

Tying Metabolic Branches With Histone Tails Using Systems Biology

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ABSTRACT: Histone modifications represent an innate cellular mechanism to link nutritional status to gene expression. Metabolites such as acetyl-CoA and S-adenosyl methionine influence gene expression by serving as substrates for modification of histones. Yet, we lack a predictive model for determining histone modification levels based on cellular metabolic state. The numerous metabolic pathways that intersect with histone marks makes it highly challenging to understand their interdependencies. Here, we highlight new systems biology tools to unravel the impact of nutritional cues and metabolic fluxes on histone modifications.

KEYWORDS: Metabolism, acetylation, methylation, histone modifications, metabolic modeling, systems biology, HDACs, HDAC inhibitors

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Introduction

Cells rely on chemical modification of histones and DNA to change chromatin accessibility and regulate their transcriptional program. The levels of these modifications in a cell involve the interplay between “writers” such as histone methyltransferases and acetyltransferases and “erasers” such as histone demethylases and deacetylases. The writer and eraser enzymes differ in substrate and target specificity, making them sensitive to different metabolic stimuli^{1,2} (Figure 1). For example, DNA and histone methyltransferases use the metabolite S-adenosyl methionine (SAM) as a methyl donor and are highly responsive to substrate levels.³ Thus, alterations to metabolism of the cell can affect substrate levels in the nucleus resulting in altered histone modifications.^{2,4} However, the interconnectedness of the metabolic network makes it highly challenging to predict the impact of nutrient changes on histone modifications. For example, acetylation is sensitive to acetyl-CoA and methylation is sensitive to SAM^{1,2}; these metabolites are involved in hundreds of metabolic reactions that can compete with histone modification enzymes for these substrates. A systems biology approach is necessary to comprehend the impact of cellular metabolic state on the epigenome.

Genome scale network modeling of metabolic-epigenetic interactions

To comprehensively account for the complexities of cellular metabolism and its impact on acetylation, we recently developed a network model of metabolism and histone acetylation.³ Our model provides a mechanistic picture of how nutrient shifts or mutations in metabolic enzymes affect this epigenetic mark. Our analysis makes use of *genome-scale metabolic network models*, which

represent the mechanistic relationships between genes, proteins, and metabolites within a biological system.⁵ The genome-scale network models are manually curated from the literature and represent a map of all known metabolic reactions that happen in an organism. For example, the human network model by Duarte et al⁶ contains 3744 reactions, 1496 genes, 2004 proteins, and 2766 metabolites. Genome scale metabolic modeling has been used successfully to predict the metabolic state of various mammalian cell types, including cancer cells and stem cells, using transcriptomics or metabolomics data.^{7,8} However, these models cannot predict the impact of metabolism on other cellular processes, especially epigenetic modifications.

The metabolic network interfaces with the epigenetic machinery through key intermediate metabolites like acetyl-CoA. To integrate epigenetic modifications with the metabolic model, we added biochemical reactions corresponding to acetylation, as a proof of principle. Similar to using Google Maps, with genome-scale modeling, we can identify an optimal path through the metabolic network from nutrients to epigenetic substrates based on reaction stoichiometry. Changes in enzyme activity due to gene knockouts, differential expression, or drug inhibition will result in the use of alternate metabolic routes through the network leading to differential flux through epigenetic reactions. Although this network modeling framework was used to study acetylation in our study, this can be easily extended to other histone marks. This network model provided new fundamental insights on metabolic-epigenetic interactions, as detailed below.

Excess carbon flux supports acetylation

Given a unit of nutrient carbon, where would the cell channel it? To biomass components or to acetylation? By analyzing the



