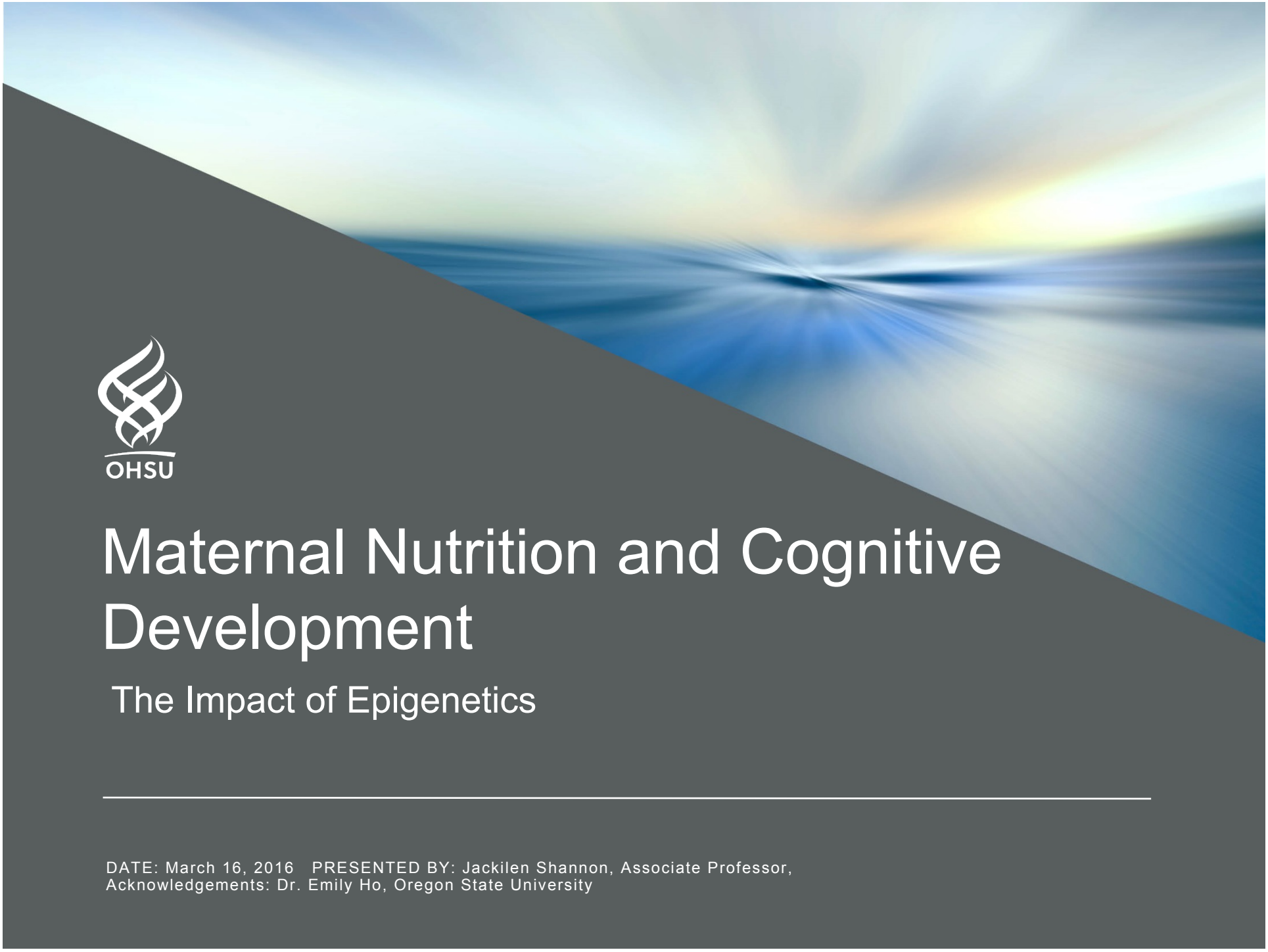

Maternal Nutrition and Cognitive Development

The Impact of Epigenetics

DATE: March 16, 2016 PRESENTED BY: Jackilen Shannon, Associate Professor,
Acknowledgements: Dr. Emily Ho, Oregon State University

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

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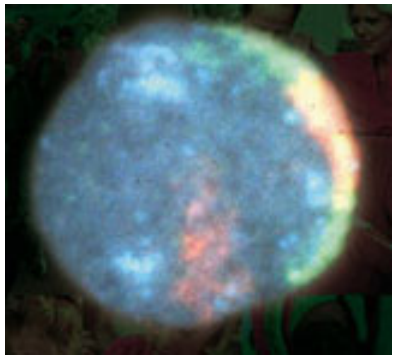
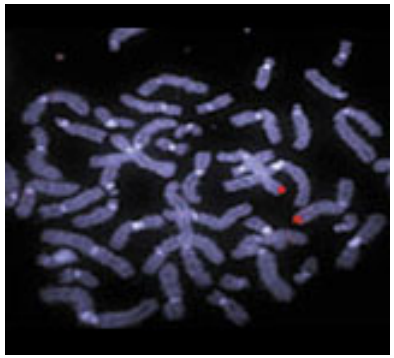
The Human Genome



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

This genetic information is packaged as chromosomes



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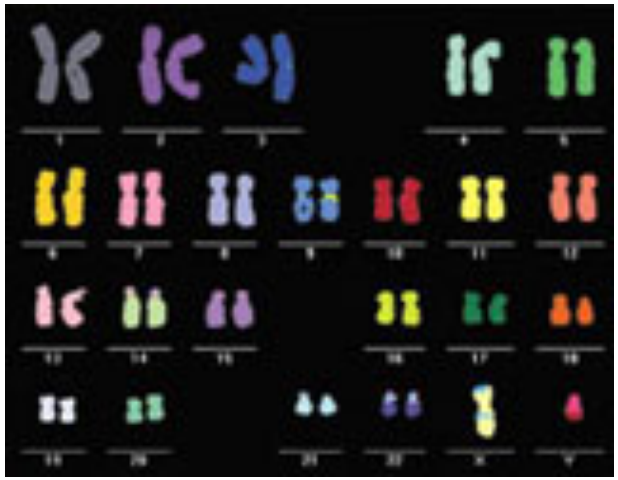

The normal human chromosome complement, or karyotype, contains two copies of the 4,000,000,000-base human genome, packaged into 22 pairs of autosomes plus the X and Y sex chromosomes. Here the human karyotype has been stained using different coloured chromosome-specific probes.

