SciMedCentral

Journal of Drug Design and Research

Review Article

Genomic Instability in Human Cancer: Current Molecular Insights and Opportunities for Prevention through Targeted Nutrition

Lynnette R. Ferguson*

Auckland Cancer Society Research Centre/Discipline of Nutrition and Dietetics, Faculty of Medical and Health Sciences, The University of Auckland

***Corresponding author**

Lynnette R. Ferguson, Auckland Cancer Society Research Centre/Discipline of Nutrition and Dietetics, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand, Tel: 64 9 923 6372 e-mail: l.ferguson@auckland.ac.nz; ORCID ID: 0000-0003-0107-4741.

Submitted: 23 March 2021

Accepted: 10 April 2021

Published: 12 April 2021

ISSN: 2379-089X

Keywords

- Genome
- Cancer
- Obesity
- Macronutrients
- Micronutrients

Abstract

Stability of the human genome is critical to the maintenance of good health, and diet plays a critical role in this. The Halifax project was an international collaboration that summarised literature on the nature of genomic stability and role of nutrients in stabilising or destabilising the genome, up to 2015. This review considers current literature in the area, to develop the most effective nutritional strategies to avoid genomic instability. Either macronutrient excess (obesity), or nutrient deficiency, can lead to genomic instability and increasing evidence suggests that both are important. However, it is important to stress that even normal weight individuals may have micronutrient deficiencies, which go undetected. Important factors affecting body weight include overall caloric intake, and the utilisation of energy. Lean meat, fish or tofu are good protein sources, when eaten in moderation. While high fat consumption may be detrimental, the ratio of long chain polyunsaturated fatty acids to other fats is important, as these may become anti-inflammatory. Certain carbohydrate sources at appropriate levels may influence genomic stability, and there is general international agreement on desirable levels of vitamins and minerals. Regular consumption of a mix of fresh fruits and vegetables will help to ensure a good micronutrient balance. Metal ions including selenium, copper, zinc and iron act as co-factors for many enzymes, thereby controlling important biological processes. Vitamin D deficiency is common, and usually detrimental, but is unusual in requiring exposure to sunlight for effective synthesis in the human body.

INTRODUCTION

The human genome plays a fundamental role in human health and protection against disease. Genomic instability is a hallmark of cancer, reflecting a high frequency of mutations, including changes to nucleic acid sequences, chromosome rearrangements and/or aneuploidy, in chromosomal and/or in mitochondrial DNA (1,2). Stability of the genome is critical in preventing the development and/or progression of disease. The Halifax project was an international task force of 180 scientists who explored the causes and implications of genomic instability, especially in relation to cancer (1). One of the subgroups of this taskforce considered the role of diet in this process (2). As well as the exact sources of proteins, fats and carbohydrates, genomic instability may result from caloric excess or restriction, the dietary balance of macro and micronutrients and/or supplementation with various nutrients, phytochemicals or nutrient formulations.

Some of the mechanisms involved in genomic instability, as found by this working group, are reproduced (with permission) in (**Figure 1**). The current review provides an update of reference 2, except for phytochemicals, which are an important topic in their own right.

Malnutrition

Obesity has been defined as a state of positive energy balance, with a body mass index exceeding 30kg/m^2 in adults, and the 95th percentile in children. The dysregulation of adipose tissue can lead to molecular changes, which in turn can result in high reactive oxygen species (ROS) and lipid peroxidation. Both ROS and lipid peroxidation are caused by increased insulin, fatty acid and glucose levels, or indirectly via inflammation (3). The by-products of the oxidative degradation of lipids, such as malondialdehyde, 4-hydroxynonenol and acrolein, and also the secondary bile acid metabolites (e.g. deoxycholic acid and lithocholic acid) associated with activities of the gut microbiota, can themselves lead to a destabilised genome. Obesity-induced adipose tissue expansion leads to a variety of signals, including adipocyte death and hypoxia, thereby initiating an inflammatory response. An overall nutrient deficiency, leading to excess weight reduction, can also lead to genomic instability. Hawkes

