The glucose sensing GPR1-GPA2 pathway modulates the oscillatory behaviour of Msn2 protein in budding yeast

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Keywords: (Ras/cAMP pathway, PKA, nucleo-citoplasmic oscillations)

Abstract:
The cAMP/PKA pathway plays an important role in many important processes in budding yeast, such as stress resistance, proliferation, morphogenesis, apoptosis and aging. The central component is adenylate cyclase (Cyr1), which catalyzes the synthesis of cAMP, which in turn activates protein kinase A (PKA). Adenylate cyclase activity is controlled by the Ras proteins, and by the Gpa2 protein, alpha subunit of a heterotrimeric G protein, activated by the Gpr1 receptor that respond to extracellular glucose. Activated Ras and Gpa2 proteins cooperate to stimulate adenylate cyclase in order to generate cAMP. We have previously made and simulated a dynamic model of the Ras/cAMP/PKA pathway and our results suggest the existence of stable oscillatory states (Pescini et al. Biotechnol Adv 30, 99-107, 2012).

Stochastic oscillation related to activity of the pathway were reported by looking at the nuclear localization of the trascription factors Msn2 and Msn4 (Gamedia-Torres et al Curr Biol 17, 1044-9, 2007) . In particular Medvedik et. al. (PloS Biol 5, 2330-41,2007) reported stable oscillations of the nuclear accumulation of Msn2 in condition of limited glucose availabiliy.
We were able to reproduce the periodic nuclear accumulation of Msn2-GFP protein in yeast cells under condition of limiting glucose, and we used this approach to investigate the role played by Gpr1-Gpa2 pathway on the insurgence of the oscillations. In fact an improvement of the model that takes in account the interplay of Gpr1-Gpa2, developed few years ago (Betta R, Thesis 2018) suggests that this pathway modulate negatively the oscillations of cAMP.
To verify these hypothesis we investigated the nucleo-cytoplasmic oscillations of Msn2-GFP, induced by low-glucose, in a wild-type and in a *gpa2*Δ mutant of budding yeast. The deletion of GPA2 gene caused an increase of the frequency of the oscillation and of the fraction of cells that presented nucleo-cytoplasmic oscillations, suggesting that the Gpr1-Gpa2 pathway exerts and inhibitory role on the oscillatory behavior.