Epigenetics, Fetal Programming, and Transgenerational Effects
Human Genome Project

- Humans aren’t that complicated genetically
- Most of the DNA is “junk”
- Has not changed medicine
- What went wrong?
Epigenetics

• Changes in gene expression without affecting the DNA code itself

• Induced by environmental factors
  – Diet is largest factor

• Can occur throughout a lifetime
  – Largest impact is during fetal and post-natal development
Environmental Factors That Cause Epigenetic Changes

- Diet
- Exercise
- Pollution
- Stress
Players in Epigenetics

- Histone Modification
  - Acetylation
  - Methylation
- DNA Methylation
  - CpG islands in DNA structure
- MicroRNAs
  - Gene silencing by RNA interference
Fetal Programming

- Maternal under-nutrition
- Maternal over-nutrition
- Paternal under-nutrition
- Paternal over-nutrition
Benefits of Fetal Programming

• Fine-tuning of fetus for future environment

• Allows the next generation to adapt to very different environments

• Mismatched signals generate increased risk for chronic disease
Maternal Under-nutrition

- Dutch Famine (1944-1945)
  - Obesity
  - Diabetes
  - CVD
- Leningrad Famine (1943-1945)
  - No obesity
- Protein restriction
  - Obesity
Catch Up Phase in Low Birth Weight Induces Hyperinsulinemia

- Obesity
- Diabetes
- Heart disease
Maternal Over-nutrition

• Maternal obesity
  – 30% of reproductive age women are obese
  – Obesity no barrier to reproductive success

• Gestational diabetes
  – Elevated insulin due to insulin resistance of the mother
Hyperinsulinemia Is Established at Birth By Over-nutrition

- Obesity
- Diabetes
- Heart disease
Maternal Stress

• Protein restriction
  – Can increase corticosteroid production

• Excess corticosteroid production
  – Creates insulin resistance and increased hyperinsulinemia
Maternal Inflammation

- Imbalance in omega-6 to omega-3 fatty acids during prenatal development

- Increased maternal inflammation generates increased maternal corticosteroids
Transgenerational Changes
Lifetime of Epigenetic Marks During Fetal Nutrition

• Appear to last up to three generations after removal of driving force

• If constantly reinforced by the diet and environment they may become permanent
Players

- Endocrine disruptors
- Gut microbe disruption
- Stress
- Omega-6 fatty acids
Endocrine Disruptors

- DES
- PCBs
- BPA
Endocrine Disruptors Have Trans-generational Epigenetic Effects

- PCBs
- BPA
Gut Microbe Disruption

• Low-fiber diet causes irreversible depletion of gut bacteria
  – Change seen within weeks
  – 1/3 of species don’t return even on high-fiber diet

• Trans-generational effects
  – 75% reduction in species by 4th generation
  – 2/3 of species don’t return even on high-fiber diet

Sonnenburg et al Nature 529 (2016)
Additional Negative Epigenetic Factors

• Oxidative stress

• Psychological stress
Trans-Generational Epigenetic Changes Caused by Excess Omega-6 Fatty Acids
Obesity

Hannbauer et al, Cardio Psychiatry and Neurology (2009)
Fatty Liver

Hannbauer et al Cardio Psychiatry and Neurology (2009)
Heart Disease

Hannbauer et al Cardio Psychiatry and Neurology (2009)
Rise of Omega-6 Fatty Acids in the US Diet

Blasbalg et al AJCN 93: 950 (2011)
Single Generation Impact of Increased Omega-6 Fatty Acids In The Diet
Increased Omega-6 Fetal Intake

Adding Omega-3 Fats Can Only Partially Reverse Effects

AA/EPA Ratio in Different Italian Age Groups

Figure 2: The AA/EPA and total omega-6/omega-3 ratios in whole blood of healthy subjects not using fish oil supplements and grouped by age. Mean ± S.E; Student’s t-test: * p < 0.05 vs 0-20; § p < 0.05 vs 21-40; §§ p < 0.01 vs 21-40, number of subjects as in Table 1.

Cellular Inflammation Can Leave Epigenetic Marks

- Altered microRNA expression
- DNA methylation by increased IL-6
  - Gasche et al Int J Cancer 129: 1053 (2011)
- Histone modification
The Likely Suspect

• Increased expression of NF-κB
  – Gene transcription factor
  – Master inflammatory switch
Dietary Controls on NF-κB Activity

Omega-6 and Saturated Fatty Acids, Excess Carbs Calories, and Epigenetic Effects

Zone Diet, Omega-3 Fatty Acids and Polyphenols
Can The Zone Diet Turn Off Cellular Inflammation Induced by Epigenetic Changes?
Gene Expression Can Change Rapidly

Brattbakk et al Omics 15 (2011)
Other Positive Short-term Epigenetic Factors

• Exercise
  – 7,000 genes are affected by methylation after 3 months of exercise
  – 5,000 genes in on leg cycling
    • Lindholm et al. Epigenetics 9:1557 (2014)

• Meditation
  – Specific down-regulation of inflammatory genes
    • Kaliman et al. Psychoneuroendocrinology 40:96 (2014)
Holding Back An Epigenetic Flood

• Reduce omega-6 fats in the diet
• Increase protein and reduce glycemic load of the diet and maintain it
• Take adequate omega-3 fats to lower the AA/EPA ratio and increase resolution
• Consume adequate polyphenols
• Exercise
• Stress reduction
Summary

• Dietary changes may be inducing trans-generational changes in inflammatory gene expression via epigenetics

• It may take several generations to reverse these epigenetic changes

• Obesity, diabetes, and heart disease will likely accelerate in the future unless there is a radical dietary change
A New Even More Powerful Message

- Diet and environment can **turn on** inflammatory genes and induce rapid epigenetic changes

- Diet and lifestyle can **turn off** inflammatory genes and hold back inflammatory consequences of epigenetic changes