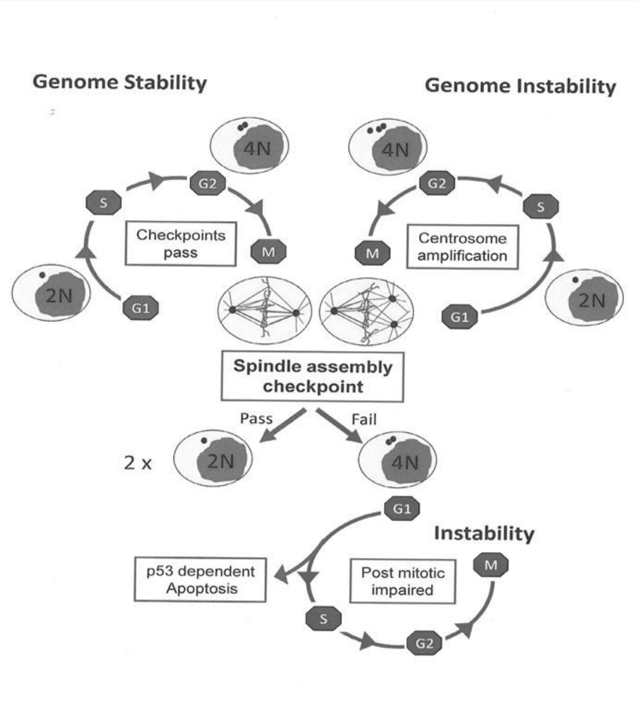

Figure 1 In a dividing cell, the centrosome and genomic material are replicated concurrently. Equal segregation of chromosomes, and genome stability (in grey), requires the completion of the spindle assembly checkpoint. Ectopic amplification of centrosomes (in black) and the failure of the spindle assembly checkpoint, may result in a tetraploid state that can progress through the cell cycle, should the p53-dependent post-mitotic checkpoint fail to induce apoptosis.

and co-workers (4) proposed ten double duty actions, with the potential to reduce undernutrition, obesity and diet-related non-communicable diseases (NCDs). They found that all of these health problems are intrinsically linked through early-life nutrition, diet diversity (or lack thereof), food environments and socioeconomic factors. They suggested a framework to design double-duty approaches and strategies, defining the first steps that are required.

A commentary on this review (4), subsequently published by Osendarp and co-workers (5) expressed some concerns that, despite micronutrient imbalance having been recognised as an element of malnutrition, it had not been included in the estimates. These authors stressed that micronutrient deficiencies are also prevalent in normal-weight and overweight populations. Both food insecurity and energy-dense obesogenic foods result in micronutrient-poor diets. In addition, both overweight and obesity can further exacerbate the risk of such deficiencies through several physiological processes. For example, autophagy appears to be an important process, which operates during starvation, and especially maintains the integrity of mitochondrial DNA (6). The inhibition of autophagy promotes oxidative stress, genomic instability and tumorigenesis. There is no question but that caloric restriction without malnutrition can often be beneficial, by modulating telomere erosion, epigenetic alterations, proteolysis imbalance, impaired nutrient sensing and abnormal intracellular communication (7). However, an overall deficiency of a range of nutrients will have adverse effects long term on good health and genome integrity.

A recent special issue of Frontiers in Psychiatry focussed on extreme eating behaviours, which lead to obesity and anorexia nervosa (8). It revealed that these are an increasing global health threat, with a rising prevalence.

Macronutrients

Proteins are essential nutrients, important to our bodies, by forming tendons and ligaments as collagen, breaking down our food as digestive enzymes and protecting us from infection as antibodies (9). Consuming adequate protein in the diet is essential, since our bodies do not store these as they do the other macronutrients. Protein sources include meats and dairy products, fish and eggs, grains, legumes and nuts. It is important to stress, however, that although there are environmental pressures suggesting a reduction of animal proteins in the diet and their replacement with plant proteins, these sources are not equivalent (10). Animal proteins are richer in leucine than are plant proteins, and therefore better able to influence anabolic protein metabolism, and thereby influence genomic stability. Nevertheless, many common sources of animal protein are also high in saturated fats, which are likely to be detrimental in relation to genome stability.

