Science Webinar Series
The Epigenetics Challenge
DNA Methylation Research from Basics to Biomarkers

21 October, 2010

Brought to you by the Science/AAAS Business Office

Participating Experts:

Dr. Michael Teitell
David Geffen School of Medicine at UCLA
Los Angeles, CA

Dr. Adam R. Karpf
Roswell Park Cancer Institute
Buffalo, NY

Dr. Alex Meissner
Broad Institute of MIT and Harvard
Cambridge, MA

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NEW ENGLAND BioLabs Inc.
DNA Methylation in Cancer

Michael A. Teitell, M.D., Ph.D.

Chief, Division of Pediatric and Neonatal Pathology
David Geffen School of Medicine at UCLA
Outline

• Epigenetics

• Some DNA methylation basics

• Overview of DNA methylation in cancer

• Several methods for analyzing DNA methylation

• DNA methylation in TCL1 B cell malignancies
Epigenetics

- Heritable, reversible modifications of DNA and chromatin that do not change the primary nucleotide sequence
- DNA methylation
  - $\text{CH}_3$ on the 5‘C of cytosine
  - $\text{CH}_2\text{OH}$ (TET1)
- Histone modifications
  - Acetylation, Methylation, Phosphorylation
  - Ubiquitylation, Sumoylation
- ? Others (e.g. microRNAs)
 Genome Project: 4 of 5 NTs Sequenced

- Cytosine may contain a 5′ –CH₃, usually within a CpG dinucleotide sequence

- 5mC not distinguishable from C by usual methods of DNA sequencing
Roles of DNA Methylation

- X-chromosome inactivation

- Genomic imprinting (~200 fetal and placental genes)

- Suppression of parasitic sequence and repetitive elements (ALU, LINE, SINE, transposons)

- Regulation of gene expression
DNA Methylation Can Block TF Binding
DNA Methylation & Chromatin Structure

Euchromatin: Gene is active

Transcription factors bind

RNA polymerase transcribes the gene

DNA wound around histones

- Acetylation (H3-Lys9)
- Histone Deacetylation
- Methylation (Lys9, Su(VAR))
- HP1/DNMTs (1,3b)
- Methyl-CpG binding proteins & associated co-repressors

Gene is inactive: no transcription

Chromatin structural changes

Change C to 5mC

Compaction to heterochromatin (slow, reversible, spreading)

UCLA Jonsson Comprehensive Cancer Center
**De Novo & Maintenance Methylation**

**De Novo**
- Cytosine
- Dnmt 3b
- SAM
- 5-Methylcytosine

**Pre-implantation embryos**
- Germ Cells
- (Somatic Cells Aging)

**Maintenance**
- CGGC
- CH₃
- DNA Replication
- CH₃
- CG
- GC
- CH₃
- SAM

**Demethylation (AID)**
- CH₃
- CG
- GC
- CH₃

**DNA Replication**
- DNA Replication
Prokaryotes versus Humans/Mice

Prokaryotes (all DNA)

CCWGG (dcm) and/or GATC (dam) sites

Humans/Mice (50-60% of genes, “housekeeping”)

Promoter

CpG Islands

CpG Suppression
Normal versus Cancer Cells

Global de-methylation and CpG island hypermethylation
(CpG island demethylation)

Normal Cells

CpG Islands

Cancer Cells

CpG Islands
Deamination Links Genetics and Epigenetics

CpG islands protected; CpG suppression outside of islands
Knudson’s “Two-Hit” Hypothesis in Cancer

Hereditary or Sporadic

LOH

Transformation

Mut Del

Mut Meth

Meth Del

Homozygous Meth/Del/Mut
Strategies for detecting DNA methylation are based mainly upon three approaches or their combinations:

1. Digestion of DNA with methylation sensitive and insensitive enzymes, followed by identification (gel-sizing, PCR)

2. Chemical modification of DNA by bisulfite in alkali, followed by identification (PCR, microarray, next-generation sequencing)

