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| Title: | Allosteric inhibition of MTHFR prevents futile SAM cycling and maintains nucleotide pools in one-carbon metabolism |
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| Abstract: | Methylenetetrahydrofolate reductase (MTHFR) links the folate cycle to the methionine cycle in one-carbon metabolism. The enzyme is known to be allosterically inhibited by SAM for decades, but the importance of this regulatory control to one-carbon metabolism has never been adequately understood. To shed light on this issue, we exchanged selected amino acid residues in a highly conserved stretch within the regulatory region of yeast MTHFR to create a series of feedback-insensitive, deregulated mutants. These were exploited to investigate the impact of defective allosteric regulation on one-carbon metabolism. We observed a strong growth defect in the presence of methionine. Biochemical and metabolite analysis revealed that both the folate and methionine cycles were affected in these mutants, as was the transsulfuration pathway, leading also to a disruption in redox homeostasis. The major consequences, however, appeared to be in the depletion of nucleotides. 13C isotope labeling and metabolic studies revealed that the deregulated MTHFR cells undergo continuous transmethylation of homocysteine by methyltetrahydrofolate (CH3THF) to form methionine. This reaction also drives SAM formation and further depletes ATP reserves. SAM was then cycled back to methionine, leading to futile cycles of SAM synthesis and recycling and explaining the necessity for MTHFR to be regulated by SAM. The study has yielded valuable new insights into the regulation of one-carbon metabolism, and the mutants appear as powerful new tools to further dissect out the intersection of one-carbon metabolism with various pathways both in yeasts and in humans |
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