The most common source of protein in a western diet may be red meat. However, it is important to note that a considerable amount of evidence has associated higher red meat consumption, especially processed red meat, with an increased risk of diseases associated with genomic instability. Mosley and co-workers (11) conducted a large meta-analysis that particularly associated high consumption of processed red meat (such as bacon, hot dogs and sausages) with negative health outcomes. They also suggested that components of red and processed meats such as saturated fats and potential carcinogens including polycyclic aromatic hydrocarbons (caused by high temperature cooking), sodium, and preservatives could contribute to adverse health outcomes. They further suggested examples of animal protein sources that are economically viable would include the use of insects or of stem cells harvested from animal tissue, but then grown in a laboratory.

Like proteins, fats are also key macronutrients, serving both structural and metabolic functions (12). Although not recommended at high levels, the body requires some fats from foods. As well as being a major source of energy, fats help the absorption of some vitamins and minerals. They help to build cell membranes and the sheaths surrounding nerves. Fats are also essential for effective blood clotting, muscle movement, and the control of inflammation. However, it is important to avoid eating trans-fats (13). These are a by-product of hydrogenation, a process used to turn healthy oils into solids such as margarine and vegetable shortening, and to prevent them from becoming rancid. However, high consumption of trans-fats has been linked to inflammation and other detrimental health effects. Foods containing significant amounts of these types of fats are now banned in the USA, and a number of other countries.

A saturated fat is one in which the fatty acid chains have mostly single bonds. Most animal fats (e.g. from cream, cheese and butter) fall into this classification, and they generally tend to be solids at room temperature. They are also the most calorie dense type of fat. There is good evidence that a maternal diet high in saturated fats leads to significant levels of inflammation and a tendency towards genomic instability in the offspring. At later stages in life, such a diet also leads to an increased risk of cancer and other diseases associated with genomic instability (13). Part of the reason for this is that high consumption of saturated fats tends to be associated with increased risks of obesity, itself a significant factor in destabilising the genome, as discussed previously.

Polyunsaturated fatty acids such as long chain omega-3 polyunsaturated fatty acids (n-3 PUFA), have generally been associated associated with beneficial effects on immune regulatory functions, thereby enhancing genomic stability. Animal studies have shown that diets enriched in two such acids, *eicosapentaenoic acid (*EPA) and/or *docosahexaenoic acid (*DHA) lead to positive effects for chronic conditions (14). N-3 PUFA are beneficial in reducing inflammation, especially in people with inflammatory disorders (15). These fatty acids are used as dietary supplements for a range of chronic conditions. N-3 PUFA act as precursors of pro-resolving mediators such as resolvins, protectins and maresins, which stimulate anti-inflammatory mechanisms. In addition, the sum of *EPA* and *DHA* in erythrocyte membranes and expressed as a percentage of total erythrocyte fatty acids (the Omega-3 Index), is used as a risk factor measure for example for diseases associated with genomic instability, such as cancer.

Monounsaturated fatty acids (MUFA) can come from either plant or animal sources (16). Major plant sources of MUFA include olive oil, nuts, salad dressing, fried foods, margarine, milk chocolate, and avocados. Animal sources of MUFA come mainly from red (beef and pork) and processed meats (41–42%), dairy products, butter, poultry, eggs, and fish. It is significant that, at least in the USA, a high consumption of plant-based MUFA was associated with a decreased risk of diseases associated with genomic instability, while the converse was true for animal-based products (16).

One type of MUFA, generally considered beneficial in maintaining genomic stability, is Oleic acid, which occurs naturally in various animal and vegetable fats and oils. It is important for at least some of the beneficial properties associated with either virgin or extra virgin olive oil (17). In particular, extra virgin olive oil has been emphasised for its' beneficial health properties (18). However, some of these benefits should be attributed to a polyphenol component of this oil.

