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Role of the fission yeast cell integrity MAPK pathway in response to glucose limitation

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Abstract

Background: Glucose is a signaling molecule which regulates multiple events in eukaryotic organisms and the most preferred carbon source in the fission yeast *Schizosaccharomyces pombe*. The ability of this yeast to grow in the absence of glucose becomes strongly limited due to lack of enzymes of the glyoxylate cycle that support diauxic growth. The stress-activated protein kinase (SAPK) pathway and its effectors, Sty1 MAPK and transcription factor Atf1, play a critical role in the adaptation of fission yeast to grow on alternative non-fermentable carbon sources by inducing the expression of *fbp1*$^{+}$ gene, coding for the gluconeogenic enzyme fructose-1,6-bisphosphatase. The cell integrity Pmk1 pathway is another MAPK cascade that regulates various processes in fission yeast, including cell wall construction, cytokinesis, and ionic homeostasis. Pmk1 pathway also becomes strongly activated in response to glucose deprivation but its role during glucose exhaustion and ensuing adaptation to respiratory metabolism is currently unknown.

Results: We found that Pmk1 activation in the absence of glucose takes place only after complete depletion of this carbon source and that such activation is not related to an endogenous oxidative stress. Notably, Pmk1 MAPK activation relies on *de novo* protein synthesis, is independent on known upstream activators of the pathway like Rho2 GTPase, and involves PKC ortholog Pck2. Also, the Glucose/cAMP pathway is required operative for full activation of the Pmk1 signaling cascade. Mutants lacking Pmk1 displayed a partial growth defect in respiratory media which was not observed in the presence of glucose. This phenotype was accompanied by a decreased and delayed expression of transcription factor Atf1 and target genes *fbp1*$^{+}$ and *pyp2*$^{+}$. Intriguingly, the kinetics of Sty1 activation in Pmk1-less cells was clearly altered during growth adaptation to non-fermentable carbon sources.

Conclusions: Unknown upstream elements mediate Pck2-dependent signal transduction of glucose withdrawal to the cell integrity MAPK pathway. This signaling cascade reinforces the adaptive response of fission yeast to such nutritional stress by enhancing the activity of the SAPK pathway.

Keywords: Fission yeast, Glucose, MAPK, Pmk1, Sty1

Background

In addition to its role as energy source, glucose is a powerful signaling molecule which modulates many cellular responses in eukaryotic organisms, ranging from cell cycle control and differentiation to transcriptional and translational regulation [1]. The regulatory pathways involved in such signaling become particularly patent in simple eukaryotic organisms like budding or fission yeasts, where this sugar is the preferred carbon source for vegetative growth [2]. In the fission yeast *Schizosaccharomyces pombe* glucose may be fermented under aerobic conditions (Crabtree effect), and a reduction in its concentration strongly affects cell metabolism and gene expression [3]. Moreover, fission yeast cells lack enzymes of the glyoxylate cycle to maintain diauxic growth in the absence of glucose, and this feature limits to glycerol or gluconate their ability to grow on non-sugar carbon sources [4,5]. Hence, as soon as glucose disappears and respiration of the fermentation products becomes impaired *S. pombe* undergoes a nutritional stress [3].

Evidence has accumulated to support a key role of mitogen-activated protein kinase (MAPK) signaling

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