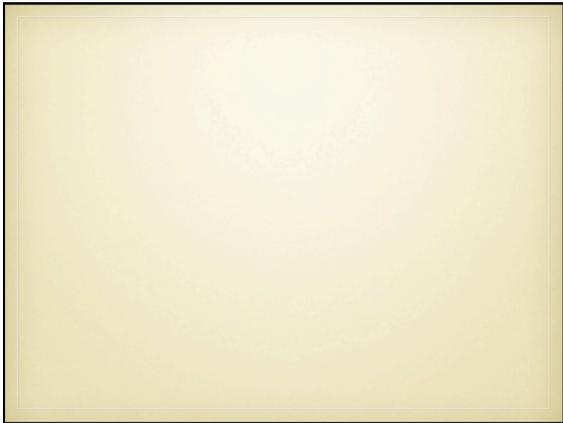


EPIGENETICS & BREASTFEEDING: THE POTENTIAL LONG- TERM IMPACT OF BREASTFEEDING ON FUTURE HEALTH

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UP TO 5 GENERATIONS

Every mother contains her daughter in herself and every daughter her mother. Every woman extends backwards into her mother and forward into her daughter. ~ Carl Jung



TRADITIONAL THINKING

HOW DOES EPIGENETICS WORK?

- Est. 100,000 genes
- Only 21,000 genes
- Not even as complex as plants
- Same genes can cause different phenotypes
- How do we explain?

HOW DOES EPIGENETICS WORK

Only 1-2% of disease comes directly from genetic origin. Our genes do not direct our lives because our genes cannot turn themselves off and on. Only the environment can do that!

WHAT IS EPIGENETICS?

- Literally means above the gene.
- How our environment influences genetic expression.
- Genome = DNA
- Epigenome = Phenotype

WHAT IS EPIGENETICS?

- Genome (Hard Drive)
- Epigenome (Software)
- Phenotype (Program)

THE EPIGENETIC SWITCH

- Flip Switch
 - Environmental and chemical exposures
 - Nutrition
 - Emotions, thoughts, beliefs
 - Stress

HOW DOES EPIGENETICS WORK?

- DNA Methylation
- Histone Modification
- mRNA
- Phosphorylation
- Ubiquitylation
- Sumolyation

METHYLATION

NUCLEOTIDES
Rungs of the ladder

- @30 million genes that can be methylated



HISTONES

- 50 trillion cells in body
- 6 linear feet of DNA in each one



HISTONE MODIFICATION/ CHROMATIN

Histones

This is Chromatin!!!
Solves the packaging problem.

HISTONE MODIFICATION

- Deacetylated, condensed genes, difficult to access
- Acetylated, decompressed, easy access to genes

Canani, 2011

Acetyl group

DNA Accessible,

MESSENGER RNA

- Messenger between DNA and Proteins that express genes through down regulation or translation

LET'S GET VISUAL

EPIGENOME AS TRANSLATOR

- Translator – How do cells differentiate the DNA?
- The Epigenome!

EPIGENOME AS TRANSLATOR

Epigenetic Marks

Fundamental
Period of
Development

Conception

By Full Gestation

NUTRIGENOMICS

- Nutrients can directly or via hormonal activity influence the expression of genes
- An entire new field now called nutrigenomics
- What is the most important first food?

EPIGENETICS AT WORK

- Breastmilk
- Micro-biome Changes
- Other Env. Factors
- Health
- Food that goes in changes the enzymes in the gut
- Fermentation of proteins of polysaccharides
- Methyls and Acetyl Groups

BREASTMILK AND THE MICROBIOME

BIFIDOBACTERIUM, PROMOTE + DIGESTION

- Artificial milk fed infants have completely different pH. Changes pH (from an **acidic base** of 5.1-5.4 to more **alkaline** of 5.9-7.3 which allows putrefactive bacteria)
- Change the fermentation process and methyl groups available to body

HIGH LEVELS OF E COLI, STREPTOCOCCI, CLOSTRIDIA, AND BACTERIOIDES

BREASTMILK AND THE MICROBIOME

- Optimal digestion/immune support the following is required:
 - Amino acids cystein and methionine
 - Uptake of selenium

Rich in sulphur amino acids = Higher cystein levels = Healthy genomic expression

(Waly, 2012)

BREASTFEEDING AND THE PHENOTYPE



(Canani, 2011)

ANIMAL RESEARCH

- Mouse studies
- Agouti mice (Dolinoy, 2006; Jirtle, 2000)

BREASTMILK'S EPIGENETIC INFLUENCE

- Lactoferrin –
- Prostaglandin –
- LCPUFA n-3 and Cholesterol – Non Alcoholic Fatty Liver
- Oligosaccharides – NEC, Immune Disorders, Obesity

Verduci, Nutrients 2014

WHY DOES IT WORK?