It is important to recognise that high intakes of some undesirable fats may be unintentional. An example that has aroused media attention in recent years has been the suggestions from some regulatory bodies about the possibility of increasing the use of cow's milk in the diet (19). This has been considered an integral part of the Western diet, partly because of its' high calcium and vitamin D content, both micronutrients considered to be important in development, bone health and the prevention of fractures. Cow's milk is important during early childhood feeding in situations where adequate human breastmilk is not available. However, not all milk is the same. For example, milk from grass-fed cows has a beneficial ratio of N-3 PUFA to less desirable N-6 PUFA, whereas large-scale industrial milk production does not lead to these beneficial ratios. Particularly given the decreased overall intake of total fats now recommended (19), milk is one of the foods coming under scrutiny.

Carbohydrates include sugars, such as the monosaccharides fructose (fruit sugar) and glucose (starch sugar) and the disaccharides sucrose (cane or beet sugar) and lactose (milk sugar) (20). These add sweetness to foods, but their high calorie content means that an excess can too easily lead to obesity. These dietary components and related glycation end-products increase chromosomal damage, and thereby genomic instability (21).

Complex carbohydrates consist of three or more sugars (oligosaccharides or polysaccharides) that form complex structures and take longer to digest than simple sugars. Resistant starch is a fraction of starch in the diet that is neither digested nor absorbed in the small intestine, but instead is fermented in the colon to produce short chain fatty acids. Vahdat and co-workers (22) conducted a meta-analysis of randomised controlled trials of resistant starch dietary intervention studies in humans, to show beneficial effects on inflammatory biomarkers, thereby enhancing genomic stability.

Dietary fibre is a term describing non-absorbed plant carbohydrates and small amounts of associated non-carbohydrate components (23). In general, the most beneficial types of dietary fibre come from intact plant cell walls from unprocessed food plants (whole grain cereals, fruits and vegetables), and there is good evidence supporting significant health benefits when these represent a significant proportion of the diet (24).

Micronutrients

There are currently thirteen different vitamins recognised as important for the maintenance of optimal human health, largely through their antioxidant activities (25, 26). Fresh fruits and vegetables are generally considered as desirable sources of several of these vitamins and related antioxidants (26), although these authors warn that poor postharvest storage conditions may lead to their breakdown. Two of the B vitamins, B9 (folate) and B12 have been particularly identified as playing key roles in the maintenance of one carbon metabolism, critical in protection against disease (27). These same two vitamins are also essential for the maintenance of optimal telomere length and mitochondrial DNA copy number (28).

Ascorbic acid (Vitamin C) also plays a critical role in protection against genomic instability. As summarised by Berretta and co-authors (29), this vitamin acts as an antioxidant, as well as being a co-factor for several key enzymatic functions. These authors emphasise that humans cannot synthesise vitamin C, and it is important to maintain levels through diet or dietary supplements. A review of recent literature shows that vitamin C supplementation could play a critical role in reducing oxidative stress in patients with severe illnesses (29). Both the B and C vitamins are water soluble, and excreted from the body in the urine. Thus, it is important to maintain a regular supply of these.

Vitamins A, D. E and K are fat-soluble, and may stay in the body for some time. Vitamin D appears particularly important in protecting against genomic instability. Very little vitamin D is contained in food, with humans deriving around 90% of their requirements from exposure to sunlight (30). These authors emphasised the importance of vitamin D on DNA methylation, and subsequent implications for maintenance of genomic stability. Martens et al. (31) discuss the active vitamin D metabolite (1,25dihydroxyvitamin D3), emphasising its' significant role on immune function and related downstream events. Karanova and co-authors (32) found that high dose vitamin D supplementation improved circulation and reduced inflammation in a highly vulnerable group of subjects.

