Title:	Thiol trapping and metabolic redistribution of sulfur metabolites enable cells to overcome cysteine overload
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Abstract:	Cysteine is an essential requirement in living organisms. However, due to its reactive thiol side chain, elevated levels of intracellular cysteine can be toxic and therefore need to be rapidly eliminated from the cellular milieu. In mammals and many other organisms, excess cysteine is believed to be primarily eliminated by the cysteine dioxygenase dependent oxidative degradation of cysteine, followed by the removal of the oxidative products. However, other mechanisms of tackling excess cysteine are also likely to exist, but have not thus far been explored. In this study, we use Saccharomyces cerevisiae, which naturally lacks a cysteine dioxygenase, to investigate mechanisms for tackling cysteine overload. Overexpressing the high affinity cysteine transporter, YCT1, enabled yeast cells to rapidly accumulate high levels of intracellular cysteine. Using targeted metabolite analysis, we observe that cysteine is initially rapidly interconverted to non-reactive cystine in vivo. A time course revealed that cells systematically convert excess cysteine to inert thiol forms; initially to cystine, and subsequently to cystathionine, S-Adenosyl-L-homocysteine (SAH) and S-Adenosyl L-methionine (SAM), in addition to eventually accumulating glutathione (GSH) and polyamines. Microarray based gene expression studies revealed the upregulation of arginine/ornithine biosynthesis a few hours after the cysteine overload, and suggest that the non-toxic, non-reactive thiol based metabolic products are eventually utilized for amino acid and polyamine biogenesis, thereby enabling cell growth. Thus, cells can handle potentially toxic amounts of cysteine by a combination of thiol trapping, metabolic redistribution to non-reactive thiols and subsequent consumption for anabolism.
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