

Effect of DNA methylation on the reactivity of DNA alkylating agents

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In mammalian species, CpG dinucleotides are highly methylated with 60–90% methylation at the 5–position of cytosine. The pattern of DNA methylation in a cell dramatically affects the function of the DNA by switching genes on or off. Abnormal methylation events occur during aging and in the development of many cancers. Methylated CpG was reported recently to affect the reactivity of agents (mitomycin C and benzo [a] pyrenediolepoxide) that can form guanine adducts in DNA. It was suggested that the enhanced reactivity is attributed to either a local charge effect, making 2–amino group of guanine more nucleophilic, or to a local conformational change, rendering it more accessible. In this study, we further examined the alkylation reactivity of various DNA alkylating agents at methylated DNA sites by using DNA strand breakage assay. The results suggest different mechanisms of adduct formation at methylated DNA depending upon which groove is attacked by those drug molecules.

[PD1–57] [10/17/2002 (Thr) 09:30 – 12:30 / Hall C]

Anti-angiogenic and anti-tumor activity of 2'–hydroxy–4'–methoxychalcone

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In the previous study, we reported that 2'–hydroxy–4'–methoxychalcone, synthetic chalcone inhibited PGE2 production in TPA–stimulated rat peritoneal macrophages by inhibiting the induction of COX–2 protein. The present study was carried out to clarify whether 2'–hydroxy–4'–methoxychalcone inhibit angiogenesis by the experimental methods in vitro and in vivo. 2'–Hydroxy–4'–methoxychalcone decreased angiogenesis of both chick embryos in the chorioallantoic membrane assay and basic fibroblast growth factor–induced vessel formation in the mouse Matrigel plug assay. 2'–Hydroxy–4'–methoxychalcone also reduced the proliferation of calf pulmonary arterial endothelial (CPAE) cells, and found to possess relatively weak gelatinase / collagenase inhibitory activity in vitro. 2'–Hydroxy–4'–methoxychalcone exhibited a strong anti-proliferative activity and was almost equipotent to that of genistein, a reference drug. 2'–Hydroxy–4'–methoxychalcone, when administered s.c. at a dose of 30 mg/kg for 20 days to mice implanted with murine Lewis lung carcinoma (LLC), caused a significant inhibition of tumor volume by 27.2%. 2'–Hydroxy–4'–methoxychalcone, when treated i. p. at the same dosage for 10 days to ICR mice bearing sarcoma 180, caused a significant suppression in tumor weight by 33.7%.

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Ligand–Based Virtual Screening for inhibitors of PTP–1B with Antihyperglycemic properties

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Protein–tyrosine phosphatase 1B(PTP–1B), which plays a key role in insulin signaling, is rising as a fascinating target for type 2 diabetes and obesity. Many scientists in structural biology solved the three dimensional X–ray Crystal structure of this type of enzyme, so we could easily get the active site structure of PTP–1B or complex structure with ligand. Our virtual screening study for PTP–1B exactly based on these crystal structures from public database. We collected suitable complex structures and analyzed the critical properties of the binding interaction between active site and ligands. As a next step, we prepared some logical query set which possess above properties. Finally, we conducted the database search with our queries and have got a number of Hits and confirmed to be a potential skeleton of the lead through the enzyme assay.

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