



Nutrition, disease and underlying molecular mechanisms

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Abstract: Although a number of factors can influence the regulation, precision and efficacy of vital biological pathways, the role of diet/nutrition cannot be ignored. Nutrition provides energy and raw material for essential life processes. A balanced diet leads to healthy outcome at not only systemic but also at cellular and molecular levels. Healthy food can also significantly impact repair and healing in biological system. However, certain types and amounts of diet are also risk factor for various ailments. Modern dietary patterns as well as lack of physical activity are impacting global disease pattern. Nutrigenomics has revealed the functional interaction between nutrients (macronutrients and micronutrients) and individual genomes. This article reviews the recent scientific literature to understand if and how nutrition would help in the maintenance of genomic integrity, proper immune surveillance and prevention of cancer.

Keywords: Inflammation; cancer; DNA damage; nutrients; nutrigenomics; nutrigenetics

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Introduction

There are about 50 to 70 trillion cells in our body and each cell is performing its respective function under the highly complex network of biological system (1). DNA molecules contain the necessary information for the biological activity such as making thousands of proteins, hormones and components of other biochemical reactions, which are involved in various functions in our body. Changes in DNA sequence, structure and malfunction of the DNA repair and maintenance mechanisms can lead to a variety of health hazards including cancer (2). Therefore, the mechanisms which contribute to the maintenance of genomic integrity and stability, play an important role in the prevention of diseases including cancer. Immune system provides another important shield against extrinsic as well as intrinsic threats to a living organism. Body's immune response activates the process of inflammation under the influence of wounds,

infections and/or any damage to tissue. At cellular level, inflammation emphasizes signaling to repair as well as heal damaged tissue. Moreover, it acts as defender against the foreign invaders for instance bacteria and viruses. Immune surveillance also helps eliminate precancerous/transformed cells from body. However, chronic inflammation can also activate mechanisms which disrupt genomic integrity and stability thus contributing on oncogenic transformation. In this article, we highlight the role of nutrition in the etiology of various diseases and the underlying mechanisms.

Diet is not only essential for survival of living organisms but the type of diet and quantity of diet impacts the performance, accuracy and lifespan of different biological systems and overall health and lifespan of living organism.

Aging

The process of aging is regulated by genetic makeup as

well as environment in which the organism lives. Human chromosomes end with specialized DNA-protein structures called telomeres. The length of DNA in telomeres shortens with each cell division. When telomeres shorten to a critical length, the cell undergoes replicative senescence. Therefore, telomere length can determine the lifespan of an organism and progressive shortening of telomeres with cell division provides the molecular basis of organismal aging. However, the pace of aging which is set by the rate of telomere shortening, depends on genetic makeup, environment and lifestyle factors of human beings. Aging is also influenced by the accumulation of free radicals which interact with and cause damage to DNA and thus increase the rate of telomere shortening (3). Stem cells play a potent role in maintaining the homeostatic balance throughout life by replacing lost and dead cells with new pool of functional cells. Reactive oxygen species (ROS) also play significant task in the regulation of homeostatic balance. Oxidative stress is well known for its behavior in modulating different stem cell properties, such as proliferation, differentiation, self-renewal and senescence (4). The choice of diet can markedly impact the level of intracellular oxidative stress. A diet rich in antioxidants can reduce pace of aging by protecting DNA and telomeres from oxidative damage.

Nervous system

N-methyl-D-Aspartate glutamate receptors (NMDARs) are important structural and functional unit of neuronal networks and brain cognitive abilities, which are impacted by diet. NMDARs are the heterogeneous subunits. Their composition is associated with the regulatory sites and their efficiency is regulated by the influence of numerous allosteric modulations including enzymes like serine racemase (SR) (5). Recent studies indicate that SR acts as an important regulatory factor that regulates the production of D-serine amino acids and acts as main co-agonist in the activation of NMDAR. SR dysregulation is associated with the psychiatric and neurological diseases such as depression, amyotrophic lateral sclerosis and schizophrenia (5). It has been demonstrated that a diet enriched with omega-3 polyunsaturated fatty acids can substantially reverse the age-associated decline in the levels of glutamate receptor in the forebrain of rats (6). The data obtained indicate that an eight-week modified feeding schedule reversed the age-related impairments in long-term potentiation and depolarization-induced glutamate transmitter release. There is also report that the concentrations of both docosahexaenoic acid and

