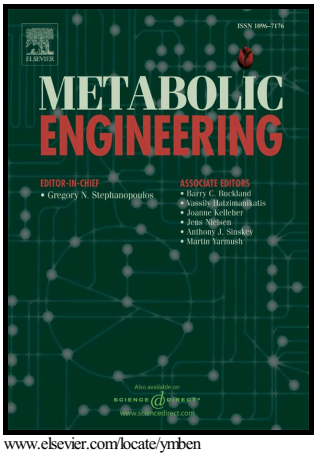

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Douglas McCloskey, Sibei Xu, Troy E. Sandberg, Elizabeth Brunk, Ying Hefner, Richard Szubin, Adam M. Feist, Bernhard O. Palsson

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Adaptation to the coupling of glycolysis to toxic methylglyoxal production in *tpiA* deletion strains of *Escherichia coli* requires synchronized and counterintuitive genetic changes[☆]

Douglas McCloskey[1,2], Sibei Xu[1], Troy E. Sandberg[1], Elizabeth Brunk[1], Ying Hefner[1], Richard Szubin[1], Adam M. Feist[1,2,] , and Bernhard O. Palsson[1,2,]*

[1]Department of Bioengineering, University of California - San Diego, La Jolla, CA 92093, USA.

[2]Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, 2800 Lyngby, Denmark.

*Corresponding author, Department of Bioengineering, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0412, USA. Tel.: 858-534-5668; Fax: 858-822-3120. palsson@ucsd.edu

Abstract

Methylglyoxal is a highly toxic metabolite that can be produced in all living organisms. Methylglyoxal was artificially elevated by removal of the tpiA gene from a growth optimized *Escherichia coli* strain. The initial response to elevated methylglyoxal and its toxicity was characterized, and detoxification mechanisms were studied using adaptive laboratory evolution. We found that: 1) Multi-omics analysis revealed biological consequences of methylglyoxal toxicity, which included attack on macromolecules including DNA and RNA and perturbation of nucleotide levels; 2) Counter-intuitive cross-talk between carbon starvation and inorganic phosphate signalling was revealed in the tpiA deletion strain that required mutations in inorganic phosphate signalling mechanisms to alleviate; and 3) The split flux through lower glycolysis depleted glycolytic intermediates requiring a host of synchronized and coordinated mutations in non-intuitive network locations in order to re-adjust the metabolic flux map to achieve optimal

☆ Adaptive laboratory evolution, *tpiA* gene knockout, mutation analysis, multi-omics data integration, systems biology, *E. coli*