DNA methylation and Epigenetics:

Nutrition and the availability of methyl donors
Epigenetics definitions

Epigenetics involves genetic control by factors other than the DNA sequence\(^1\). The epigenome is made up of chemical compounds and proteins which attach to DNA and direct actions such as turning genes on and off\(^2\). When epigenomic compounds attach to DNA and modify its function, they are said to have ‘marked’ the genome\(^2\).

DNA methylation and histone acetylation/deacetylation are two important epigenetic mechanisms that lead to changes in gene expression\(^1\).

**Nutritional epigenetics**: Nutrient-induced change in epigenetic patterns that can alter gene expression and hence, long term health outcomes\(^3\).

DNA methylation and histone modification: two important epigenetic mechanisms

**Histone modifications:** histone acetylation/de-acetylation affects chromatin structure. Chromatin needs to be open for gene transcription to take place.
- **Closed chromatin** – transcription is impeded
- **Open chromatin** – transcription is possible

**DNA methylation**
Methyl group added to DNA through action of DNA methyltransferase (DNMT) enzymes

What is DNA methylation?

• DNA methylation is the addition of a methyl group to DNA in a reaction catalyzed by DNMTs.
• Methyl groups are donated for these reactions by S-adenosylmethionine (SAMe).
• DNA methylation usually silences a gene – acting as an off-switch.

DNA methylation: good or bad?

• In certain areas of the genome e.g. transposable elements, DNA methylation (silencing of the gene) is important to prevent genome instability associated with the expression of these elements.
• However, DNA methylation of other areas of the genome, such as tumor suppressor genes, may be associated with negative health outcomes.
Histone modification: another form of gene expression regulation

Histone de-acetylation leads to stronger interaction between histone and DNA. This results in closed chromatin structure that limits the access of transcription machinery to DNA and hence, inhibition of gene expression. Histone acetylation has the opposite effects.

DNA methylation across the life-span

• *In utero* development is a critical phase in the establishment of DNA methylation patterns. These epigenetic modifications have lifelong impact on health and risk of disease. Establishment of DNA methylation patterns *in utero* is known as imprinting$^1$.

• DNA methylation continues throughout an individual’s life and interesting age-related epigenetic drift has been described. This epigenetic drift is characterized by loss of DNA methylation in some parts of the genome (hypo-methylation) accompanied by gain of DNA methylation (hyper-methylation) in other parts of the genome, e.g. tumor suppressor genes. DNA methylation has been used to predict chronological age.$^{2,3,4}$

3) Bjornsson HT, Sigurdsson MI, Fallin MD et al., Epigenetic differences arise during the lifetime of monozygotic twins *JAMA*, 2008;299(24):2877-83
Altered DNA methylation patterns have been associated with some diseases

**Cancer:** Loss of imprinting, activation of normally silenced genes, methylation of tumor suppressor genes, and chromosomal instability have all been described in cancer\(^1,2,3\).

**Metabolic diseases:** Similar to aging, global hypo-methylation in combination with hyper-methylation of specific loci have been shown to be associated with cardiovascular diseases, diabetes type II, cancer and other diseases\(^4,5,6\).

**Oxidative stress:** Oxidative stress has been linked to altered DNA methylation status in healthy aging and diseases\(^7,8\).

5) Clarke-Harris R, Wilkin TJ, Hosking J et al., PGC1α promoter methylation in blood at 5-7 years predicts adiposity from 9 to 14 years (EarlyBird 50). *Diabetes*, 2014; 63(7):2528-37
Methyl donors are generated through the 1-carbon metabolism

- To generate a methyl group donor, the cell relies on 1-carbon metabolism which comprises the folate and methionine cycles.

- These cycles function interdependently and produce SAMe, the universal methyl group donor.

- 1-carbon metabolism is dependent on key nutrients intake.

1-Carbon metabolism links nutrition to DNA Methylation

Nutrients such as folate (in 5-MTHF form), vitamin B12, choline and betaine are required for homocysteine to methionine conversion and the generation of SAMe.

MTHFR is a critical enzyme in the folate cycle, and is involved in the formation of 5-MTHF.

Single nucleotide polymorphisms (SNPs) in the *MTHFR* gene are common and can influence folate pathway activity

- **The C667T mutation (rs1801133) is the most common SNP in the *MTHFR* gene, and causes an alanine to valine switch at codon 22 leading to a thermolabile enzyme and reduced MTHFR enzyme activity**¹
  - TT = 30% of expected MTHFR enzyme activity
  - CT = 65% of expected MTHFR enzyme activity

- **Individuals with T allele have lower phosphatidylcholine, suggesting a greater reliance on betaine pathway**²

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1) http://www.snpedia.com/index.php/Rs1801133
2) Veenema K, Solis C, Li R et al., Adequate Intake levels of choline are sufficient for preventing elevations in serum markers of liver dysfunction in Mexican American men but are not optimal for minimizing plasma total homocysteine increases after a methionine load. *Am J Clin Nutr*, 2008;88(3):685-92
Phytonutrients and epigenetics

In addition to nutrients involved in 1–carbon metabolism, there are many dietary ingredients with epigenetic and chromatin remodeling properties.

**Sulforaphane** (from broccoli) has been shown *in vitro* to act as a HDAC inhibitor

**EGCG** (from green tea) has been shown *in vitro* to inhibit DNMT activity and DNA demethylation

**Genistein** (from soy) has been shown to influence DNA methylation patterns *in vitro* and in human studies

**Curcumin** has been shown to inhibit DNMT activity *in vitro*

**Cocoapolyphenols** has been shown to influence DNA methylation patterns in human white blood cells

Summary and conclusions

- Epigenetic changes like DNA methylation and histone modification play an important role in the regulation of gene expression.
- Epigenetic changes can have ‘positive’ and ‘negative’ effects on health, depending on what gene has been affected. ‘Optimal’ epigenetic patterns for health have not been well defined.
- Dietary nutrients are critical for the generation of methyl group donors through 1-carbon metabolism. Maintaining adequate status of these nutrients (which may vary depending on an individual’s genetics) is important.
- Other vitamins, mineral and phytonutrients also play a role as co-factors in the generation of methyl group donors, and can also influence the activity of the enzymes catalysing DNA methylation reactions and histone modifications.
- A greater understanding of the nutritional and metabolic factors that influence epigenetic patterns will help to fully harness the power of epigenetics to influence health and prevent disease.