arachidonic acid, two main polyunsaturated fatty acids in neuronal membranes, were decreased in the hippocampus of aged rats, and were restored by dietary manipulation with omega-3 fatty acids (7). Similarly, patients diagnosed with glioblastoma (primary brain tumor) have a limited life expectancy (ranging from 8 to 15 months). The therapies have not led to encouraging results for glioblastoma patients. The ketogenic diet (KD) has shed light on promising results in animal models. On the other hand, it not possible to depict judgment on the effectiveness of diet due to limited number of studies with small sample size. KD is low carbohydrate and high fat diet. It is evident that brain tumor cells consume glucose extensively because it is a sole energy source. Therefore, potential results may be achieved when glucose metabolism is targeted (8). The first leading neurodegenerative disorder is Alzheimer's disease (AD) all over the world (9). The second leading disorder, Parkinson's disease (PD), is affecting about 7-10 million people around the world. Causative mechanisms which are responsible to cause PD are still unknown but raised levels of oxidative stress by overproduction of ROS are the most acceptable pathogenic contributor. ROS causes oxidative damage to lipids, proteins and DNA, which subsequently leads to the neurodegeneration. Studies represents that different effective strategies have been developed to slow or stop the progression of PD, but unfortunately still no effective cure for PD is available (9).

Liver

Hepatic encephalopathy (HE) is a chronic liver disease accompanied with acute or chronic complications. HE leads to vast range of neurological symptoms including cognitive impairment of different severity and motor disturbances. Ammonia-induced senescence in the astrocytes involves GADD45 α , p53 activation and raised levels of cell cycle inhibitory factor and glutamine synthesis-dependent formation of ROS (10). Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is the third most cause of cancer-associated deaths (11). Liver cirrhosis is the most significant risk factor (70-90%) in patients suffering from HCC (12). The most relatable factors are chronic viral hepatitis B (HBV) and C (HCV) connected with hepatocarcinogenesis. Apart from viral hepatitis fatty liver disease is closely linked with nutritional factors, particularly in industrialized countries. Moreover, high consumption of alcohol is one of the most important risk

