JMGCB
ISSN:3032-1085
https://doi.org/10.61796/jmgcb.v1i9.918

DNA INSTABILITY ASSOCIATED WITH FOLATE DEfiCIENCY

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Received: Jul 22, 2024; Accepted: Aug 29, 2024; Published: Sep 17, 2024;

Abstract: Folate, also referred to as Vitamin B9, is a type of vitamin that dissolves in water and plays a central role in preserving the integrity of DNA molecules and gene expression through the construction of DNA and methylation. Folate cannot be synthesised in vivo and must be obtained from the diet, particularly fruits and green leafy vegetables. deficiency of folate increases the risk of DNA stability due to uracil misincorporation into the DNA backbone and chromosome breaks, it can lead to the accumulation of deoxyuridine monophosphate (dUMP) which impairs the pathway of dTMP synthesis. in addition, it reduces the availability of methyl donors which causes impaired methylation patterns. Finally, it can generate oxidative stress leading to mtDNA damage and eventually to genomic instability. Different studies and measurement methods have produced varying evidence on the connection between folate and DNA stability, So we encourage to increase in folic acid intake for at-risk groups, but more rigorous human studies are needed before scientifically based public health recommendations about dietary requirements can be made.

Keywords: Folate Deficiency DNA instaibility, Vitamin B9

Introduction

Folate is a water-soluble vitamin that falls within the B vitamin group. It is an essential component of one-carbon metabolism, which regulates a number of processes including DNA repair, apoptosis, cell development, and differentiation [1]. The primary source of folate in our diets is vegetables, along with certain fruit varieties, green leafy vegetables, fortified foods, and grain products. Through the substrate or spontaneous action of cofactor enzymes involved in DNA synthesis, repair, and methylation, micronutrients are critical for preserving genomic integrity [2]. The process of one-carbon nutritional metabolism in a variety of biological molecules, including methyltetrahydrofolate, pyridoxal phosphate, and methyl-cobalamin, is dependent on vitamins B9, B6, and B12.

Deoxyuridine monophosphate must be converted into deoxythymine monophosphate by this procedure. It entails the remethylation of hemocysteine to methionine, which produces S-adenosyl methionine in the end. In order to preserve DNA methylation patterns, this is necessary [3]. Genomic instability has been linked to vitamin deficiencies; this is mostly caused by uracil being incorporated into DNA, which induces micronuclei. The method known as cytokinesis block micronucleus cytometry (CBMNcyt) may be used to quantify these micronuclei [4]. Chromosome abnormalities include chromosomal rearrangement, telomere attrition, and entire chromosome loss events are linked to deficiencies in pyridoxine and folate [5]. A lack of these vitamins makes cells more vulnerable to other genotoxins causing DNA damage. Growing in folic acid-deficient RPMI increases the sensitivity of B lymphoblastoid WIL2-NS cells to radiation-induced DNA damage (1.5 Gy). When

compared to controls developing in regular RPMI, they undergo an approximately two-fold increase in MNi and nucleoplasmic bridges (NPBs) [6]. Since many clinical illnesses are linked to altered metabolic states, it is crucial to take into account how vitamin shortages may modify cellular responses to other genotoxic stressors [7].

Dietary folate may be absorbed at a rate of between 10 and 98%. It is influenced by a number of variables, including as the dietary matrix, alcoholism, the pH of the colon, and the activity of enzymes [8]. To quantify the difference in absorption between folic acid and folate, one uses a folate equivalent.

Adults in the UAS are advised to consume 400 mg of dietary folate equivalents (DFE) per day. Dietary folate and 0.6 mg of folate supplemented with food or 0.5 mg of additional folic acid taken on an empty stomach are both equal to one microgram of dietary folic acid equivalents (DFE). One-fifth of the quantity that causes a vitamin B12 deficiency, or 1,000 mg of folic acid per day, is the highest dosage recommended [9]. Approximately 5 percent of Americans are overdosing on certain nutrients, mostly via dietary supplements [10].