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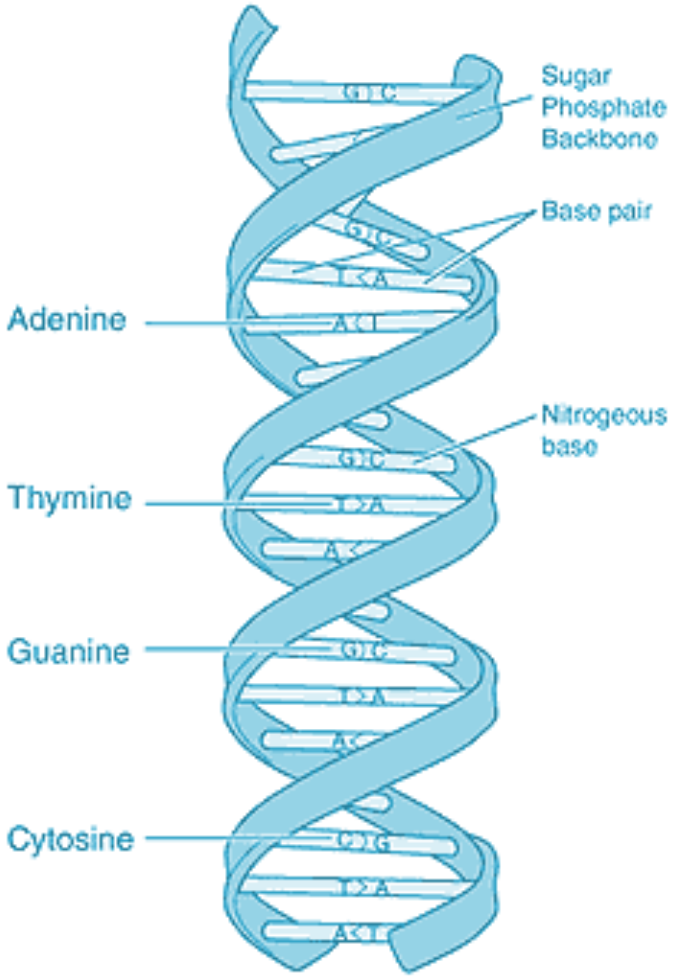
- Each chromosome contains many genes
- Gene= segment of a chromosome that encodes for instructions that allow a cell to produce a specific protein
- Genes are composed of DNA, which exists as 2 complementary strands containing adenine (A), thymine (T), cytosine (C), or guanine (G).



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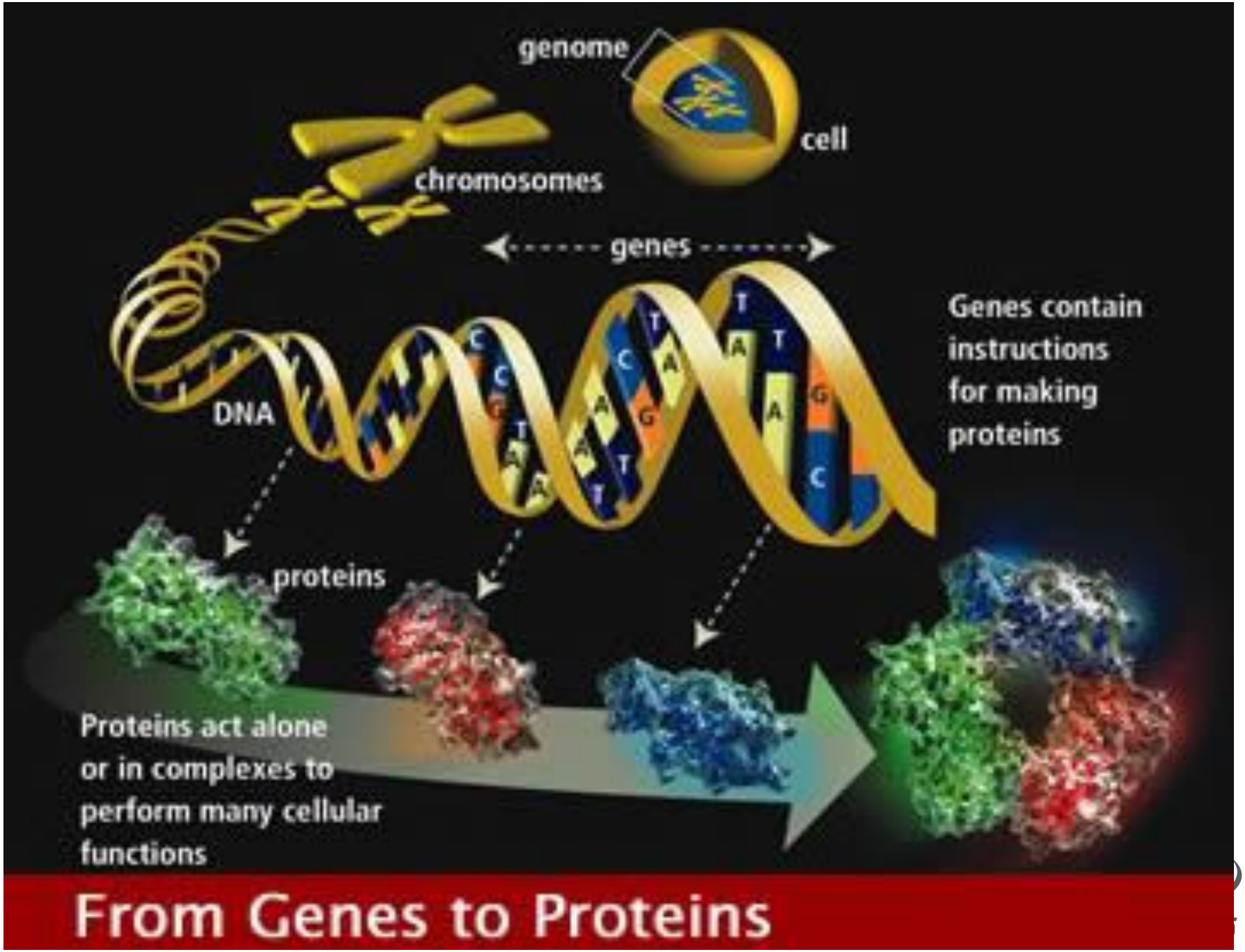
genome
cell
chromosomes
genes
DNA
Genes contain instructions for making proteins
proteins
Proteins act alone or in complexes to perform many cellular functions
From Genes to Proteins

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.

