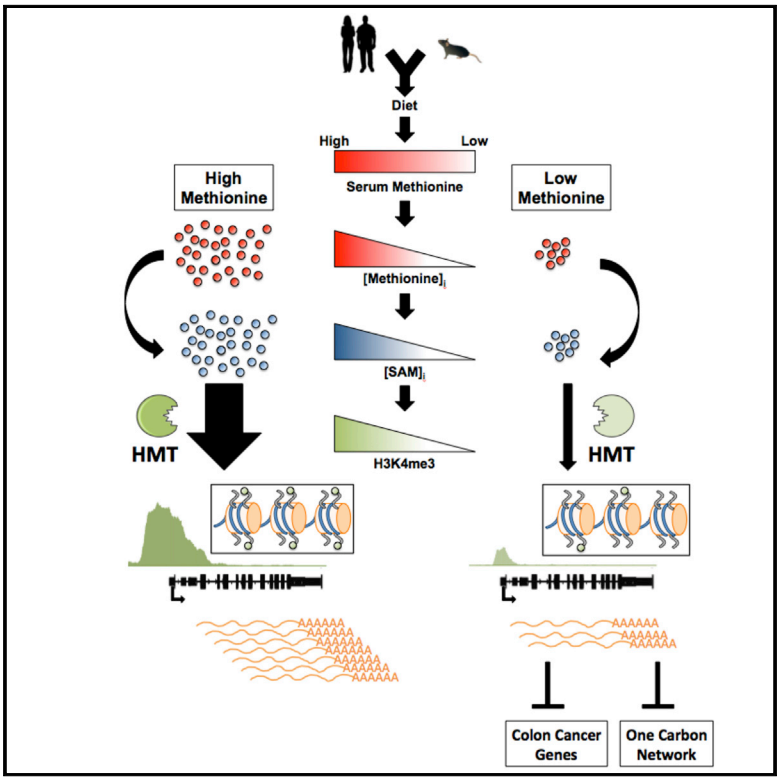
Article

Cell Metabolism

Histone Methylation Dynamics and Gene Regulation Occur through the Sensing of One-Carbon Metabolism

Graphical Abstract



Authors

Samantha J. Mentch, Mahya Mehrmohamadi, Lei Huang, ..., Anna E. Thalacker-Mercer, Sailendra N. Nichenametla, Jason W. Locasale

Correspondence

jason.locasale@duke.edu

In Brief

Mentch et al. show that modulation of methionine metabolism, by altering nutrient availability, regulates SAM and SAH levels to drive specific histone methylation events that affect gene expression. Methionine cycle alterations can be sustained by diet in vivo and modulate histone methylation in the liver.

Highlights

- Histone methylation dynamics occur in response to changes in SAM and SAH
- Metabolism-regulated histone methylation affects gene expression
- Diet alters methionine metabolism and histone methylation in the liver
- Variation in human serum MET occurs at levels needed to alter histone methylation

Accession Numbers

GSE72131

Mentch et al., 2015, Cell Metabolism 22, 861–873
November 3, 2015 ©2015 Elsevier Inc.
http://dx.doi.org/10.1016/j.cmet.2015.08.024

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Histone Methylation Dynamics and Gene Regulation Occur through the Sensing of One-Carbon Metabolism

Samantha J. Mentch,[1,7,8,9] Mahya Mehrmohamadi,[2,7,8,9] Lei Huang,[3] Xiaojing Liu,[4] Diwakar Gupta,[4] Dwight Mattocks,[5] Paola Gómez Padilla,[4] Gene Ables,[5] Marcas M. Bamman,[6] Anna E. Thalacker-Mercer,[4] Sailendra N. Nichenametla,[5] and Jason W. Locasale[1,2,3,7,8,9,*]
[1]Department of Molecular Biology and Genetics, Field of Biochemistry, Molecular, and Cell Biology
[2]Department of Molecular Biology and Genetics, Field of Genomics, Genetics and Development
[3]Department of Biological Statistics and Computational Biology, Field of Computational Biology
[4]Division of Nutritional Sciences
Cornell University, Ithaca, NY 14853, USA
[5]Orentreich Foundation for the Advancement of Science, Cold Spring, NY 10516, USA
[6]UAB Center for Exercise Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, USA
[7]Duke Cancer Institute
[8]Duke Molecular Physiology Institute
[9]Department of Pharmacology and Cancer Biology
Duke University School of Medicine, Durham, NC 27710, USA
*Correspondence: jason.locasale@duke.edu
http://dx.doi.org/10.1016/j.cmet.2015.08.024

SUMMARY

S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) link one-carbon metabolism to methylation status. However, it is unknown whether regulation of SAM and SAH by nutrient availability can be directly sensed to alter the kinetics of key histone methylation marks. We provide evidence that the status of methionine metabolism is sufficient to determine levels of histone methylation by modulating SAM and SAH. This dynamic interaction led to rapid changes in H3K4me3, altered gene transcription, provided feedback regulation to one-carbon metabolism, and could be fully recovered upon restoration of methionine. Modulation of methionine in diet led to changes in metabolism and histone methylation in the liver. In humans, methionine variability in fasting serum was commensurate with concentrations needed for these dynamics and could be partly explained by diet. Together these findings demonstrate that flux through methionine metabolism and the sensing of methionine availability may allow direct communication to the chromatin state in cells.

INTRODUCTION

Alterations in the methylation status of proteins, nucleic acids, and metabolites contribute to the pathogenesis of many of the major human pathophysiological conditions including cancer, obesity, and aging (Bergman and Cedar, 2013; Greer and Shi, 2012; Kraus et al., 2014). When these changes affect the methylation of histones and nucleic acids that determine the epigenetic status in cells, they can affect the expression of thousands of genes (Barth and Imhof, 2010). Changes in methylation status occur because of differences in the enzyme activity of methyltransferases and demethylases. Genes that encode these enzymes are frequently altered in pathological states, leading to alterations in methylation (Chi et al., 2010; Dawson and Kouzarides, 2012). It has also been long established that S-adenosylmethionine (SAM) is the universal methyl donor for these enzymes that transfer its methyl group to yield S-adenosylhomocysteine (SAH) and a methylated substrate (Finkelstein, 1990). The methylation of this substrate provides a link between the metabolism that regulates SAM and SAH, which may act through product inhibition of a methyltransferase, and the epigenetic status of cells (Gut and Verdin, 2013; Katada et al., 2012; Teperino et al., 2010).

SAM and SAH are intermediate metabolites in a metabolic pathway that is a subset of a larger network collectively referred to as one-carbon metabolism (Locasale, 2013). One-carbon metabolism integrates nutrients from diverse sources such as glucose, serine, threonine, methionine, and choline and processes them into distinct outputs that achieve diverse biological functions. Whether the concentrations of SAM and SAH or their ratio ever reach values that could affect methyltransferase activity has been controversial. Some studies have concluded that their concentrations do not reach limiting values (Hoffman et al., 1979). Recent studies, however, have provided evidence that aberrant expression of NNMT, an enzyme that metabolizes SAM, has profound biological consequences resulting from changes in histone methylation (Kraus et al., 2014; Ulanovskaya et al., 2013). Others have found that only the levels of SAH correlated with methylation status (Caudill et al., 2001), including a recent finding that investigated threonine metabolism in mouse pluripotent stem cells and demonstrated that threonine catabolism affected both pyruvate and glycine metabolism and altered histone methylation (Shyh-Chang et al., 2013). Although this study was the first to our knowledge to document the influence of an amino acid on histone methylation, this effect was shown to occur through indirect pathways involving energy production