

Abstract

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Low dietary folate initiates intestinal tumors in mice, with altered expression of G2-M checkpoint regulators polo-like kinase 1 and cell division cycle 25c.

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OBJECTIVE: Clinical reports have suggested that low dietary folate increases risk for colorectal cancer. Animal studies for investigation of folate and tumorigenesis have used carcinogen induction or mice with germ-line mutations.

METHODS: We have developed a new spontaneous tumor model in which mice, with or without a null allele in a key folate-metabolizing enzyme, methylenetetrahydrofolate reductase (Mthfr), develop intestinal tumors due to low dietary folate alone.

RESULTS: On folate-deficient diets, 12.5% of Mthfr(+/+) mice and 28.1% of Mthfr(+/-) mice developed tumors; mice on control diets were negative. Dietary and genotype effects on tumor development were significant. To investigate mechanisms of folate-dependent tumorigenesis, we examined levels of DNA damage and gene expression of two genes involved in DNA damage response and G(2)-M checkpoint regulation, polo-like kinase 1 (Plk1) and cell division cycle 25c (Cdc25c). Folate deficiency increased DNA damage and decreased expression of both genes (assessed by quantitative reverse transcription-PCR and immunofluorescence) in normal intestine compared with levels in mice on control diets. An immunofluorescence assay for CDC25c activity (phosphorylated CDC2) also found CDC25c activity to be decreased in folate-deficient normal intestine. In tumors, however, Plk1 and Cdc25c mRNA were found to be higher (11- and 3-fold, respectively) compared with normal intestine from folate-deficient mice; immunofluorescence studies of PLK1, CDC25c, and phosphorylated CDC2 supported these findings.

CONCLUSIONS: Our data suggest that folate deficiency can initiate tumor development, that Mthfr mutation can enhance this phenomenon, and that altered expression of Plk1 and Cdc25c may contribute to folate-dependent intestinal tumorigenesis.

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