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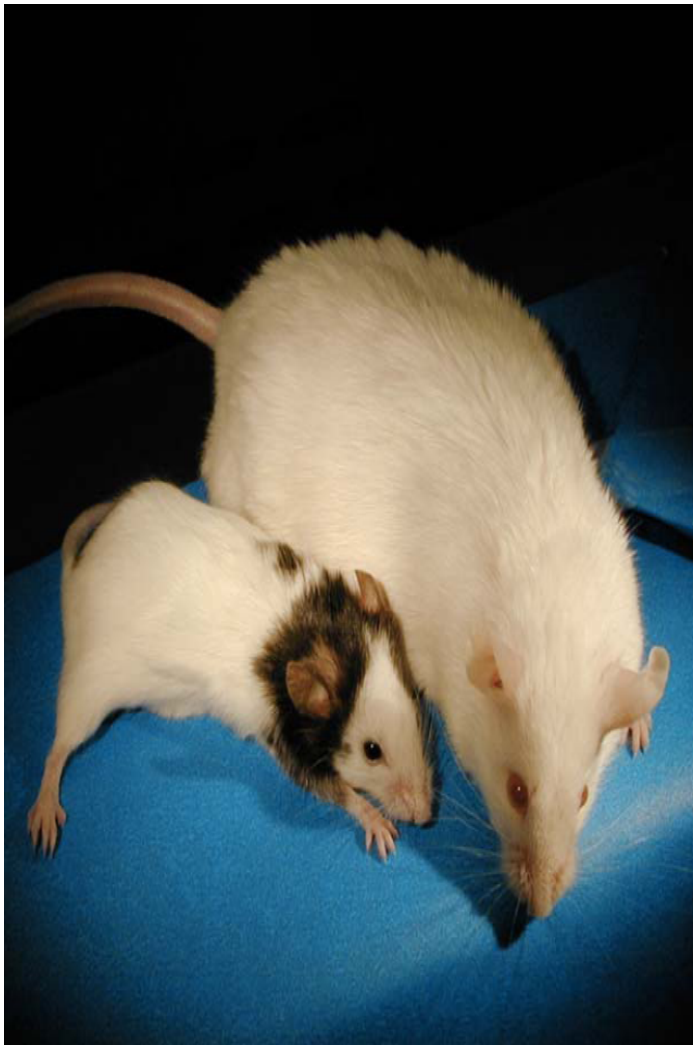
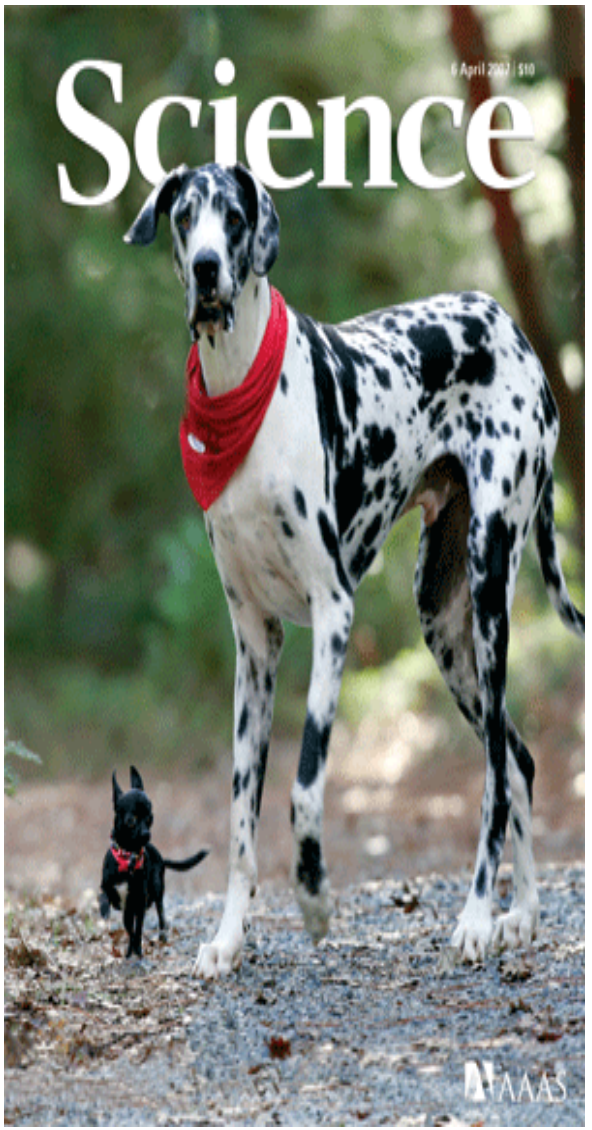
No Change to DNA – Big Effect



Small Change to DNA – Big Effect



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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

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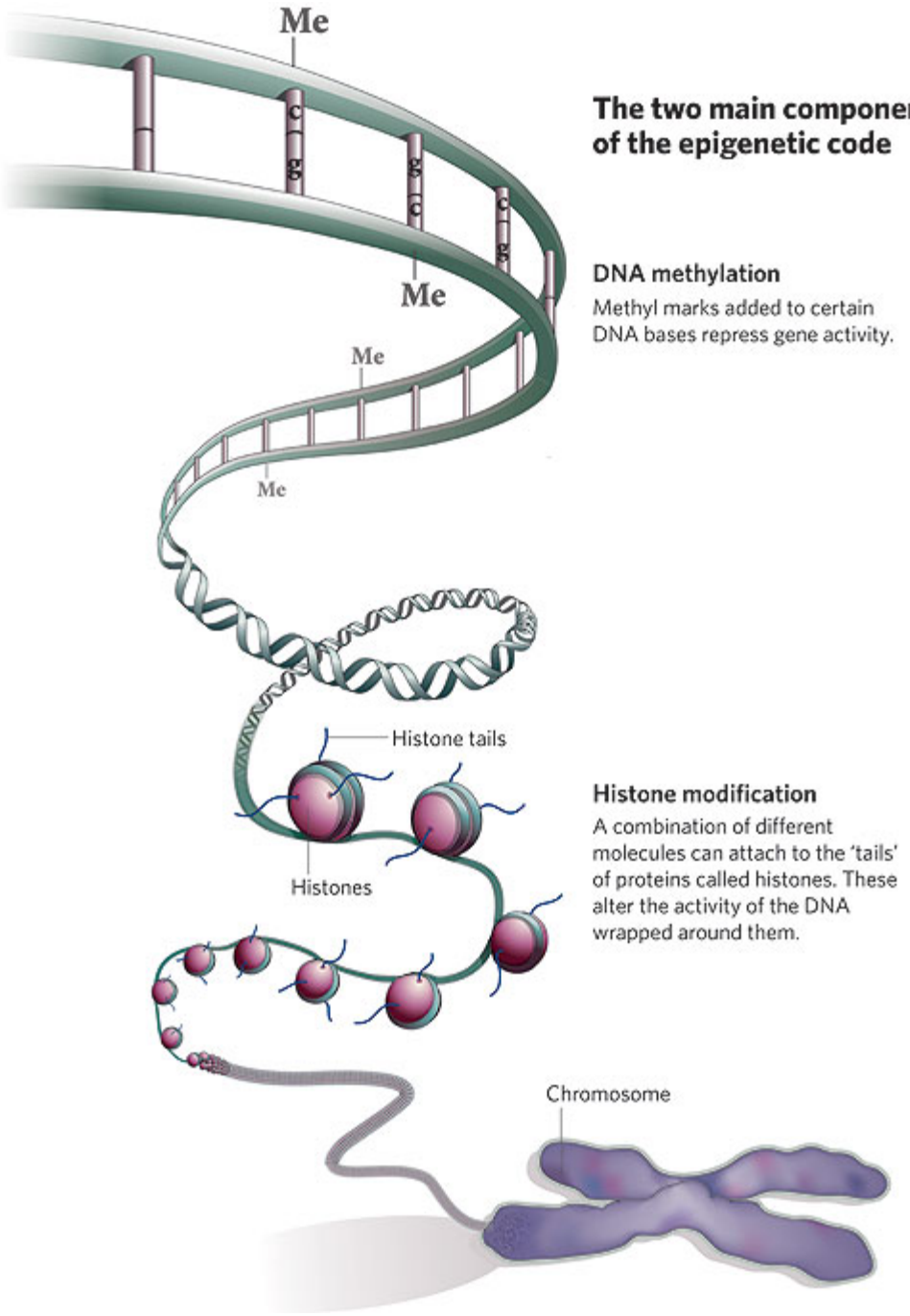
The Epigenetic Revolution



