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SUPPRESSION BY CHLOROPHYLL, BUT PROMOTION BY CHLOROPHYLLIN, OF COLON CARCINOGENESIS IN THE FISHER 344 RAT

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The carcinogens 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) and 1,2-dimethylhydrazine (DMH) induce colon tumors in the Fisher 344 rat that contain mutations in Ctnnb1, the gene for b-catenin, but the pattern of mutation differs from that found in human colon cancers. In both species, mutations affect the glycogen synthase kinase 3 β (GSK-3 β) consensus region of β-catenin, but whereas they directly substitute critical Ser/Thr phosphorylation sites in human colon cancers, the majority of mutations cluster around Ser^{33} in the rat tumors. Chlorophyllin (CHLIN), the water soluble salt of chlorophyll (CHL), was found at a low dose to promote the colon tumors induced by DMH, but not those induced by IQ. Unexpectedly, the pattern of b-catenin mutation was altered in the promoted tumors; most of the mutations directly substituted critical Ser/Thr residues in the GSK-3 β motif (i.e. Ser^{37}, Thr^{41}, Ser^{45}). In addition, tumors with mutations in this region had increased mRNA and protein levels of three gene targets of b-catenin involved in cell proliferation, *cyclin D1, c-Myc,* and c-*Jun,* compared to both normal colon tissue and tumors expressing wild-type β-catenin. Although CHLIN is commonly used in experiments it differs from CHL found in plants in that it is a copper salt that lacks the phytol side chain present in chlorophyll. To investigate the effects of CHLIN, CHL, copper, and phytol on colon carcinogenesis, an aberrant crypt foci (ACF) study was conducted. Fisher 344 rats were initiated with the carcinogens IQ and azoxymethane (AOM) and then given comparable levels of CHLIN, CHL, copper, or phytol. CHL suppressed the formation of AOM induced ACF, and mildly suppressed IQ induced ACF while CHLIN, copper, and phytol did not suppress nor promote.

In summary, CHLIN was found not to be protective against IQ or DMH induced colon carcinogenesis and can be promotional at low doses. However, CHL was found to suppress IQ and AOM induced ACF. These results seem to indicate that the amount of chlorophyll or chlorophullin given as well as the form may influence the development of colon carcinogenesis. Supported by NIH grant CA65525 and CA80176.