3. Purification of the methylated or unmethylated fraction of the genome using antibodies, followed by identification (PCR, microarray, next-generation sequencing)
# Methods of DNA Methylation Detection

Mainly sequence-specific analysis (incomplete listing):

<table>
<thead>
<tr>
<th>Technique Name</th>
<th>Method</th>
<th>Abbrev</th>
<th>Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nearest Neighbor Analysis</td>
<td>HPLC</td>
<td>NNA</td>
<td>Absorbance</td>
</tr>
<tr>
<td>Methylation-Sensitive Restriction Enzyme Analysis</td>
<td>MSRE</td>
<td>MSREA</td>
<td>SB</td>
</tr>
<tr>
<td>Genomic Bisulfite Sequencing</td>
<td>B</td>
<td>GBS</td>
<td>Sanger Seq</td>
</tr>
<tr>
<td>Combined Bisulfite Restriction Analysis</td>
<td>B+M</td>
<td>COBRA</td>
<td>PCR</td>
</tr>
<tr>
<td>Methylation-Specific PCR</td>
<td>B</td>
<td>MSP</td>
<td>PCR</td>
</tr>
<tr>
<td>MethylLight</td>
<td>B</td>
<td></td>
<td>QPCR</td>
</tr>
<tr>
<td>Methylation-Sensitive Single Nucleotide Primer Extension</td>
<td>B</td>
<td>Ms-SNuPE</td>
<td></td>
</tr>
<tr>
<td>Methylation-sensitive single conformational analysis</td>
<td>B</td>
<td></td>
<td>MS-SSCA</td>
</tr>
</tbody>
</table>

*HPLC = high performance liquid chromatography  
MSRE = methylation sensitive restriction enzyme  
B = bisulphite conversion  
B+M = B plus methyl-sensitive restriction enzyme  
SB = Southern blot*

**Methods of DNA Methylation Detection**

Genome-wide DNA methylation profiling (incomplete listing):

<table>
<thead>
<tr>
<th>Technique Name</th>
<th>Method</th>
<th>Abbrev</th>
<th>Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Restriction Landmark Genomic Scanning</td>
<td>MSRE</td>
<td>RLGS</td>
<td>2D-electrophoresis</td>
</tr>
<tr>
<td>- Methylated CpG Island Amplification</td>
<td>MSRE</td>
<td>MCA</td>
<td>RDA</td>
</tr>
<tr>
<td>- Differential Methylation Hybridization</td>
<td>MSRE</td>
<td>DMH</td>
<td>microarray</td>
</tr>
<tr>
<td>- Methylation-Specific Oligo Hybridization</td>
<td>B</td>
<td>MSO</td>
<td>microarray</td>
</tr>
<tr>
<td>- Gene Expression profiling</td>
<td>ADC</td>
<td>GEP</td>
<td>microarray</td>
</tr>
<tr>
<td>- Methylated-CpG Island Recovery Assay</td>
<td>MBD</td>
<td>MIRA</td>
<td>microarray</td>
</tr>
<tr>
<td>- Methyl-DNA Immunoprecipitation-chip</td>
<td>5mC-Ab</td>
<td>MeDIP</td>
<td>microarray</td>
</tr>
<tr>
<td>- Methyl-DNA Immunoprecipitation-Seq</td>
<td>5mC-Ab</td>
<td>MeDIP</td>
<td>next-gen sequencing</td>
</tr>
</tbody>
</table>

MSRE = methylation sensitive restriction enzyme digestion  
RDA = representational difference analysis  
B = bisulphite conversion  
ADC = 5-aza-2′-deoxycytadine  
MBD = methyl binding domain protein  
5mC-Ab = 5-methylcytosine antibody

Most Lymphomas Originate from GC B Cells

Lymph Node Germinal Center

- Mantle Zone
  - Non-responding naïve B cells

- Follicle Center
  - Proliferation
  - SHM (C→U)
  - Selection (Death)
  - CSR (DSBs)
  - Differentiation

- Post-GC
  - Memory B and plasma cells

What Transforming Genes are Implicated?

