Epigenetic mechanisms and DOHaD

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Developmental origins of health and disease

GENE-ENVIRONMENT INTERACTION

EPIGENETICS
Epigenetic: heritable changes in gene expression caused by mechanisms that do not depend on changes in DNA sequences
### Genetics and disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sequence 1</th>
<th>Sequence 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (G/G)</td>
<td>AGATTCA<strong>G</strong>GCATATT</td>
<td>AGATTCA<strong>G</strong>GCATATT</td>
</tr>
<tr>
<td>Carrier (G/A)</td>
<td>AGATTCA<strong>G</strong>GCATATT</td>
<td>AGATTCA<strong>A</strong>GCATATT</td>
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<tr>
<td>Disease (A/A)</td>
<td>AGATTCA<strong>A</strong>GCATATT</td>
<td>AGATTCA<strong>A</strong>GCATATT</td>
</tr>
</tbody>
</table>
Epigenetics and disease

Adapted from Petronis et. al., 2003
Epigenetic mechanisms in mammalian development

- Lineage commitment
- Retrotransposon silencing
- X Chromosome inactivation
- Genomic imprinting
Review of epigenetics mechanisms

**EPIGENETIC MECHANISMS**
are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

**DNA methylation**
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

**Histone modification**
The binding of epigenetic factors to histone “tails” alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

**CHROMATIN**

**HEALTH ENDPOINTS**
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

**EPIGENETIC FACTOR**

Histones are proteins around which DNA can wind for compaction and gene regulation.
F0

multigenerational (directly exposed)

F1

F2

transgenerational (no direct exposure)

F3

Adapted from Xin F. et al (2015) Seminars in Cell and Developmental Biology
Epigenetic mechanisms in mammalian development

- Lineage commitment
- Retrotransposon silencing
- X Chromosome inactivation
- Genomic imprinting
Genomic Imprinting
The unequal expression of the maternal and paternal alleles of a gene
Dosage is important!

Normal

Too much!

Not enough!
Abnormal imprinting disrupts development

Fetal growth

Placental development
Tunster et al (2011)

Growth
Beckwith-Wiedemann Syndrome

Neurobehavioral development
Prader-Willi Syndrome
Angelman Syndrome
A model of environmental exposure: Bisphenol A is ubiquitous in the environment.
MOUSE
CHR 7

**H19/Igf2** domain:

- insulin-like growth factor
- fetal growth
- misregulation linked to disease

- BPA exposure alters DNA methylation and expression (Susiarjo et al 2013: PLoS Genetics)
Susiarjo et al (2015): Endocrinology

Igf2 normally expressed

Healthy

Igf2 overproduced

Adult onset obesity
Glucose intolerance
Insulin resistance