Ethanol from plants may become cheaper, thanks to insights into fungus metabolism

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Credit: AI-generated image (disclaimer)

Efficient industrial fermentation of the plant sugar called xylose is critical to the cost-effective production of biofuels and other chemicals. However, most microorganisms cannot ferment xylose; and industrial microbiologists have yet to expose the secrets behind the extraordinary success of the current microbial champion of xylose fermentation, the

fungus Scheffersomyces stipitis.

Publication of the genomic sequence of S. stipitis five years ago was but the first step towards this elusive goal. Rajagopalan Srinivasan and his co-workers at the A*STAR Institute of Chemical and Engineering Sciences, Singapore, have taken a critical next step by reconciling the annotated DNA sequence of S. stipitis with its biochemistry and physiology. The more holistic view of the metabolism of S. stipitis that emerges from their model suggests rational approaches to both improve the unique metabolic capabilities of S. stipitis and transfer these to other industrially important microbes. "If successful, such initiatives would substantially improve the efficiency with which energy could be extracted from agricultural and forest residues," explains Srinivasan.

Rational engineering of more efficient xylose metabolism has been hindered by the complexity of the metabolic network: mRNA abundance, protein abundance, and metabolite-regulated protein activity all contribute to the regulation of metabolism. Perturbation of the metabolic network by modifying the expression of just one or a few genes usually has only minimal effects and often has unanticipated negative consequences.

To identify the most promising approaches to optimize xylose fermentation, Srinivasan and his co-workers combined information from the annotated genome sequence, pathway databases, and published studies with their own data, which they collected by determining the macromolecular composition of S. stipitis cells under various growth conditions. They used all of this information to generate a mathematical model that represents the relationships between 814 genes, 971 metabolites and 1,371 reactions.

In silico analysis of the model predicted that xylose-driven growth of S. stipitis is restrained by a limited capacity to regenerate a nucleotide

cofactor when the oxygen supply is limited. The researchers validated this prediction experimentally and proposed specific strategies to overcome the bottleneck. The model also provided insights into the roles of super-complexes in channeling the flow of electrons during mitochondrial respiration.

Incorporation of thermodynamic constraints, enzyme kinetics information, and high-throughput transcriptomic, proteomic and metabolomic data will enhance the predictive capacity of the model. "Refinement of our metabolic model will help metabolic engineers to propose other testable strategies to increase the efficiency of xylose fermentation in S. stipitis and other industrial microbes," Srinivasan says.

More information: Balagurunathan, B., Jonnalagadda, S., Tan, L. & Srinivasan, R. Reconstruction and analysis of a genome-scale metabolic model for Scheffersomyces stipitis. *Microbial Cell Factories* 11, 27 (2012). dx.doi.org/10.1186/1475-2859-11-27

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