Nutrition in Health and Disease course

15 hours, 1 credit.

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Nutritional Genomics and Epigenetics: Diet, Gene Regulation, Health, and Chronic Disease

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I. Foundational Definitions and The Non-Genetic Code

A. The Epigenetic Code

The human genome contains critical information that is not fully described by the DNA sequence alone. This is known as epigenetic information (from the Greek, meaning “on” or “over”).

1. **Epigenetics:** Epigenetics is defined as any changes in our DNA that impact gene expression and regulation. Epigenetics refers to a collection of mechanisms that define the phenotype of a cell without affecting the genotype (the DNA sequence). This information fundamentally affects the way in which the sequence information in DNA is used.
2. **Health Importance:** The epigenetic signal is essential to the identity and the healthy functioning of cells. Epigenetic change has been implicated in a wide range of health outcomes, including cancer, cognition, cardiovascular disease, diabetes, and reproductive function.
3. **Heritability:** A key characteristic is that the epigenetic signal is heritable and can be passed from a somatic cell to its daughter cell during mitosis (Somatic cell division), and even across generations during meiosis (Gamete formation).

B. Nutritional Genomics (Nutrigenomics)

Nutritional genomics (or nutrigenomics) is the field describing genomic studies that relate nutritional factors to the regulation of genes that influence cellular processes genome-wide. This field includes all genetic factors, including epigenetic events, as they modulate individual genes and gene networks.

- **Phenotypic Expression:** The phenotypes of health or disease are manifestations of gene expression. Nutritional science focuses on how dietary conditions produce changes that define this phenotypic expression.

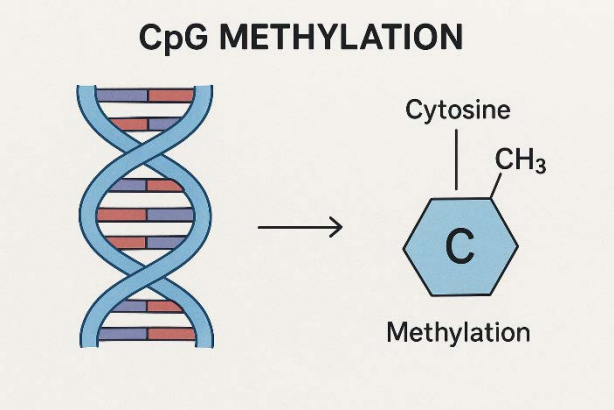
II. Molecular Mechanisms Linking Diet to Disease Risk

Epigenetic regulation is critical because it controls the accessibility of genetic information to the cell's transcriptional machinery. Nutrition directly influences these mechanisms by altering the availability of molecular substrates.

A. DNA Methylation (The Primary Nutritional Target)

DNA methylation [1]is the most widely studied epigenetic mechanism in relation to nutrition.

1. **Mechanism:** Methylation in mammalian cells occurs at a CpG site (a cytosine located to a 5' guanosine).
2. **Control of Transcription:** When CpG sequences located in gene promoters are methylated, the affinity of the transcription factor (TF) for the target gene is altered, substantially altering the transcription rate.
3. **Methyl Donor Pathway:** The ultimate methyl donor for epigenetic methylation reactions is the metabolite S-adenosylmethionine (SA), which is derived from the folate-methylation cycle.



B. Nutritional Substrates that Influence Epigenetic Status

Nutritional and genetic factors that affect the folate-methylation cycle also influence epigenetic marking:

- **Folate and Vitamins:** Poor folate status and elevated homocysteine have been linked to human lymphocyte hypomethylation (decreased overall methylation). Mutation in the methylenetetrahydrofolate gene, which is involved in providing methyl groups, interacts with folate status to influence methylation.
- **Alcohol:** Alcohol is known to interact with methyl group metabolism, leading to altered methylation in animal models and measurable variation in humans.
- **Phytochemicals:** Compounds like sulforaphane (from cruciferous vegetables) inhibit histone deacetylase, an enzyme involved in histone modification. Polyphenols (green tea, coffee, soybeans) are thought to influence epigenetic status by having a direct effect on the methyltransferases (enzymes that add methyl groups to DNA).

