Cyclooxygenase-2 (COX-2) is an inducible enzyme expressed in response to a variety of cytokines and other proinflammatory stimuli. It has been known that aberrant up-regulation of COX-2 is associated with resistance to apoptosis. Contrary to the above notion, treatment of MCF10A-*ras* cells with the anti-tumor agent ET-18-O-CH_3 caused increased expression of COX-2 and its mRNA transcript, while inducing apoptosis as revealed by proteolytic cleavage of poly(ADP-ribose)polymerase, caspase-3 activation, and positive TUNEL staining. To determine whether the ET-18-O-CH_3-induced apoptosis is associated with up-regulation of COX-2 expression, the selective COX-2 inhibitor celecoxib was used. Celecoxib treatment attenuated ET-18-O-CH_3-induced apoptosis as well as COX-2 expression and PGE_2 production, suggesting that induction of COX-2 by ET-18-O-CH_3 is causally linked to the induction of apoptosis. In another study, PGE_2 and 15-deoxy-$\Delta^{12, 14}$ prostaglandin J_2 (15d-PGJ_2) induced apoptosis in MCF10A-*ras* cells. ET-18-O-CH_3 induced expression of EP2 receptor and peroxisome proliferator-activated receptorγ(PPARγ). GW9662, an antagonist of PPARγ, suppressed the ET-18-O-CH_3-induced COX-2 expression. These findings suggest that ET-18-O-CH_3 induces COX-2 expression through interaction with PPARγ that PGE_2 and 15d-PGJ_2 accumulated as a consequence of COX-2 up-regulation may mediate apoptosis in ET-18-O-CH_3-treated MCF10A-*ras* cells.

[PC1-7] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Flexible docking of stereoisomers of allyl substituted penam sulfones into metallo-β-lactamase with QXP

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Bacterial β-lactamases provide resistance to β-lactams by hydrolyzing the β-lactam bond. On the basis of their catalytic mechanisms, β-lactamases are divided into two major groups. Class A, C and D which belong to the first goup require serine in the active site and class B which is the second group require Zn(II) for their activity. Among class B enzymes, *Bacteroides fragilis* β-lactamase (CcrA enzyme) require two Zn(II) ions per monomer for maximal enzymatic activities. Using the computer docking program, QXP, one known β-lactamase inhibitors, sulbactam, and two sets of α and β isomers of novel allyl substituted derivatives of sulbactam were docked into the *Bacteroides fragilis* β-lactamase. The docking results demonstrated that isomers having β configuration at C-6 with high biological activity proven experimentally docked well into the active site but those with little or no activities - sulbactam and isomers having α configuration at C-6 - were not docked. The docking results also provided potential binding modes for each isomer. These results suggest that not only the stereoisomers can be selected but also the effect of metal ion in a protein could be elucidated by the docking study.

[PC1-8] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Flexible docking of novel antitumor agents into human topoisomerase I-DNA complex with FlexiDock

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DNA topoisomerases catalyze changes in DNA topology through cycles of transient DNA strand breakage and religation. During this process, the active site tyrosine in human DNA topoisomerase I(Top I) becomes covalently linked to the 3'-ends of a single-stranded nick in the DNA duplex. Stabilization of the Top I-DNA cleavable complex is the common initial event leading to the cytotoxicity of top I inhibitors. Using the flexible docking program FlexiDock, novel antitumor agents with benzoindole-dione structure were docked into the human Top I-DNA complex. Among 16 agents tested, five with IC_{50} between 0.1 and 5 uM were docked well, intercalating DNA and forming up to 5 H-bonding to Top I-DNA complex. Out of four agents with moderate activity with IC_{50} below 20 uM, three were docked while one was not. The remaining seven agents with IC_{50} over 20 uM were either not docked or docked with different binding modes. The well docked structures showed similar intercalative binding modes with the known Top I inhibitors, such as camptothecin and topotecan. These results suggest that benzoindole-dione series of antitumor agents probably inhibit Top I by trapping reversible Top I-DNA cleavable complex, presenting the mechanism of its activity.