Methods

The passage describes various methods used to study the effects of folate deficiency on DNA stability and its link to cancer. The primary methods involve analyzing the metabolic pathways of folate, particularly its role in one-carbon metabolism, DNA synthesis, and methylation processes. The method known as cytokinesis block micronucleus cytometry (CBMNcyt) is highlighted as a way to quantify micronuclei caused by DNA damage, specifically from uracil incorporation into DNA. Additionally, experiments on folate-deficient RPMI media showed increased sensitivity to DNA damage, resulting in higher incidences of micronuclei and nucleoplasmic bridges. The passage also touches on the importance of assays like deoxyuridine suppression tests and elevated homocysteine levels to assess folate deficiency, and mentions research on laboratory animals, human studies, and in vitro models to investigate the impacts of folate deficiency on genomic stability and the subsequent risk of cancer development.

Results and Discussion

Folate pathway

Our diets often include folate as polyglutamate, which is made up of glutamine chains, pteridine, and para-aminobenzoate. The brush border of the first segment of the small intestine is where the enterocytes absorb the monoglutamate form that is produced by hydrolyzing the polyglutamates. Dihydrofolate reductase (DHFR) must convert folate present in the cell to tetrahydrofolate (THF) in order for it to have cofactor activity [11].

THF is a key component of one-carbon metabolism and a bioavailable precursor of folic acid. THF serves as a one-carbon carrier, while serine is used to create 5,10-methylene-THF and glycine. The latter serves as a cofactor, supplying the necessary methyl group for the crucial DNA synthesis step of converting dUMP to dTMP. 5,10-methylene-THF is changed into 5-methyl-THF, which is then changed into S-adenosylmetonine (SAM), serving as a methyl donor for homocysteine remethylation and cellular methylation processes. A low folate level may have a number of detrimental impacts on the body. First of all, it may cause dUMP to build up and impede the dTMP production pathway. Second, it may make methyl donors less available, which would disrupt the methylation pattern. In the end, this may result in extreme oxidation, damage to mitochondrial DNA, and eventually genetic instability [12].

Folate deficiency

As a vitamin, folic acid is essential for the survival of cells in animals. It has to be received from food since it cannot be manufactured in vivo. Although there are a number of techniques for determining folic acid levels, serum levels are often used to show recent consumption. The range for determining folate insufficiency is less than 7 nmol/liter to less than 10 nmol/liter.

Less than 315 to 363 nmol/L of red blood cell folate indicates a deficit and represents a folate status across several months [13]. Other techniques to assess folate status include elevated urine foraminoglutamate excretion tests and deoxyuridine suppression tests. Moreover, elevated homocysteine levels may operate as a useful marker of folate status. In order to be absorbed, dietary folate containing polyglutamate side chains must first be reduced and then hydrolyzed. The body may readily absorb folic acid, even if it is present as an oxidized form of pterylmonoglutamate [14].

Causes Folic Acid Deficiency

Overview of Folic Acid Absorption and Requirements

The name "folate" refers to a group of chemical forms of the vitamin that have one end of a P-aminobenzene molecule attached to a pteridine ring and the other end of the P-aminobenzene molecule linked to a single glutamic acid molecule. Naturally, the Y carboxyl group of glutamine is joined by a peptide bond to roughly (one to six) extra glutamine molecules found in meals. Folic acid has to undergo hydrolysis by conjugation at the intestinal brush boundary in order to be absorbed. High dosages of folic acid cause the intestinal folate transport mechanisms to become saturated, which reduces the efficiency of absorption; nonetheless, modest quantities of the monoglutamine form are absorbed by passive diffusion [15]. Folic acid's bioavailability is about half that of its crystalline form. In general, folic acid that is contained in food is less stable than folic acid. Biopsies of well-nourished males revealed that their stocks of folate ranged from 12 to 28 mg, with the liver containing half of this amount. Bile excretes large quantities of folic acid, most of which is reabsorbed in the small intestine. When it comes to folic acid, renal reabsorption works quite well. Accompanying folic acid Urine containing folic acid is regarded as a breakdown product. Stools lose part of their folic acid content, but they also include some that is produced by gut bacteria [17]. Reduced blood serum folate levels are a clear indicator of poor folate consumption or low absorption. This is followed by erythrocyte reduction due to elevated plasma homocysteine levels, and finally megaloblastic anemia. The Institute of Medicine's recommendations for the recommended daily amount of folic acid—400 mg for adults and between 150 and 400 mg for infants and young adults—have been the basis for the World Health Organization's guidelines [18].

