The Antifolate Activity of Tea Catechins

To the Editor:

In the March 15, 2005, issue of Cancer Research, Navarro-Perán et al. (1) described how epigallocatechin gallate (EGCG) inhibits the key folate enzyme dihydrofolate reductase (DHFR).

This study is of tremendous interest. The authors point to the recognized benefits of green tea containing EGCG as a functional food that may be both anticarcinogenic as well as antimicrobial. The mechanisms they focus on parallel those that are used by methotrexate and sulfonamides, respectively. This, as they point out, could explain why an excess of gallated polyphenols associated with high maternal tea consumption is linked to neural tube defects (2). It is difficult, however, to reconcile preventative health benefits with a mechanism of action that mimics that of methotrexate, an antifolate that is only efficacious because of its extreme toxicity.

There is an alternative mechanism that might explain a preventative role for EGCG in the etiology of cancer that was not discussed by Navarro-Perán et al. (1). A mild inhibition of DHFR may well reduce the regeneration of tetrahydrofolate for cellular one-carbon transfer reactions, including those destined for nucleotide synthesis as the authors indicate; however, the actual beneficial effect of EGCG could stem from an accumulation of dihydrofolate.

Dihydrofolate is an allosteric inhibitor of methylenetetrahydrofolate reductase. If, under folate-replete conditions, EGCG causes an accumulation of dihydrofolate, this could inhibit methylenetetrahydrofolate reductase and redirect one-carbon units from methionine into thymidylate biosynthesis. This promotes stable DNA production with fewer chromosomal breakages (3).

However, irrespective of whether this putative mechanism does explain the preventative health benefits of green tea consumption, it does raise the question of whether EGCG could have any long-term negative effects in folate-deplete individuals because folate shortage and perturbations of methylenetetrahydrofolate reductase activity are actually likely to promote chromosome instability via uracil misincorporation (3). Perhaps then, it is fortuitous that green tea is also purported to be a good source of folate (4)!

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References
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