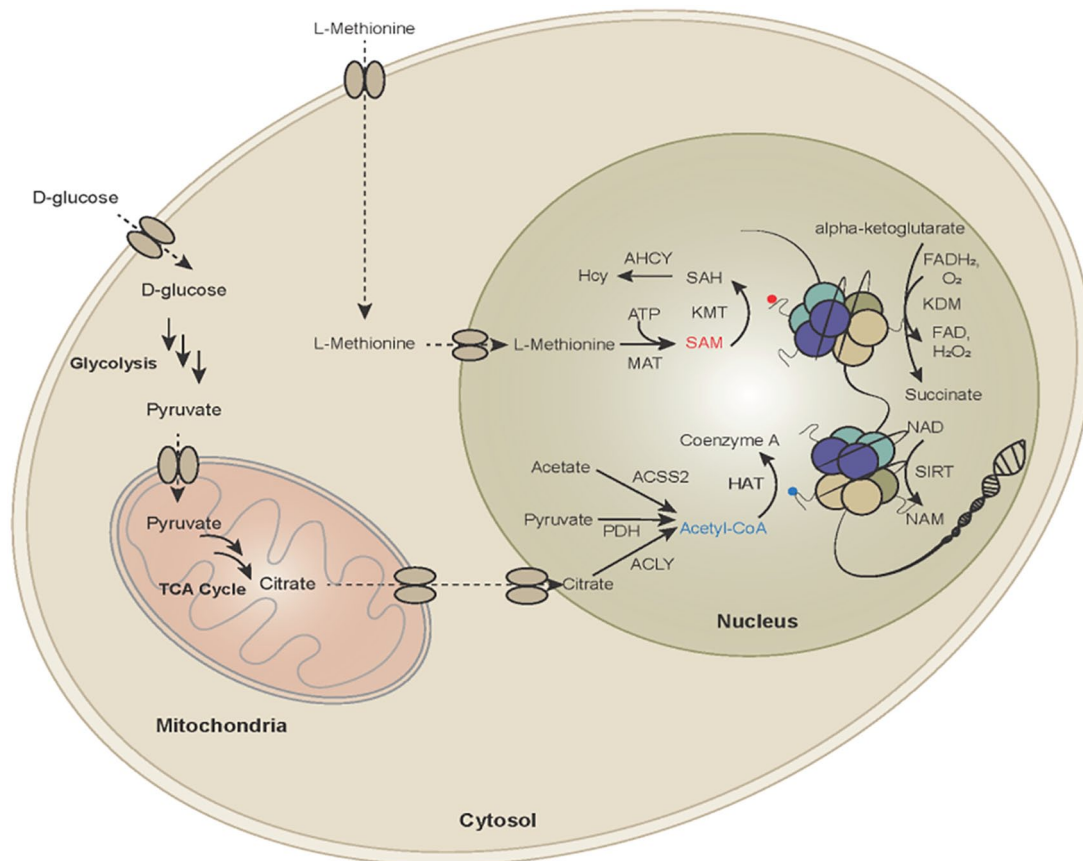


Figure 1. Metabolic dependencies of histone acetylation and methylation. Enzymes that catalyze post-translational modifications of histone tails (writers—histone methyltransferases [KMT] and acetyltransferases (HAT or KAT), erasers—histone demethylases (KDM) and deacetylases (HDAC, SIRT)) use key metabolic intermediates (SAM, Acetyl-CoA) as substrates). The availability and flux of these metabolic substrates in the nucleus impact levels of histone modifications, which subsequently influences gene expression, thus linking gene regulation with the metabolic status of the cell.

impact of various nutrient sources on the levels of histone acetylation in mammalian cells, our model revealed that histone acetylation levels reflect the level of excess carbon flux that is available beyond the requirement for biomass synthesis. The metabolic model recapitulated known effect of addition or depletion of nutrients, including glucose, amino acids and fatty acids, on acetylation. Surprisingly, certain starvation conditions resulted in increased acetylation. For example, lack of amino acids in the culture media did not reduce acetylation. However, lack of glucose and pyruvate greatly impaired acetylation levels. These results suggest that excess carbon availability relative to nitrogen is predictive of acetylation levels. Cells primarily use nutrient carbon and nitrogen sources for biomass synthesis first, and excess carbon, if available, is used for supporting acetylation.