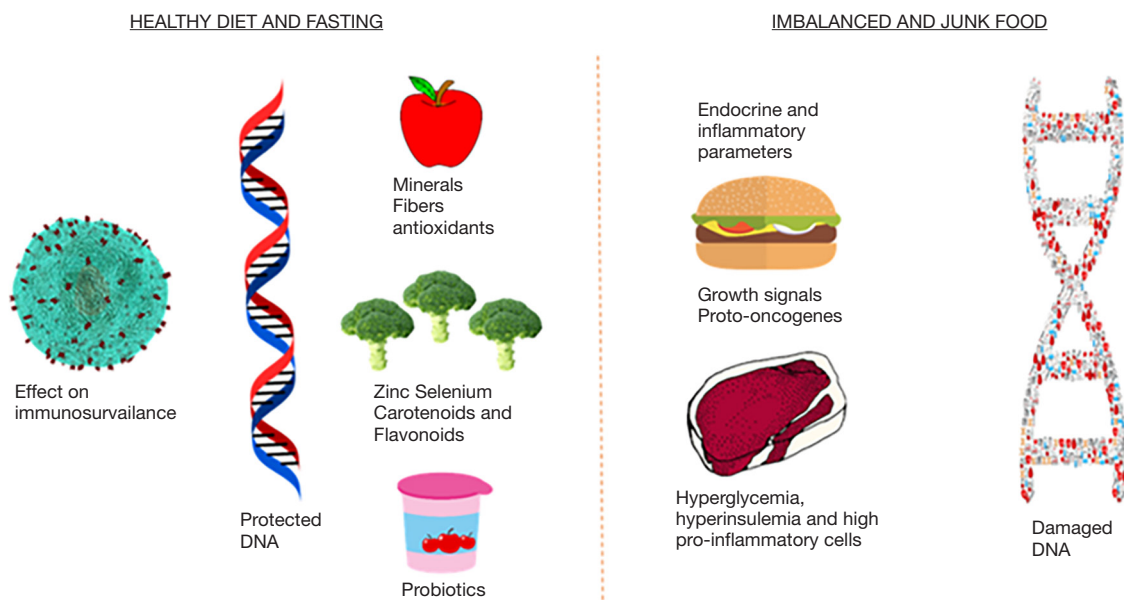


Figure 1 Food intake and cancer prevention. Different dietary components have different actions in the human body. Healthy diet (containing antioxidant and anti-inflammatory molecules) has direct protective role on DNA and other biological material. Overnutrition and imbalanced diet can expose cells of a living organism to toxic substances. Some of the harmful substances are present as the ingredient/s in unhealthy diet, whereas others are produced as byproduct of food metabolism. These harmful substances can disrupt genomic integrity, immune surveillance and/or endocrine function/balance causing many diseases.

factors for development of HCC and liver cirrhosis (13). Studies have shown that coffee consumption has an inverse association with the risk for HCC (14-18). A rationalized meta-analysis reported a risk decline in 40% for any coffee consumption (19). Nutritionally, white meat and fish have less saturated fats and cholesterol compared with red meat and are rich source of poly-unsaturated fatty acid (PUFA). Significant confirmation shows that n-3 PUFA has anti-inflammatory activity by inhibiting TNF and IL-1 synthesis (20). The n-3 PUFA have been reported to hinder HCC growth *in vitro* through the blockage of cyclooxygenase-2 and β -catenin (21).

Nutrients help vital cellular processes

Synthesis of building blocks is required for vital reactions in our body. Since nutrition provides energy and raw material for these building blocks, the type of diet plays an important role in vital cellular processes. For example, vitamin A is an important nutrient for healthy eyes and calcium is essential for bone strength. Vitamins B3, B12 and folic acid in a sufficient amount are required for synthesis of DNA (22). Shortage of these vitamins leads to the poor production of DNA which

could impact the maintenance of genomic integrity, stability and cell viability. Many other nutrients play important role such as zinc is important for forming finger like structure of DNA (23) and selenium plays important role as component of certain tumor suppressor genes (24,25) (Figure 1). Deficiency in folic acid is associated with a number of abnormalities including genetic damage, premature aging, heart disease and certain types of cancers (26). Deficiency in vitamin D may lead to osteoporosis and is also associated with diseases such as cancer (27), diabetes (28,29) or multiple sclerosis (30).

Impact of dietary factors on inflammation & DNA damage and integrity

DNA may get damaged in variety of ways by interfering the normal activity of genes. The damage may include free radicals, replication error in DNA or transcriptional error; aging and wrinkled skin are the signs of DNA damage. DNA damage may occur in all organs at different rates that increases the chance of systemic abnormality (31,32).

Unstable molecules such as free radicals are responsible for aging and DNA damage. Free radicals are formed in body as a by-product of different biochemical process

such as break down of food, infection and detoxification of hazardous chemicals. Some pollutants, such as cigarette smoke, automobile exhaust, copy machines fumes and some other free air pollutants. UV radiation and X-rays are also responsible for the generation of free radicals. Different theories suggest that each body cell is capable for generating thousands of free radicals. The damage of free radicals does not appear until age twenty-seven. After that, the damage of free radicals starts appearing. As the number of free radicals increase, they accumulate in different position on DNA. The damage from cigarette smoking is located in lungs where high level of DNA mutation can occur (33,34).

