

A synergistic effect of therapeutic stem cells expressing a suicide enzyme, cytosine deaminase, with a prodrug and interferon-beta in the inhibition of endometrial cancer cell growth *In vitro*

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In recent, gene-directed enzyme/prodrug therapies (GEPT) have been highly regarded as an alternative means of gene therapy in anti-cancer treatments. As one of GEPT, *cytosine deaminase (CD)/5-fluorocytosine (5-FC)* system induces metabolic suicide of cancer cells following administration of prodrug 5-FC which is converted to a toxic agent, 5-fluorouracil(5-FU) by *CD*. In addition, human *interferon-beta (IFN-b)* gene presents antitumor effect by expressing *IFN-b*, a immunotherapeutic cytokine. In this study, we explored the therapeutic efficacy of *CD/5-FC* system and human *IFN-b* gene that were engineered into the human neural stem cell lines having the inherent tumor-tropic properties. Parental stem cell, HB1.F3, was modified by *E.coli CD* gene and human *interferon-beta (IFN-b)* gene to produce engineered stem cells, HB1.F3.CD and HB1.F3.CD.IFN-b, respectively. Endometrial Ishikawa cancer cell lines and engineered stem cells were cultured in 10% FBS containing DMEM. Using RT-PCR, we confirmed *CD* and *IFN-b* gene expressions in the engineered stem cells and of chemoattractant molecules such as SCF, CXCR4, c-kit, VEGF, and VEGFR2, in cancer cell lines. In a migration assay using modified transwells, HB1.F3.CD and HB1.F3.CD.IFN-b were effectively migrated to endometrial Ishikawa cancer cell lines, which can be attributed to chemoattractants secreted by cancer cells. In the cytotoxicity test using co-culture system and MTT assay, the viability of endometrial Ishikawa cancer cells was decreased in the presence of engineered stem cells. Especially, the viable cancer cells was more effectively reduced when co-cultured with HB1.F3.CD.IFN-b rather than HB1.F3.CD., which means that the fusion of *CD* and *IFN-b* genes may have a synergic antitumor effect. These results suggest that engineered stem cells expressing *CD* and/or *IFN-b* may have a therapeutic potential against endometrial cancer cells *in vitro* via a strong tumor tropism of stem cells and a cytotoxic effect of engineered gene products. Furthermore, our data provide proof for the use of genetically modified stem cell-based gene therapy through a targeted delivery of therapeutic gene products to endometrial cancer sites.

Biography

Nam-Hee Kang 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.