Insufficient intake of folate

The primary food sources of folate are vegetables, certain types of fruits, and green leafy vegetables, fortified grains, and grain products. The true dietary folate content is reduced if the digestion process of folate is not optimal. It is expected that there will be a severe decrease in folate content among the population whose diet depends on unfortified wheat and rice as a staple food. On the other hand, studies indicate that eating one cup of cooked beans or six pieces of cornbread can provide about 70% of the daily recommended amount of folate for adult women [19].

Alcoholism

It is common for alcoholics to have insufficient dietary intake of folate. Research and clinical experiments have been conducted on laboratory animals have demonstrated the important effects of chronic alcoholics on the balance of folate in the body [20].

Chronic alcoholism is associated with reduced folate levels in patients, as seen by elevated hemocystitin levels and a folate deficit in erythrocytes and blood serum [21].When the amount of booze consumed by alcoholics surpasses 80 grams per day, their levels of folic acid fall. Alcoholics

with liver illness have higher levels of folate insufficiency than non-alcoholics do. Chronic alcoholism patients who have inadequate folic acid intake, poor intestinal absorption, and low hepatic absorption and storage are among the many variables that lead to folate deficiency [22]..

Folate losses in food preparation

The folate present in food can be relatively affected by food preparation methods, including high temperature and oxidation. Therefore, significant losses can occur in food preparation when it boiling vegetables and legumes destroys up to 80% of folate content [23]. Cutting and grinding processes when preparing food can increase the bioavailability of folate, but the presence of ascorbic acid present in foods can improve the stability of folate [24]. There is insufficient information and no adequate studies about the effect of food preparation on folate status.

Medication

Some medications can antagonize the folate: Methotrexate, sulfasalazine, phenytoin, and trimethoprim can antagonize folate utilization. These drugs prevent the absorption of folate or its conversion to its active form, which leads to a deficiency of folate in the body [25].

Mechanism of DNA instability by folate deficiency

A deficit in folate may affect DNA stability in two ways. One method is by modified DNA methylation, where folate, specifically 5-methyltetrahydrofolate (5-methyl THF), acts as methyl in the remethylation process that transforms homocysteine into methionine and then S-adenosylmethionine (SAM). Transcription of genes is controlled by SAM via the methylation of certain cytosines in DNA. A lack of folate causes cellular SAM to be depleted, which may cause hypomethylation of DNA and potentially trigger the development of proto-oncogenes, which can culminate in cancer. Less research has been done on the second method that folate may impact DNA stability than the first. A methyl group is donated to uracil by folate in the form of 10,5-methylene THF, which transforms it into thymine, an essential amino acid for DNA synthesis and repair. A lack of folate may result in uracil being incorrectly incorporated into DNA, which can induce mutagenesis. A separate process, however, may also lead to DNA instability: when a cell attempts to heal itself, it breaks the DNA molecule in order to get rid of the uracil. An ongoing folate deficiency may lead to abnormalities in the precursor of deoxynucleotide triphosphate.throughout the course of what is known as "the catastrophic repair cycle." It is possible for the uracil to be misincorporated and subsequently repaired, although this may cause double strand breaks, chromosomal damage, and even cancer. Studies conducted on humans, animals, and in vitro models of DNA stability provide evidence in favor of the theory that folic acid inhibits cancer[26]..

