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Micronutrient, Genome Stability and Degenerative Diseases: Nutrigenomics Concept of Disease Prevention - An Overview

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ABSTRACT

Diet is a key factor in determining genomic stability is more important than previously imagined because it impacts on all relevant pathways like exposure to dietary carcinogens, DNA repair, DNA synthesis, epigenetic damage and apoptosis. Recent research focuses into how a single micronutrient deficiency is leading to genomic instability and development of degenerative diseases in various stages of life.The study aimed at finding the nutrigenomic mechanism of how a marginal deficiency of any single micronutrient is interrupting in DNA repairing, methylation and synthesis by taking nutrient-nutrient and nutrient-gene interaction into consideration. It also focuses on how recommended dietary allowance is important in achieving DNA integrity and genome stability to prevent degenerative diseases.Exhaustive review of research papers in genome health nutrigenomicsis involved in this study to explore, assimilate and analyze data to understand the importance of micronutrient in maintaining methylation of CpG sequence and preventing DNA oxidation or uracil misincorporation in DNA to stop disease occurrence in individuals.The study finds a direct link between micronutrient deficiency and increased epigenomic damage, resulting into elevated risk for adverse health outcomes during various stages of life like infertility, tumor development and cancer. The overview study concludes with a vision for a paradigm shift in disease prevention strategy based on diagnosis and micro-nutritional intervention of genome or epigenome damage on an individual basis, i.e. personalized prevention of degenerative diseases in genome health clinic.

Key words: Nutrigenomics, DNA integrity, Epigenomic damage, Degenerative diseases.

INTRODUCTION

Fundamental cause of many degenerative diseases and lifestyle disorders like cancer, diabetes, neurological dysfunction, cardio-vascular diseases (CVDs) & Obesity is DNA damage and genomic instability.[1] Micronutrients by acting as co-factor or substrates for enzyme play an important role in protecting DNA damage, DNA repair, methylation of CpG island and lead to cell apoptosis and formation of cancer which can be explained by the mechanism of nutrient-nutrient or nutrient-gene interaction. These observations led to emergence of Nutrigenomics study in preventing degenerative diseases by maintaining genetic stability and genome integrity with optimum intake and utilization of micronutrients. The Principal cause of degenerative diseases can be managed by individual dietary intervention with exact dosage of single micronutrient or multiple micronutrients. DNA methylation[2] is one of the strongest parameters in describing the mechanism of degenerative disease occurrence. Aberrant DNA methylation has been associated with common acquired immunodeficiency, cancer, CVDs, diabetes and neurological diseases, indicating important functions of DNA methylation in these disorders.[2] Strong evidences are found to describe epigenome damage as potent biomarker

in detecting degenerative disease state of body. The Recommended Dietary Allowance (RDA) of each single micro-nutrient and their effect on genome stability has taken into account to describe the role of their deficiency in disease occurrence. Personalized dosage recommendation of 'Nutriome'[3] (Combination of Micronutrients) can prevent DNA damage and following degenerative diseases by incorporating the concept of 'Genome Health Clinic'[4] in the area of Nutritional Science.

The overview aims to discuss the importance and utilization of micronutrients in preventing degenerative diseases by maintaining genome integrity and epigenetic stability in the next following sections –

1. DNA methylation and its association with degenerative diseases.
2. Micronutrient deficiency and resulting aberrant DNA methylation by explaining nutrient-gene interaction.
3. RDA of single micronutrient and 'Nutriome' concept in disease prevention.
4. Genome health clinic and its implication in 'Nutrigenomics'.

DNA methylation and its association with degenerative diseases

DNA methylation occurs by covalent addition of a methyl group at the 5' carbon of the cytosine ring, resulting into the formation of 5-methylcytosine.[2] These methyl groups project into the groove of DNA and effectively inhibit transcription. In mammalian DNA, 5-methylcytosine is found in approximately 4% of genomic DNA, primarily at cytosine-guanine dinucleotides (CpGs)[2]. Such CpG sites are found more frequently at small stretches of DNA called CpG islands. [2]These islands are typically found in or near promoter regions of genes where transcription is initiated.[2] DNA methylation is the fundamental mechanism for the epigenetic control of gene expression and genomic integrity.[2] Aberrant DNA methylation is thus one of the most prominent causes of developing degenerative diseases in human.