- 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)

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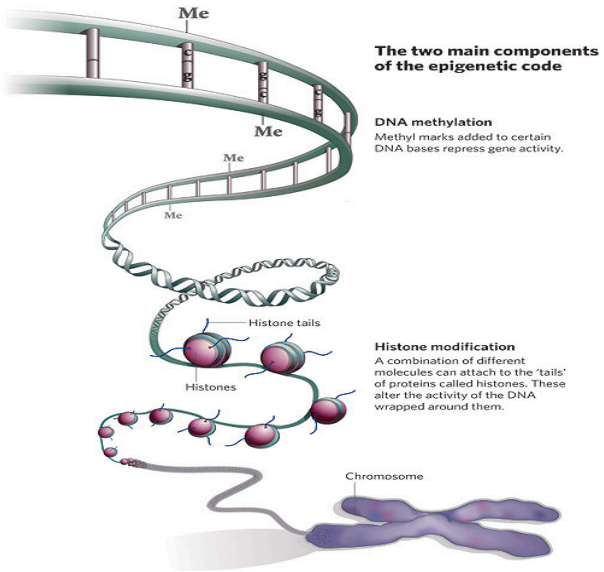
Nutrition and Epigenetics What we know from animal models

- Effects of early nutrition in the honey bee.



Not all Jelly is equal

Nutritional Control of Reproductive Status in Honeybees via DNA Methylation **R. Kucharski**[*], **J. Maleszka**[*], **S. Foret, R. Maleszka**[†] *Science* 28 Mar 2008:

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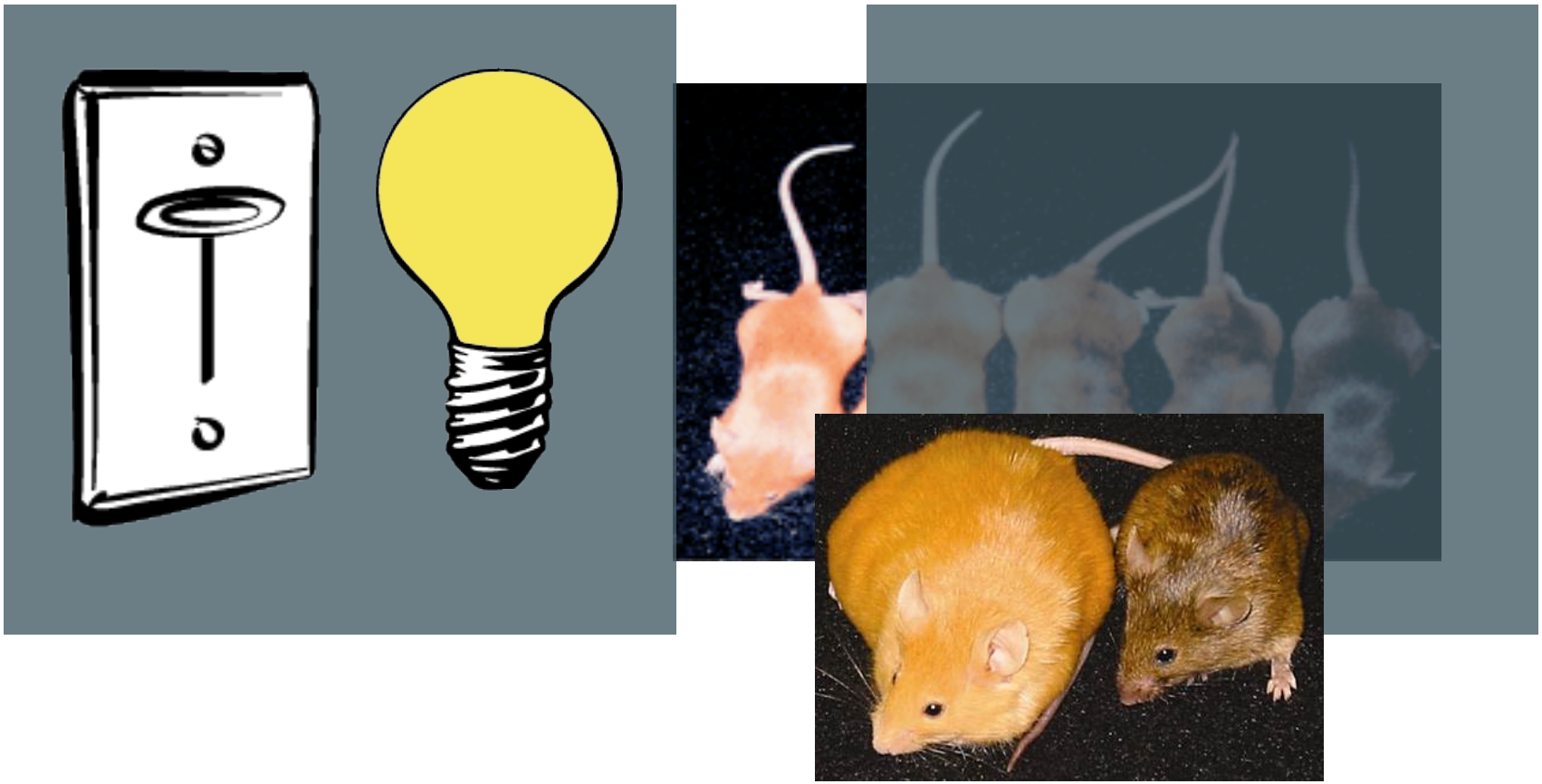
Epigenetics – In living color…



The murine *agouti* gene encodes a paracrine signaling molecule that signals follicular melanocytes to switch from producing black pigment to yellow pigment.

