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Review Article

The role of folic acid in carcinogenesis, diagnosis, and treatment of cancer

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ABSTRACT

Introduction: Folic acid, also known as folate, is one of the water-soluble B vitamins which its derivatives are involved in many metabolic reactions as cofactor, that are mostly contributed in cell growth. Regarding the role of derived cofactors from this vitamin in reactions such as methylation, production of thymidine and purines; seems that there is a relationship between this vitamin and cancer.

Methods: We searched Medline/Pubmed, Scopus, Embase and Web of Science (2000-2017) using term folic acid, carcinogenesis, diagnose and treatment. Our focused was on the articles published within the past 5 years and type of study in culture media, animal models and clinical trials were in our favor.

Results: Candidate mechanisms in carcinogenesis for folic acid include 1: changes in DNA and RNA methylation 2: Damage to the integrity and stability of DNA 3: disruption in repair system of DNA.

Conclusion: Folic acid in carcinogenesis acts as a double-edged sword**.** The activity type of folic acid depends on the physiological conditions, dosage of the vitamin, age, individual genotypes, target tissues and stage of the disease in patients. High growth rate of cancer cells leads to increase in cell requests of the vitamin, and on the other hand the cells enhance the number of receptors improving the vitamin absorption. Therefore, increasing number of cell surface receptors, it can be applied for non-invasive diagnosis and target therapy.

Introduction

Folic acid is one of the water-soluble B vitamins acting as a cofactor to participate in many biochemical reactions such as one-carbon transfer (1). Mammals cannot synthesize this vitamin and it must be obtained from food sources or foods fortified with folic acid. Folic acid is oxidized and monoglutaryl form of vitamin B9 and its synthetic form of the vitamin is used in commercially fortified foods or supplements (2). Folic acid is more stable than the folate natural form of vitamin B9 (3). Folate cofactors with coenzymes which are derived from B2, B6, and B12 vitamins and it is essential for catabolism of one-carbon compounds (4). Biochemically, the one-carbon units are transferred from serine or glycine to tetrahydrofolate to form methylene-tetrahydrofolate (5). Then this material is involved in the below-mentioned processes: a) Production of thymidine and entering this organic base to structure of DNA. b) Production of purines, basic precursors of the RNA and DNA that is oxidized to formyl-tetrahydrofolate. c) Reduction to methyl-tetrahydrofolate which is necessary for

homocysteine-methionine conversion by methylation that majority of this material turns to the S-adenosylmethionine, as general donor of methyl groups to DNA, RNA, hormones, neurotransmitters, membrane lipids and proteins (6). Figure 1 shows the reactions that folic acid and its metabolites which are involved in this reaction (7). The relationship between folic acid deficiency and various diseases has been demonstrated in humans and it can also be noted to congenital neural tube defects, atherosclerosis, and cancer (1, 8, 9). Although some epidemiological studies, along with studies on animal models had shown that folic acid can have a protective effect against carcinogenesis, especially in the colon cancer cases (10-11), but recent epidemiological studies revealed a paradox results in this regard, and some studies showed a direct relationship between high intake of folic acid and risk of breast cancer (12-14). Stolzenberg *et al.* have reported an increased risk of breast cancer by 32% in postmenopausal women who had high intake of folic acid (14). Also, another study (15) suggests that folic acid can make some causes to the development of leukemia. In this research we tried to describe the relationship between folic acid and cancer and discuss about new findings of literature

Methods

We searched Medline/Pubmed, Scopus, Embase and Web of Science (2000-2017) using the term folic acid, carcinogenesis, diagnose and treatment. Our concern was the articles published within the past 5 years and type of the studies in culture media, animal models and clinical trials were also in our favor.

