DNA methylation in relation to aging, cancer and dietary factors

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DNA methylation refers to the enzymatic addition of methyl groups to DNA. It occurs by covalent transfer of a methyl group from S-adenosyl methionine to cytosine (at the 5'-position) residues in the dinucleotide sequence CpG. This can be seen in a fairly large percentage of CpG dinucleotide sequences.

Landscape of Epigenetics

DNA methylation lies in the landscape of epigenetics. As opposed to the term genome, epigenome consists of DNA-associated proteins, and the patterns of DNA methylation. The extent of DNA methylation correlates with the extent of gene inactivation. Epigenetic studies encompass all those aspects that bring about a change in gene function due to DNA methylation, and due to modifications in proteins intimately associated with DNA. In recent years such studies have thrown light on the mysteries surrounding aging and cancer, which are related to the aberration in control of gene action. Histone deacetylation and chromatin remodeling, RNA inhibition, RNA modification, and DNA rearrangement also lie within the purview of epigenetic mechanisms.

Environmental factors and DNA methylation

Some environmental factors that affect DNA methylation include diet, proteins, drugs, and hormones. Epigenetic DNA modifications provide genomic plasticity and short-term adaptation of each generation to their environment. Induced methylation changes produce altered gene response upon subsequent hormonal stimulation. The gene-specific DNA methylation state may be maintained by transmission through mitosis and meiosis. In certain type of cancer, different kinds of alterations in DNA methylation patterns are observed. These include: (1) global hypomethylation, and (2) regional hypermethylation. Regional hypermethylation occurs by specific regional changes in chromatin structure, whereas global demethylation is caused by a general increase in demethylation activity. In cancer cells there is also a deregulated level of expression of DNA methyltransferases.

Hypermethylation and hypomethylation

Hypermethylation silences growth regulatory genes so that there may not be uncontrolled growth whereas hypomethylation leads to activation of genes required for metastasis. Aberrant DNA hypermethylation in gene promoter regions leads to gene silencing, whereas global hypomethylation events result in chromosomal instability and oncogene activation. DNA hypomethylation can increase gene expression, particularly when occurring in the promoter region CpG sites. Hypomethylation may result from DNA excision repair. DNA hypomethylation in pericentromeric satellite regions of the chromosome is known to result in centromeric decondensation and enhanced chromosomal recombination in precancerous conditions and hepatocellular carcinomas. During the development and progression of malignant neoplasia, a global hypomethylation is often accompanied by a locus-specific hypermethylation.

Dietary factors and DNA methylation

Recent studies have also revealed that dietary factors can modulate DNA methylation, and thereby play a role in aging and tumorigenesis. Thus, it may not be unreasonable to suppose that DNA methylation serves as an important common link between aging, cancer, and nutrition. Certain pharmacologic agents are known to induce DNA hypomethylation or inhibit histone deacetylation. These agents can modify epigenetic events by restoring the defective expression of selected components called 'tumor recognition complex' in cancer cells.

Dichloroacetic acid (DCA), a liver carcinogen, induces DNA hypomethylation in mouse liver. Short-term exposure to arsenic has long-term effects in genome-wide DNA hypomethylation, which enhances genetic instability.

Vitamin B12 and folic acid, which act as coenzymes, also determine DNA hypomethylation. There is a possibility that sequence-specific alterations of DNA methylation in critical cancer-related genes might be due to folate deficiency. Folate plays a significant role in the prevention of chromosome breakage and hypomethylation of DNA. Deficiency of folate leads to demethylation of heterochromatin causing structural centromere defects that could induce abnormal distribution of replicated chromosomes during nuclear division. A depletion of folates, lipotropes, including methionine, choline, betaine and S-adenosylmethionine, leads to the hypomethylation of oncogenes, resulting in DNA strand breaks, and thereby increases carcinogenesis.

Selenium deprivation ameliorates some of the effects of folate deficiency, probably by shunting the buildup of homocysteine (as a result of folate deficiency) to glutathione.

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