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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

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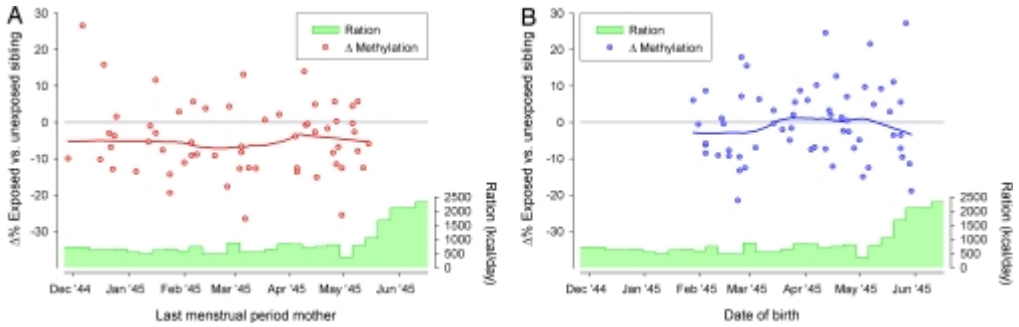
Maternal Diet has Epigenetic Effect on Offspring Health

Persistent epigenetic differences associated with prenatal exposure to famine in humans

Bastiaan T. Heijmans[a,1,2], Elmar W. Tobi[a,2], Aryeh D. Stein[b], Hein Putter[c], Gerard J. Blauw[d], Ezra S. Susser[e,f], P. Eline Slagboom[a], and L. H. Lumey[e,1]



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

Cardiovascular and Metabolic Risk

ORIGINAL ARTICLE

Impaired Insulin Secretion After Prenatal Exposure to the Dutch Famine

Susanne R. de Rooij, msc[1]
Rebecca C. Painter, md, msc[1]
David I.W. Phillips, md, frcp[2]
Clive Osmond, phd[2]
Robert P.J. Michels, md, phd[3]
Ian F. Godsland, phd[4]
Patrick M.M. Bossuyt, phd[1]
Otto P. Bleker, md, phd, frcog[5]
Tessa J. Roseboom, phd[1]

birth weight babies and babies exposed to maternal gestational diabetes are also at increased risk for type 2 diabetes (17,18).

The results of most low–birth weight studies imply that the impaired glucose

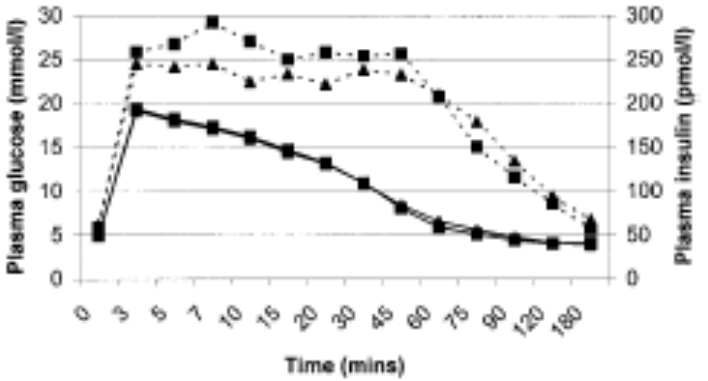


Figure 1—*Geometric means of plasma glucose (solid line) and insulin (dotted lines) concentrations during the intravenous glucose test for people who were exposed (▲) or unexposed (■) to famine in utero.*

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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….

nature neuroscience

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

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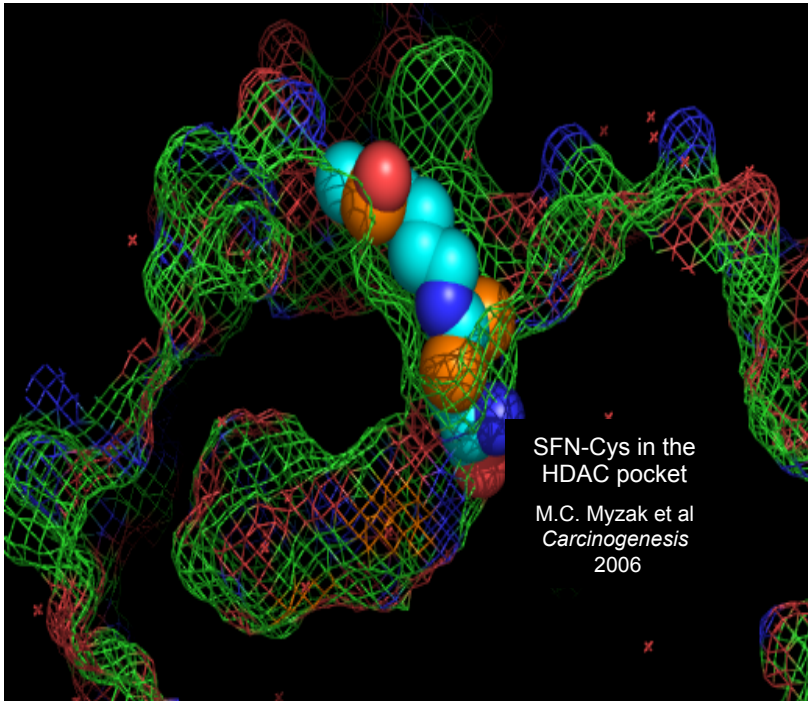
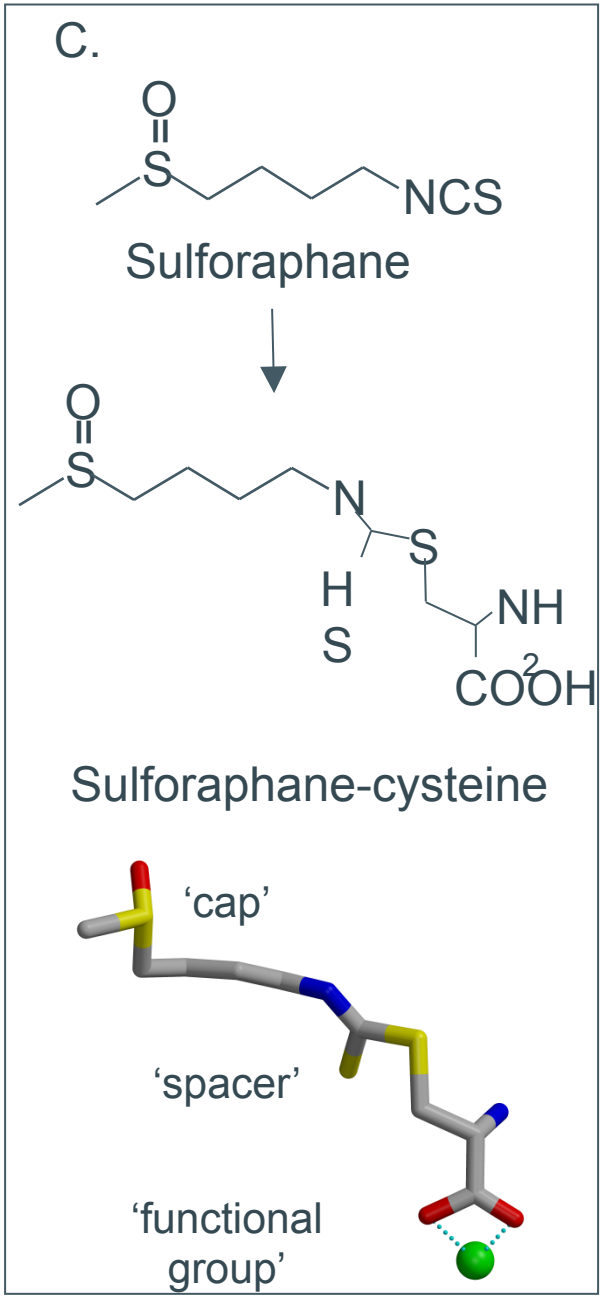
Reducing Cancer Risk through Diet and Epigenetics





