Epigenetics: How Nutrients Affect Gene Expression.

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Evolution of Nutritional Medicine

- The “Naturalistic Era” (400 B.C.-1750 AD), Hippocrates hypothesized about the body’s “innate heat” and coined his famous phrase “Let food be your medicine and medicine be your food.”

- The late 1700’s ushered in the “Chemical-Analytical Era” (1750-1900) highlighted by Lavoisier’s calorimetry studies and how food is metabolized by oxidation to carbon dioxide, water and heat.

- The “Biological Era” (1900-present) was founded on advances in chemistry, biochemistry and understanding of the metabolic pathways. Once understanding of macronutrients was developed and better tools developed, nutrition scientists turned attention to the understanding of micronutrients, mineral and vitamin nutrition.

- The “Cellular Era” of the late 20th century (after 1955) focused on understanding functions of essential nutrients and the roles of micronutrients (vitamins and minerals) as cofactors for enzymes and hormones and their subsequent roles in metabolic pathways.

- The coming era of “Molecular and Cellular” is developing in the 21st century. It has been spurred on by the sequencing of the human genome, but is not yet ready for application. Here is a glimpse of the future of nutritional science and personalized medicine.
Nutrient-Gene Interaction and Nutrigenomics

- Nutrigenomics corresponds to the use of biochemistry, physiology, nutrition, genomics, proteomics, metabolomics, transcriptomics, and epigenomics to seek and explain the existing reciprocal interactions between genes and nutrients at a molecular level.

- The discovery of gene-nutrient interactions will aid the prescription of customized diets according to each individual's genotype.

- In the future, it may be possible to reduce the symptoms of existing diseases or to prevent future illnesses, especially for the common chronic diseases of aging and possibly the aging process itself.
Brain Health: The New Frontier

- Brain health in aging, autism, eating disorders, Alzheimer’s disease, schizophrenia, Parkinson’s disease and brain tumors are related to individual variability in numerous protein-coding and non-coding regions of the genome.
- However, genotype does not necessarily determine neurological phenotype because the epigenome modulates gene expression in response to endogenous and exogenous regulators, throughout the life-cycle.
- Studies using both genome-wide analysis of multiple genes and comprehensive analysis of specific genes are providing new insights into genetic and epigenetic mechanisms underlying nutrition and neuroscience.
NUTRITIONAL FACTORS
Dietary pattern e.g. Mediterranean / Western Specific foods • Phytochemicals • Alcohol Macronutrients • Micronutrients Methyl donors - methionine, choline, folate Energy status - energy intake, physical activity

Recent Advances in Genomic & Epigenomic Technologies
Non-coding RNAs: e.g. microRNAs, long non-coding RNAs

Novel Approaches to Nutrition, Epigenetics & Neuroscience
Gene x Environment: e.g. serotonin, genetics & epigenetics

INSIGHTS INTO NUTRITION & BRAIN DISORDERS
Mental health & well-being • Cognitive function • Memory Autistic spectrum disorders • Depression • Eating disorders Schizophrenia • Bipolar disorder • Alzheimer's disease Parkinson's disease • Brain tumours
Many chronic nutrition related diseases originate from metabolic imbalance.

Oxidative stress

Inflammatory stress

metabolic stress

What is happening here? Can we identify, quantify and modulate these processes?
Single nucleotide polymorphisms (SNPs) are variations in the coding of a DNA sequence that occur as a result of a single nucleotide change. They are the most frequent type of genetic variation, with about 10 million identified in the human genome.
Chart reflecting the course of hereditary hemochromatosis. This graph depicts the clinical course of iron overload due to hereditary hemochromatosis. The Y axis reflects increasing amounts of iron concentration in the body and the X axis reflects increasing age in years from birth to age 60. The diagonal line shows that as a person’s iron concentration increases over time, the effects of iron on the body are initially seen as non-specific symptoms, followed by more serious signs of organ damage, bronze diabetes, and ultimately early death.

Slope depends on individual.
After two decades of intensive research, the genetic complexity of hereditary hemochromatosis is still unfolding. The majority of hereditary hemochromatosis cases are due to C282Y homozygosity. The C282Y mutation, caused by a guanine to adenine transition at nucleotide 845 (TGC—TAC), results in the substitution of cysteine (C) by tyrosine (Y) at amino acid position 282 in the HFE protein product. The C282Y mutation alters HFE protein structure, disrupting its transport to and presentation on the cell surface.
Glutathione S-Transferases - Genetics

- Deletion polymorphisms in $GSTM1$ and $GSTT1$ abolish isozyme activity
- In Caucasians, $GSTM1$ absent in 50-60% and $GSTT1$ absent in 10-20%
- In Chinese, $GSTM1$ and $GSTT1$ both absent in 50-60%
- $GSTM1$ and $GSTT1$ null genotypes alone confers at best a modest increased risk of certain cancers
Brassica Vegetables Increase Serum GST-\(\alpha\) Among \(GSTM1\)-null Individuals

Adjusted LS-means ± SE
Genetics of Body-Weight Regulation

New Discoveries in Obesity Research
Using RNA interference (RNAi)

Well-Adapted to Starvation and Fighting Infection: Poorly Adapted to Overnutrition and Excess Inflammation

Evolution of Man

1900

2002

?

