Editorial

Folic acid and colorectal cancer

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Folic acid is necessary for the synthesis of nucleotides and plays a pivotal role in the repair mechanisms of DNA. Derangements in DNA methylation provokes alterations in proto-oncogenes expression with potentially detrimental effects on cellular proliferation. S-adenosyl-methionine (SAM) constitutes the major donor of methyl groups in humans and its production depends on folic acid and methionine. Methyl-tetrahydrofolic acid is essential for the synthesis of methionine. As a consequence, methionine deficiency leads to folic acid depletion, as the organism attempts to replete the body stores of the former. Green vegetables and liver constitute major natural sources of folic acid.

The importance of folic acid in DNA synthesis and repair led to the assumption that its deficiency could trigger neoplasia. There is some evidence that folic acid deficiency predisposes to the development of certain malignancies, such as in the stomach, esophagus, breast, lungs and female genital system. The most important correlation, however, seems to exist with colorectal cancer and its precancerous lesions (adenomas).[1] The first epidemiological studies came from patients with ulcerative colitis.[2] Many other studies followed thereafter, and there is now enough evidence to support that low folate intake in combination with high alcohol intake increases the risk for colorectal cancer by 3,3 times.[3] There are few studies that failed to prove such a correlation.[4] Lashner *et al*[5] showed that after supplementation of folic acid for 6 months in patients with ulcerative colitis there was a 28% decrease in the risk for colorectal cancer. It seems that both sexes are equally predisposed. This correlation remains controversial for rectal cancer and colorectal adenomas. Although low folate levels predispose to the development of adenomas,[6] a prospective study from the same group showed that folate supplementation did not reduce the relapse rate at 2 years.[7]

Moderate and heavy alcohol consumption has been correlated with an increased risk for colorectal cancer. The suggested mechanisms of carcinogenesis include the increased catabolism of methionine as well as the depletion of mucosal folate due to alcohol metabolism to acetaldehyde from the colonic flora.[1]

The correlation between mucosal folate levels and colorectal cancer remains controversial. Kim *et al*[8] reported reduced folate levels in the normal mucosa adjacent to adenomas but not to hyperplastic polyps. These data gave rise to the concept that mucosal folate deficiency precedes the development of colorectal neoplasia but contradict other studies where no reduction of folate levels of the normal mucosa was found except a slight reduction in polyps and cancers.[9]

There are several aetiopathogenetic mechanisms to explain the role of folate deficiency in carcinogenesis: a) Derangement of nucleotide incorporation in DNA, particularly of uracil in RNA. Animal studies have shown that this derangement leads to mutations of oncogenes and tumour suppressor genes. b) Impairment in DNA methylation and cellular proliferation: Folate is essential in the synthesis of pyrimidines and purines and in preserving adequate levels of SAM. Its deficiency per se or in combination with other dietetic components that serve as methyl donors such as choline, leads to DNA hypomethylation especially in promoter areas, resulting in altered gene expression. c) Enhanced gene expression: DNA hypomethylation enhances the expression of oncogenes such as *ras* and *c-myc* that regulate cellular proliferation. d) DNA disruption-resulting from DNA hypomethylation-that leads to mutations and derangements in chromosome positioning during mitosis. Animal studies

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in rats have shown that folate deficiency leads to DNA disruption in genes such as APC and p53. e) Structural alterations of chromatin that render chromosomes prone to damage during mitosis (loss or duplication). This phenomenon is common in colorectal but not in other cancers.

Methylene-tetrahydrofolate reductase (MTHFR) catalyses the conversion of 5,10 methylene-tetrahydrofolic into 5-methyl-tetrahydrofolic acid. This enzyme has recently attracted much scientific interest as it shows genetic polymorphism.[1] 10% to 12% of the population carries a mutation of the gene that encodes for MTHFR (substitution of cytosine 667 by thymine). Individuals heterozygous for the mutation demonstrate 65% of the normal enzyme activity whilst homozygous only 30%. This latter group may have an increased risk of colorectal cancer in case of folate deficiency due to DNA hypomethylation. Although a reduced risk for adenomas is reported in homozygous with reduced folate intake,[10] this does not seem to be the case with colorectal cancer where the frequency is low.[11] Of course, in this latter study this subgroup of homozygous individuals reported high folate and low alcohol intake.

Several theories have been developed in order to explain these contradictory results. The correlation between homozygous for the mutation state and adenomas is expected as a result of reduced methylation capacity. It is well known that the imbalance between pyrimidine deoxy-nucleotides in favor of dUMP may lead to mutation. The reduced activity of MTHFR prevents the depletion of 5,10 methylene-tetrahydrofolic acid and therefore increases its intracellular stores, thus preserving the balance between dUMP and dTMP. Although this theory explains the reduced incidence of colorectal cancer in homozygous individuals, a more satisfactory explanation is the following: The evolution of an adenoma to cancer includes a complex process of DNA methylation which is impaired in homozygous. On this basis, folate supplementation could enhance the evolution of the adenoma to carcinoma.

Today, there is plenty of evidence to support that reduced folate intake predisposes to the development of colorectal cancer. The great importance of folate in diet has led many nations to adopt the artificial enriching of foods with folate. Once more the protective role of fresh fruits and vegetables in preventing colorectal cancer is evident. More intensive research is needed however in order to clarify the role of folate in the adenoma to carcinoma sequence.

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