The Epigenetics of Obesity: Individual, Social, and Environmental Influences

K. J. Claycombe, Ph.D.
What can happen to our gene(s) that would cause obesity?
Modification via Epigenetic alterations
Individual Influences

Environmental Influences

Social Influences
Early-life determinants of overweight and obesity

Environmental

- Maternal nutrition
- In utero growth restriction
- Maternal smoking

- Paternal/maternal overweight/obesity
- Genetic factors
- Parental diet and physical activity

- Large birthweight
- Rapid growth Catch up

- Sedentary
- TV viewing
- Built environment

- Short sleep duration
- Low SES education

- Breastfeeding infant feeding
- Unhealthy food and beverages
- Marketing advertising

- Food prices
- Food insecurity

- Neglect/abuse
Epigenetics

- Epigenetics is an \textit{inheritable changes} that affects gene expression without DNA base pair sequence changes.

- Examples of epigenetic phenomena:
  - DNA methylation
  - histone modifications
  - chromatin remodeling
Maternal diet, infection, stress and inflammatory immune function regulation

- Stress
- Environmental Pollutants
- Smoking/Alcohol
- Nutritional Status
- Maternal Obesity
- Maternal Infection
You are what your grandmother ate— inherited effects of *in utero* undernourishment

Jennifer Sargent

Published online 29 July 2014
“What your **grandparents** ate could affect your health”

For example, when a **paternal grandmother** experienced drastic changes in food availability as a child, then granddaughters had an increased risk for cardiovascular mortality as an adult.

*Bygren et al. BMC Genetics 2014, 15:12*  
http://www.biomedcentral.com/1471-2156/15/12
Don’t blame the mothers
Headlines in the press reveal how these findings are often simplified to focus on the maternal impact: ‘Mother’s diet during pregnancy alters baby’s DNA’ (BBC), ‘Grandma’s Experiences Leave a Mark on Your Genes’ (Discover), and ‘Pregnant 9/11 survivors transmitted trauma to their children’ (The Guardian). Factors such as the paternal contribution, family life and social environment receive less attention.
A Control development and postnatal nutrition in fathers.

B Current High Fat or Low Protein Diet

C History of Exposure to Maternal Caloric Restriction

You Are What Your Dad Ate

Cell Metabolism

Volume 13, Issue 2, 2 February 2011, Pages 115–117
Do prenatal experiences shape culinary tastes?

Pregnant volunteers consumed plain flavored or garlic capsules around 24 weeks of pregnancy.

Sniffed unlabeled bottles of amniotic fluid and breast milk.

Volunteers easily sniffed out which came from the garlic consumer.
Babies born from two groups of volunteers who consumed plain flavored or garlic capsules

Videotape images were generated when babies were given garlic milk
Other Supporting Evidence
(Animal Study)

Other supporting evidence (animal study)

Pregnant Wistar rats

Maintained on their respective diets throughout pregnancy and lactation

After weaning, offspring were fed either control chow or junk diets for either 3 weeks and for 3 months

Conclusions:
Mice whose mothers had a junk food diet developed **altered development of the central reward system**, resulting in **increased fat intake** and altered response of the reward system to excessive junk-food intake in postnatal life.
Example of Basic Science Studies of Epigenetics
Obesity and Epigenetics of Adipose tissue
(USDA ARS Research Program)
LP fed dams and offspring Phenotypes


**increased fat deposition and altered feeding behavior**

**impaired glucose homeostasis, dyslipidaemia**
- (Burdge et al., Prostaglandins Leukot Essent Fatty Acids 2008; 78: 73–79)

**impaired immunity**
- (Calder and Yaqoob, Nutr Res 2000; 20: 995–1005)

**increased susceptibility to oxidative stress**
- (Langley-Evans and Sculley, Mech Ageing Dev 2005; 126: 804–812)
Intrauterine growth restriction and catch-up growth

Maternal undernutrition

Low birth weight

Increased propensity for catch-up growth

Normal diet

Normal weight

Normal growth

Sutton et al., Endocrinology 2010;151(4):1570-80
Maternal undernutrition

Low birth weight

High Fat diet

Increased propensity for catch up growth

Epigenetic Programming?
Animal model of obesity and epigenetics
Experimental Design

Experimental Diet (12 wks)

