Mitochondrial ATP Generation is More Proteome Efficient than Glycolysis

CABBI
CENTER FOR ADVANCED BIOENERGY AND BIOPRODUCTS INNOVATION

Background/Objective

Metabolic efficiency profoundly influences organismal fitness. Non-photosynthetic organisms like yeast generate energy (ATP) mainly through glycolysis (fermentation) and respiration. Despite respiration being more energy efficient, some cells favor glycolysis even when oxygen is available, known as the 'Crabtree effect' in yeast. A leading explanation is that glycolysis produces ATP more efficiently per unit mass of protein, achieving the same metabolic flux using fewer enzymes, and so allowing faster growth. While the proteome efficiency of glycolysis versus respiration has been tested in *Escherichia coli*, it has not been measured rigorously in any eukaryote. Here, we measured it in *Saccharomyces cerevisiae* and *Issatchenkia orientalis*.

Approach

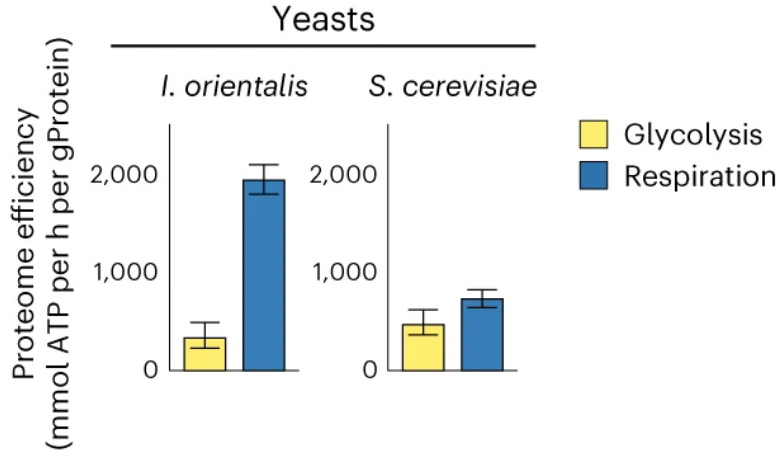
Quantitative fluxomics data, from 13C metabolic flux analysis and large-scale metabolic models, as well as quantitative proteomics data, were generated and used to compare their proteome efficiency for glycolysis and respiration, reflecting the cell's ATP gain for its overall protein investment in the pathway.

Results

Metabolic fluxes diverged markedly between *I. orientalis* (more respiratory) and *S. cerevisiae* (more glycolytic). Respiration was more proteome-efficient than aerobic glycolysis. When oxygen was available, different respiratory yeasts grew faster than aerobic glycolytic yeasts. Glycolytic flux correlated with high glycolytic protein expression and promoted hypoxic growth. Thus, aerobic glycolysis emerges from cells maintaining a proteome conducive to both aerobic and hypoxic growth.

Significance/Impacts

This work revamps our basic science understanding of the original biofuel pathway: aerobic glycolysis. It supports that non-model aerobic yeasts like *I. orientalis* are high value chassis for bioengineering, both because they deploy more efficient ATP production routes than aerobic glycolysis and because their aerobic capacity renders them superior for producing oxidized products like organic acids.



Proteome efficiency by glycolysis (yellow) and respiration (blue) in yeasts *I. orientalis* and *S. cerevisiae*.

Shen, et al. 2024. "Mitochondrial ATP Generation is More Proteome Efficient than Glycolysis." *Nature Chemical Biology*. DOI: 10.1038/s41589-024-01571-y.