Evolution reveals a glutathione-dependent mechanism of 3-hydroxypropionic acid tolerance

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 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 followed by functional analysis identified the causal mutation in SFA1 gene encoding S-(hydroxymethyl)glutathione dehydrogenase. Based on our findings, we propose that 3HP toxicity is mediated by 3-hydroxypropionic aldehyde (reuterin) and that glutathione-dependent reactions are used for reuterin detoxification. The identified molecular response to 3HP and reuterin may well be a general mechanism for handling resistance to organic acid and aldehydes by living cells.