[PC3-1] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

C2-phytoceramide and Dimethylphytosphingosine induces cell death and apoptosis in human breast cancer cells, MDA-MB-231

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Sphingolipid metabolites have been implicated as an important component of cell signalling, such as cell proliferation, differentiation and apoptosis. But the roles of phytoceramide and its deraivatives are very poorly understood, even though they are abundant in plants, yeasts and animals including humans. We investigated the effects of N-acetyl-C2-phytosphingosine(NAPS) and the analogue of N,N-dimethylsphingosine(DMS), N,N-dimethylphytosphingosine(DMPS), on cell growth inhibition and apoptosis. NAPS and DMPS has the cytotoxic effect on MDA-MB-231 cells in a time- and dose-dependent manner and more toxic than their sphingosine analogues, C2-ceramide and DMS, respectively. Significant apoptosis is induced by treatment of DMPS with 5uM that is detectable at 48 h.
Apoptotic cell death by NAPS and DMPS is mediated by caspase 3. Caspase 3 activity is increased by NAPS(50uM) up to 6-fold at 3 h after treatment , but only 3-fold increased by C2-ceramide. Our results show that the structural difference of hydroxyl group at C-4 of the sphingoid long-chain base is critical for the cytotoxicity and apoptosis.

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Estrogen receptor is downregulated by expression of HIF-1a/VP16

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Estrogen Receptor is a ligand-activated transcription factor. The concentration of the receptor is a major component that regulates expression of estrogen-responsive genes.We have studied mechanism of estrogen receptor alpha (ERα) downregulation by HIF-1 using HIF-1α/VP16 constructs. ERαis known to be downregulated under hypoxic condition. Transcriptional response under hypoxia is mediated through Hypoxia-inducible factor-1 (HIF-1), a transcription factor that is usullaly degraded but stabilized under hypoxia. We have constructed HIF-1α/VP16 known to be active under normoxia. The HIF-1α/VP16 hybrid protein consisting of DNA-binding and dimerization domains from the HIF-1αsubunit transcriptional activation domain from herpes simplex virus VP16 protein was constructed to create a strong, constitutive transcriptional activator. We have found that ERα was downregulated at the levels of ligand-binding and protein. Expression of HIF-1α/VP16 decreased basal and 17β-estradial-induced estrogen response element-dependent reporter gene activity in COS-ER probably due to decreased level of