UCLA Jonsson Comprehensive Cancer Center
### TCL1 in GC B Cell Tumors and a Mouse Model

**Genetic/Viral Lesions**

<table>
<thead>
<tr>
<th>Genetic/Viral Lesions</th>
<th>Zinc Finger (c-MYC), EBV(+)</th>
<th>p53, EBV(+)</th>
<th>p53, c-MYC</th>
<th>p53, EBV(+)</th>
<th>p53, c-MYC</th>
<th>p53, EBV(+)</th>
<th>p53, c-MYC, EBV(+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Number</td>
<td>DLBCL #1</td>
<td>DLBCL #2</td>
<td>BL</td>
<td>DLBCL #4</td>
<td>DLBCL #5</td>
<td>DLBCL #6</td>
<td>DLBCL #7</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>Spleen</td>
<td><strong>TCL1</strong></td>
<td>Liver</td>
<td>Spleen</td>
<td>Liver</td>
<td>Liver</td>
</tr>
</tbody>
</table>

**Sample Number**

- DLBCL #1
- DLBCL #2
- DLBCL #3
- BL
- DLBCL #4
- DLBCL #5
- DLBCL #6
- DLBCL #7
- DLBCL #8

**#4: TCL1 (+)**

**TCL1 is Repressed in GC and post-GC B Cells**

**Question:**

Do epigenetic changes cooperate with TCL1 to transform B cells?

Restriction Landmark Genomic Scanning (RLGS)

NotI (GCGGCCGC)

No digestion or labeling if NotI is methylated

1st dimension 60 cm agarose tube gel

$\text{N}$

NotI digest gDNA, fill in with radiolabeled nucleotides

Cut with EcoRV

2nd dimension

5% PAGE Slab Gel

Final exposure area 35 x 43 cm (~ 2000 spots/gene fragments)

Dr. Christoph Plass
DKFZ, Heidelberg
Germany

DNA Hypermethylation Detected by RLGS

DNA Hypermethylation Detected by RLGS

115 genetic loci identified as DNA hypermethylated by RLGS (spot decrease or loss) in up to 11 tumors

Genomic Bisulfite Sequencing

5'-METHYL-CYTOSINE

5CH₃ Blocks Sodium Bisulfite Conversion of Cytosine to Uracil
Genomic Bisulfite Sequencing

\[ \text{C} - \text{CH}_3 - \text{C} \downarrow \text{Sodium Bisulfite Treatment} \]

\[ \text{C} - \text{CH}_3 - \text{U} \downarrow \text{PCR and (Subclone or Restriction Cut)} \]

\[ \text{XXXXXX} \quad \text{G} \quad \text{XXXXX} \quad \text{A} \quad \text{XXXX} \]
Spry2 is DNA Methylated in TCL1 B Cell Tumors

Bisulfite Sequencing Confirmation

Sanchez, Oncogene, 2008

Frank, et al., Blood 113: 2478-2487, 2009
Spry2 is Silenced in TCL1 B Cell Lymphomas

**Spry2 RNA expression**

**Spry2 reactivation**

*SPRY2* is also DNA methylated and silenced in human lymphoma samples and transformed B cell lines and is epigenetically reactivated.

Frank, et al., Blood 113:2478-2487, 2009
TCL1 Augments RAS-MAPK-ERK Signaling

TCL1 & SPRY2 Regulate ERK Signaling in B Cells

TCL1 augments B cell proliferation and survival by co-activating PI3K/AKT (not shown) and RAS/MAPK/ERK signaling pathways

Frank, et al., Blood 113:2478-2487, 2009
Distinct DNA Methylation in TCL1-Driven B-CLL

CD19+ B cells and PBLs

CLL Patient samples

Pcdh10
Foxd3
Fign
Axin1
Pkp4
Dlx1
EphA7
Spry2

0% 90%

0.2 0.4 0.6 0.8 1.0

TCL1: B-CLL
MYC: T/NK cell leukemia
IL15: T cell leukemia

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Broad Institute of MIT and Harvard  
Cambridge, MA
DNA hypomethylation, cancer germline antigens, and ovarian cancer

