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Research Interests

Folate is an essential nutrient that is required for the synthesis of DNA precursors and S-adenosylmethionine, a cofactor required for cellular methylation reactions. Intracellular folate concentrations are tightly regulated, and cells do not accumulate high levels of folate. Therefore, cells are highly susceptible to becoming folate-deficient. The underlying biochemical mechanisms that regulate cellular folate concentrations have not been established, but evidence suggests a role for folate catabolism in the regulation of intracellular folate concentrations. The expression of the cDNA encoding for the enzyme methenyltetrahydrofolate synthetase (MTHFS) decreases total cellular folate by accelerating the rates of folate catabolism. Recombinant mouse MTHFS protein copurifies with both Cu^{2+} and an oxidized NADA derivative, which can function as electron acceptors for folate catabolism. Mouse MTHFS protein reconstituted with Cu^{2+} and oxidized NADA results in an active protein complex capable of catabolizing 5-methylTHF to pABG, and this is the first evidence for MTHFS-mediated folate catabolism *in vitro*. MTHFS activity was determined in 14 sets of animal tumors and surrounding normal tissue, and the activity was found to be increased between 2- and 24-fold in all 14 sets of animal tumor samples relative to controls, suggesting that elevated rates of folate catabolism associated with increased MTHFS activity are responsible for the folate deficiency observed in most cancers. Therefore, alterations in the regulation of intracellular folate levels, specifically resulting from accelerated folate catabolism rates, may be an early event that is responsible for the loss of methylation common in many types of cancer. Folate catabolism is the newly identified parameter that directly affects the regulation of cellular folate concentrations.

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