FO

2 wk Gestation

20% protein 20% protein

Lactation

20% protein

F1

Experimental Diet (12 wks)

Normal Energy

High Energy

2 wk Gestation

8% protein 8% protein

Lactation

8% protein

High Energy

Normal Energy
2 wk  |  Gestation  |  Lactation
---|---|---
20% protein  |  20% protein  |  20% protein

Experimental Diet (12 wks)

- Normal Energy
- High Energy

2 wk  |  Gestation  |  Lactation
---|---|---
8% protein  |  8% protein  |  8% protein

Experimental Diet (12 wks)

- Normal Energy
- High Energy

Adaptive and compensatory programming
2 wk Gestation, Lactation

20% protein, 20% protein, 20% protein
8% protein, 8% protein, 8% protein

Experimental Diet (12 wks)

At Birth, at weaning

Body weight (g)

Weight (g)
How to measure fat tissue changes over time in live animals?

Magnetic Resonance Imaging (EchoMRI)
Quantitate fat mass measurement by Echo MRI.
Low Adipose Tissue Weight and **Catch-up Growth**
Adipose tissue mass fold increase

Claycombe et al., accepted, J Nutr. 2013
Effects of prenatal and postnatal diet on imprinted gene expression?
Igf2/H19 Locus

- Insulin-like growth factor 2 (IGF2) was the first imprinted gene identified (Cell, 64:849-859, 1991)
- IGF2 is a major fetal growth factor (Nature 417:945-948, 2002)
- Epigenetics is an inheritable changes that affects gene expression without DNA base pair sequence changes (e.g. DNA methylation, histone modifications)
Effects of LP prenatal and HF postnatal diet on Adipose Tissue IGF2 mRNA Expression

Claycombe et al., J Nutr. 2013
CTCF - CCCTC motif binding factor

1-4 CpG sites/CTCF
IGF2 transcription activation

NORMALLY: methylation is present in the ICR so there is no CTCF binding and hence Igf2 expression activated.
IGF2 transcription repression

With less methylation or hypomethylation of the ICR there is CTCF binding and Igf2 expression repressed.
ICR/ H19 DMR Methylation in Adipose Tissue

![Graph showing methylation levels and statistical significance](image)
Effects of LP prenatal and HF postnatal diet on Adipose Tissue Dnmt3a mRNA Expression
Is there metabolic phenotype associated with catch-up growth?
Effects of LP prenatal and HF postnatal diet on GT

Effects of LP prenatal and HF postnatal diet on Plasma Insulin Concentrations

Adipose Tissue
Mitochondrial Copy Number

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<th>Condition</th>
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<th>Post</th>
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ANOVA
- Pre: NS
- Post: p=0.06
- Pre x Post: NS

Visceral

Subcutaneous
Effects of LP prenatal and HF postnatal diet on Adipose Tissue **IGF2 mRNA Expression**
Adipose Tissue Growth and Regulators

- Normal
- Obesity

Increase in adipose tissue mass
Adipose Tissue Growth and Regulators

IGF2

Normal
Increase in adipose tissue mass
Obesity

IGF2
Adipose Tissue Growth and Regulators

High Fat Diet

IGF2

Increase in adipose tissue mass

IGF2

Normal Obesity
Adipose Tissue Growth and Regulators

High Fat Diet + Exercise

Normal: Increase in adipose tissue mass

Obesity: IGF2

IGF2
Maternal Conditions

High Fat Diet and Obesity

Developmental Influences of Maternal Diet and Exercise

Epigenetic Changes

Decreased Numbers of Beige Adipocytes and Decreased Energy Utilization

F1 Response

Promote Obesity and Insulin Resistance

Modulators?

Test of Maternal exercise (Human study)
Maternal LP Diet

Skeletal muscle
SDH, SIRT3, mt respiration

Adipose tissue
SDH, SIRT3, mt respiration
IGF2

Endocrine cross talk

Insulin Resistance

Brain and BAT
UCP-1, PPAR-a

Brain and BAT
Hypothalamus
Leptin

Sympathetic tone

Energy expenditure

White adipose tissue

Lipolysis

Brown adipose tissue

Insulin Resistance

SDH, SIRT3, mt respiration

IGF2
Other metabolic tissues?
Effects of LP prenatal diet on Muscle Metabolism and mt Function
Effects of LP prenatal diet on Brown adipose tissue function
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