Mitochondria are dependent on the majority of the oxidative phosphorylation (OXPHOS) system for the nuclear genome and are also used to maintain and replicate mitochondrial DNA (mtDNA) as well as organelles proliferation and destruction (35). When DNA damage occurs, it triggers different abnormalities, for example, detaching and subsequent mitochondrial autophagy, loss of DNA repair, histopathology and other degenerative infections (36). Thus, damage to the mitochondrial genome results in deleteriously stable changes and impaired integrity. Therefore, maintaining the integrity of mtDNA is the foundation of healthy life. Nutrition may play a crucial role in controlling mtDNA integrity and expanding life expectancy.

Malnourishment and DNA damage

Hunger and malnutrition is one of the most overwhelming problems faced by several countries. Nearly 30% people suffer from one or more form of starvation (37). The terrible results of malnourishment consist of death, disability, and stunted mental and physical growth. Among the children in the developed countries, about 60% of the 10.9 million deaths per year are identified with lack of healthy sustenance (38). The underlying causes of malnutrition include poverty and inequality. Nutrition planning can only eliminate these causes that require political and social action. Various food supplements counteract ailing health as well as diminish different chronic abnormalities (39).

The link between diet and genomic instability suggests an important or preventive effect of various dietary factors. DNA damage, epigenome and chromosomal levels are the underlying causes of developmental and degenerative disorders. Hundreds of genes intricate and maintain the genomic integrity (40). Protein encoded by

DNA translation and DNA repair or detoxification of potentially genetic toxins rely on the cofactors necessary for optimal function, present in the diet (41). Excessive genomic instability caused by micronutrients deficiencies can be diagnosed by using DNA damage biomarkers, and can optimize nutritional status by reducing genomics and epigenome damage rates after diagnostic intervention (42).

Folic acid, B-complex, and other minerals in DNA synthesis and repair

Micronutrients (vitamins and minerals) are required as cofactor for protein associated with DNA synthesis and repair, counteracting oxidative damage to DNA. Any deficiency of micronutrients such as folic acid, B-complex, iron, zinc other minerals lead to cytotoxic lesion or oxidative damage. Lack of micronutrients can lead to DNA damage, malignant growth and other degenerative abnormalities (43). Folic acid inadequacy causes accumulation of uracil into human DNA prompting chromosomal breaks. Such chromosomal breaks are robust prognostic factor for human cancer. Folic acid deficiency can be a main cause of acute lymphoblastic leukemia. Folic acid administration can reverse humans' high DNA uracil levels and chromosome breaks (44). Like folate deficiency, B12 deficiency leads to accumulation of uracil in DNA and chromosomal breaks. These two defects may play a synergistic role. Studies have shown that B12 supplements are important for limiting chromosome breaks (45). B6 insufficiency attributes towards stroke and atherosclerosis and is also associated with chromosomal breaks. B6 supplements reduces these risks (46).

Niacin (VitaminB3) helps to repair DNA breakage defects by keeping up nicotinamide adenine dinucleotide (NAD) levels, thereby maintaining ploy-ADP ribose reaction to DNA damage (47). Niacin deficiency can impair DNA gaps and repair so it is expected that synergistic action of folate and antioxidant deficiency prompts DNA damage and malignant growth (48). Selenium is essential for enzyme resistance to oxidants and insufficient selenium can cause oxidative DNA damage. Selenium plays an important role in preventing cancer (49). Zinc deficiency is a cause of human esophageal cancer. The consequences are an increase DNA oxidation, DNA breaks and increase chromosomal damage (50).