Results

Folic acid and carcinogenesis; Mechanistic of folic acid's carcinogenesis

Modification in DNA methylation

DNA methylation is a chemical modification which occurs in the covalent addition of a methyl group at carbon 5 of cytosine, it was previously thought and it can only happen in sequence of 5'CG 3', called a CpG dinucleotides or islands, but now, it states that the addition also occurs in CpA and CpT islands (16). Since human genome is not methylated monotonously, DNA methylation can alter gene activity without modifying the gene sequence (17), so the increase of DNA methylation level in the promoter region can be reduced in gene expression. In the vertebrate more than 4% of genome which is methylated in CpG sequences that are considered as of palindromic sequences. While the cells highly maintain their methylation pattern**;** Inappropriate DNA methylation of tumor suppressor genes plays a critical role in carcinogenesis. Reduction in the level of DNA methylation of oncogenes is an important finding in tumorigenesis that has been observed in cancers of the colon, stomach, cervix, prostate and breast (17, 18). It is unexpected and amazing observed that DNA methylation pattern which is hardly protected by cells; it is disturbed by modifying the amount of folate in both animals and human beings. In this regard, Jacob et al showed that the hypomethylation of DNA can be induced by a long-term diet with folate deficiency in the volunteers (19). Hypo-methylation of certain genes is important than whole genome in carcinogenesis. For example, it has been shown that the P53 gene (exons 5-8) which is hypo-methylated is induced by folate deficiency. It is previously marked that in human cancers is more likely to have mutations in this part of P 53 (20). Recent results exhibited that the methylation changes at the special position may lead to subsequent mutation. Methylated cytosine in the carbon position number 5 is unstable compared to none methylated form**.** Hydrolytic deamination of 5-methylcytosine causes a mutation of the G/T mismatch, then lead to transition mutation (C→T), so we can conclude that methylation determines hot spots for mutation of DNA in the human (21). However, in contrast to the idea, it should be noted that deamination of non-methylated cytosine to uracil can be achieved especially when the S-adenosylmethionine level is low and can also be the result of a lack of folic acid. In Lubecka-Pietruszewska *et al.* study (22) showed that folic acid causes hyper-methylation of PTEN, APC and RARbeta2 tumor suppressor genes that the hyper-methylation suppresses the expression of these genes. So translational repression by hyper-methylation of promoter can disable **t**umor suppressor genes in cancer and so the folate deficiency can reduce methylation of these genes

Modification in RNA methylation

Variety of RNAs, like DNA, is methylated by S-adenosylmethionine. RNA methylation may occur in the cap of mRNA and in some cases may be in internal nucleotides (23). The methylation patterns are strongly maintained by cells and it seems to contribute into the stability of RNA and the

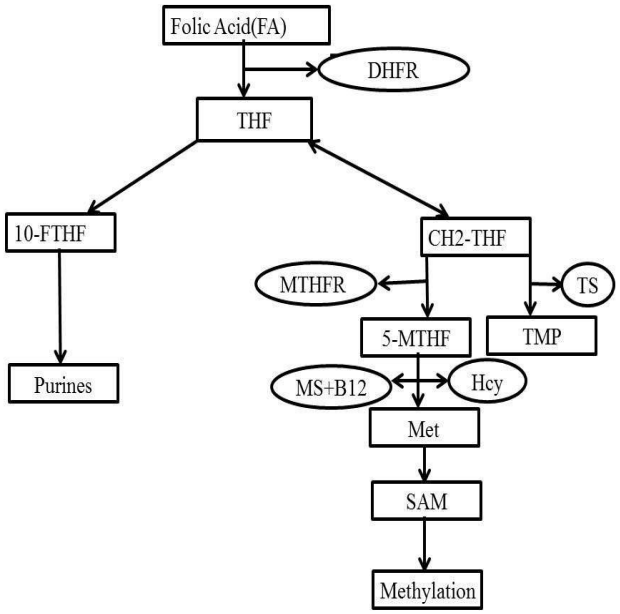

Figure 1. Folic acid metabolism and its role in biosynthesis of purines,thymine and methylation reaction (7). **FA**: Folic Acid, **DHFR**:dihydrofolate reductase, **THF**: tetrahydrofolate, **10-FTHF**: 10-formyl- THF, **HCY**: homocysteine, **MS**: methionine synthase, **MTHFR**: methylenetetrahydro-folate reductase, **SAM**: Sadenosyl methionine,**TS**: thymidylate synthase.

facilitated exit of RNA from the nucleus to the cytoplasm for translation and protein synthesis. It has recently been observed that folate deficiency leads to demethylation of SnRNAs that these types of RNA are required for mRNA maturation (24). There are evidences suggesting that the activities of tRNA methylating enzymes are different in tumor tissues from normal tissues. It is not clear yet that changes in methylation of RNA molecules are a causative role in the development of cancer or an event that takes place along with the development of cancer (25).

