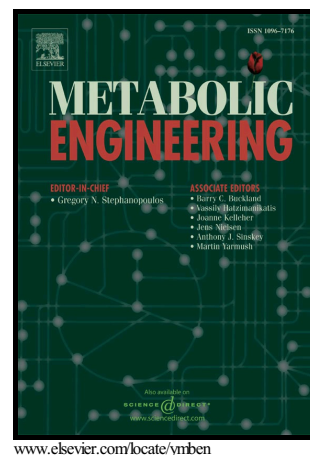


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Adaptation to the coupling of glycolysis to toxic methylglyoxal production in *tpiA* deletion strains of *Escherichia coli* requires synchronized and counterintuitive genetic changes[☆]

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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*

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