Obesity, osteoarthritis and metabolic syndrome

Changes in lifestyle and environmental exposures are

major factors in pathogenesis and metabolic syndrome. Moreover, obesity and metabolic syndrome associated with inflammation, dyslipidemia, and insulin resistant or fully developed diabetes and an increased risk of cardiovascular disorders, are also affected by genetic susceptibility (51). Such metabolic factors may increase the risk of obesity induced osteoarthritis (52). Obesity predominantly is a natural consequence of over-nutrition and sedentary life styles. Persistent obesity can deregulate metabolic processes and severely affects the process of controlling blood sugar, blood pressure and blood lipids thus it is referred to as metabolic syndrome (53). Obesity is also considered to be a risk factor for osteoarthritis. It's contribution may be due to different astringent mechanism leading to cartilage destruction. Despite this, recent advances have shown the adipose cells create large number of elements called adipokines that have a key role in the development and progression of osteoarthritis (54).

Popkin and Doak (55) reported that in several developed countries the prevalence of obesity has increased from 2.3% to 19.6% over the last 10 decades. The obesity rate in the Middle East, Pacific island, Australia and China has increased since 1980 (56). With the support of government and legislative work, various health strategies consisting of individual and community initiatives, will also help to minimize the incidence of obesity and metabolic disorders in developing countries.

Malnutrition, inflammation, and immunodeficiency

Microbial diseases of cells initiate a provocative reaction. The underlying impression of disease is mediated by innate pattern recognition receptors (PRRs) which contain Toll-like receptor (TLRs), RIG like receptors (RLRs), NOD like receptors (NLRs) and C-type lectin receptors (CLRs). This intracellular signaling cascade activated by these PRRs causes transcription expression to eliminate the pathogens and infected cells. However, this system is abnormally activated by induction of autoimmunity and immunodeficiency (57).

Immunodeficiency is a state in which immune system fighting ability is impaired or completely absent against the infectious diseases and cancer. Immunodeficiency is caused by absence of elements of the immune system including lymphocytes, phagocytic cells and complement system. Immunodeficiency can be primary such as Bruton's disease or secondary disease caused by HIV

infection. Primary immunodeficiency disease is caused by intrinsic defects in immune cells including T-cells, complements constituents and phagocytic cells. Recurrent pneumonia caused by extracellular bacteria indicates a lack of antibodies. Moreover, recurrent fungal infections may be caused by lack of T-lymphocytes (58). Secondary immunodeficiency may be caused by drugs that affect the function of T and B lymphocytes. The most common secondary immunodeficiency is caused by HIV and lead to acquired immunodeficiency syndrome (AIDS) which has varying prevalence rates worldwide. AIDS primarily affects CD4+ T cells and down-regulation of cellular immune response occurs that produces devious infections and cancers which are threatening to human health (59). Most immunodeficiency is congenital and X-linked autosomal recessive inheritance patterns such as immunodeficiency with ataxia-telangiectasia are autosomal recessive disease instigated by mutations in genes encoding DNA repair enzymes. Defects result from the cleavage of chromosomes 14 of the T-cell receptor (TCR) and Ig-heavy chain gene loci (60).

Malnutrition deficiency is the cause of secondary deficiency such as protein malnutrition affects cell mediated immunity, phagocytosis and consumption of microorganism is intact but the ability of phagocytic cells to kill intracellular organisms is impaired. Nutrition deficiencies may lead to cancer, chronic kidney disease, multiple injuries and chronic infections. Zinc and iron deficiency have multiple effects on immunity including delayed reduction of cutaneous hypersensitivity.

Vitamin supplements (B6, B12), selenium and copper are also important for immune system. It is now believed that oxidative stress is associated with all provocative diseases (joint inflammation, vasculitis glomerulonephritis and adult respiratory diseases), ischemic diseases, AIDS, emphysema, organ transplantation, gastric ulcer, high blood pressure, neurological disorder (Alzheimer's disease, Parkinson's disease, muscular dystrophy) and so on (61). Oxidative stress occurs due to irregularities between antioxidant defense and free radical production. Higher production of ROS in body can alter DNA structure, leading to modification of proteins and lipids, activation of induced transcription factors and production of pro-inflammatory and anti-inflammatory cytokines (62). Antioxidant can reduce oxidative stress by directly scavenging ROS or inhibiting cell proliferation. B-carotene prevents UV-induced carcinogenesis. β -carotene may have an anticancer impact by altering the liver metabolism of cancer-causing agents (63).