With Apologies to Stephen Jay Gould
Nutrients (dietary signals) → Signalling through sensor mechanisms → Genes (normal genotype) → Normal phenotype → Homeostasis

Nutrients (dietary signals) → Signalling through sensor mechanisms → Genes (sensitive genotype) → Sensitive phenotype → Onset of disease

‘Hit 1’ Metabolic stress

‘Hit 2’ Proinflammatory stress

‘Healthy’ signatures

‘Stress’ signatures
Nutrients (fatty acids) → Gene expression → Biomarkers → Lipidomics → Proteomics
Methyl Donors Affect Gene Expression

- Folate, vitamin B-12, methionine, choline, and betaine can affect DNA methylation and histone methylation through altering 1-carbon metabolism.
- Two metabolites of 1-carbon metabolism can affect methylation of DNA and histones: S-adenosylmethionine (AdoMet)\(^5\), which is a methyl donor for methylation reactions, and S-adenosylhomocysteine (AdoHcy), which is a product inhibitor of methyltransferases.
- Any nutrient, bioactive component, or condition that can affect AdoMet or AdoHcy levels in the tissue can alter the methylation of DNA and histones.
DNA Methyltransferase (Dnmt’s)

- DNA methylation, which modifies a cytosine base at the CpG dinucleotide residues with methyl groups, is catalyzed by Dnmt and regulates gene expression patterns by altering chromatin structures.
- Currently, 5 different Dnmt are known: Dnmt1, Dnmt2, Dnmt 3a, Dnmt3b and DnmtL.
- By affecting these Dnmt during our lifetime, nutrients and bioactive food components can change global DNA methylation, which is associated with chromosomal integrity, as well as gene-specific promoter DNA methylation, which is closely associated with gene expression.
Bioactive Food Components in the DNA Methylation Process

- **Nutrients**
- **SAM**
- **SAH**
- **CpG**
- **Me-CpG**
- **DNA Methyltransferase**
- **DNA Demethylation**
- **Nutrients?**
- **Aging, Disease**
Epigenetic Mechanisms

Epigenetic mechanisms are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histones are proteins around which DNA can wind for compaction and gene regulation.

Health endpoints
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

Histone modification
The binding of epigenetic factors to histone “tails” alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.
Maternal Supplements with zinc methionine betaine choline, folate B_{12}

High risk cancer, diabetes, obesity & reduced lifespan

Lower risk of cancer, diabetes, obesity and prolonged life

Cooney J Nutr 2002;132:2393S-2400S.
Other Bioactives

- Genistein from soy and green tea catechins affect DNA methyltransferases.
- Resveratrol, butyrate, sulforaphane, and diallyl sulfide inhibit Histone Deacetylase (HDAC).
- Curcumin inhibits histone acetyltransferases (HAT).
- Altered enzyme activity by these compounds may affect physiologic and pathologic processes during our lifetime by altering gene expression without changing base sequences.
Early Nutrition Programming Reduces Disease Risk

- Barker Hypothesis: “Responsiveness to their mother’s condition before birth may condition individuals so they are best suited to the environment forecast by cues available early in life”

In Utero  Neonatal Life  Adult  Aging
Match → Match → Match → Match
Match → Mismatch → Chronic Disease
Honeybee Epigenetics

• In honeybee colonies, whether an individual becomes a queen or a worker depends not on genotype but on its diet during development.

• Female honeybee larvae develop into either a queen or worker phenotype, and determination of phenotype is due entirely to dietary-induced DNA methylation by royal jelly.

• This mixture of proteins, sugars and fatty acids, including 10-hydroxydecanoic acid and phenyl butyrate, reduces DNA methyltransferase 3 expression, leading to altered DNA methylation patterns that induce the queen bee phenotype.
Dr. Kilmer McCully, Dislocated Lenses, and Atherosclerosis
Folic Acid

Nucleotide biosynthesis

5,10-methylene-tetrahydrofolate reductase (MTHFR)

5,10-methylene-tetrahydrofolate

5-methyl-tetrahydrofolate

Homocysteine

Cystathionine synthese plus vitamin B₆

Cystathionine

S-adenosyl-homocysteine

Methionine

Methionine synthase plus vitamin B₁₂, MSR

Methyltransferases

S-adenosyl-methionine

Methylated DNA, proteins, lipids

DNA, proteins, lipids

Folic acid receptors
NATURE MAKES A CHOICE

Chronic Diseases vs. Reproduction
Susceptibility to cardiovascular disease

MTHFR 677 TT polymorphism, along with folate and vitamin B12 deficiency, elevates the level of homocysteine, which is an independent risk factor for cardiovascular diseases.

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<tr>
<td>Value</td>
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Enzyme activity (in per cent)

Risk Genotype (TT)
- ▲ Absent
- ▲ Present

Populations with MTHFR 677 TT genotype may be selectively targeted for folate and/or vitamin B12 supplementation.

Source: The Institute of Genomics and Integrative Biology, Delhi
Mortality increases markedly at Homocysteine greater than 15 umol/liter
The Omics of Nutrition

Bioactive Food Components

- Nutrigenetics
  - Nutritional Epigenomics
  - Nutritional Transcriptomics
  - Proteomics
  - Metabolomics

- DNA
- RNA
- Protein
- Metabolite
Proteomics Technologies

Critical to Understanding the Physiological Effects of Bioactive Food Components Captures information about:

1. Gene expression patterns
2. Post-translational modifications
3. Cross-talk within and across cells.
• New Analytical Skills for Nutritional Status/Metabolomics

• Utilize implantable biosensors to:
  • Monitor response to nutritional intervention within cell

• Use imaging technologies to identify response in whole body or single cells
Interrelations between Functional Foods, Nutrigenomics and Human genotypes.
Response

Nutritional

Supranutritional

Exposure

Typical Intakes

Immune Enhancement

Cell Cycle Inhibition Apoptosis

Carcinogen Metabolism

Anti-oxidant

Toxicity

THANK YOU!!!!

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