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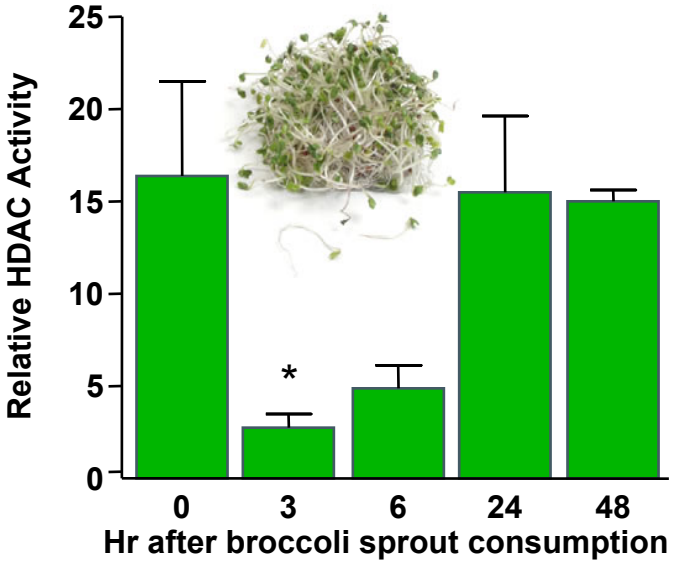
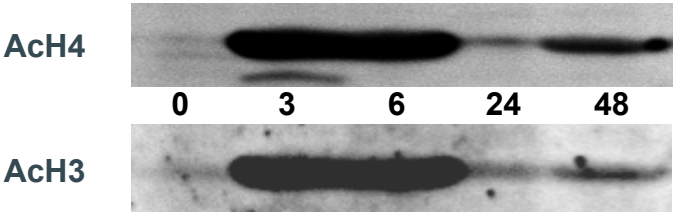
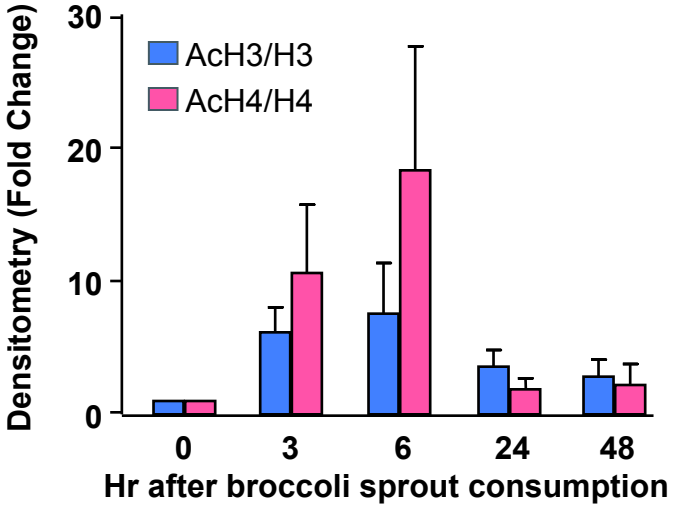
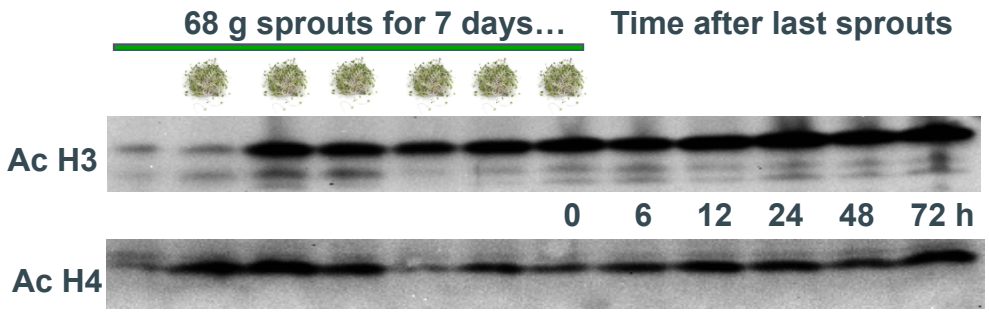
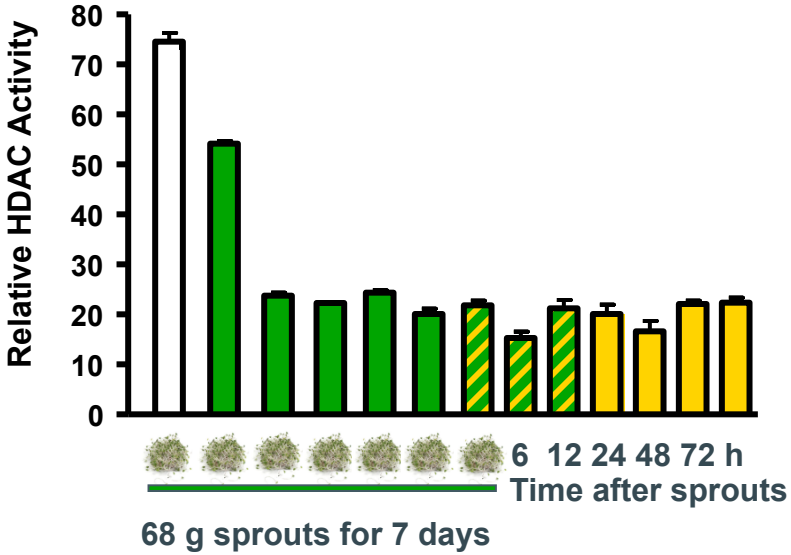
HDAC inhibition in human PBMC











