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[Lab. of Biochemistry]

ICRF-193, a Catalytic Inhibitor of DNA Topoisomerase II , Delays the Cell Cycle Progression from Metaphase, but not from Anaphase to the G1 Phase in Mammalian Cells.

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We have shown previously that ICRF-193, a catalytic inhibitor of DNA topoisomerase II (topo II), delays cell cycle progression in HeLa S3 cells. We report here that the delay of the transition in M phase is observed when HeLa S3 cells were treated with ICRF-193 during metaphase, but not thereafter. ICRF-193 also delayed the degradation of cyclin B in the transition from M to G1 phase, while in Chinese hamster ovary (CHO) cells the drug did not delay the progression in M phase. Since HeLa S3 and CHO cells are 'stringent' and 'relaxed' in mitotic control, respectively, it is suggested that under topo II inhibition, the M phase checkpoint operates through an inability for chromosome segregation.

[Carcinogenesis, 18, 957-965 (1997)]

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Chemoprevention of Azoxymethane-induced Rat Colon Carcinogenesis by the Naturally Occurring Flavonoids, Diosmin and Hesperidin.

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The modulating effects of dietary feeding of flavonoids, diosmin and hesperidin, both alone and in combination, during the initiation and post-initiation phases on colon carcinogenesis initiated with azoxymethane (AOM), were investigated in male F344 rats. Animals were initiated with AOM by weekly s. c. injections of 15 mg/kg body wt for 3 weeks to induced colon neoplasia. Feeding of two flavonoids, both alone and in combination, significantly inhibited the development of aberrant crypt foci, the 5'-BrdU labeling index, ODC activity and blood polyamine levels. These results indicate that diosmin and hesperidine, both alone and in combination, act as a chemopreventive agent against colon carcinogenesis, and such effects may be partly due to suppression of cell proliferation in the colonic crypts, although precise mechanisms should be clarified.

[Carcinogenesis, 18, 1113-1118 (1997)]

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A Xanthine Oxidase Inhibitor 1'-Acetoxychavicol Acetate Inhibits Azoxymethane-induced Colonic Aberrant Crypt Foci in Rats.

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The modifying effect of dietary administration of a xanthine oxidase inhibitor 1'-acetoxychavicol acetate (ACA) present in an edible plant *Languas galanga* in Thailand on the development of azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) was investigated in male F344 rats. Feeding of ACA caused significant reduction in the frequency of ACF. Such inhibition might be associated with suppression of the proliferation biomarkers expression such as ODC activity, number of silver-stained nucleolar organizer regions' protein and blood polyamine content. These results indicate that ACA could inhibit the development of AOM-induced ACF through its suppression of cell proliferation in the colonic mucosa and ACA might be a possible chemopreventive agent against colon tumorigenesis.

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[Lab. of Biochemistry]

Identification of Amino Acid Residues Responsible for Difference in Substrate Specificity and Inhibitor Sensitivity Between Two Human Liver Dihydrodiol Dehydrogenase Isoenzymes by Site-directed Mutagenesis.

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Human liver dihydrodiol dehydrogenase isoenzymes (DD1, DD2), in which only seven amino acid residues are substituted, differ remarkably in specificity for steroidal substrates and inhibitor sensitivity. In this study we performed site-directed mutagenesis of the seven residues of DD1 to corresponding residues of DD2. Of these mutations, only the replacement of Leu-54 with Val produced an enzyme that had almost the same properties as DD2. No significant changes were observed in the other mutant enzymes. An additional site-directed mutagenesis of Tyr-55 of DD1 to Phe yielded an inactive protein, suggesting the catalytically important role of this residue. Thus a residue at a position before the catalytic Tyr residue might play a key role in determining the orientation of substrates and inhibitors.