- We are constantly adapting for optimal survival.
- The fetus is preparing for optimal survival outside the womb.
- The newborn is managing its new environment and adjusting to cues.

UNIQUE MICROBIOME/ NUTRITIONALLY IMPACTED

EPIGENETICS AND THE MICROBIOME

Step 1

Step 2

Step 3

Step 4

- Microbiome Differences
 - Vaginal vs. Cesarean
- Emergent Cesarean vs Planned Cesarean
- Homebirth vs. Hospital birth
- Breastfed vs. Formula Fed

How Does Bacteria Get into Breastmilk???

GALT/MALT

Fernandez, 2012

- “The human gut contains a diverse community of bacteria that colonise the large intestine in the days following birth and vastly outnumber our own cells. These so-called gut microbiota constitute a virtual organ within an organ, and influence many bodily functions.” Costandi, 2012
- Breastmilk
- Nutrition
- Immune Function
- Microbiome

How Similar Are Our Biomes?

Williams et al., in press

HMOs -OLIGOSACCHARIDES MARVELS NEWEST HEROS

- HMO – Human Milk Oligosaccharides
- Can't be used by baby
- There to feed our bacteria
- Genetically driven
- Influenced by geography

200 Different Types

SUPER HERO'S OF MILK

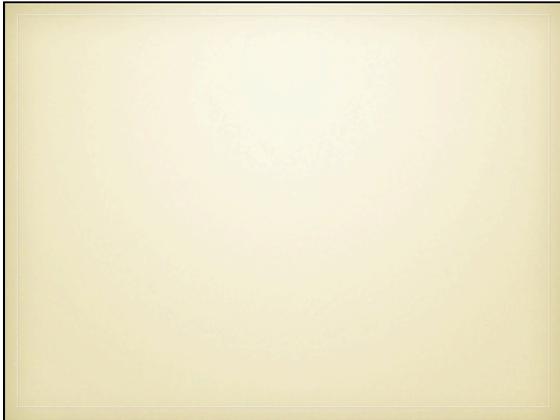
- Bouncers – bacteria latch on and get a ride out of gut
- Immune Tuners – Dial down immune in gut so bacteria can establish hold
- Feeders –Providing unique nourishment

WHY IS IT IMPORTANT?

Gomez-Gallego et al. 2016

Germ Free Rats are Depressed

Rats raised germ-free have different production of key brain neuron fertilizers that help with neuroregeneration, neuroplasticity, and repair than do rats that are (like most animals) colonized with gut bacteria.



BREASTMILK AND BRAIN INFLAMMATION

- Reduces inflammatory responses in infant
- Until the Immune system catches up, takes care of immune response
- Without this, the gut communicate an inflammatory state via cytokines through Vagus Nerve
- Stimulate **microglia to direct tryptophan** away from production of **serotonin and melatonin**

BABY BUILDING CAN HAVE LONG TERM CONSEQUENCES

- Depression is thought to represent a hypercortisolemic state which may result from elevated levels of inflammatory cytokines

MOTHERS ARE ARCHITECTS

STUDIES IN REVIEW

- Chung, *Transitory Mammary Glands*, 2005
- Dos Santos et al. Mammary Gland Memory, 2015
- Obermann-Borst et al. Duration of breastfeeding and gender are associated with methylation of the LEPTIN gene in very young children. 2013.
- Ozkan et al.: Milk kinship hypothesis in light of epigenetic knowledge. *Clinical Epigenetics* 2012, 4-14.
- Kosaka et al.: microRNA as a new immune-regulatory agent in breast milk. *Silence*, 2010,1:7.

