Fundamentals of Epigenetics

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Epigenetic Epidemiology of the Developmental Origins Hypothesis
Robert A. Waterland and Karin B. Michels
2007 Ann Rev Nutr

Epigenetic Mechanisms Affecting Regulation of Energy Balance: Many Questions, Few Answers
Robert A. Waterland
2014 Ann Rev Nutr
Where Health Begins

Obesity, Cancer and Heart Attacks: How Your Odds Are Set in the Womb
Metabolic Imprinting: Adaptive responses to early nutrition

- Susceptibility limited to critical period of development
- Persistent effect lasting through adulthood
- Specific and measurable outcome
- Quantitative relationship between exposure and outcome
Metabolic Imprinting - Potential Mechanisms

• Alterations in organ structure
• Alterations in cell number or ploidy
• Clonal selection
• Epigenetics (metabolic differentiation)

Waterland & Garza 1999 *Am J Clin Nutr*
EPIGENETICS: Mitotically heritable, stable alterations in gene expression *potential* that are NOT caused by changes in DNA sequence

Epigenetics: “Above” genetics
Epigenetic Mechanisms

• Cytosine Methylation

• Histone Modifications?
  - Henikoff & Shilatifard 2011 *Trends in Genetics*

• Autoregulatory Transcription Factors
  - Riggs & Porter 1996 in *Epigenetic mechanisms of gene regulation*

• Non-coding RNA

*Waterland & Michels 2007 Ann Rev Nutr*
Why Focus on DNA Methylation?

- Most stable epigenetic mark
- Known mechanism of mitotic heritability
- Can be measured in minute quantities of DNA
- Can be measured molecule-specifically
  - Enables precise assessment of allelic regulation
Establishment and Maintenance of DNA Methylation

- Most cytosines within CpG dinucleotides are methylated

![Chemical structure of Cytosine and 5-Methylcytosine]

- Tissue-specific patterns of CpG methylation are established during development

- Methylation requires dietary methyl donors and cofactors

- Mitotically heritable

Waterland & Michels 2007 *Ann Rev Nutr*
Is epigenetic dysregulation contributing to the obesity epidemic?
Epigenetic Dysregulation Causes Obesity

Cloning

Prader-Willi Syndrome

- Infantile hypotonia
- Gonadal hypoplasia
- Feeding difficulties
- Hyperphagia
- Obesity
- Moderate MR
- Behavioral problems
- Short stature
- Small hands and feet

Tamashiro KL et al, Nat Med 2002
The Agouti Sisters
The Agouti Sisters
Obstacles to Understanding Epigenetic Contribution to Human Obesity

• Genetic variation influences epigenetic variation

• Epigenetic regulation is largely cell type-specific

• Epigenetic regulatory regions poorly characterized

• Disease process can affect epigenetic mechanisms
  - Causation vs. association

Waterland 2014 Ann Rev Nutr
Waterland & Michels 2007 Ann Rev Nutr
Tissue-specific Enhancer Activity in the Human Genome

Kundaje et al 2015 Nature
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Developmentally Programmed 3’ CpG Island Methylation Confers Tissue- and Cell-Type-Specific Transcriptional Activation

Da-Hai Yu, Carol Ware, Robert A. Waterland, Jiexin Zhang, Miao-Hsueh Chen, Manasi Gadhkari, Govindarajan Kunde-Ramamoorthy, Lagina M. Nosavanh, Lanlan Shen

Yu et al 2013 Mol Cell Biol
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Interpretation and Significance: The Way Forward

- Controlled studies in animal models are urgently needed to understand developmental programming of energy balance

- Considerations for design of human studies
  - Assess epigenetic variation in context of genetic variation
  - Study appropriate tissues (or confirm systemic variation – Metastable epialleles)
  - Focus on genomic regions of functional interindividual variation
  - Perform prospective studies to enable causal inference

Waterland 2014 Ann Rev Nutr
Waterland & Michels 2007 Ann Rev Nutr
Genetically Identical, Epigenetically Different