Wesselink et al. (33) considered the importance of magnesium and calcium in vitamin D metabolism, showing the lowest risk of mortality in colorectal cancer patients with sufficient vitamin D (>50nmol/L) and a high magnesium intake. Calcium intake appeared to be less important in this context. A moderate intake of magnesium (without vitamin D) beneficially influenced the intestinal microbiome in rats, likely to have flow on effects for genomic stability (34). In a pre-diabetic rodent model, chromium supplementation directly enhanced genomic stability (35). Serra and co-workers (36) stress the importance of metals, including selenium, copper, zinc and iron, and discuss how they act as co-factors for many enzymes, and control biological processes by binding to receptors and transcription factors. However, too high levels can be detrimental.

CONCLUSIONS

Appropriate selection, quantities and balance of macronutrients and micronutrients is essential to the maintenance of genomic stability. Malnutrition, whether it manifests as excess weight or emaciation, presents a high risk for genomic instability. Protein quality is more important than quantity, and the nature as well as the amount of dietary fats is critical. Unrefined carbohydrates also have important functions. A balanced mix of vitamins and minerals is largely, but not exclusively, provided by a diverse range of fresh whole grains, fruits and vegetables.

REFERENCES

1. Block KI, Gyllenhaal C, Lowe L, et al. Designing a broad-spectrum integrative approach for cancer prevention and treatment. Semin Cancer Biol. 2015; 35: S276-S304.
2. Ferguson LR, Chen H, Collins AR, et al. Genomic instability in human cancer: Molecular insights and opportunities for therapeutic attack and prevention through diet and nutrition. Semin Cancer Biol. 2015; 35: S5-S24.
3. Zatteralle F, Lungo M.,Naderi J. et al. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. Front Physiol. 2020 10: 1607.
4. Hawkes C, Ruel MT, Salm L, ET AL. Double-duty actions: seizing programme and policy opportunities to address malnutrition in all its forms. Lancet 2020; 395: 142-155.
5. Osendarp SJM, Brown KH, Neufeld LM, et al. The double burden of malnutrition-further perspective. Lancet. 2020 Sep 19; 396: 813.
6. Clementi E, Inglin L, Beebe E, et al. Persistent DNA damage triggers activation of the integrated stress response to promote cell survival under nutrient restriction. BMC Biol. 2020; 18: 36.
7. Castejón M, Plaza A, Martinez-Romero J, et al. Energy restriction and colorectal cancer: A call for additional research. Nutrients. 2020; 12: 114.
8. Aggarwal R, Bains K. Protein, lysine and vitamin D: critical role in muscle and bone health. Crit Rev Food Sci Nutr. 2020: 1-12.
9. Bailey HM, Mathai JK, Berg EP, Stein HH. Most meat products have digestible indispensable amino acid scores that are greater than 100, but processing may increase or reduce protein quality. Br J Nutr. 2020; 24: 1-9.
10. Mosley D, Su T, Murff HJ, et al. Meat intake, meat cooking methods, and meat-derived mutagen exposure and risk of sessile serrated lesions. Am J Clin Nutr. 2020; Jun 1;111(6):1244-1251.
11. Calder PC. Eicosanoids. Essays Biochem. 2020; 64: 423-441.
12. Bojková B, Winklewski PJ, Wszedybyl-Winklewska M. Dietary fat and cancer. Which is good, which is bad, and the body of evidence. Int J Mol Sci. 2020; 9:21(11):4114.
13. Calder PC. Eicosapentaenoic and docosahexaenoic acid derived specialised pro-resolving mediators: Concentrations in humans and the effects of age, sex, disease and increased omega-3 fatty acid intake. Biochimie. 2020; 178: 105-123.
14. Calder PC. N-3 PUFA and inflammation: from membrane to nucleus and from bench to bedside. Proc Nutr Soc. 2020: 1-13.
15. Ferreri C, Sansone A, Ferreri R, et al. Fatty acids and membrane lipidomics in oncology: A cross-road of nutritional, signalling and metabolic pathways. Metabolites. 2020; 10: 345.
16. De Santis S, Cariello M, Piccinin E, et al. Extra virgin olive oil: Lesson from nutrigenomics Nutrients. 2020; 11: 2085.
17. Marta Farràs M, Canyelles M, Fitó M, et al. Effects of virgin olive oil and phenol-enriched virgin olive oils on lipoprotein atherogenicity. Nutrients 2020; 12: 601.
18. Willett WC, Ludwig DS. Milk and health. N Engl J Med. 2020; 382: 644-654.
19. Satokari R. High intake of sugar and the balance between pro- and anti-inflammatory gut bacteria. Nutrients. 2020; 121348.
20. Deo P, McCullough CL, Almond T. et al. Dietary sugars and related endogenous advanced glycation end-products increase chromosomal DNA damage in WIL2-NS cells, measured using cytokinesis-block micronucleus cytome assay. Mutagenesis. 2020; 35: 169-177.
21. Vahdat M, Hosseini SA, Khalatbari Mohseni G, et al. Effects of resistant starch interventions on circulating inflammatory biomarkers: a systematic review and meta-analysis of randomized controlled trials. Nutr J. 2020; 19: 33.
22. Augustin LSA, Aas AM, Astrup A, et al. Dietary fibre consensus from the International Carbohydrate Quality Consortium (ICQC). Nutrients. 2020; 12: 2553.
23. Barber TM, Kabisch S, Pfeiffer AFH, Weickert MO. The health benefits of dietary fibre. Nutrients. 2020; 12: 3209.
24. Niforou A, Konstantinidou V, Naska A. Genetic variants shaping inter-individual differences in response to dietary intakes - A narrative review of the case of vitamins. Front Nutr. 2020; 7.
25. Meitha K, Pramesti Y, Suhandono S. Reactive oxygen species and antioxidants in postharvest vegetables and fruits. Int J Food Sci. 2020.
26. Lyon P, Strippoli V, Fang B, Cimmino L. B vitamins and one-carbon metabolism: Implications in human health and disease. Nutrients. 2020 12: 2867.
27. Praveen G, Shalini T, Sivaprasad M, Reddy GB. Relative telomere length

