Bax, a member of Bcl-2 family, has been known to promote apoptotic cell death induced by a wide variety of stimuli. Recently, we have shown that the level of Bax protein was significantly increased during ceramide-induced apoptosis in HL-60 cells. Here we show that Bax translocates from the cytosol to the mitochondria following ceramide treatment. Bax translocation occurred in concert with the release of cytochrome c and poly(ADP-ribose) polymerase. Furthermore, Bax-depleted HL-60 cells generated by using Bax antisense oligonucleotides demonstrated inhibition of cell death induced by ceramide, providing direct evidence that Bax plays a pivotal role in ceramide-induced apoptosis.

[PC3-6] [ 10/20/2000 (Fri) 15:30 - 16:30 / [Hall B] ]

## Role of Reactive Oxygen Species in Arsenite -induced Tumor Promotion

Jeong DG[o], Bae GU, Lee HY[*], Hong SY[§], Lee HW, Han JW

Lab. of Biochemistry, College of Pharmacy, Sungkyunkwan University. College of Medicine, Konyang University *. College of Life Science and Natural Resources, Sungkyunkwan University §

Arsenite is a potent carcinogen that may act as a tumor promoter in the carcinogenic process. However, the mechanism of arsenite-induced tumor promotion has not been definitely revealed. Recently, arsenite is believed to be associated with upregulation of growth factor signaling pathway. In the previous study, we reported that reactive oxygen species (ROS) play a key role in cell signaling pathway as an important signaling intermediator. Therefore, we aimed to determine the role of ROS in the signaling pathway activated by arsenite. Arsenite treatment stimulated MAPK and $p70^{S6K}$, which was accompanied with increase in intracellular ROS production. The predominant ROS produced appeared to be hydrogen peroxide ($H_2O_2$), because the arsenite-induced increase in fluorescence was completely abolished by treatment with catalase. The elimination of $H_2O_2$ by catalase inhibited the arsenite-induced activation of $p70^{S6K}$, and MAPK indicating possible role of ROS in the arsenite-induced activation of $p70^{S6K}$, and MAPK signaling pathway. Furthermore, activation of $p70^{S6K}$ by arsenite was significantly blocked by specific inhibitors such as rapamycin, wortmannin and LY294002. Taken together, these results suggest that $H_2O_2$ may be a pivotal mediator in arsenite-induced tumor promotion through the growth factor signaling pathway.

[PC3-7] [ 10/20/2000 (Fri) 15:30 - 16:30 / [Hall B] ]

## Effects of histone deacetylase inhibitors on angiogenesis

Ahn SH[o1], Han JW[2], Lee HW[2], Hong SY[1]

Department of Genetic Engineering[1], College of Pharmacy[2], Sungkyunkwan University, Aju University Hospital[3]

The reversible acetylation - deacetylation of histones is thought to play a crucial role in transcriptional control in eukaryotic cells. Apicidin was isolated from Fusarium sp. as a potent histone deacetylase (HDAC) inhibitor. We have reported Apicidin and its derivatives have the anti-angiogenic effects on chorioallantoic membrane (CAM) assay. Apicidin and its derivatives suppressed in vitro angiogenesis by interfering tube formation and sprouting of human umbilical vein endotherial cells (HUVECs) and ECV304 cell lines. We examined the effect of Apicidin, Apicidin02 and Apicidin07 on the expression of angiogenic factors such as VEGF, bFGF, TNF-α, angiopoietin-1, angiopoietin-2, angiogenin, TGF-α and TGF-β in cultured HUVEC and ECV304. Reverse transcriptase-polymerase chain reaction indicated that Apicidin and its derivatives modulate the mRNA expression of angiogenic factors in dose-dependent manner.