



COLLEGE OF INTEGRATIVE MEDICINE

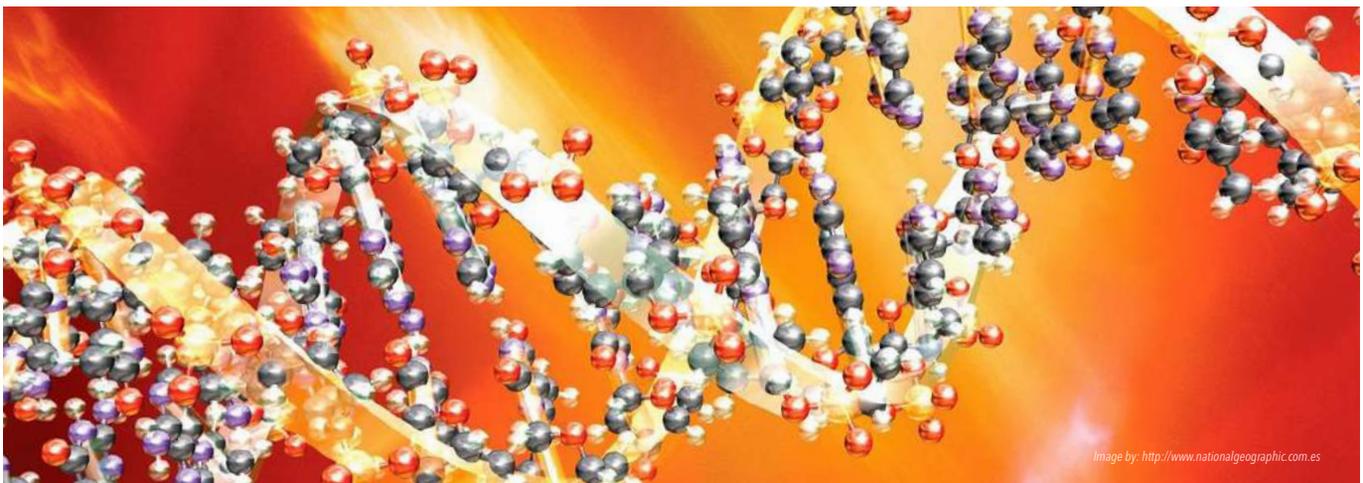
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DNA Methylation and Cancer: Is it Hypo- or Hypermethylation or Both?

(Article adapted from College of Integrative Medicine Module 25 CIHP2504 Integrative Oncology)

Dr. Wayne Sodano DC, DABCI, DACBN, CFMP, BCTN

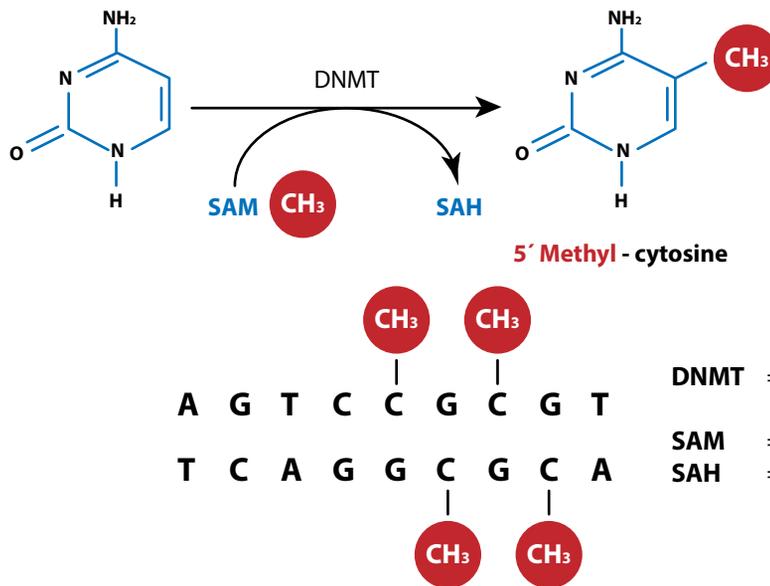


"Epigenetics can be defined as somatically heritable states of gene expression resulting from changes in chromatin structure without alteration in the DNA sequence, including DNA methylation, histone modification, and chromatin remodeling."ⁱ "DNA methylation is probably the most widely studied epigenetic mechanism in relation to nutrition. Methylation in mammalian cells takes place at a cytosine located 5' to a guanosine (i.e. CpG site)ⁱⁱ (DNA methylation is the covalent addition of a methyl group to the carbon-5 position of the cytosine bases adjacent to guanine bases (i.e. CpG dinucleotide) (see figure 1). "More than half of human genes initiate transcription from the genome with an elevated content of CpG dinucleotides and G+C base pairs referred to as 'CpG island' or 'CG island'. In contrast to the rest of the genome, where CpG dinucleotides are heavily methylated and so rapidly lost through deamination, CpG sites within promoter CpG islands are normally free from methylation and do not have an elevated mutation rate."ⁱⁱⁱ "The distribution of methylated and nonmethylated CpG dinucleotides is not random; rather it conforms to a pattern. Certain genomic sites, such as pericentromeric regions, imprinted regions, and genes on the inactive X chromosome in females, are hypermethylated, whereas other sites, such as CpG islands, which are often associated with gene promoter regions, are hypomethylated."^{iv}

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DNMT = DNA Methyltransferase
(Maintenance of DNA methylation).