MC Myzak et al *Exp Biol Med* 2007

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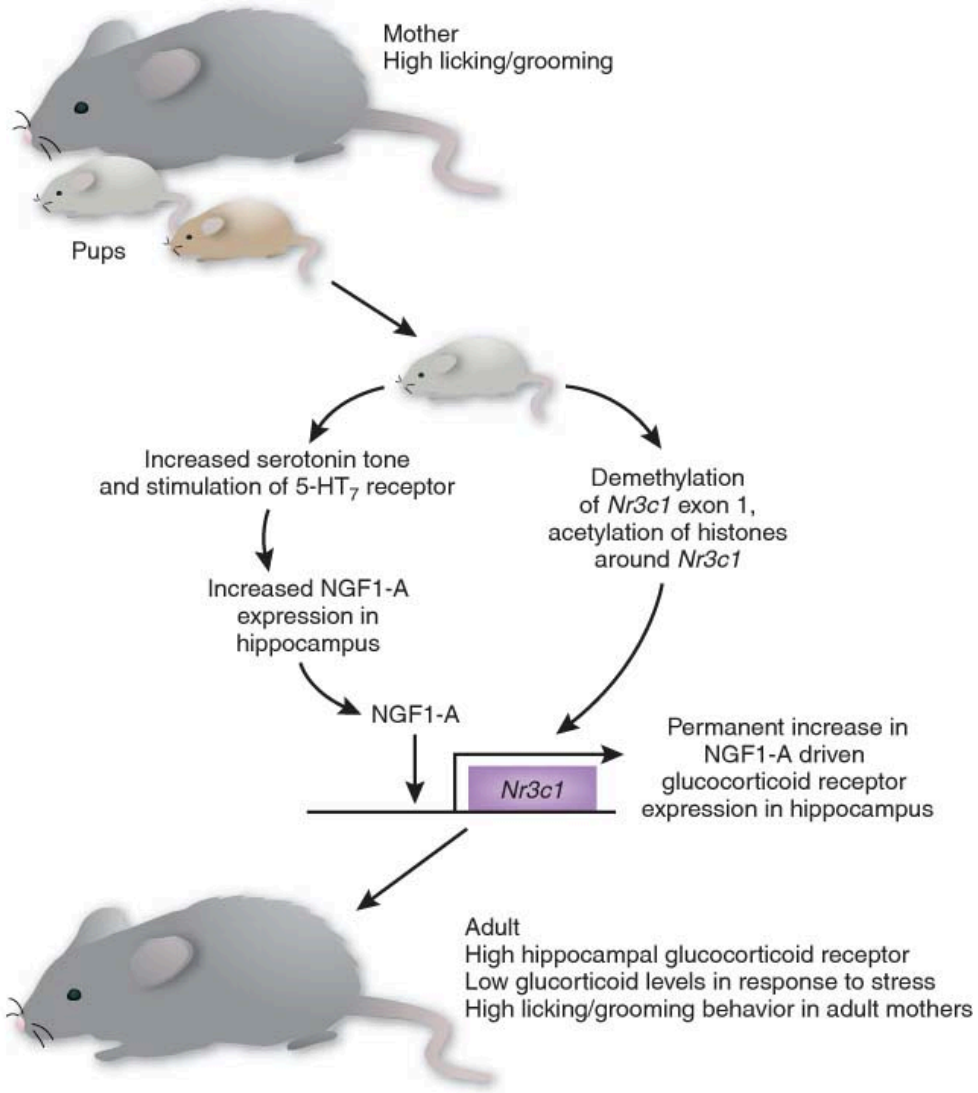
Epigenetic/Fetal Programming Effects on the Brain

Best evidence for Maternal Care



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What about Prenatal Diet and Cognitive Development Evidence from Schizophrenia

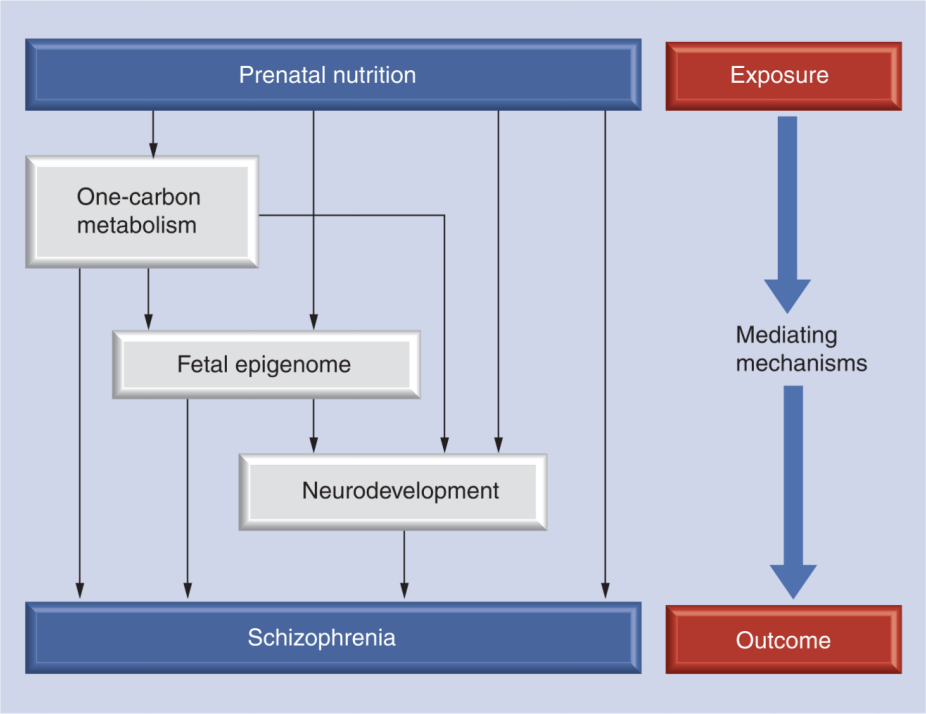

Figure 1. Potential mediating mechanisms linking prenatal nutrition with later schizophrenia development