The association between aberrant DNA methylation and some degenerative diseases In cancer

DNA methylation is an important regulatory factor for gene transcription, and its role in carcinogenesis has been a topic of consideration in Medical Science in the last few years. Alterations in DNA methylation are common in a variety of tumor progression. Hypermethylation of DNA represses transcription of the promoter regions of tumor suppressor genes and that leads to gene silencing, is most extensively studied in the field of cancer. Global hypomethylation has also been recognized as a cause of oncogenesis.

DNA hypermethylation and cancer

Reports of hypermethylation in cancer far outnumber the reports of hypomethylation in cancer. There are several protective mechanisms that prevent the hypermethylation of the CpG islands. [6] These include active transcription, active demethylation, replication timing, and local

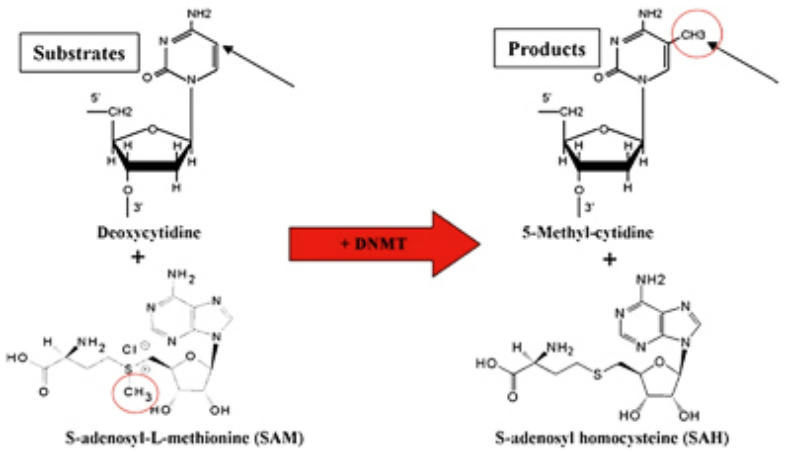

Fig. 1: DNA Methylation

chromatin structure preventing access to the DNA methyltransferase. To date, numerous genes have been found to undergo hypermethylation in cancer. The genes that are susceptible are those which are involved in cell cycle regulation ($p16^{INK4a}$, $p15^{INK4a}$, Rb, $p14^{ARF}$) genes associated with DNA repair (BRCA1, MGMT), apoptosis (DAPK, TMS1), drug resistance, detoxification, differentiation, angiogenesis and metastasis.[6]

DNA hypomethylation and cancer

Hypomethylation is the second kind of methylation that is related to tumor production and carcinogenesis. It is common in solid tumors such as metastatic hepatocellular carcinoma, in cervical cancer, prostate tumors and leukemia[7]. The pericentreheretochromatin regions on chromosomes 1 and 16 are heavily hypomethylated in patients with immunodeficiency, centromeric instability and facial abnormalities and in many cancers.[7] This chromatin instability is due to a mutation, DNMT3b which has been found in these patients. Hypomethylation also activates oncogenes such as CMYC and H-RAS.[7]

In Atherosclerosis or other Cardio-vascular diseases

DNA methylation has emerged with an important role as a distinct and crucial mechanism to regulate genes, governing cell proliferation in atherosclerosis.[9] Aberrant methylation is resulting into aging and age related plaque formation in older individuals as methylation affects large number of CpG islands.[9] In old people age-related methylation is an important contributor as it up regulates atherosclerosis susceptible genes and down regulates atherosclerosis protective genes.[9] Genome hypomethylation of bulk chromatin has been observed in aged tissues *in vivo*.[9] Age related hypomethylation is thus the contributor of cancer and CVDs.[9]

In Type 2 Diabetes

DNA methylation is a major regulator of transcriptional activity and is involved in the regulation of expression in a broad variety of genes. Differentiation of T helper cell 1 (TH1) and T helper cell 2 (TH2) and their striking differences in their pattern of cytokine expression is taken into account.[10] This sub-type specific expression pattern is maintained in Th1 and Th2 cells in the absence of stimulation by antigen or cytokines Interleukin -12 (IL-12) and Interleukin – 4 (IL-4) respectively.[10] The persistence of these expression patterns is thought to be due to epigenetic changes in chromatin structure, locus accessibility and DNA methylation.[10] So, DNA methylation can be considered as a stable

