14 October 2016

**Yeast evolved for enhanced xylose utilization reveal interactions between cell-signaling pathways and iron-sulfur cluster biogenesis**

Understanding how yeast cells adapt to non-preferential carbon sources uncovers potential genetic engineering strategies for improved biofuel production.

**The Science**

A stress-tolerant yeast strain was evolved for enhanced xylose utilization under aerobic or anaerobic growth conditions, the causative mutations identified by whole-genome sequencing, and systems-level effects of the mutations on cellular metabolism were analyzed. Rapid xylose utilization was found to be dependent upon genetic interactions among four genes, uncovering a surprising connection between Fe-S cluster assembly and cell signaling that facilitates aerobic respiration and anaerobic fermentation of xylose.

**The Impact**

The yeast *Saccharomyces cerevisiae*, an important microbial biocatalyst, efficiently converts glucose in lignocellulosic biomass to biofuel whereas other prevalent carbon sources such as xylose are typically poorly utilized. Analysis of genetic alterations that shift metabolism toward use of non-preferential carbon sources identified new cellular connections that may be exploited for improved biofuel production efficiency.

**Summary**

Efficient conversion of all the sugars present in lignocellulosic biomass to biofuel is a remaining challenge for the biofuels industry. In order to identify factors that influence xylose utilization, a stress-tolerant yeast strain was evolved for enhanced growth on xylose under aerobic or anaerobic growth conditions. Rapid xylose conversion was found to be dependent on genetic interactions among four genes: a xylose reductase (*GRE3*), a component of MAP Kinase signaling (*HOG1*), a regulator of Protein Kinase A (PKA) signaling (*IRA2*), and a scaffolding protein for mitochondrial iron-sulfur (Fe-S) cluster biogenesis (*ISU1*). Genetic interactions between the *HOG1* and *ISU1* mutations enabled aerobic respiration of xylose and other non-fermentable carbon sources, a finding supported by proteomic analyses that showed elevated mitochondrial respiratory proteins under these conditions. In contrast, the *IRA2* mutation only impacted anaerobic xylose use and required the loss of *ISU1* function, indicating a previously unknown connection between PKA signaling, Fe-S cluster biogenesis, and anaerobiosis. Taken together this study provides new insights on routes to improved xylose utilization in yeast and deeper knowledge of the signaling that governs sugar utilization.

**Contacts (BER PM)**

N. Kent Peters
Program Manager, Office of Biological and Environmental Research
kent.peters@science.doe.gov, 301-903-5549

**(PI Contact)**

Trey Sato
University of Wisconsin - Madison
[tksato@glbrc.wisc.edu](tksato%40glbrc.wisc.edu)

**Funding**

This work was funded by the DOE Great Lakes Bioenergy Research Center (DOE BER Office of Science DE-FC02-07ER64494), the Pew Charitable Trusts, and the Alexander von Humboldt Foundation. Additional author support was provided by a predoctoral NSF fellowship.

**Publications**

Sato, T. K. *et al.* Directed evolution reveals unexpected epistatic interactions that alter metabolic regulation and enable anaerobic xylose use by *Saccharomyces cerevisiae*. *PLOS Genetics* (2016) [DOI: 10.1371/journal.pgen.1006372]

**Related Links**

<http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1006372>

<https://www.glbrc.org/news/super-yeast-has-power-improve-economics-biofuels>

**PM Recommendation for SC Web Publication**

[Yes or No]