Metabolic regulation in *Issatchenkia orientalis* revealed by integrative omics

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Project Goals: Understand metabolic regulation in I. orientalis

Omics technologies hold the potential to rapidly understand less studied organisms. Here we examine the potential to integrate proteomics, metabolomics, and fluxomics to dissect metabolic regulation in a non-model yeast of industrial metabolic engineering interest, *Issatchenkia orientalis*. Despite diverging from *Saccharomyces cerevisiae* 250 million years ago, *I. orientalis* responds similarly to nutrient limitation. Systematic identification of meaningful metabolic enzyme regulation from the multi-omics data revealed similar metabolic regulatory logic to the model yeast. This logic is, however, implemented through different allosteric regulatory events, suggesting convergent evolution. Among these is inhibition of the glycolytic enzyme glyceraldehyde dehydrogenase by ATP, which we also verified biochemically. By understanding the specific enzymatic regulatory events controlling metabolic flux in *I. orientalis,* we lay the groundwork for future rational and efficient engineering. More generally, we demonstrate the capacity for integrated omics to rapidly advance metabolic regulatory understanding in less studied microbes.

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