Metabolic Regulation of the Epigenome: Chromatin Adaptation to Methyl-Metabolite Depletion

Spencer Haws
Denu Laboratory
Madison Scholars Symposium
5-8-19
Integration of Metabolism and Epigenetics


**Euchromatin**
“Transcriptionally Active”
H3ac, H4ac, H3K4me...

**Heterochromatin**
“Transcriptionally Repressive”
H3K9me, H3K27me, H4K20me...

Integration of Metabolism and Epigenetics


Table 4. Spearman’s rank correlations between plasma concentrations and dietary intakes of amino acids

<table>
<thead>
<tr>
<th>Amino Acids</th>
<th>Sample size</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branched-chain essential amino acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoleucine</td>
<td>392</td>
<td>0.10</td>
<td>0.05</td>
</tr>
<tr>
<td>Leucine</td>
<td>392</td>
<td>0.16</td>
<td>0.001</td>
</tr>
<tr>
<td>Valine</td>
<td>392</td>
<td>0.14</td>
<td>0.01</td>
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<tr>
<td>Other essential amino acids</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>392</td>
<td>-0.02</td>
<td>0.7</td>
</tr>
<tr>
<td>Lysine</td>
<td>381</td>
<td>0.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Methionine</td>
<td>392</td>
<td>0.19</td>
<td>0.0002</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>299</td>
<td>0.05</td>
<td>0.4</td>
</tr>
<tr>
<td>Threonine</td>
<td>392</td>
<td>0.06</td>
<td>0.2</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>390</td>
<td>0.16</td>
<td>0.001</td>
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<tr>
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<td>0.003</td>
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<td>0.12</td>
<td>0.02</td>
</tr>
<tr>
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</tr>
<tr>
<td>Tyrosine</td>
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<td>0.0007</td>
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*Conventional P-values are shown and those marked in bold were significant after Bonferroni correction (P < 0.0029).

Modified from Schmidt et al. (2015) EJCN.
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SAM Depletion Leads to Decreased Histone Methylation Abundance

Gap in the Field: All current studies focus on PTM susceptibility to methyl-metabolite depletion.

Project Focus: Identify and characterize adaptive chromatin responses to methyl-metabolite depletion.


Kera et al. (2013) *J. Biol. Chem.*
Initial Experimental Approach
Methyl-Metabolite Depletion Stimulates Conserved Epigenetic Response

Histone methylation dynamically responds to methyl-metabolite depletion.
H3K9 Mono-methylation is an Adaptive Response to Methyl-Metabolite Depletion
H3K9me1 is a Prominent Pre-Deposition Histone PTM


Rivera et al. (2015) NAR.

H3K9 Mono-methylation is an Adaptive Response to Methyl-Metabolite Depletion

H3K9me1 is actively maintained in response to methyl-metabolite depletion… but why?
H3K9me1 is Required to Support Constitutive Heterochromatin


Approaches for Investigating Heterochromatin Stability

MNase Accessibility Assay

[Diagram showing the MNase Accessibility Assay]
Approaches for Investigating Heterochromatin Stability

MNase Accessibility Assay

Transcript Abundance of Constitutively Repressed DNA Elements

Saksouk et al. (2015) *Epigenetics and Chromatin*.
Global Heterochromatin Instability is Exacerbated by Inhibition of H3K9 Mono-methylation

UNC0642

A

B

% of Total Nucleosome Species

0hr
24hr MR DMSO
24hr MR UNC0642

pentα
tetra-
tri-
di-
mono-

735bp
588bp
441bp
294bp
147bp
De-repression of Repetitive and Retrotransposable DNA Elements is also Exacerbated by Inhibition of H3K9 Mono-Methylation

Active H3K9 mono-methylation is required to preserve global and site-specific heterochromatin stability.
Proposed Model of Chromatin Adaptation to SAM Depletion

- SAM producing and consuming pathways dictate histone methylation profiles.

- *De novo* methylation of H3K9me1 is an adaptive epigenetic response to methyl-donor depletion.

- *De novo* H3K9me1 attenuates losses in heterochromatin stability.

- Epigenetic persistence to metabolic stress requires an active chromatin response.
Experimental Approach for \textit{in vivo} Validation

Analyses Performed

A. Histone proteomics

B. DNA element mRNA abundance

C. In vivo metabolic tests
   A. GTT
   B. MRI
Epigenetic Adaptation and Persistence to Diet-Induced SAM Depletion is Conserved Across the Lifespan
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Acknowledgments

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Lily Miller
Sydney Thomas
Yiming Qin

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Dudley Lamming: UW-Madison
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