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Monosialylated ganlioside GM3 regulates tumor phenotype and sensitizes to anti-tumor agent-induced apoptosis

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Glycosphingolipids (GSLs) are ubiquitous components of plasma membrane in all mammalian cells, and they are concentrated in specialized microdomains for cell signaling. Gangliosides, GSLs with sugar chains containing sialic acid, have been implicated in fundamental cell processes such as proliferation, differentiation, adhesion and signal transduction. One of these, ganglioside GM3 is a precursor for simple and complex gangliosides and inhibits growth of several cancer cells and induces cell cycle arrest by regulating cellular signal pathways. GM3 suppresses tumor suppressor PTEN-mediated cancer cell proliferation. GM3 induces transcription factor AP-2α-mediated PTEN expression in colon cancer cells. The enhanced expression of PTEN by GM3 in both HCT116 and p53-null HCT116 cells has been shown to be not associated with p53 function. Thus, to further determine the mechanism underlying the regulation of PTEN gene expression by GM3, we characterized the promoter region of the PTEN gene. Promoter analysis of the PTEN gene showed that the AP-2α is essential for the expression of PTEN in GM3-stimulated colon cancer cells. Moreover, AP-2α siRNA diminished the PTEN expression. The transient expression of AP-2α results in the induction of PTEN transcription in AP-2α-negative colon cancer cells. Additionally, GM3 induced AP-2α-mediated PTEN expression through the inhibition of autocrine-ligand-mediated EGFR activation. On the other hand, Cisplatin (CDDP) is a well known chemotherapeutic agent against several cancers. CDDP induces apoptosis of HCT116 cells, modulating the activation of JNK/p38 and mitochondria-dependent apoptosis signals. When the expression levels of different gangliosides in HCT116 cells were checked with or without CDDP, CDDP augmented expression of GM3 synthase only and its product GM3 among the gangliosides. The reduction of GM3 synthase level by ectopic expression of GM3 small interfering RNA (siRNA) and PDMP treatment rescued HCT116 cells from CDDP-induced apoptosis. The apoptotic sensitivity to CDDP was remarkably increased in GM3 synthase-transfected HCT116 cells. In addition, GM3 synthase-transfected cells treated with CDDP exhibited the increased accumulation of intracellular ROS and Ca2+ compared with controls. These results suggest that the AP-2α transcription factor is required for the ganglioside GM3-stimulated transcriptional regulation of PTEN gene and GM3 acts as a mediator of oxidative apoptosis of HCT116 cells induced by CDDP.

Biography

Cheorl-Ho Kim has completed his Ph.D. at the age of 28 years from The University of Tokyo and Senior Scientist Studies from Korea Research Institute of Bioscience and Biotechnology. He is a professor of molecular glycobiology, SungKyunKwan University, Korea, a leading organization of Korea, which is cooperated with the Samsung Group. He has published more than 320 papers in reputed journals and serving as an editorial board member, executive editor and editor-in chief of the international journals.

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