Damage to the integrity and stability of DNA

Folic acid deficiency induces broken chromosome**,** and these breaks can increase the risk of cancer in Studies in cell culture and animal models suggest that folic acid deficiency increases the broken parts in phosphodiester bonds in chromosomal DNA that is molecular basis for the breaking. There are mechanisms that explain folic acid deficiency causes of such breaks (26). Folic acid deficiency causes decreased production of thymine nucleotides from uracil and it cause the lack of balance between the nucleotides and an increase wrong entrée of uracil in DNA structure because most DNA polymerases are not differentiate between deoxyribose uridylate and thymidylate. DNA repair systems delete entered uracils of DNA strand by the glycosilase and it causes broken that these broken cause genome instability. It is observed that DNA breaks without repair cause cell transformation in the culture medium and increased risk of cancer. High presence of uracil in DNA increases the breakdown of chromosomes and also it has been observed plentifully in patients with folate deficiency which by folic acid supplements is reversible (27). However it should also be noted that in the viruses that are known to be carcinogenic and their genome integrate into the genomes of their hosts and it is possible methylation of host genome also induces blocking the process, while hypomethylation and broken chromosomal causes can increase the entry of the genome of viruses into the genome of normal cells (28).

Disorders in DNA repair system

Folate deficiency induces an imbalance in the source of deoxynucleotides and the wrong entry of uracil in DNA that this misplaced entry causes to enter an abnormal DNA to process of DNA replication and the imposition of dependence on the repair system (29). Cells growing in culture media with folate deficiency demonstrate these chromosomal aberrations, but cells that grow in a medium containing hypoxanthine demonstrate much lower damages. Hypoxanthine is a precursor for the synthesis of purines that steps needed to the folic acid were covered during the synthesis of purines (30). In another study, folic acid deficiency with alkylating agents' acts synergistically in generating somatic mutations, and also with gamma rays and beta in creating chromosomal breakages (31). It is observed that in the excision repair system that it is defective in conditions of folic acid deficiency. In squamous cell cancer of colon it is compared with normal squamous cells in its normal patterns of DNA methylation that some abnormalities are observed which may occur in folic acid deficiency eventually affecting the effectiveness of DNA repair system, because DNA methylation play an important role in repairmen of DNA strand for changes after replication (32).

Antioxidant role of folic acid

Aging is a risk factor for many diseases such as cancer. Studies show that nutrients, especially vitamins can prevent aging process and therefore prevent diseases that have been associated with cancer. Vitamins are the most effective factor in preventing oxidative reactions (33, 34). Some studies introduce folic acid as free radical scavenger and an anti-cancer role is also considered for it (31). In a

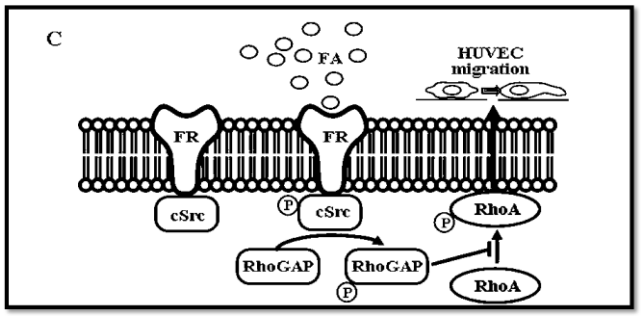

Figure 2. FR: Folic acid Receptor, **HUVEC**: Human Umbilical Vein Endothelial Cells, **RhoGAP***:* Rap-activated Rho GTPase- activating Protein, **RhoA**: Ras homolog gene family, member A, **cSrc**: SRC: proto-oncogene tyrosine-

study on *Caenorhabditis elegans* as an experimental model it has been showed that folic acid can be assumed as anti-oxidants and its antioxidant properties could increase the lifetime (35).