SAM = S - Adenosmethionine

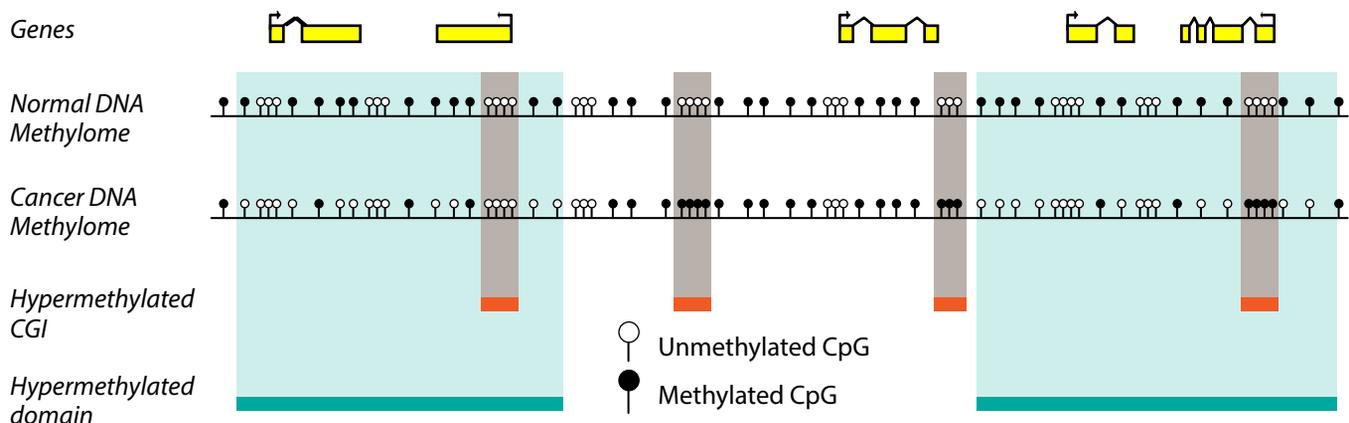
SAH = S - Adenosylhomocysteine

"A common observation in human tumors is epigenetic change, including altered methylation of DNA and the histones associated with DNA. Hypomethylation in tumor cells is thought to be an early trigger that predisposes cells to genomic instability and hypermethylation of specific genes thought to be involved in carcinogenesis and disease progression."^v "Certain imprinted genes are known tumor suppressors involved in cell proliferation. (An individual normally has one active copy of an imprinted gene. Improper imprinting can result in an individual having two

active copies or two inactive copies. This can lead to severe developmental abnormalities, cancer, and other problems.) Loss of imprinting (gain or loss of DNA methylation or loss of allele-specific gene expression) is also a common characteristic of many cancer types, including breast, lung, colon, liver, and ovary. Imprinting syndromes, in which the imprint is disrupted or absent, are associated with diabetes and cancer risk, in addition to impairment of normal function that leads to obesity and impaired cognitive development."^{vi}

Reprogramming of DNA Methylation Patterns in Cancer^{vii}

Cancer Pattern: The red bars indicate hypermethylation of the CpG islands and blue bars indicate global hypomethylation.



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Reprogramming of DNA methylation patterns in cancer. Frequently observed changes to the DNA methylome in cancer are depicted for a portion of a hypothetical genome. CpG dinucleotides are depicted as open (unmethylated cytosine) or filled (5-methylcytosine). In healthy somatic cells ("Normal DNA methylome") the background level of CpG methylation throughout the bulk genome is high, while CGIs (CpG islands) are infrequently methylated. In cancer, CGIs frequently become hypermethylated (red bars and boxes), and CpG methylation is reduced across large genomic domains (blue bars and boxes). Focal CGI hypermethylation frequently occurs within larger hypomethylated domains. Only unmethylated and 5-methylcytosine are shown for simplicity. ^{viii}

Cancer exhibits at least 2 types of methylation defects; hypomethylation, characterized by a global loss of methylation, and hypermethylation of CpG islands (cytosine-phosphate-guanosine) of regulatory regions of tumor suppressor genes.^{ix} [The CG island is a short stretch of DNA in which the frequency of CG sequence is higher than other regions. It is also called the CpG island, where 'p' indicates that C and G are connected by a phosphate bond. CpG islands are often located around the promoters of housekeeping genes (essential for general cell function) or other genes frequently expressed in a cell.] At these locations (i.e. the CG islands), the CG sequence is not methylated. By contrast, the CG sequences in inactive genes are usually methylated to suppress their function. Global hypomethylation and hypermethylation of CpG islands appear to independent processes.

