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The expressions of fusion genes, cytosine deaminase and interferon-beta, in genetically engineered stem cells migrated to breast cancer cells and induced their cell growth inhibition

Bo-Rim YI and Kyung-Chul CHOI

College of Veterinary Medicine, Chungbuk National University, Republic of Korea

Recent studies of genetically engineered stem cells (GESTECs) have received a great deal of attention as an alternative potent anti-tumor treatment to various human cancers. In this study, human neural stem cells (HB1.F3) having a powerful tumor tropism were engineered as GESTECs to harbor fusion genes, a bacterial *cytosine deaminase (CD)* gene and a human *interferon-beta (IFN-b)* gene which are related with the cytotoxic effect on cancer cells. *CD* gene is a suicide gene expressing *cytosine deaminase* that can convert a non-toxic prodrug, 5-fluorocytosine (5-FC), to an active form, 5-fluorouracil (5-FU. Also, human *interferon-beta (IFN-b)* was well known as a cytokine to have an antitumor effect. In the present work, we evaluated the coupling effect of CD and IFN-b genes in the cytotoxicity on breast cancer cells (MDA-MB-231 and MCF-7) with tumor targeting capacity of these GESTECs. Cancer cells (MDA-MB-231 and MCF-7) and GESTECs (HB1.F3.CD, and HB1.F3.CD. IFN-b) were cultured in RPMI and DMEM containing 10% FBS. Expressions of *CD* and *IFN-b* genes and chemoattractant ligands such as SCF/c-kit, VEGF/VEGFR2, and SDF-1/CXCR4, were identified in these GESTECs and breast cancer cells, respectively by RT-PCR method. To evaluate migratory ability of these GESTECs, we performed a modified transwell assay where both HB1.F3.CD and HB1.F3.CD.IFN-b cells migrated selectively toward breast cancer cells, MCF-7 and MDA-MB-231. Migration capacity of these GESTECs can be attributed to a strong tumor tropism of stem cells toward chemoattractants secreted by cancer cells. In addition, using MTT assay, we tested cytotoxic effect of engineered stem cells against breast cancer cells *in vitro*. The viability of breast cancer cells was significantly reduced by co-culture with HB1.F3.CD and HB1.F3.CD.IFN-b in the presence of a prodrug, 5-FC. More potent inhibition was observed by HB1.F3.CD.IFN-b compared to HB1.F3.CD, which means that 5-FU (converted from 5-FC by *CD*) and *IFN-b* affected cancer cells synergically. These data provide a promise that these GESTECs expressing fusion genes, *CD* and/or *IFN-b,* may have a therapeutic potential against breast cancer cells *in vitro* via their strong anticancer effect and tumor tropism. A further study is needed to prove *in vivo* efficacy for human breast cancer therapy by applying these GESTECs in a xenograft animal model. Also, immuno-deficient, transgenic or knockout mouse models can be employed to elucidate a mystery of therapeutic usefulness of these GESTECs.

Biography

Bo-Rim Yi is doing her master course at the Laboratory of Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University (Cheongju, Republic of Korea). Kyung-Chul Choi completed his Ph.D. from the University of British Columbia (Vancouver, BC, Canada) and postdoctoral studies from the Cornell University (Ithaca, NY, USA). He has published more than 100 papers in peer-review journals and is an Associate Professor and Department Head in the program of pre-veterinary medicine, College of Veterinary Medicine, Chungbuk National University.