Maternal Nutrition and Cognitive Development

The Impact of Epigenetics

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Presentation Overview

- Review of Genetics and Epigenetics
- Epigenetic Effects of the Maternal Diet
- Examples from Animal models and Observational Studies/ Natural Experiments
- How Diet and Epigenetics may Impact Cognitive Development
The Human Genome

The nucleus of a single cell contains all the genetic information required to make the human body.

This genetic information is packaged as chromosomes.
The normal human chromosome complement, or karyotype, contains two copies of the 4,000,000,000-base human genome, packaged into 22 pairs of autosomes plus the X and Y sex chromosomes. Here the human karyotype has been stained using different coloured chromosome-specific probes.
• Each chromosome contains many genes
• Gene = segment of a chromosome that encodes for instructions that allow a cell to produce a specific protein
• Genes are composed of DNA, which exists as 2 complementary strands containing adenine (A), thymine (T), cytosine (C), or guanine (G).
From Genes to Proteins

Genes contain instructions for making proteins.

Proteins act alone or in complexes to perform many cellular functions.
Human Genetic Variation

• Any 2 individuals share 99.9% of their DNA sequence
  – Approximately 1 difference every 1000 base pairs
  – Many of these variations are: Single Nucleotide Polymorphisms (SNP’s)

These small differences are responsible for human diversity including our appearance, as well as medically important variations including susceptibility to disease.
No Change to DNA – Big Effect

Small Change to DNA – Big Effect
Genetic v. Epigenetic Modifications

• A **genetic** modification in DNA (such as that induced by a genotoxic agent) can mutate a gene in such a way that the protein product is **non-functional**

• An **epigenetic** modification does not change the sequence of DNA; rather, it changes how a gene is expressed

• Epigenetic modifications can be **reversed**, so genes can be turned back **on**
• Methylation of CpG islands
• Changes in chromatin – “histone code”
  ➢ Methylation of histones
  ➢ Phosphorylation of histones
  ➢ Ubiquitination of histones
  ➢ Biotinylation of histones
  ➢ Acetylation of histones…

Catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs)
Nutrition and Epigenetics
What we know from animal models

• Effects of early nutrition in the honey bee.

Nutritional Control of Reproductive Status in Honeybees via DNA Methylation R. Kucharski*, J. Maleszka*, S. Foret, R. Maleszka†Science 28 Mar 2008:
The murine *agouti* gene encodes a paracrine signaling molecule that signals follicular melanocytes to switch from producing black pigment to yellow pigment.
Are you what your mother eats?

- Dutch Hongerwinter famine (late 1944-May 1945)
- Children conceived during famine were small and underweight
- As adults, increased susceptibility to insulin resistance, metabolic syndrome and obesity -- The Thrifty Gene
Maternal Diet has Epigenetic Effect on Offspring Health

Persistent epigenetic differences associated with prenatal exposure to famine in humans

Bastiaan T. Heijmans1,2, Elmar W. Tobin3,7, Anyeh D. Stein4, Hein Putter4, Gerard J. Blauw5, Ezra S. Sussert2, and L. H. Lumey5,6

Difference in IGF2 DMR methylation between individuals prenatally exposed to famine and their same-sex sibling. (A) Periconceptional exposure: Difference in methylation according to the mother's last menstrual period (a common estimate of conception) before conception of the famine-exposed individual. (B) Exposure late in gestation: Difference in methylation according to the date of birth of the famine-exposed individual. To describe the difference in methylation according to estimated conception and birth dates, a lowess curve (red or blue) is drawn. The average distributed rations (in kcal/day) between December 1944 and June 1945 are depicted in green.

PNAS 2008
Fetal Programming vs. Epigenetics

- Fetus makes adaptations through programming to “prepare” for postnatal environment in response to signals.
  - Epigenetic marks get laid down during embryogenesis
  - Prenatal exposures may have long lasting effects.

- Epigenetics provides the molecular basis for fetal programming
  BUT epigenetics can occur throughout the lifespan.
  - BACK TO THE BEES....

Reversible switching between epigenetic states in honeybee behavioral subcastes
Brian R Herb, Florian Wolschin, Kasper D Hansen, Martin J Aryee, Ben Langmead, Rafael Irizarry, Gro V Amdam & Andrew P Feinberg
Reducing Cancer Risk through Diet and Epigenetics

SFN-Cys in the HDAC pocket
M.C. Myzak et al Carcinogenesis 2006
HDAC inhibition in human PBMC

Epigenetic/Fetal Programming Effects on the Brain

Best evidence for Maternal Care
What about Prenatal Diet and Cognitive Development
Evidence from Schizophrenia

- Dutch Famine and The Great Chinese Famine Epidemiologic studies
  - Maternal exposure to famine associated with offspring increase risk
    - neural tube defects
    - schizophrenia/schizoid personality disorder

Figure 1. Potential mediating mechanisms linking prenatal nutrition with later schizophrenia development
What about Prenatal Diet
Evidence from Obesity and Inflammation
DOES PRENATAL OMEGA-3 supplementation (DHA) improve cognitive development: Infants and toddlers: YES

Task 1: Infants: Habituation

Until 6 mos of age faster habituation= better attention/cognition, seen here in high omega 3 group

Task 2: Toddlers: Free play with single object look duration: Concentration

During second year of life longer concentration on single object play predicts later IQ and executive function development, seen here again in high omega 3 supplementation group

Source: Columbo et al 2004, Child Development 75, 1254
What Next?

• How do we apply the science of diet, epigenetics and brain development in developing interventions?
• Where to start?
• What to measure?