and mitochondrial DNA copy number variation with age: Association with plasma folate and vitamin B12. Mitochondrion. 2020; 51: 79-87.

28. Berretta M, Quagliariello V, Maurea N, et al. Multiple effects of ascorbic acid against chronic diseases: Updated evidence from preclinical and clinical studies. Antioxidants (Basel). 2020 ; 9: 1182.

29. Ong LTC, Booth DR, Parnell GP. Vitamin D and its effects on DNA methylation in development, aging, and disease. Mol Nutr Food Res. 2020: e2000437.

30. Martens PJ, Gysemans C, Verstuyf A, Mathieu AC. Vitamin D's effect on immune function. Nutrients. 2020; 12: 1248.

31. Karonova T, Stepanova A, Bystrova A, Jude EB. High-dose Vitamin D supplementation improves microcirculation and reduces inflammation in diabetic neuropathy patients. Nutrients. 2020; 12: 2518.

32. Wesselink E, Kok DE, Bours MJL, et al. Vitamin D, magnesium, calcium, and their interaction in relation to colorectal cancer recurrence and all-cause mortality. Am J Clin Nutr. 2020; 111: 1007-1017.

33. García-Legorreta A, Soriano-Pérez LA, Flores-Buendía AM, et al. Effect of dietary magnesium content on intestinal microbiota of rats. Nutrients. 2020; 12: 2889.

34. Molz P, Molz WA, Dallemole DR,et al. Potential ameliorative effects of chromium supplementation on glucose metabolism, obesity, and genomic stability in pre-diabetic rat model. Biol Trace Elem Res. 2020; 199: 1893:1899.

35. Serra M, Columbano A, Ammarah U, Mazzone M, Menga A. Understanding Metal Dynamics Between Cancer Cells and Macrophages: Competition or Synergism? Front Oncol. 2020; 10: 646.

Cite this article

Ferguson LR (2021) Genomic Instability in Human Cancer: Current Molecular Insights and Opportunities for Prevention through Targeted Nutrition. J Drug Des Res 8(1): 1080.