Folate Deficiency Impaired DNA Repair

Mammalian cells include two different kinds of DNA repair systems: mismatch repair and excision repair. In the first mechanism, short sequences and damaged bases are eliminated and replaced with fresh, normal bases. The mismatch repair process, on the other hand, is specifically designed to rectify mistakes that arise during DNA replication. Recent research in prokaryotic cells has shown that the two repair processes are not entirely independent. Mismatch repair's molecular mechanisms are associated with the excision repair system, specifically with transcription-coupled repair, one of its subtypes [27].

Carcinogenesis evolves as a result of compromised DNA repair. One such theory is that a shortage in folate causes a fault in DNA or impairs the DNA repair process. This theory is reinforced by findings on cultured cells, which show that a lack of folate in these conditions resulted in chromosomal defects, breaks in the DNA strand, and an increased susceptibility to genetic mutations [28–31]. Research conducted on lab mice suggests that a deficiency of folate may result in a

malfunction in the P53 gene, which is particular to a break in the DNA strand [32]. Given that p53 controls both the cell cycle and the DNA repair process, any alteration to the p53 gene's structure may be seen as an extra way to compromise DNA repair [33]. It is unclear exactly what metabolic process led to this aberration in the DNA [34]. The problem might have to do with the one-carbon group that folate offers, which is needed for the production of pyrimidine and purine. Human folate insufficiency is brought on by chromosomal breaks and improper uracil incorporation into DNA. This bolsters the theory that they also have an impact on persons who operate [35].

Folate and Risk of Cancer

Epidemiological studies have indicated that elevated consumption or levels of folate have been shown to guard against various types of cancer development,much evidence from in vitro, animal, and human studies has shown that folate deficiency is closely associated with DNA strand breakage, poor DNA repair, and an increase in mutations and aberrant DNA methylation [36].

Given the role of folate in one-carbon metabolism, extensive studies have been conducted on folate for its possible role in the development of cancer. For the methionine pathway folate is required in the form of 5-methytetrahydrofolate (5-MTHF) and cobalamin for converting homocysteine to methionine. Then, methionine is transformed into the compound called S-adenosylmethionine SAM. SAM is considered the main contributor of methyl in many body reactions, such as methylation of both nucleic acids DNA and RNA. A decrease in sufficient production of SAM will lead to a decrease in the CpG islands in the DNA, and this will affect many processes, including a change in the gene expression of tumor-suppressing genes as well as oncogenes and gene transcription [37]. Moreover, folate deficiency can impair the process of converting deoxyuridine monophosphate (dUMP) into deoxythymine monophosphate (dTMP), the nucleic acid necessary in the process of building and repairing DNA. Misincorporated uracil for thymine can ultimately lead to instability of the DNA and thus breakage of the DNA strands and an error in the DNA repair. Folate and cancer relationships remain uncertain, while there is evidence that anti-folate agents are used as a treatment for cancer [38].

Conclusion

Conventional epidemiologic studies indicate deficient folate status associated with an increased risk of instability of the genetic material of cells. There are two main mechanisms by which folate is thought to moderate DNA stability: The first hypothesis is that folate deficiency makes DNA hypomethylation and oncogene activation. The second hypothesis is that folate deficiency leads to continuous misincorperated of uracil during DNA synthesis leading to a catastrophic DNA repair cycle, DNA strand breakage, and chromosome damage. This is supported by evidence from cellular and animal studies.

References

[1]. A. Randomized, P. Controlled, and C. Trial, "Protective effect of folic acid on oxidative DNA damage," Medicine (Baltimore), vol. 94, no. 45, pp. 1–10, 2015, doi: 10.1097/MD.0000000000001872.

[2]. M. Fenech, "Folate (vitamin B9) and vitamin B12 and their function in the maintenance of nuclear and mitochondrial genome integrity," Mutat. Res., vol. 733, pp. 21–33, 2012.

[3]. C. E. Clare, A. H. Brassington, W. Y. Kwong, et al., "One-carbon metabolism: linking nutritional biochemistry to epigenetic pro-programming of long-term development," Annu. Rev. Anim. Biosci., vol. 7, pp. 263–287, 2019, doi: 10.1146/annurev-animal-020518-115206.