- 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

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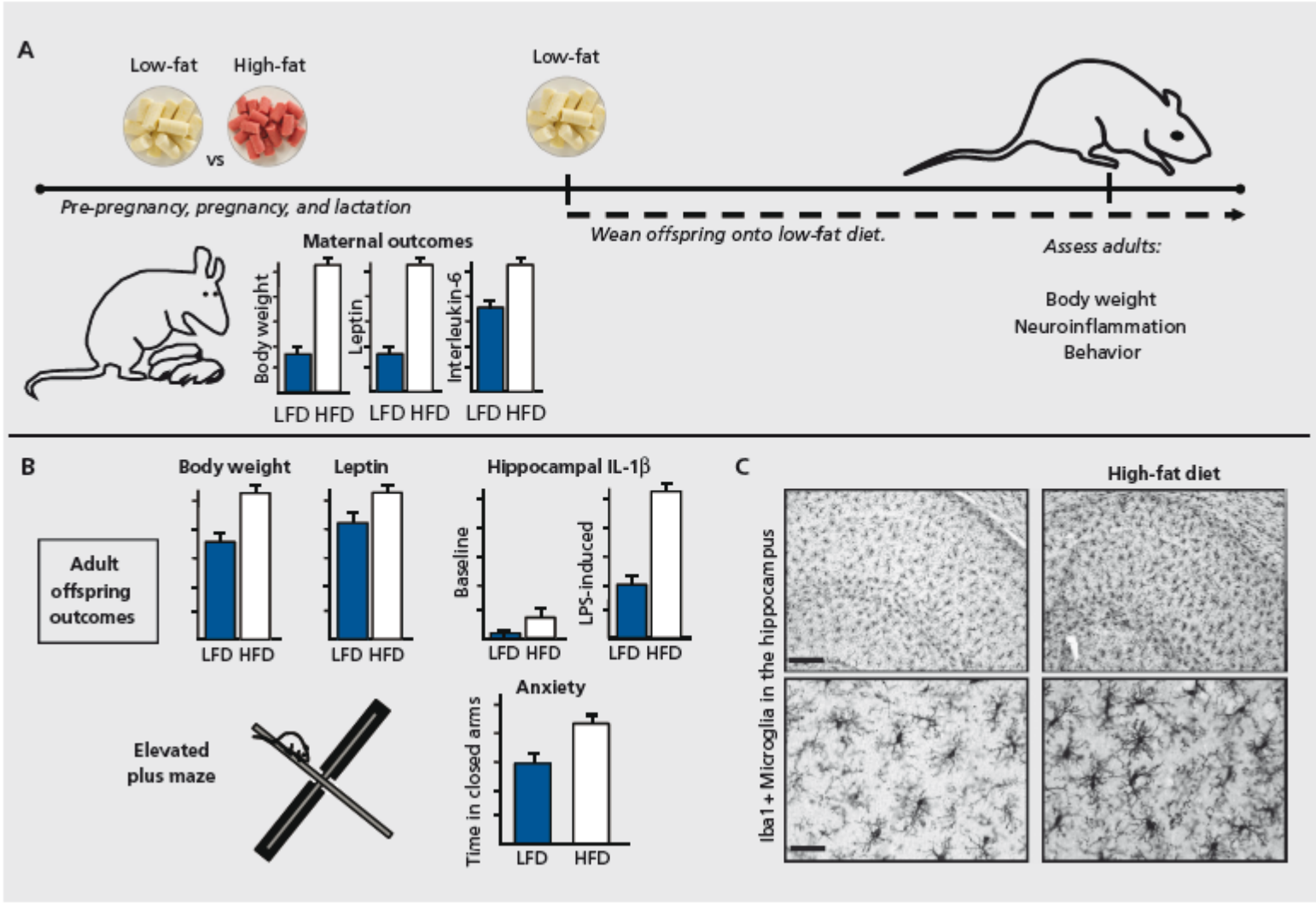
What about Prenatal Diet
Evidence from Obesity and Inflammation



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DOES PRENATAL OMEGA-3 supplementation (DHA) improve cognitive development: Infants and toddlers: YES

Task 1: Infants: Habituation

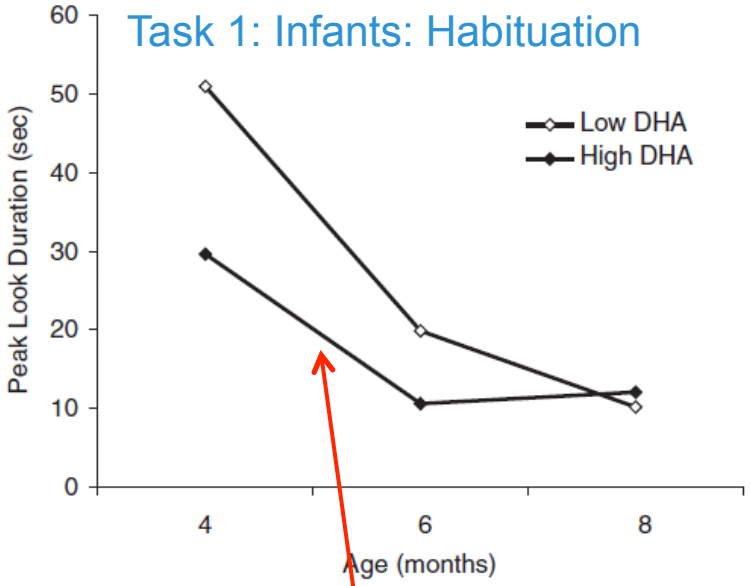

Figure 1. Developmental course of look duration for infants born to mothers with high and low maternal docosahexaenoic acid (DHA) at delivery.

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

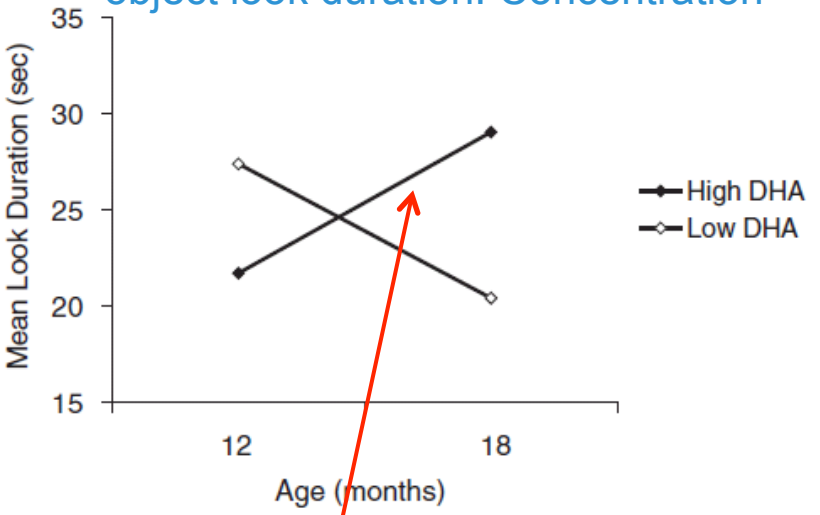

Figure 3. Developmental course of look duration during single-object, free-play sessions at 12 and 18 months as a function of high and low maternal docosahexaenoic acid (DHA) at delivery.

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

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What Next?

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

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