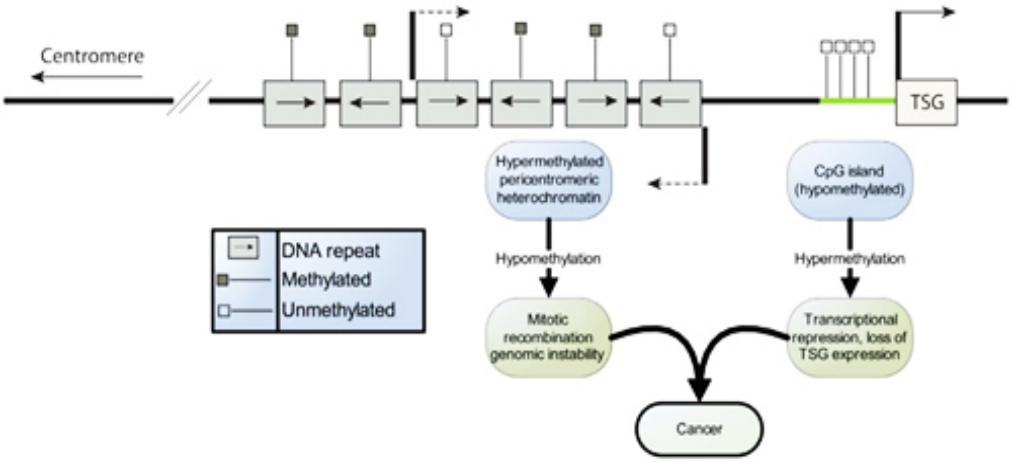

Fig. 2: This region of genomic DNA contains hypermethylated heterochromatin and an actively transcribed Tumor Suppressor Gene (TSG). A hallmark of tumor cells is the conversion of repeat rich regions from hypermethylated to hypomethylated, culminating in genomic instability resulting from increased mitotic recombination. Additionally, the CpG island located upstream of the TSG is hypomethylated, allowing for transcription. However, during oncogenesis, the CpG islands become hypermethylated, resulting in a loss of expression and a progression toward cancer.

cellular memory for the maintenance of cytosine expression patterns and T cell memory. [10]According to many scientific evidences, DNA methylation memory is involved in maintaining gene expression patterns associated with insulin resistance in type – 2 diabetes mellitus. Prenatal glucose and insulin level in mothers influences the risk of developing type – 2 diabetes later in life, independent of the maternal type of diabetes and therefore independent of genetic predisposition.[10] This indicates the presence of cellular memory in insulin target tissues such as adipose tissue, skeletal muscle and liver.[10]

On the other hand, a general defect in DNA methylation in erythrocytes of diabetic patient is due to decreased level of SAM, major donour of methyl group in methylation procedure.[10]

These two observations justify that methylation plays as important role in regulating gene expression, most likely including the expression of these genes essential for the strict maintenance of normal blood glucose level. DNA methylation profiling is one of the most important biomarkers to identify type - 2 diabetes now-a-days as the phenomena is likely to be involved in the propagation of insulin resistance in insulin receptor cells. [10]

Micro-nutrient deficiency and DNA damage

According to animal studies, it is evident that, nutrients especially vitamins and minerals are essential for maintaining genomic stability and DNA methylation process. [11] Specific nutrient-nutrient and nutrient-gene interactions are involved in maintaining chromosomal integrity and DNA function. [12] DNA damage arises from intermediates of oxygen reduction. [12] Alternatively, free radicals can attack other cellular components such as lipids to generate reactive intermediates that couple to DNA bases.[12] Endogenous DNA lesions lead to genotoxicity and mutations causing carcinogenesis and tumor promotion. [12] The increased level of reactive oxygen species is higher in the absence of anti-oxidant nutrients like Vitamin – A, Vitamin – C & Vitamin – E. Incomplete scavenging of reactive oxygen species is causing aberration of DNA and mutagenicity in long term deficiency of these micronutrients. Some studies have found that Vitamin – D deficiency is resulting to cause unstable chromosomal structure and breaking of DNA double strands. [13] Zinc, a key constituent or co-factor over 300 mammalian proteins, is specifically important in host defense against the initiation and progression of cancer. [14] Dietary deficiency of zinc leads to double strand DNA breaks and oxidative modifications to DNA that increases risk of cancer development. [14] Vitamin – B_{12} deficiency leads to less extensive incorporation of uracil and causes chromosome break. [12]

Folate deficiency affects DNA stability principally through two potential pathways namely uracil misincorporation[15] and DNA hypomethylnation[2]. Two forms of folate – 5,10-Methyleneterahydrofolate and 5 – Methylenetetrahydrofolate are involved in these two processes respectively. [2,15]