Adam R. Karpf, Ph.D.
Department of Pharmacology and Therapeutics
Roswell Park Cancer Institute
Altered DNA methylation in cancer

I. Classical CpG islands
II. CpG poor intergenic regions
III. Select CpG-rich gene promoters

Normal Cells

Tumor cells

Tumor Suppressor Gene Silencing
Repetitive DNA element activation
Cancer-germline antigen gene activation
Causes and consequences of DNA hypomethylation in cancer

- Loss of DNMT function
- Demethylase activation
- Altered chromatin structure

Genomic DNA hypomethylation

- Oncogene activation
- Genomic instability
- CG antigen gene activation
Global DNA hypomethylation induces genomic instability

HCT116
DNMT
Knockout
Cell Lines

Aneuploidy

Chromosomal Rearrangements

DNMT1-/-
DNMT3b-/-
(DKO) Cells
Global DNA hypomethylation induces cancer-germline antigen genes

Decitabine (5-aza-2’-deoxycytidine) Treatment

HCT116 DNMT Knockout Cell Lines
Cancer-germline (a.k.a. cancer-testis) antigens

• ~150 members, X-linked and autosomal. Often exist in multi-gene families

• Restricted expression to germ cells and cancers

• Immunogenic: Cell-mediated and humoral responses in cancer patients

• Vaccines in clinical trials: MAGE-A3, NY-ESO-1

• Potentially Oncogenic Functions: e.g. negative regulation of p53; androgen receptor activation

• Heterogeneous expression in tumors
CG antigen (NY-ESO-1) expression correlates with promoter DNA methylation status in epithelial ovarian cancer (EOC)

Traditional Bisulfite Sequencing = 41 CpG sites

Bisulfite Pyrosequencing = 15 CpG sites
CG antigen (NY-ESO-1) expression heterogeneity in EOC and promoter DNA methylation status
Coordinated CG gene and global DNA hypomethylation in EOC

A

P<0.0001

% XAGE-1 methylation vs. % BORIS methylation

B

P<0.0001

% Alu methylation vs. % LINE-1 methylation

C

P<0.0001

% NY-ESO-1 methylation vs. % LINE-1 methylation

Bisulfite Pyrosequencing
Association of global and CG antigen promoter hypomethylation with advanced disease stage in EOC

\[ P < 0.01 \]
NY-ESO-1 is a target for immunotherapy of EOC

• NY-ESO-1 vaccines are undergoing Phase I/II trials in EOC

• Vaccines are safe and promote, antibody, CD8+ and CD4+ T-cell responses in vivo

• One key limitation is lack of antigen expression, antigen loss, and expression heterogeneity

• Another key limitation is MHC I expression loss

• Epigenetic modulatory drugs could overcome these limitations
Epigenetic modulators 5-aza + TSA robustly induces NY-ESO-1 expression in EOC cell lines

A2780 Cells

qRT-PCR

Western
Potential routes for epigenetic therapy augmentation of CG antigen immunotherapy

Epigenetic Therapy
DNMTi (e.g. decitabine) + HDACi (e.g. depsipeptide) or HMTi (e.g. BIX-01294) or EZH2i (e.g. DZnep)

CG antigen vaccines
↑CG antigen genes
↑HLA Class I
↑Co-stimulatory molecules

Adoptive cell transfer therapy

Enhanced Anti-tumor Immune Responses
Humoral responses
Cell-mediated responses
Summary

• Global DNA hypomethylation is common in cancer

• Global DNA hypomethylation is associated with genomic instability and advanced disease stage

• In EOC, global DNA hypomethylation coordinately effects repetitive DNA elements and CG antigen gene promoters