[4]. J. W. Crott, S. T. Mashiyama, B. N. Ames, et al., "The effect of folic acid deficiency and MTHFR C677T polymorphism on chromosome damage in human lymphocytes in vitro," Cancer Epidemiol. Biomarkers Prev., vol. 10, pp. 1089–1096, 2001.
[5]. X. Wu, W. Xu, T. Zhou, et al., "The role of genetic polymorphisms as related to one-carbon metabolism, vitamin B6, and gene-nutrient interactions in maintaining genomic stability and cell viability in Chinese breast cancer patients," Int. J. Mol. Sci., vol. 17, no. 1003, pp. 1–10, 2016.
[6]. C. F. Bull, G. Mayrhofer, N. J. O'Callaghan, et al., "Folate deficiency induces dysfunctional long and short telomeres; both states are associated with hypomethylation and DNA damage in human WIL2-NS cells," Cancer Prev. Res. (Phila), vol. 7, pp. 128–138, 2014.
[7]. L. Donnellan, et al., "Folic acid deficiency increases sensitivity to DNA damage by glucose and methylglyoxal," Mutagenesis, vol. 37, no. 1, pp. 24–33, 2022, doi: 10.1093/mutage/geab036.
[8]. S. S. Gropper and J. L. Smith, Advanced Nutrition and Human Metabolism, 6th ed., Belmont, CA: Wadsworth, 2013, pp. 344–353. [Online]. Available: https://www.cengage.co.uk/books/9781133104056/.
[9]. National Institutes of Health, "Folate: Dietary Supplement Fact Sheet," [Online]. Available: https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/. [Accessed: Jun. 6, 2018].
[10]. R. Pieroth, et al., "Folate and its impact on cancer risk," Curr. Nutr. Rep., vol. 7, pp. 70–84, 2018.
[11]. C. Galeone, V. Edefonti, M. Parpinel, R. Talamini, and A. F. Olshan, "Folate intake and the risk of oral cavity and pharyngeal cancer: A pooled analysis within the ENHANCE Consortium," Cancer Epidemiol. Biomarkers Prev., vol. 136, no. 4, pp. 904–914, 2016.
[12]. X. Wang, J. Yu, and J. Wang, "Neural tube defects and folate deficiency: Is DNA repair defective?," Int. J. Mol. Sci., vol. 24, no. 3, pp. 2220, 2023.
[13]. L. H. Allen, "Causes of vitamin B12 and folate deficiency," Food Nutr. Bull., vol. 29, no. 2, suppl. 1, pp. S20–S34, 2008.
[14]. L. B. Bailey, P. J. Stover, H. McNulty, et al., "Biomarkers of nutrition for development—folate review," J. Nutr., vol. 145, no. 7, pp. 1636S–1680S, 2015.
[15]. S. C. Liew, "Folic acid and diseases—supplement it or not?," Rev. Assoc. Med. Bras., vol. 62, no. 1, pp. 90–100, 2016.
[16]. Y. Lin, et al., "Quantitation of in vivo human folate metabolism," Am. J. Clin. Nutr., vol. 80, no. 3, pp. 680–691, 2004.
[17]. A. M. Molloy, et al., "Effects of folate and vitamin B12 deficiencies during pregnancy on fetal, infant, and child development," Food Nutr. Bull., vol. 29, no. 2, suppl. 1, pp. S101–S111, 2008.
[18]. Institute of Medicine, Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline, Washington, DC: National Academy Press, 2000.
[19]. L. H. Allen, "Causes of vitamin B12 and folate deficiency," Food Nutr. Bull., vol. 29, no. 2, suppl. 1, pp. S20–S34, 2008.
[20]. C. H. Halsted, et al., "Metabolic interactions of alcohol and folate," J. Nutr., vol. 132, no. 8, pp. 2367S–2372S, 2002.
[21]. J. A. Villanueva, A. M. Devlin, and C. H. Halsted, "Reduced folate carrier: tissue distribution and effects of chronic ethanol intake in the micropig," Alcohol Clin. Exp. Res., vol. 25, pp.