A proposed molecular mechanism linking early nutrition, bacterial metabolites, epigenetics, and obesity.
Mona Mischke, and Torsten Plösch Am J Physiol Regul Integr Comp Physiol 2013;304:R1065-R1069

Butyrate is a short chain fatty acid, contributing to fat accumulation hyper-acetylation

AMERICAN JOURNAL OF PHYSIOLOGY
 Regulatory, Integrative and Comparative Physiology

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MAMMARY GROWTH YIELDS

- Energy restriction (all essential nutrients but caloric reduction) has significant biological impact on animals
 - Retardation of aging
 - Reduction of cancer
 - Reduction late life disease
- Energy restriction shifts physiology to energy-conserving and away from energy-wasteful metabolic pathways
- Refeeding then causes accelerated anabolism, increased growth

MAMMARY GROWTH YIELDS

Early in history this been practicing this for years, called stairstepping

- Energy restriction followed by refeeding during pre-puberty, puberty and gestation. Increases yields by up to 10%
- Two groups in trial – Rats (mammary secretory cells)
 - Group One-dietary restrictions for first 10 days gestation
 - Same minerals, protein and vitamin, just energy restriction at 60% of mean intake
 - Group Two

MAMMARY GROWTH YIELDS

- Restricted energy led to:
 - More Milk!
 - Increased elevation of gene expression (proliferation and differentiation)
 - Increased cell proliferation
 - Refeeding during last trimester most impact

THE EPIGENOME HELPS BREAST TISSUE “REMEMBER”

Breast Tissue	12	Gland
6		

(Dos Santos, 2015)

DURATION OF BREASTFEEDING AND LEP

- DNA methylation of LEP
- Responsible for appetite regulation and fat metabolism
- Formula feeding dims down the Leptin producing gene

Obermann-Borst et al.

DURATION OF BREASTFEEDING AND LEP

- Maternal Education, Breastfeeding Duration, Constitutional Factors at 17 mo. old
- Measured DNA methylation of LEP in whole blood and also serum leptin
 - 120 Couplets, 99 BF Info
 - 75% BF
 - 14% < 1 mo.
 - 22% > 1-3 mo.
 - 21% > 3-6 mo.
 - 18% > 6 mo.

MILK KINSHIP AND EPIGENETICS

- Does wet nursing or milk sharing cause consanguinity?

Oksan et al.

- Why is this a possibility? (approximately 30 to 100 nm in diameter)
 - Exosomes in breastmilk
 - Tiny endosome-derived membrane vesicles that are released into the extracellular environment
 - Genetic material such as microRNA

MIRNA IN BREASTMILK



- High levels of miRNA in breastmilk in first six months of lactation
- Approximately 1.3×10^7 copies/liter/day of miR-181a
- Allow for transfer of genetic material (outside sexual reproduction)

Kosaka et al.

3 MILK KINSHIP AND EPIGENETICS

- Presence of exosome containing microRNA
- miRNAs involved in negative gene regulation
- Single miRNA species can affect expression of many proteins
- Control expression of epigenetic regulators such as affecting methyls and histones

IMMUNE CELL REGULATION AND METABOLISM

- Rich with mRNAs that promote cellular differentiation and proliferation, tissue identity, metabolism, and developmental programming

Karlsson, Oskar, et al. "Detection of long non-coding RNAs in human breastmilk extracellular vesicles: Implications for early child development." *Epigenetics* 11.10 (2016): 721-729.
 Alsweid, M.; Lai, C.T.; Harman, P.E.; Geddes, D.T.; Kakulas, F. Human milk miRNAs primarily originate from the mammary gland resulting in unique miRNA profiles of fractionated milk. *Sci. Rep.* 2016, 6, 20680

- Either functional role or a nutritional role.
 - Functional - Absorbed by the suckling baby to imply specific actions: for example, to modulate and shape the immune system by regulating T-cells, inducing B-cell differentiation, and preventing the development of allergies
 - Nutritional hypothesis suggests miRNAs simply provide nutrition

Melnik, 2016; Na, 2015; Alsaweed, 2015

DAY TO NIGHT

FROM WOMB TO MILK

Floris, 2016

MIRNA IN BREASTMILK

- miRNAs survive harsh conditions
 - Prolonged room temp.
 - Acidic conditions
 - Rnase digestion
 - Boiling!!!!
- Delivers miRNA to infants through the gut of the infant

MIRNA IN BREASTMILK

- Influence is strongest before age of 2
 - Inadequacy of immune system to reject genetic material
 - Increased plasticity
 - Increased vulnerability of epigenome during developmental period

MILK KINSHIP AND EPIGENETICS

- Stem Cells – MaSC (Mammary Stem Cell)
- Ingests **thousands to millions** with each feeding
- Can turn into many types of cells - bone, fat, liver, insulin
- Stem cells gradually get methylated (turning off parts) until they are very specific – become one type of cell

• What Does Epigenetics Have to Do With Attachment?