Paradoxical outcomes of folic acid deficiency in normal and cancerous tissues

Epidemiological and laboratory evidences showed that folic acid deficiency in normal tissues causes that these tissues to be susceptible to neoplastic transformation and on the other hand folic acid supplements prevents the development and progression of tumors in normal tissues (36). Most of the evidences demonstrated that folic acid deficiency increases the amount of DNA strand breakages, defects in the DNA repair system, mutation and deviation in DNA methylation patterns, so folic acid supplements can compensate some of the defects and help to correct these issues (37). Considering folic acid as a cofactor for enzymes involved in purine synthesis and thymidylate plays an important role in the synthesis/replication of DNA. Thus folic acid deficiency in cells with rapidly growth can cause a dysfunction of the DNA synthesis. In neoplastic cells, DNA replication and cell division carried out with an increased rate; therefore, interference with the metabolism of folic acid causes interferes with DNA synthesis and causes cell growth inhibition. This is the base of cancer chemotherapy, so some of the anti-folate agents such as methotrexate and 5-fluorouracil are applied in this regard. In addition, studies have shown that folic acid deficiency prevents the progression of pre-existing tumors (38).

Folic acid and colon cancer

The role of folic acid has been well studied in carcinogenesis and progression of colon cancer. Case-control studies suggest an inverse relationship between the daily intake of folic acid and the risk of colon cancer and also its progression. Some studies showed low levels of folic acid in neoplasms. A study in Michigan in United States showed that Folic acid prevents cancer cell growth through block epidermal growth factor receptor [EGFR] signaling and pathway-dependent growth. It should be noted that an overgrowth of cells in the gastrointestinal tract is a central and a main event in the carcinogenesis and tyrosine kinases particularly EGFR play an important role in the regulation of cell proliferation. On the other hand there is evidence stating that a major role for EGFR is played in colon cancer. For example, over-expression of EGFR in neoplastic cells of colon also increases the activity of EGFR in colonic mucosa of patients with ulcerative colitis, adenomatous polyps and colon cancer. In this research, the amount of changes in the level of gene expression was measuredand the activity of EGFR that was induced by folic acid and it was observed that the expression and activity of EGFR reduced affected by folic acid (39). Another study (40) evaluated the effect of folic acid on insulin-like growth factor I (IGF-I) receptor gene expression in colon cancer cell line. IGF-I receptor plays a critical role in colon cancer creation and its progression. This receptor has an anti apoptotic role, which is coupled with some intra-cellular pathways such as phosphatidyl inositol 3-kinase as a tyrosine kinase receptor. High expression of this gene can also be observed in primary tumors and colon cancer derived cell lines. Increasing the serum level of IGF-R is accompanied with adenomatous polyps even in upgraded adenomas. The results showed that folic acid can reduce the expression of this receptor which is folic acid dose-dependent, and also it is induced by decreasing in activity of promoter of IGF-I gene receptor.

Folic acid and angiogenesis

Angiogenesis is a generation process of new vessels from current ones performed by growth and migration of endothelial cells in a process which is called germination. However this process in the time of fetus is common, but it rarely happens in adults except in the time of wound healing and reproduction cycle in women (41). Reaching to nutritious materials and oxygen for all cells is possible when they are near the vessels in distance of 100-20 micro meters, so in development of a cancer, the process of angiogenesis for tumors especially metastatic ones, is very important (42). Recent studies have shown that folic acid is able to cease the angiogenesis process in two steps: I) Proliferation of endothelial cells by activating the cSrc/ERK-2/NF-κB/p53 pathway

which is related to folic acid receptors (43). II) Inhibiting the cell migration by preventing the action of ras homolog gene family, member A (RhoA) which is performed by activating the cSrc/p190RhoGAP-signaling pathway which is in association with folic acid receptors. In this way, folic acid provokes the activation of cSrc by binding to its cellular receptors, and then the activation of cSrc induces activating RhoGAP and activation of RhoGAP prevents activating RhoA and inactivating RhoA prevents cell migration (Figure 2) (44).