• Tumors that show DNA hypomethylation may be amenable to treatment with CG antigen directed vaccines, either alone or in combination with epigenetic modulators
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Genome-Scale DNA Methylation Mapping

- Identifying differentially methylated regions
- Establishing reference maps

Alexander Meissner
Categories for DNA methylation profiling

>20 different methods…

I. Bisulfite conversion (Illumina Infinium, RRBS,…)

II. Digestion with methylation sensitive restriction enzymes (HELP, CHARM,…)

III. Capture of methylated DNA fragments using a recombinant methyl-DNA binding domain or a monoclonal anti-methyl-cytosine antibody (MBD-Cap-Seq, meDIP-Seq)
DNA Methylation in Cancer

DNA Methylation in human stem cells (ES, iPS,...)

NIH Roadmap Reference Epigenome Mapping Center
(Broad, UCSF, UCSD and UWash)

Produce semi-comprehensive epigenomes from human cells and tissues:

Genome  Epigenome Environment  Phenotype, Disease
DNA Methylation in Cancer

DNA Methylation in human stem cells

NIH Roadmap Reference Epigenome Mapping Center

We are interested in DNA methylation differences

Which method provides the most accurate and effective identification of differentially methylated regions (DMRs)?

Goal: Benchmark four methods (MeDIP, MethylCap, RRBS, Infinium) on two pairs of two samples: a colon normal/tumor pair and two human ES cell lines
### Summary of Experiments

#### MeDIP

<table>
<thead>
<tr>
<th>Sample name</th>
<th>#lanes</th>
<th>#reads (total)</th>
<th>#reads (aligned)</th>
<th>Alignment rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUES6 ES cell line</td>
<td>2</td>
<td>37,086,239</td>
<td>22,798,831</td>
<td>61.5%</td>
</tr>
<tr>
<td>HUES8 ES cell line</td>
<td>2</td>
<td>36,078,308</td>
<td>24,266,670</td>
<td>67.3%</td>
</tr>
<tr>
<td>Primary colon tumor</td>
<td>2</td>
<td>33,453,797</td>
<td>18,582,183</td>
<td>55.5%</td>
</tr>
<tr>
<td>Matched normal colon tissue</td>
<td>2</td>
<td>37,789,936</td>
<td>21,793,567</td>
<td>57.7%</td>
</tr>
</tbody>
</table>

#### MethylCap

<table>
<thead>
<tr>
<th>Sample name</th>
<th>#lanes</th>
<th>#reads (total)</th>
<th>#reads (aligned)</th>
<th>Alignment rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUES6 ES cell line</td>
<td>3</td>
<td>38,436,495</td>
<td>23,401,511</td>
<td>60.9%</td>
</tr>
<tr>
<td>HUES8 ES cell line</td>
<td>3</td>
<td>38,735,596</td>
<td>21,670,301</td>
<td>55.9%</td>
</tr>
<tr>
<td>Primary colon tumor</td>
<td>3</td>
<td>37,718,830</td>
<td>23,206,054</td>
<td>61.5%</td>
</tr>
<tr>
<td>Matched normal colon tissue</td>
<td>3</td>
<td>38,330,519</td>
<td>22,724,002</td>
<td>59.3%</td>
</tr>
</tbody>
</table>

#### RRBS

<table>
<thead>
<tr>
<th>Sample name</th>
<th>#lanes</th>
<th>#reads (total)</th>
<th>#reads (aligned)</th>
<th>Alignment rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUES6 ES cell line</td>
<td>2</td>
<td>30,004,147</td>
<td>12,150,905</td>
<td>40.5%</td>
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<tr>
<td>HUES8 ES cell line</td>
<td>2</td>
<td>28,395,040</td>
<td>12,670,034</td>
<td>44.6%</td>
</tr>
<tr>
<td>Primary colon tumor</td>
<td>4</td>
<td>40,015,958</td>
<td>9,545,423</td>
<td>23.9%</td>
</tr>
<tr>
<td>Matched normal colon tissue</td>
<td>4</td>
<td>32,072,287</td>
<td>6,214,732</td>
<td>19.4%</td>
</tr>
</tbody>
</table>