415–420, 2001.
[22]. H. Tilg and A. M. Diehl, "Cytokines in alcoholic and nonalcoholic steatohepatitis," N. Engl. J. Med., vol. 343, no. 20, pp. 1467–1476, 2000.
[23]. D. J. McKillop, K. Pentieva, D. Daly, J. M. McPartlin, J. Hughes, J. J. Strain, J. M. Scott, and H. McNulty, "The effect of different cooking methods on folate retention in various foods that are amongst the major contributors to folate intake in the UK diet," Br. J. Nutr., vol. 88, pp. 681–688, 2002.
[24]. J. Dang, "Folate retention in selected processed legumes," Food Chem., vol. 68, pp. 295–298, 2000.
[25]. R. Green and A. Datta Mitra, "Megaloblastic anemias: nutritional and other causes," Med. Clin. North Am., vol. 101, no. 2, pp. 297–317, 2017.
[26]. S. J. Duthie, et al., "Impact of folate deficiency on DNA stability," J. Nutr., vol. 132, no. 8, pp. 2444S–2449S, 2002.
[27]. I. Mellon and G. N. Champe, "Products of DNA mismatch repair genes mutS and mutL are required for transcription-coupled nucleotide-excision repair of the lactose operon in Escherichia coli," Proc. Natl. Acad. Sci. USA, vol. 93, pp. 1292–1297, 1996.
[28]. J. B. Mason and T. Levesque, "Folate: effects on carcinogenesis and the potential for cancer chemoprevention," Oncology, vol. 10, pp. 1727–1743, 1996.
[29]. M. Cravo, P. Fidalgo, A. D. Pereira, et al., "DNA methylation as an intermediate biomarker in colorectal cancer: modulation by folic acid supplementation," Eur. J. Cancer Prev., vol. 3, pp. 473–479, 1994.
[30]. G. A. Paspatis and D. G. Karamanolis, "Folate supplementation and adenomatous colonic polyps," Dis. Colon Rectum, vol. 37, pp. 1340–1341, 1994.
[31]. B. Libbus, L. Borman, C. H. Ventrone, et al., "Nutritional folate-deficiency in Chinese hamster ovary cells," Cancer Genet. Cytogenet., vol. 46, pp. 231–242, 1990.
[32]. R. Branda and F. Blickensderfer, "Folate deficiency increases genetic damage caused by alkylating agents and irradiation in Chinese hamster ovary cells," Cancer Res., vol. 53, pp. 5401–5408, 1993.
[33]. Y. I. Kim, I. P. Pogribny, A. G. Basnakian, et al., "Folate deficiency in rats induces DNA strand breaks and hypomethylation within the p53 tumour suppressor gene," Am. J. Clin. Nutr., vol. 65, pp. 46–52, 1997.
[34]. B. Shane and E. L. R. Stokstad, "Vitamin B12-folate interrelationships," Annu. Rev. Nutr., vol. 5, pp. 115–141, 1985.
[35]. B. C. Blount, M. M. Mack, C. M. Wehr, et al., "Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage," Proc. Natl. Acad. Sci. USA, vol. 94, pp. 3290–3295, 1997.
[36]. L. Y. Tomita, "Folate and cancer: is there any association?," J. Inborn Errors Metab. Screening, vol. 4, pp. e160016, 2019, doi: 10.1177/2326409816678180.
[37]. A. Melse-Boonstra, C. E. West, M. B. Katan, F. J. Kok, and P. Verhoef, "Bioavailability of heptaglutamyl relative to monoglutamyl folic acid in healthy adults," Am. J. Clin. Nutr., vol. 79, pp. 424–429, 2004.
[38]. N. Craig, S. Johnson, K. Komachi, et al., "Basic genetic mechanisms," in Molecular Biology of the Cell, B. Alberts, D. Bray, J. Lewis, et al., Eds., New York and London: Garland Publishing, 1994, pp. 223–290.