Metabolic cost of acetylation

There are a billion potential acetylation sites in the mammalian nucleus.⁹ Although this is a very big number, an equal number of acetyl-coA units are synthesized and consumed by the cell in an hour in the cytoplasm.¹⁰ As only a small number of histones are acetylated,¹¹ redirecting a small fraction of cytosolic carbon flux used for acetyl-coA metabolism to the nucleus is sufficient to support acetylation. Thus, the burden of histone acetylation

on cellular metabolism is relatively small. In contrast to the flux of acetyl-coA, the steady-state concentration of acetyl-coA is relatively low.¹⁰ Hence, increased acetylation will likely be accompanied by rewiring of metabolic fluxes.

Metabolic state influences drug sensitivity

As acetylation depends on the metabolic state of the cell, it is foreseeable that the efficacy of drugs that disrupt histone acetylation will also be influenced by cellular metabolic state. Histone deacetylase inhibitors are widely used for treating many cancers, neurodegenerative diseases, and immune disorders.¹² Their primary mode of action is by blocking histone deacetylation, resulting in hyper acetylation, and subsequently cell death.

We found that the growth inhibition of HeLa cells by Vorinostat—a deacetylase inhibitor—changed significantly when cells were grown in different nutrient conditions. Strikingly, the extent of growth inhibition was directly proportional to the extent of acetylation flux predicted by our metabolic model in each growth condition. This effect was also observed in a panel of diverse cell lines from different tissue lineages with inherently distinct metabolic activities. Cell lines predicted by the model to have high acetylation

were more sensitive to various deacetylase inhibitors. This observation can be potentially used to selectively target specific cancer cells based on their metabolism.

Impact of metabolic fluxes on histone methylation

Similar to acetylases, the kinetic properties of histone methyltransferases make them sensitive to levels of their substrate, SAM.⁴ Hence, histone methylation is also sensitive to cellular metabolism. A similar genome-scale modeling framework was used to predict the impact of metabolic state on methylation in a related study by Chandrasekaran et al.⁷ As histone methylation plays a central role in early embryonic development, genome scale metabolic modeling was applied to characterize the metabolism of naïve and primed murine pluripotent stem cells. The naïve and primed stem cells represent two fundamental steps during embryonic development with distinct pluripotency potential (i.e. ability to differentiate into various cell types). By combining metabolomics data from each stem cell type with metabolic network models, this study revealed the activation of the one-carbon metabolic pathway in embryonic stem cells transitioning from naïve to primed pluripotent state. The metabolic model predicted that the activation of the one-carbon metabolic pathway would result in increased flux through the synthesis of SAM. The model revealed that this flux supports extensive histone methylation. The model prediction was validated using tracing of ¹³C labeled glucose and serine. Furthermore, perturbing SAM flux using inhibitors of SAM synthesis lead to altered histone methylation levels in naïve and primed cells consistent with the model predictions. Thus, genome scale modeling enables the simulation of the influence of various metabolic alterations on SAM synthesis and ultimately histone methylation.

Future directions

A key limitation of the model of metabolic-epigenetic interactions in Shen et al³ and Chandrasekaran et al⁷ is that it is predictive of only bulk histone marks and does not account for modifications in specific histone sites such as K9 or K27. Different histone sites can have differing sensitivities to metabolic substrates. Furthermore, although this model focuses on “writers,” we lack a similar model for deacetylation or demethylation enzymes that are sensitive to the redox molecules NADH and FADH (Figure 1). Future models need to account for the dynamic interplay between writers and erasers in each metabolic condition. Finally, another limitation is that the current model does not account for other chromatin marks such as succinylation, malonylation, crotonylation, and sugar modifications.¹³ These modifications also use metabolic substrates and are potentially sensitive to metabolic state. Expanding this modeling framework to other modifications and incorporating the competition between different modifications can provide a

comprehensive picture of how histone modifications sense and respond to metabolic alterations. Furthermore, understanding the transcriptomic and chromatin state of the cell along with its metabolism can help unravel the feedback regulation of metabolism by histone modifications. Two recent studies have simulated the impact of transcriptome changes due to altered chromatin modifications on metabolic pathways using genome-scale network modeling.^{14,15} Hence, in combination with the model used in Shen et al, these tools can help simulate the reciprocal regulation of metabolic and epigenetic machinery.

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Author Contributions

SC wrote the manuscript.

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