A-13

Development of DNA Vaccine Against Human Breast Cancer

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Abstract

Breast cancer is the most common malignancy among women in most parts of the world, including Malaysia. While the specific etiology of breast cancer remains unknown, DNA vaccines directed at eliciting an immune response toward tumours appear to offer promise for both the prophylactic and therapeutic treatment of cancer. The ultimate goal of cancer immunotherapy is to induce effective tumour-specific cellular immunity that can inhibit and block the growth and metastasis of cancer cells. Thus, development of a DNA vaccine that induces Th1 response may be required for effective cancer immunotherapy. In this study, DNA plasmids encoding human breast tumour associated antigen, MUC-1 and an anti-cancer cytokine, interleukin-18 (IL-18) are being investigated as potential candidates for the development of a vaccine against human breast cancer. Both the cDNAs of MUC-1 and IL-18 were cloned into mammalian expression plasmid, pVAX1. MUC-1 cDNA was subcloned from pcDNA3/MUC-1 recombinant plasmid, whereas IL-18 cDNA was reverse-transcribed from Chang human liver cells' total RNA. The immunogenicity of these clones was then tested in dendritic cell (DC) and mouse models. In the dendritic cell study, autologous T cells were stimulated in vitro with untransfected DCs or with DCs transfected with plasmids expressing various genes to investigate the capacity of gene-modified DCs to prime naive T cells, as measured by T cell proliferation response and mixed leukocyte reaction. The most remarkable T cell proliferation was observed after stimulation with IL-18 + MUC-1-DC with Stimulation Index (S.I.) of 1.94 (versus S.I. 0.96 for negative control). In addition, enhanced cytotoxic activity of these stimulated T cells as the effector cells was also augmented against the target cells, T-47D and MDA-MB-231 human breast cancer cell lines. At Effector: Target (E:T) ratio of 10:1, 87 % of T cell cytotoxicity was observed in T-47D and 79 % in MDA-MB-231 when T cell stimulated with IL-18 + MUC-1-DCs, respectively. Administration of pVAX1/MUC-1 combined with pVAX/IL-18 showed induction of strong and long term antibody response specific against MUC-1 in BALB/c mice. The antibody level of MUC-1 still remained at high level (~20,000 ng/ml) after 2 months. Most importantly, administration with combination of pVAX1/ MUC-1 and pVAX1/ IL-18 led to potent generation of Th1 cytokines, IL-18 and IFN-γ.

More than 12,500 pg/ ml of IL-18 was detected at day 42 and about 30,000 pg/ ml of IFN-γ at day 63 after administration with combination of pVAX1/ MUC-1 and pVAX1/ IL-18. These results indicate that DNA plasmids expressing both tumour antigen MUC-1 and cytokine IL-18 are potential to be used as a vaccine and its application in immunization may be an effective strategy for a successful therapeutic vaccination against human breast cancer.