

Modeling PDC1 and PDC5 expression as a function of thiamine availability in yeast *S. cerevisiae*

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Abstract

The two pyruvate decarboxylase isozymes Pdc1 and Pdc5 convert pyruvate to acetaldehyde in the first dedicated step towards ethanol in the metabolism of the yeast *S. cerevisiae*. Recent experimental data indicate that in the presence of glucose expression of both *PDC1* and *PDC5* is regulated by availability of thiamine pyrophosphate (ThDP or B1 vitamin), the cofactor for the enzyme. In the presence of ThDP in the growth medium only *PDC1* is expressed, while in its absence expression of *PDC5* is stimulated and that of *PDC1* diminished such that both genes are expressed to similar levels. However, in cells where *PDC1* is deleted *PDC5* expression is independent of ThDP availability. Hence it appears that yeast cells have a system that controls the level of ThDP-dependent (iso)enzymes in accordance of the availability of the cofactor, probably to ensure that critical reactions can be performed even under ThDP limitation.

In this project we want to investigate this ThDP homeostasis system by means of a first mathematical model. The model includes known components involved in the regulation of *PDC1* and *PDC5* as well as other ThDP-dependent enzymes (such as Tk11, Pda1 and Kgd1). Currently the model is able to reproduce experimental observations regarding the expression levels of *PDC1* and *PDC5*, in a qualitative and semi-quantitative manner in steady-state behavior where parameters were manually fitted. Simulations of the model have led to two somewhat contradictory hypotheses: assuming that the affinity of the other enzymes to ThDP is higher than the affinity of Pdc1, the model suggests that the affinity of Pdc5 to ThDP is higher than that of Pdc1. Assuming that the affinity of the other enzymes to ThDP is in the same range of, or lower than that of Pdc1, the model suggests that the affinity of Pdc5 to ThDP is lower than that of Pdc1. The model also suggests that the formation of heteromers between Pdc1 and Pdc5 would be beneficial for the distribution of ThDP between the different enzymes. In silico 3D structural studies are undertaken in order to support this hypothesis.

Future work comprises the measurement/estimation of enzyme affinities to ThDP and kinetic rate constants. Our goal is to elucidate in detail this apparently unique cellular control system where availability and production of an enzyme cofactor is coordinated with the production of different isoforms of an enzyme using this cofactor.