Vitamins C help to prevent cancer. Its mechanism may influence carcinogenesis because of its antioxidative character, blocks formation of nitrosamines, enhances immune response, and accelerates detoxification process of liver (64). Vitamins E is a main antioxidant that increases body fluid, antibody production, anti-bacterial infection, cell mediated immunity, T-lymphocyte, tumor necrosis factor (TNF), inhibition of mutagens formation, repair of membranes and blocks microcell line formation. Consequently, vitamin E can be used to prevent malignant growth and repress carcinogenesis by stimulating the immune system (65). Therefore, nutrition may help to expand the inflammatory response to the borders of exposure to pathogens, toxins and tissue damage. Dietary components such as vitamins, antioxidants, plant flavonoids, prebiotics and probiotics all have the potential to modify the susceptibility of chronic inflammation and may work in treatment.

Diverse type of nutrients affects the performance of DNA. Several nutrients such as zinc, folic acid, vitamin D, flavonoids and carotenoids are affecting DNA health. Different vitamins affect the DNA health such as vitamin A influences the growth and differentiation of cells. Vitamin B complex is involved in DNA repair, synthesis and regulation. Other important vitamins are vitamin C, D and E. Minerals such as zinc, chromium and selenium are important for the DNA health (66,67).

Action of dietary supplements on cancer

Number of genes have been identified which are cancer causing and can be suppressed through a variety of mechanisms. *p53* gene is one of the cancer suppressor genes. *p53* gene is involved in inhibition of cancer cells, when activated. Mutations of *p53* gene have been identified in more than fifty types of cancers. Other factors involved are folic acid and selenium that help in maintaining normal activity and genetic stability of *p53*. Another gene, GST which codes for glutathione-S-transferase enzymes is also involved in preventing cancer. It functions as antioxidant that helps in protection from free radical damage. It also provides protection from breakdown of hazardous chemicals. VDR (Vitamin D Receptor) polymorphism is also associated with an increased risk in breast, prostate and colon cancer (68-70).

To some extent, cancer can be controlled through variety life styles and nutrient supplements. Vegetables and fruits provide low risk from most cancers. Herbs are rich source

of antioxidants, which help in protecting DNA damage. Another powerful antioxidant is glutathione peroxidase and its important component is selenium. These selenium molecules protect the DNA from free radicals. Natural succinate, a form of vitamin E has potent anticancer effect (71). DNA repair processes and oncogenes suppression are maintained by vitamin B6 and B12. Coenzymes Q10 is a vitamin like nutrient that act as a protective antioxidant. It boosts the activity of immune cells to fight cancer cells (72). For the treatment of cancer, some nutritionally oriented physicians use large amount of vitamins and minerals with the combination of other conventional medical therapies. Cervical cancer has been treated by using vitamin E, co-enzyme Q10, vitamin C, beta carotene, mixed carotenoids and vitamin A in combination with medical therapy. These nutrients do not affect the cancer but boost the immune system of patient to fight against cancerous cells (73).

Conclusion

Natural antioxidants in diet play a crucial role in multiple metabolic pathways affecting disease progression. Plant-based diet, fruit and vegetables, are rich source of fiber, antioxidants and healthy fatty acids which are connected with decreased risk of any disorder. Many substances present in fruit and vegetables are protective in nature for biological system. Hence, the entire effect is not likely to be due to any single phytochemical or nutrient.

The components of balanced diet such as bioactive compounds can rewire the expression of gene which could be up or down regulated. Nutrient intake is considered significant to alleviate the risk of onset of a disease based on the individual's genetic profile. Nutrigenetics/genomics may be employed to manipulate a personalized diet for each patient. Several studies have reported altered metabolism in all disorders, particularly in cancer showing high usage of metabolic energy along with elevated production of ROS. Food molecules act as ligand against several targets in biological system. These targets could be extracellular as well as intracellular.

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