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Disialyl ST8Sia I (GD3 synthase) accumulates GD2 ganglioside and suppress ICAM-1-mediated invasiveness in human breast cancer MDA-MB231 cells

Jun-Young Park¹, Kyung-Min Kwon, Choong-Hwan Kwak, Sun-Hyung Ha, Fukushi Abekura, Young-Choon Lee and Cheorl-Ho Kim¹Sungkyunkwan University, Korea²Dong-A University, Korea

Gangliosides are sialylated glycosphingolipids which are ubiquitously expressed in mammalian plasma membranes and they play crucial roles in cellular interaction, adhesion, differentiation and apoptosis. To synthesize gangliosides in cells, lactosyl ceramide is processed by different pathways composed of various glycosyltransferases or sialyltransferases. One of these sialyltransferases, GD3 synthase (ST8Sia I), is a key enzyme which controls GD3 biosynthesis from its precursor ganglioside GM3. The steady state level of GD3 expression also depends on other enzymes such as GD2 synthase and GT3 synthase. Thus, the relationship between a ganglioside and its related enzymes is linked to its glycosylation pattern in the cell membrane. The GD3 is expressed weakly in normal tissues, and expressed almost exclusively during development or under pathological conditions such as neuronal disorders. In addition, GD3 promotes tumor progression by influencing cellular proliferation, adhesion and metastasis in malignant tumors. However, GD3 is also known to induce apoptosis by transiently accumulating in the cytosol to contribute to mitochondria damage in the early stages of apoptosis. Fas-mediated apoptosis was also induced by GD3 in lymphoid cells. Therefore, the significance of the biological functions of the ganglioside GD3 in cancer cells is still controversial. Although the disialoganglioside GD3 has been considered to be involved in tumor progression or suppression in various tumor cells, the significance of the biological functions of GD3 in breast cancer cells is still controversial. This prompted us to study the possible relationship(s) between GD3 expression and the metastatic potential of a breast cancer MDA-MB231 cells. The human GD3 synthase cDNA was transfected into MDA-MB231 cells, and G-418 bulk selection was used to select cells stably overexpressing the GD3 synthase. *In vitro* invasion potentials of the GD3 synthase over-expressing cells (pc3-GD3s) were significantly suppressed when compared with control cells. Expression of intercellular adhesion molecule-1 (ICAM-1; CD54) was down-regulated in the pc3-GD3s cells and the decrease in ICAM-1 expression is directly related to the decrease in invasiveness of the pc3-GD3s cells. Then, we investigated signaling pathways known to control ICAM-1 expression. No difference was observed in the phosphorylation of ERK and p38 between the pc3-GD3s and control cells (pc3), but the activation of AKT was inhibited in pc3-GD3s, and not in the control (pc3). In addition, the composition of total gangliosides was changed between control (pc3) and pc3-GD3s cells, as confirmed by HPTLC. The pc3-GD3s cells had an accumulation of the GD2 instead of the GD3. RT-PCR results showed that not only GD3 synthase, but also GM2/GD2 synthase (β 4-GalNc T) expression was increased in pc3-GD3s cells. Overexpression of GD3 synthase suppresses the invasive potential of human breast cancer MDA-MB-231 cells through down-regulation of ICAM-1, which may be influenced by accumulation of the GD2 ganglioside.

Biography

Jun-Young Park graduated from Biological Science Department, Myungji University, Yongin, Gyeonggi-do, Korea in 2014. Presently, he is a master-doctor coursed student at the Molecular and Cellular Glycobiology Lab, Department of Biological Science, Sungkyunkwan University, Suwon under supervisor Prof Cheorl-Ho Kim. His research interest is glycan structure and biosynthesis of glycoproteins, glycoconjugates, glycolipids and anti-inflammatory mechanism.

wnsdud2057@naver.com

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