Uracil misincorporation

5,10 – Methylenetetrahydrofolate donates a methyl group to uracil, converting it to thymine, which is used for DNA synthesis and repair. If folate is limited, imbalances in the DNA precursor pool occur, and uracil may be not incorporated properly into DNA. Subsequent miscorporationleads to double strand breaks, chromosomal damage and cancer. [15]

DNA hypomethylation

Folate affects gene expression by regulating cellular S-Adenosylmethionine (SAM) levels. 5-Methyltetrahydrofolate serves as methyl donour in the remethylation of homocysteine to methionine, which then converts into SAM. SAM methylates specific cytosines in DNA, and this regulates gene transcription. As a result of folate deficiency SAM is depleted, which in turn induces DNA hypomethylation and potentially induces proto-oncogene expression leading to cancer.[2,15]

RDA of single micronutrient and 'Nutriome' concept in disease prevention

Recommended Dietary Allowance (RDA) or Dietary Reference Value (DRV) is intended to provide guidance for the appropriate intake of nutrients for prevention of diseases. RDA of single micronutrient or multiple micronutrients in combination is important to maintain the chromosomal health of individuals.[3] DNA instability related degenerative diseases are causing not because of food insecurity but because of deficiency of single micronutrient or micronutrient combination. DNA damage at

the base sequence and chromosome level is a fundamental cause of development and propagation of degenerative diseases and multiple micronutrient deficiency &their interaction with genes is powerfully established as influencing factor for causing DNA damage. In this context, to fulfill this deficiency, optimum supplementation of micronutrient is needed in preventing DNA damage and resulting degenerative diseases. 'Nutriome' is the combination of micronutrients in specific recommended value which has taken into consideration for fulfilling this deficiency in the scope of Nutrigenomics study. But the biggest challenge is to identify, formulate and establish the combination of micronutrient with proper dosage after assessing single gene-single micronutrient and whole genome-whole micronutrient interaction in individuals.[16] RDA of each micronutrient should be revised and optimum dosage should be evaluated in personalized basis to balance the internal micronutrient environment and genome integrity.

Genome health clinic and its implication in 'Nutrigenomics

Poor nutrition has been linked to cause many degenerative diseases including cancer, heart diseases and diabetes. Significant chronic metabolic disruption may occur when consumption of a micronutrient is below the RDA level. Nutrigenomic study has aimed for devising ways to personalize nutritional requirements and optimize genome stability by appropriately matching the genome with the nutriome; thus offering a setup of 'Genome health clinic' to implement the nutriome project in individuals. Genome health clinic studies development of dietary pattern, functional foods and supplements that are designed to improve genome health maintenance in individuals with specific genetic backgrounds.[4,16] It aims to achieve an optimum health strategy based on the diagnosis and individualized nutritional prevention of genome damage. Nutrigenomics within its scope of research has targeted to take up genome health clinic concept to formulate a personalized nutrition pattern with proper recommended value of single micronutrient or nutriome in preventing micronutrient deficiency related degenerative disease occurrence.

DISCUSSION

Nutrients can reverse or change epigenetic phenomena such as DNA methylation and histone modification thereby modifying the expression of critical genes associated with pathogenic processes, including embryonic development, aging, carcinogenesis and other degenerative diseases. Micronutrients and bio-active food molecules can modulate the epigenetic environment of body by the process of nutrient-gene interaction. Deficiency of single micronutrient or combination of micronutrient is exceptionally responsible in causing DNA double strand break, aberrant DNA methylation and degenerative diseases. Nutrigenomics can prevent these disease occurrences by explaining nutrient-gene interaction and designing individual specific dosage of single micronutrient or nutriome in genome health clinic.

CONCLUSION

Degenerative diseases include infertility, pregnancy complications, cancer, CVDs and diabetes. DNA damage and genome instability increase the risk of these diseases. Micronutrient deficiency in single or multiple forms contributes in causing genome instability to cause DNA damage and degenerative diseases. Nutritional genomics assesses the outcome of micronutrient deficiency in DNA damage, genome instability and chromosome disintegration. The science of nutrient-gene interaction strategically analyses and verifies DNA damage in causing degenerative diseases with a possible intervention of nutriome to prevent these diseases. An optimum personalized dosage of single micronutrient or nutriome can be prepared with revised RDA value to protect individuals from aberrant DNA methylation and related degenerative diseases in genome health clinic. This step can further develop a 'Public health nutrigenomics' strategy where genome health clinic can be accessed by global population for healthy lifestyle and disease freestate.

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