

Evolution Reveals A Glutathione-dependent Mechanism Of 3-hydroxypropionic Acid Detoxification - DTU Orbit (08/11/2017)

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Biologically produced 3-hydroxypropionic acid (3HP) is a potential source for sustainable acrylates and can also find direct use as monomer in the production of biodegradable polymers. For industrial-scale production, high titer, rate and yield are essential; thus there is a need for robust cell factories tolerant to high concentration of 3HP, preferably at low pH. Through adaptive laboratory evolution we selected *S. cerevisiae* strains with improved tolerance to 3HP at pH 3.5. Genome sequencing of three independent clones identified single-nucleotide changes in the SFA1 gene encoding S-(hydroxymethyl)glutathione dehydrogenase. Introduction of the mutated SFA1 alleles or overexpression of any of the SFA1 alleles in a *sfa16* strain enabled growth in the presence of above 40 g/L 3HP. We further found that aldehyde dehydrogenase (ALD6), S-formylglutathione hydrolase (YJL068C) and glutathione play a role in 3HP detoxification. Addition of glutathione relieved growth inhibition by 3HP for several yeast species and for *E. coli*; but glutathione could not enable growth of a *S. cerevisiae* *sfa16* strain. Based on our findings we propose a 3-hydroxypropionic aldehyde-mediated mechanism underlying 3HP toxicity as well as a glutathione-dependent route for detoxification of 3-hydroxypropionic aldehyde (reuterin). The identified molecular response to 3HP and reuterin may well be a general mechanism for handling resistance to organic acids and aldehydes by living cells

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