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Global Regulation of Snf1 in *Saccharomyces cerevisiae*

A case study of experimental systems biology

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ABSTRACT

Cells commonly face environmental changes and have evolved various regulatory mechanisms to adjust their metabolism accordingly. One such key regulator in *S. cerevisiae* is the Snf1 kinase, which belongs to the conserved AMP-activated protein kinase (AMPK) family in all eukaryotes. The main function of Snf1 is to sense the energetic status in the cell and switch the cell metabolism from anabolism to catabolism through a complex regulatory network. In this study, we applied an experimental systems biology approach to study the regulation of Snf1 in *S. cerevisiae* at the global level. First, we show that the three β-subunits of Snf1 (Sip1, Sip2 and Gal83) are not redundant and found that Sip2, but not Sip1, can take over in the utilization of ethanol and glycerol when Gal83 is deleted, although both Sip1 and Sip2 isoforms can utilize acetate as the carbon source. To map the possible protein interactions of Snf1 with TORC1, a key regulator in the nitrogen catabolite repression (NCR), we assessed the global effect of deleting Snf1 and/or Tor1 under nutrient limited conditions. We show that Snf1 may regulate amino acid biosynthesis by inducing the *GDH3* encoded glutamate dehydrogenase, and therefore may represent a convergence to the TORC1 pathway. The data also suggest that Snf1 plays a larger role in the regulation of translation under the nutrient-limited conditions tested, compared to TORC1. Finally, we examined the effects of replacing the kinase domain of Snf1 with its analog from AMPK. The chimeric α1-Snf1 kinase restored the functions of Snf1, although to a lesser extent. However, this chimera fails to repress sterol biosynthesis as the native Snf1 does, and we attribute this to different phosphorylation motifs between Snf1 and AMPK. We also propose that Snf1 might repress the sterol biosynthetic genes by phosphorylating Ser272 of the transcription factor Ecm22, and therefore exerts transcriptional regulation on this process. Through these examples, we demonstrate that experimental systems biology is useful for investigating complex regulatory networks and powerful for identifying molecular targets for validation.

Keywords: Snf1, AMP-activated protein kinase (AMPK), target of rapamycin complex 1 (TORC1), catabolite repression, glucose derepression, energy homeostasis