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[1] Methylation is the process of adding a methyl group (−*CH3* to a molecule, such as DNA, proteins, or other compounds, which can change the molecule's activity.

III. Epigenetic Change in Chronic Disease

Epigenetic factors are of high interest to investigators because they are implicated in the origin of human disease.

A. Cancer and Genomic Instability

Historically, cancer is the disease in which epigenetics has been studied most extensively.

- **Common Observations:** A common finding in human tumors is epigenetic change, including altered methylation of DNA and associated histones.
- **Hypomethylation:** Hypomethylation in tumor cells is considered an early trigger that predisposes cells to genomic instability.
- **Imprinted Genes and Cancer:** Imprinted genes (genes marked specifically by the parent of origin, important in cell proliferation) are known tumor suppressors. Loss of imprinting (disrupted allele-specific gene expression) is a common characteristic of many cancer types, including breast, lung, colon, liver, and ovary.
- **Predictive Biomarkers:** Methylation changes of specific genes, such as the breast cancer 1, early onset gene (BRCA1), have been detected not only in tumor cells but also in the peripheral blood and buccal cells of women with the disease or at increased risk.

B. Cardiovascular Disease and Neurological Function

Epigenetic mechanisms are involved in the pathology of major non-communicable diseases:

- **Vascular Disease:** Patients with vascular disease have significantly altered DNA methylation compared with healthy controls. Studies in atherogenic mouse models suggest that altered methylation can precede the development of atherosclerosis.
- **Neurological Health:** Epigenetic mechanisms are implicated in Alzheimer disease, mental impairment, and normal cognitive function.

C. Genomic Imprinting and Developmental Syndromes

Genomic imprinting is critical for normal function. Imprinting syndromes, where the epigenetic mark is disrupted or absent, are associated with serious health outcomes including diabetes, cancer risk, obesity, and impaired cognitive development.

IV. Windows of Nutritional Sensitivity and Disease Risk

The epigenotype is plastic and can be modified by diet and lifestyle throughout the life span. However, specific periods of development are particularly sensitive to nutritional exposure.

A. Critical Prenatal Exposure

Epigenetic regulation is central to the coordinated development of human gametes, the early embryo, and the fetus, with the entire period before birth marked by intense epigenetic activity.

- **Folate and IGF-2:** Studies in pregnant humans have shown that mothers who took folic acid supplements during pregnancy had babies with higher methylation levels of the insulin-like growth factor-II gene IGF-2 in umbilical cord DNA. IGF-2 methylation is related to birth weight, which is itself related to the later risk of cardiovascular disease, diabetes, obesity, and cancer.
- **Famine and Long-Term Risk:** Altered IGF-2 methylation was observed in women 60 years after their prenatal exposure to famine during the Dutch Hunger Winter[2], suggesting that nutritional changes during this sensitive window can be retained for decades and are associated with increased **breast cancer risk**.

B. Clinical Relevance

- **Prediction and Biomarkers:** Epigenetic status in accessible cells (like peripheral blood or buccal cell DNA) may be useful as a predictive biomarker of disease. For this to be useful, the epigenetic status in these peripheral cells must be indicative of key epigenetic events occurring in the critical tissues and organs (liver, pancreas, heart, brain).
- **Intervention Potential:** Unlike the genotype, which is fixed, the epigenotype is plastic. This plasticity means that epigenetic changes linked to disease can be modifiable by diet and lifestyle. A better understanding of the epigenetic links between nutrition and disease is crucial for developing dietary strategies to reduce the risk of chronic disease.

End of module 2

[2] Dutch Hunger Winter: a period of famine that occurred in the Netherlands during 1944 and 1945