic yeast species, which highlights identified key players as potential pharmacological targets. Furthermore, we provide a direct link between adaptation to changing CO_2 conditions and lipid/Pkh1/2signaling in yeast, thus establishing a new signaling cascade central to metabolic adaptation.

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