Folic acid in treatment and diagnosing cancer

Folic acid cell receptors and cancers

Folic acid or folate is of a high importance to proliferation and activities of cancer cells, but it seems cancer cells need this vitamin more than other cells (45) . In order to receive enough amount of this vitamin by cancer cells, special places are provided on the surface of these cells as folate receptors. Three isoform of these receptors have also been detected: alpha beta and gamma. These receptors bind to the cell membrane surface by a glycosylphosphatidylinositol anchor (46). Alfa isoform have been investigated more than others. It has been shown that this kind of receptors has a restricted expression in normal cells, but in epithelial cell derived tumors its expression is very high, and also it has been determined that these receptors have a high expression in ovarian cancer, and this high expression is accompanied by cancer progression and fatality. The reasons for high expression of these

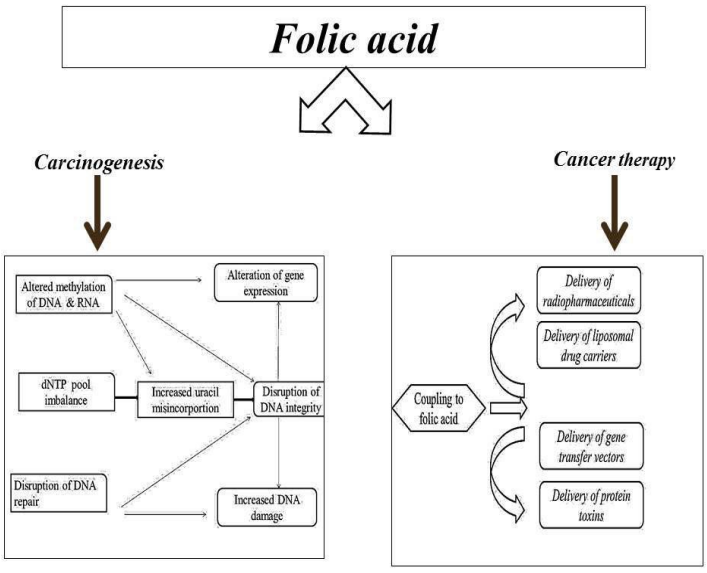

Figure 3. The role of acid folic in carcinogenesis and treatment of cancer

receptors in cancer cellsare not clear in comparison with normal cells but: I) they may adjust the folic acid uptake from circulation II) they likely effect cell proliferation through intra-cellular signaling pathways like other receptors which have phosphatidylinositol anchors (47).

Cell surface receptors of folic acid for diagnosis and treatment goals

These receptors on the cell surface can be used in the diagnosis and treatment that can be done in two ways: Coupled with monoclonal antibodies against the receptors or coupled with folic acid that in this way folic acid is considered as a ligand. Using folic acid conjugates has some advantages rather than monoclonal antibodies are as following: less immunogenicity growing small, easy access and low costs, simple chemical formulation (45), high tendency of these receptors and the lack of receptors on the surface of normal cells and high specificity in cancer tissues (48) and ligand-receptor complex can enter the cell via endocytosis so it results in facilitating the delivery of therapeutic agents to the target cells (49). Some of folic acid conjugates which can be used in experimental studies are listed below: The conjugates which are used to delivery radiotherapeutic drugs: to deliver the radionucleotides, folic acid conjugates with low molecular weight are used. Because of these conjugates small sizes and fast clearance, using them, compared to monoclonal antibodies is more advantageous (47). Therapeutic drugs deliver using folic acid conjugated liposomes: liposomes are bilayer phospholipid vesicles. Therapeutic efficiency of liposomes in carrying the drugs can be carried out by elective and specified connections to the tumor tissue. In order to effective targeting of liposomes, folic acid binds to the liposome with PEG spacer (50). Gene vector delivery: gene therapy is a promising method in treatment of humankind diseases. Some effective treatment methods have also been developed in cancer gene therapy until now. An appropriate vector should be safe with reasonable cost and stability, and they should be able to deliver the intended gene to the specified tissues. Being conjugated with folic acid can make the vector be more specific. For examples, there are folic acid paired viral vectors which have folic acid receptors (51). Protein toxins delivery: studies have shown that protein toxins conjugated with folic acid, are able to kill the cells with high expression of folic acid receptors effectively, without any harm to normal cells (52).

Conclusion

Folic acid has got a bifunctional performance in cancer and carcinogenesis depended on physiological conditions and the dosage of folic acid. In a healthy person folic acid deficiency can be resulted in genome double-stranded breaks that can be resulted in cancer, but in a person with cancer, folic acid may result in progression of cancer. Also, folic acid can be used for diagnosis and treatment of cancer in non-invasive diagnosis methods.

Ethical disclosure

Not applicable.

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Authors' contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Conflict of interest

All authors declare that there is no conflict of interests.

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