

Folate, gene expression and genomic stability

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Folate deficiency has been known to be a cause of megaloblastic anaemia since 1930. However, in the past two decades it has become evident that various methylated/reduced forms of this vitamin play a key role in DNA metabolism, specifically maintenance methylation of CpG sequences and in the synthesis of thymine, one of the four bases in DNA. Inadequate maintenance methylation of CpG has important consequences which include (a) altered methylation of CpG islands which impacts on gene expression, (b) altered structure of centromeric DNA leading to chromosome loss and aneuploidy during cell division and (c) expression of parasitic (viral) DNA sequences. These events lead to important changes in the phenotype of cells and are an initiating step in cancer. The other important role of folate (5,10-methylenetetrahydrofolate) is the synthesis of dTTP (deoxythyminetriphosphate) from dUMP (deoxyuracilmonophosphate). This reaction is important because folate deficiency increases the dUTP/dTTP ratio which results in uracil being incorporated into DNA instead of thymine. Uracil in DNA is highly mutagenic, and the cell dedicates four of eight known human DNA repair glycosylases to remove this base. Incorporation of uracil in DNA leads to excessive excision repair sites and the subsequent formation of DNA double stranded breaks which are similar to the DNA lesions caused by ionising radiation. The formation of DNA double stranded breaks leads to chromosome breakage, chromosome rearrangement and gene amplification, important events in the initiation and progression of cancer. The capacity to utilise folate is dependent on dietary intake and also on polymorphisms that affect the activity of proteins/enzymes involved in the deconjugation, conjugation, reduction, methylation and receptor transport. When vitamin B12 is oxidised or concentration is low, activity of methionine synthase is reduced, lowering SAM concentration and trapping folate as 5-methyltetrahydrofolate making folate unavailable for synthesis of dTMP and methylation of DNA. In view of the above we have dedicated our research efforts in defining the optimal concentration of folate and vitamin B12 for minimising DNA damage in human cells. To date our research suggests that chromosome damage in human lymphocytes *in vivo* is minimised when RBC concentration of folate exceeds 600 nmol/L, plasma B12 exceeds 300 pmol/L and plasma homocysteine is less than 7.5 μmol/L (1). These concentrations are achievable at above RDA intake of folic acid (700 μg) and vitamin B12 (7 μg) (1). *In vitro* studies suggest that the optimal concentration of folic acid in medium for minimising DNA damage is in excess of 60 nmol/L which is greater than the normal range of folate concentration in human plasma (15-40 nmol/L) (2). These studies suggest that current RDAs for folate and vitamin B12 may not be adequate for minimising DNA mutation. This has led to the concept that RDAs should be designed to minimise DNA damage rate because genomic instability is a causative factor in degenerative diseases such as cancer, Alzheimer's disease and accelerated ageing (3).

1. Fenech M, Aitken C and Rinaldi J. Folate, vitamin B12, homocysteine status and DNA damage in young Australian adults. *Carcinogenesis* (accelerated paper) 1998; 19: 1163-1171.
2. Crott JW, Fenech M. (2001) The effect of folic acid deficiency and MTHFR C677T polymorphism on chromosome damage in human lymphocytes *in vitro*. (submitted).
3. Fenech M. Recommended dietary allowances for genomic stability. *Mutation Res* 2001, (in press).