#### Infinium

<table>
<thead>
<tr>
<th>Sample name</th>
<th>#arrays</th>
<th>#CpGs (total)</th>
<th>#CpGs (valid)</th>
<th>#CpGs (unique)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUES6 ES cell line</td>
<td>1</td>
<td>27,578</td>
<td>27,192</td>
<td>27,192</td>
</tr>
<tr>
<td>HUES8 ES cell line</td>
<td>1</td>
<td>27,578</td>
<td>27,090</td>
<td>27,090</td>
</tr>
<tr>
<td>Primary colon tumor</td>
<td>1</td>
<td>27,578</td>
<td>27,561</td>
<td>27,561</td>
</tr>
<tr>
<td>Matched normal colon tissue</td>
<td>1</td>
<td>27,578</td>
<td>27,478</td>
<td>27,478</td>
</tr>
</tbody>
</table>
Visual Comparison

MeDIP

MethylCap

RRBS

Infinium

Low Medium High
Visual Comparison
Genomic Coverage (1): Comparison across Chromosome 21

MeDIP

MethylCap

RRBS

Infinium
Genomic Coverage (2): Key Regulatory Regions

MeDIP

- Promoter regions (2kb centered on TSS)
- CpG islands (length ≥ 700 bp)
- Whole genome (5kb sliding window)

MethylCap

- Promoter regions (2kb centered on TSS)
- CpG islands (length ≥ 700 bp)
- Whole genome (5kb sliding window)

RRBS

- Promoter regions (2kb centered on TSS)
- CpG islands (length ≥ 700 bp)
- Whole genome (5kb sliding window)

Infinium

- Promoter regions (2kb centered on TSS)
- CpG islands (length ≥ 700 bp)
- Whole genome (5kb sliding window)
Detection of DMRs

(a) MeDIP-seq read frequency for HUES6 vs. MethylCap-seq read frequency for HUES6 (Pearson's r = 0.86)

(b) MethylCap-seq read frequency for HUES6 vs. MeDIP-seq read frequency for HUES6 (Pearson's r = 0.86)

(c) RRBS measurement for HUES6 vs. MeDIP-seq read frequency for HUES6 (Pearson's r = 0.95)

(d) Venn diagram showing the overlap of MeDIP-seq, MethylCap-seq, and RRBS measurements. Higher methylation in HUES6 is shown in blue, lower methylation in HUES6 in red. The numbers inside the Venn diagram represent the number of CpG islands: MeDIP-seq: 535 (35 overlap with MethylCap-seq), 71 (overlap with RRBS), MethylCap-seq: 241 (35 overlap with MeDIP-seq), 254 (23 overlap with RRBS), RRBS: 332 (288 overlap with MethylCap-seq). Genome-wide: 44,440.
Conclusion

- MethylCap seems less prone to global bias than MeDIP
- RRBS and MethylCap are surprisingly similar in their power to detect DMRs
- Other considerations
  - RRBS works on FFPE samples and <30ng of input DNA
  - MethylCap and MeDIP provide genome-wide coverage, whereas RRBS does not
  - RRBS provides single-basepair resolution
  - The MethylCap and MeDIP protocols are simpler than RRBS
  - RRBS can be scaled to methylome sequencing
- We have refined the Epigenome Pipeline Package to handle group-wise comparison of many samples
Establishing an ES cell reference map (RRBS)

Reference: 19 High quality human ES cell lines
Test set: 11 iPS cell lines
High-quality ES cell lines span a reference corridor of pluripotent cell variation

For each gene, the “reference corridor” defines expected DNA methylation and gene expression values

Outliers could interfere with cell line function
Comparison with the reference corridor identifies cell-line specific outlier genes

Avoid cell lines with hypermethylation at key genes (e.g. CD14 for macrophages)
Meissner Lab
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Camille Sindhu
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Griet Verstappen
Jamie Webster
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