MOLECULES OF EMOTION

- Neuropeptides
- Thoughts language of brain, feels language of body
- The Emotional Quotient
 - EQ
- Lifelong happiness and health
 - Develop relationships

The Visual MD

ENTRAINMENT/SYNCHRONICITY

Care
Love
Appreciation

Stress
Anger
Frustration
Anxiety

MOLECULES OF EMOTION

- The Placenta
- Acts as a brain
- Produces Serotonin
- Affects mood, sleep, cognition and develops pancreas, heart and brain (O'Donnell, 2009)
 - Organs we associate with emotions
- Development of hindbrain, emotional brain (Tryptophan)
- Produces enzyme to break down cortisol (Mairesse, 2007)

BABIES HAVE AN EMOTIONAL LIFE

PRENATAL BRAIN AND STRESS

- Prenatal stress reduces proteins needed for synaptogenesis
- Altered expression in hippocampus (depression and anxiety)
- Increased fear response

Bogoch, 2007

MOMS BRAINS CHANGE, TOO

Kim et al., 2010;
Bartles, 2004;
Barrett, 2012;
Bauman, 2004

IT LOOKS LIKE FALLING IN LOVE

AMYGDALA RESPONSE

THE MOTHER'S NOSE

- Smell of the baby creates actual "addiction" to the baby
- Scent of baby activate caudal nucleus
 - Neural reward circuit
- Makes mothers desire to be near their babies

Lundstrom, et al
2013

THE EYES HAVE IT

- Oxytocin and Dilation



DETACHMENT

HORMONES OF PREGNANCY

- Hormones of Pregnancy
- Oxytocin
 - Bonding
 - Increase in olfactory response
- Increase in spatial memory

OXYTOCIN EXERCISE

HORMONES OF PREGNANCY

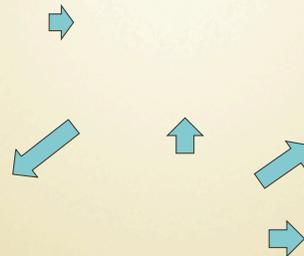
- Hormones of Pregnancy
- Progesterone and Estrogen
 - Hormones brain development-
increase maternal behavior
- Prolactin
 - Increases ability to deal with
stress (Wartella)
- Vasopressin

LET'S GET BACK TO THE PRENATAL ENVIRONMENT

EPIGENETICS AND STRESS

- Scientific Data
 - Telomeres -telomerase
 - Baboon studies
 - (Sapolsky)

STRESS



SUSTAINED STRESS IN FETUS

- Children of the 90's Study – ADHD, behavioral problems
- World Trade Center (Behrman 2006) – shorter gestation
- Flu Pandemic 1918 (Almond) - 15% less like to grad. High school, 15% more likely to be poor, 20% more likely to have heart disease
- Hongerwinter study - hippocampus
- Arab-Israeli War 1967 - schizophrenia
- China's Great Leap Forward – schizophrenia

STRESS AND PREGNANCY

- What we know about stress
 - Increases ego “me centered” behavior
 - Inability to feel gratitude, joy
 - Body holds on to fat cells, even in baby
 - Indian babies study

EPIGENOMIC INHERITANCE

- Human research - influence beyond three generations – HongerWinter winter 1944-spring 1945
 - 30% nutrition
 - Early pregnancy or late pregnancy
 - Specific epigenetic tags for diabetes

HONGER WINTER AND MOOD DISORDERS

- Schizophrenia
- Depression
- Mood Disorders

POTENTIAL BRAIN CHANGES IN BABIES DUE TO PRENATAL STRESS

- Prenatal Stress
 - Impairs HPA Axis (Hypothalamic/Pituitary/Adrenal)
 - Decrease Social Interaction
 - Anxiety
 - Learning Impairments

(Weinstock, 2014)

BRAIN CHANGES IN BABIES DUE TO PRENATAL STRESS

- Postpartum Fostering
 - Repair HPA Axis
 - Decrease Anxiety
 - **No Change Learning Deficit**
 - **No Change in Socialization**

THE BEHAVIOR OF BREASTFEEDING

- Poor nurturing = Methylation of the estrogen receptor (ER) alpha gene = future poor maternal behavior. (Champagne)
- Estrogen gene is implicated in oxytocin - key to attachment, maternal behavior and MOOD stability!!!! **Unhealthy**

Weaver and Champagne)

ULTIMATELY HUMAN MILK IS IMPORTANT

- Share Milk Systems
- Improving donations to Donor Milk sites
- Improving access to human milk for those in need.
- Wet nursing???

FUTURE GENERATIONS ARE COUNTING ON US THANK YOU, LATCH!

Questions, handouts, resources:
info@motherjourney.com
www.motherjourney.com
www.theattachmentpregnancy.com