

Abstract

J Nutr Biochem. 2008 May; 19(5): 328-335.

Moderate folate depletion modulates the expression of selected genes involved in cell cycle, intracellular signaling and folate uptake in human colonic epithelial cell lines.

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BACKGROUND: Folate deficiency may affect gene expression by disrupting DNA methylation patterns or by inducing base substitution, DNA breaks, gene deletions and gene amplification. Changes in expression may explain the inverse relationship observed between folate status and risk of colorectal cancer.

METHODS: Three cell lines derived from the normal human colon, HCEC, NCM356 and NCM460, were grown for 32-34 days in media containing 25, 50, 75 or 150 nM folic acid, and the expression of genes involved in cell-cycle checkpoints, intracellular signaling, folate uptake and cell adhesion and migration was determined.

RESULTS: Expression of Folate Receptor 1 was increased with decreasing media folate in all cell lines, as was p53, p21, p16 and beta-catenin. With decreasing folate, the expression of both E-cadherin and SMAD-4 was decreased in NCM356. APC was elevated in NCM356 but unchanged in the other lines. No changes in global methylation were detected. A significant increase in p53 exon 7-8 strand breaks was observed with decreasing folate in NCM460 cells.

CONCLUSION: The changes observed are consistent with DNA damage-induced activation of cell-cycle checkpoints and cellular adaptation to folate depletion. Folate-depletion-induced changes in the Wnt/APC pathway as well as in genes involved in cell adhesion, migration and invasion may underlie observed relationships between folate status and cancer risk.

PMID: 17681772

