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Ultrasensitive allosteric regulation of glycolytic efflux

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The fate of the last intermediate of glycolysis, phosphoenolpyruvate (PEP), controls much of cellular metabolism, e.g. the balance of glycolysis and gluconeogenesis. How are the key enzymes consuming PEP controlled? Here we examine this issue in the bacterium *Escherichia coli* and the budding yeast *Saccharomyces cerevisiae*. In both organisms, removal of glucose results in a paradoxical increased in PEP, which goes up the most of any canonical metabolite. What mechanisms lead this product of glucose to rise when glucose is removed? Enzyme activity can be regulated at the level of transcription, translation, degradation, covalent modification, and allostery.We show that allostery predominates in both organisms, with PEP consumption activated in an ultrasensitive (switch-like) manner by the upstream glycolytic intermediate fructose-1,6-bisphosphate. Mutations that eliminate this regulation do not impair growth on steady glucose, but they render the microbes defective in gluconeogenesis and ingrowth in an oscillating glucose environment. Thus, microbial central carbon metabolism is intrinsically programmed with ultrasensitive feed-forward regulation to enable rapid adaptation to changing environmental conditions.

Biography

Yifan Xu grew up in China, attending college at NanjingUniversity. He is currently a graduate student in the Rabinowitz lab at Princeton University. His research interests are in the regulation of central carbon metabolism andthe discovery of novel metabolic pathways in E. coli and yeast.

The Rabinowitz lab aims to achieve a quantitative, comprehensive understanding of cellular metabolism. The lab has developed methods for measuring most common intracellular metabolites using the state-of-the-art mass spectrometry technologyand for quantitating intracellular fluxes using isotope-tracers.These tools enable analyses of metabolic regulation and its dysregulation in disease.