"Global hypomethylation is believed to induce proto-oncogene activation and chromosomal instability, whereas regional (i.e. the CpG islands) hypermethylation is strongly associated with transcriptional silencing of tumor suppressor genes."^x "The first identified (early sign) change in DNA methylation in cancer appears to be genome-wide hypomethylation."^{xi} Genes involved in regulation of the cell cycle, DNA repair, growth signaling, angiogenesis, and apoptosis, are all known to be inactivated by hypermethylation.^{xii} The mechanism involved in the DNA methylation pattern of cancer (i.e. global hypomethylation and CpG island hypermethylation) appear to involve several participating factors such as the gene microenvironment (e.g. SNPs - especially methylation -

MTHFR), cellular and host factors (e.g. aging, inflammation and diet), and baseline genetic expression.^{xiii} DNA methylation seems to be promising in putative translational use in patients and hypermethylated promoters may serve as biomarkers.

"Several studies suggest a correlation between chronic inflammation and accelerated DNA hypermethylation (at the CpG islands). Ulcerative colitis is a condition associated with a marked increased risk of colon cancer. Issa et al. found markedly increased methylation of four genes in dysplastic epithelium form with high-grade dysplasia, compared to non-UC controls. This suggests that chronic inflammation is associated with high levels of methylation, perhaps as a result of increased cell turnover, and that inflammation bowel disease can be viewed as akin to premature aging of colorectal epithelia cells. Association between chronic inflammation and gene methylation has also been identified in cancers involving other organs."^{xiv}

The concept of global hypomethylation and CpG island hypermethylation as it related to cancer is a relatively new scientific discovery. It appears that the first step (early sign) in the process leading to potential cancer is hypomethylation of the background CpG DNA bond (i.e. the less frequent CpG DNA sequence or non CpG islands). This appears to lead to hypermethylation of the CpG islands that house the gene for expressing DNA repair, growth signaling, angiogenesis, and apoptosis. Once the islands become hypermethylated, they become inactive leading to increased cancer risk.

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Chronic inflammation, poor diet and lifestyle, genetic polymorphisms of methylation appear to be the suspects involved in altering DNA methylation toward the cancer promoting side. Unlike genetic alteration, DNA methylation is reversible making it an essential part of the integrative medicine evaluation for cancer prevention. Integrative medicine addresses the foundations of a healthy lifestyle/diet, focuses on resolving chronic inflammation, supports detoxification, prescribes stress reduction measures, and reviews genetic tests that assess methylation; invaluable tools that can lead to a reduced incidence of cancer. Most integrative medicine clinicians are trained in assessing these vital areas of patient care and I advocate that all individuals schedule a wellness appointment with such a clinician.

- i Choi S, Friso S. *Epigenetics: a New Bridge between Nutrition and Health*. *Adv Nutr*. 2010; 1: 8-16.
- ii Haggarty P. *Epigenetics*. In: Ross AC, caballero B, Cousins RJ, Tucker KL, Ziegler TR. *Modern Nutrition in Health and Disease*. 11th Ed. Baltimore: Lippincott Williams & Wilkins; 2014. p. 534.
- iii Vavouri T, Lehner B. *Human genes with CpG island promoter have a distinct transcription - associated chromatin organization*. *Genome Biology*. 2012; 13: R110.
- iv Daniel FI, Cherubini K, Yurgel LS, Zancanaro de Figueiredo, Salum FG. *The role of epigenetic transcription repression and DNA methyltransferases in cancer*. *Cancer*. 2011; 117: 677-87.
- v Haggarty P. *Epigenetics*. In: Ross AC, caballero B, Cousins RJ, Tucker KL, Ziegler TR. *Modern Nutrition in Health and Disease*. 11th Ed. Baltimore: Lippincott Williams & Wilkins; 2014. p. 535.
- vi *Ibid.*
- vii Reddington JP, Sproul D, Meehan RR. *DNA methylation reprogramming in cancer: Does it act by re-configuring the binding landscape of Polycomb repressive complexes? Bioassays Insights and Perspectives*. 2013; 36: 134-140.
- viii *Ibid.*
- ix Haggarty P. *Epigenetics*. In: Ross AC, caballero B, Cousins RJ, Tucker KL, Ziegler TR. *Modern Nutrition in Health and Disease*. 11th Ed. Baltimore: Lippincott Williams & Wilkins; 2014. p. 535.
- x Suzuki H, Tpyota M, Sato H, sonoda T, Sakauchi F, Mori M. *Roles and Causes of abnormal DNA Methylation in Gastrointestinal Cancers*. *Asian Pacific Journal of Cancer Prevention*. 2006; 7: 177-185.
- xi *Ibid.*
- xii *Ibid.*
- xiii Estecio MRH, Issa JPJ. *Dissecting DNA hypermethylation in cancer*. *FEBS Lett*. 2011 July 7; 585(13): 2078-2086.
- xiv Suzuki H, Tpyota M, Sato H, sonoda T, Sakauchi F, Mori M. *Roles and Causes of abnormal DNA Methylation in Gastrointestinal Cancers*. *Asian Pacific Journal of Cancer Prevention*. 2006; 7: 177-185.



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