[PA1-7] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

The inhibition of NO production by 5-Fluorouracil is linked to the inactivation of NF-kB in stomach cancer cells

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The antimetabolite 5-fluorouracil (5-FU) is one of the more prominent clinical antitumor agents for stomach and colorectal cancers. In the present study, we characterized the effects of 5-FU on nitric oxide (NO) production by stomach cancer cells, NCI-N87. IFN-γincreased the production of NO and pretreatment of 5-FU inhibited the production of NO in response to IFN-γin a dose dependent manner. The increased expressions of iNOS mRNA and protein by IFN-γwere completely blocked by 5-FU through the inactivation of NF-kB and the stabilization of IkBαin stomach cancer cells. These data suggest that the efficacy of 5-FU may, at least, include the inactivation of NF-kB and the inhibition of NO production.

[PA1-8] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

OST-3033, A Potent Cathepsin K Inhibitor, Inhibit Bone Resorption In Vitro

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Cathepsin K (CK), a cysteine protease that degrades type I collagen, is highly and selectively expressed in osteoclasts. CK was emerged as a potential target for antiresorptive therapy. In a search for potent CK inhibitors for the treatment of osteoporosis, we found several compounds with subnanomolar level of IC50 on CK. Among these, OST-3033 showed the superior CK inhibitory activity with an IC50 value of 0.7 nM as well as the high selectivity.
In the present studies, the effects of OST-3033 on bone resorption and bone formation were determined in osteoclastic and bone marrow stromal cell culture systems in vitro, respectively. In the bone resorption assay, osteoclast-rich cell suspensions isolated from fetal rabbit long bones were cultured on the ivory slices for 48h. The level of bone resorption was assessed by microscopy and the levels of C-terminal telopeptides of type I collagen, CTx, released from resorption pits. The bone formation was determined by measurement of the markers of enrichness of osteoblasts such as alkaline phosphatase, osteocalcin levels and bone-like nodule formation in rat bone marrow stromal cell cultures.
OST-3033 was found to inhibit osteoclastic bone resorption with an IC50 value of about 100 nM in CTx release and the treatment with OST-3033 also resulted in decrease of pit formation. The effect of OST-3033 on bone formation showed that none of alkaline phosphatase, osteocalcin levels and bone-like mineralized nodule formation was affected by up to 1 uM of OST-3033. These results indicate that OST-3033, a very potent and selective CK inhibitor, efficiently suppresses the bone resorption in vitro, and may have therapeutic potential in diseases caused by the excessive bone resorption such as osteoporosis.
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[PA1-9] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

In vitro inhibition of DDB toward CYP3A4 : inhibitory patterns are substrate -