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Ganglioside GM3-growth factor receptor interaction and cellular regulation: VEGFR-2 and TGFβR

Cheorl-Ho Kim[1], Tae-Wook Chung[1], Seok-Jo Kim[1], Choong-Hwan Kwak[1], Hee-Jung Choi[2], Ki-Tae Ha[2], Dong-Soo Kim[3] and Young-Choon Lee[4]
[1]SungKyunKwan University, Korea
[2]Pusan National University, Korea
[3]Kyung Sung University, Korea
[4]Dong-A University, Korea

Angiogenesis is closely associated with the growth and metastasis of human solid tumor, and is regulated by the balance between angiogenic stimulators and inhibitors released from tumor cells and stromal cells in the tumor microenvironment. Of the angiogenic factors, vascular endothelial growth factor (VEGF) is the most potent endothelial-specific mitogen which activates endothelial cells in tumor neovascularization. GM3 is an anti-angiogenic factor in tumor microenvironment and negatively regulates VEGF-mediated tumor angiogenesis by suppressing the activation of the VEGF receptor-2 (VEGFR-2). GM3 blocked VEGF-stimulated neovascularization in matrigel plugs and chorioallantoic membrane (CAM) assays. VEGF-mediated VEGFR-2 activation was inhibited by GM3. GM3-specific interactions with the extracellular domain (ExD) of VEGFR-2 were clearly demonstrated, and GM3 blocks VEGFR-2 dimerization and the binding between VEGF and VEGFR-2. In C57BL/6 mice inoculated with Lewis lung carcinoma cells, the intraperitoneal injection of GM3 reduced the volume of primary tumors, and an immunohistochemical study indicated that GM3 inhibits the angiogenesis and proliferation of primary tumor cells. In another case, TGF-β-induced epithelial-mesenchymal transition (EMT) induces the proliferation and migration of the human lens epithelial (HLE) cells caused by the posterior capsular opacification (PCO) after cataract surgery. The relation between GM3 and TGF-β-induced EMT in the HLE B-3 cells is poorly understood. GM3 is involved with TGF-β1-induced EMT in HLE B-3 cells. GM3 and GM3 synthase are significantly increased in TGF-β1-induced HLE B-3 cells. Transcriptional activation of GM3 synthase gene is regulated by Sp1 in HLE B-3 cells upon TGF-β1 stimulation. On the GM3-depleted experiment using by d-PDMP and shGM3, the reduced expression of ganglioside GM3 significantly suppresses the TGF-β-induced migration and EMT-related signaling in HLE B-3 cells. By exogenous treatment of GM3, the suppressed EMT-molecules and cell migration are recovered during TGF-β1-induced EMT. Finally, GM3 is interacted with TGFβRs in TGF-β1-induced HLE B-3 cells. Taken together, the results indicate that GM3 is a blocker of VEGR-VEGFR2 interaction in tumor regression and regulates the EMT by interaction with TGFβRs.

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.

hkimbio@skku.edu