Systematic inference of functional phosphorylation events in yeast metabolism

Motivation: Protein phosphorylation is a post-translational modification that affects proteins by changing their structure and conformation in a rapid and reversible way, and it is an important mechanism for metabolic regulation in cells. Phosphoproteomics enables high-throughput identification of phosphorylation events on metabolic enzymes, but identifying functional phosphorylation events still requires more detailed biochemical characterization. Therefore, development of computational methods for investigating unknown functions of a large number of phosphorylation events identified by phosphoproteomics has received increased attention.

Results: We developed a mathematical framework that describes the relationship between phosphorylation level of a metabolic enzyme and the corresponding flux through the enzyme. Using this framework, it is possible to quantitatively estimate contribution of phosphorylation events to flux changes. We showed that phosphorylation regulation analysis, combined with a systematic workflow and correlation analysis, can be used for inference of functional phosphorylation events in steady and dynamic conditions, respectively. Using this analysis, we assigned functionality to phosphorylation events of 17 metabolic enzymes in the yeast Saccharomyces cerevisiae, among which 10 are novel. Phosphorylation regulation analysis cannot only be extended for inference of other functional post-translational modifications but also be a promising scaffold for multi-omics data integration in systems biology.

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