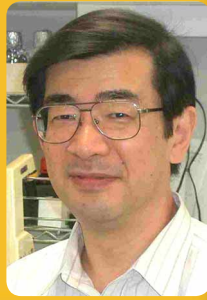


Dendritic/tumor-fusion vaccine with

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What is the function of dendritic/tumor-fusion vaccine?

Sadamu Homma: Dendritic/tumor-fusion vaccine is generated by treatment of dendritic cells (DCs) and tumor cells with polyethylene glycol (50% generally) (1,2) or an electrofusion (3,4) for both basic experiments and clinical studies. Recently, envelope of Hemagglutinating Virus of Japan (HVJ), which elicits cell membrane fusion activity, was applied to cell fusion of DCs and tumor cells in animal experiments (5). Fusion efficacy of DCs and tumor cells seems to be almost same among above procedures, all of which showed about 30-40 % of fusion efficacy. Although fusion cells (FCs) of DC and tumor cell were sometimes purified prior to administration (6), whole cell fraction of PEG-treated or electrofused cells have been inoculated to tumor bearing hosts as a tumor-specific immunostimulating agent. Tumor cells had been irradiated before cell fusion to prevent the growth in the body to which the vaccine was administered.

FCs would migrate to draining lymph nodes from injection sites, and migration capacity of FCs was reported to be almost same as unfused DCs (7). Reaching to T cell area in lymph nodes, FCs could present tumor antigens to T cells, both CD4⁺ and CD8⁺T cells, and activate tumor antigen-specific T cells. Regarding to induction of specific CD8⁺cytotoxic T lymphocytes (CTLs), FCs might be able to present tumor antigen as intrinsic one to T cells after intracellular processing of antigen, whereas antigenic peptide and MHC class I complex expressed on tumor cell surface might be utilized as it is for antigen presentation by FCs. As dendritic/tumor-fusion vaccine is composed of DC and tumor cell, it might be able to present multiple tumor antigens, which contain some known and unknown or individually specific ones, to T cells. This style might be more profitable for induction of potent anti-tumor immunity than vaccination with a single tumor antigen. About T helper cells, many reports have shown that Th1 immune condition was induced by dendritic/tumor-fusion vaccine. However, we found that Th2 immune condition, which provided humoral antibody eliciting anti-tumor activity, was also induced by dendritic/tumor-fusion vaccine in experiments using animal models of familial adenomatous polyposis (8).

If tumor cells to be fused produce immuno-suppressive agents such as TGF-beta, dendritic/tumor-fusion composed of such tumor cells could not work for induction of effective anti-tumor immunity (9). Thus, it might be necessary to check the production of immuno-suppressive cytokines or agents by tumor cells before cell fusion.

We found that FC vaccine composed of immature DC and tumor cell could efficiently induce potent anti-tumor immunity, suggesting that fusion procedure might provide functional modulation for antigen presentation of DCs (10). Recently it has been shown that matured DCs would be desirable to generate more functional dendritic/tumor-fusion vaccine (11).

Dendritic/tumor-fusion vaccine composed of allogeneic DC and tumor cell have been utilized to induce stronger anti-tumor immunity promoted by allo-immune responses (12). Allogeneic tumor cells could be also used for generation of effective dendritic/

tumor-fusion vaccine (13). It was reported that vaccination with fusions of DCs and tumor cells transduced with genes encoding immuno-stimulatory cytokines such as IL-12 or IL-18 enhanced anti-tumor activity mediated by tumor-specific T cells (14).

Has the administration of IL-12 any effects?

Sadamu Homma: In tumor treatment model of animal experiments, dendritic/tumor-fusion vaccine in combination with IL-12 showed significant therapeutic effect, in which either the vaccine or IL-12 alone did not (15). Indeed, in phase I clinical study using dendritic/tumor-fusion vaccine plus recombinant human IL-12 (rhIL-12) against human glioma showed 26.7 % of PR, 6.7 % of MR (16), while the vaccination alone showed 12.5 % of PR in radiological findings (17). Administration of low dose of IL-12 (30ng/Kg) in combination with the vaccine would be useful for the tumor suppression, and no severe adverse effects associated with the treatment have not been observed (2). Primed CD4⁺T cells received antigen presentation from DCs express more IL-12 receptor molecules. Accordingly, IL-12 would effectively enhance anti-tumor activity induced by dendritic/tumor-fusion vaccine.

We accidentally found that vaccination with dendritic/tumor-fusion vaccine composed of DC and well-differentiated hepatocellular carcinoma cell and following administration of IL-12 generated autoimmune hepatic inflammation (18). In this experimental model, vaccination alone could stimulate autoreactive CTLs to hepatocytes, but no hepatic inflammation occurred *in vivo* without administration of IL-12. Our data suggest that homing of autoreactive T cells to the liver by enhanced expression of adhesion molecules in the hepatic tissue, which had been provided by interferon-gamma induced by IL-12, plays an important role for generation of autoimmune hepatic inflammation. Accordingly, it might be possible that treatment with the vaccine and IL-12 might induce potent anti-tumor immunity as well as autoimmunity.

Is there any correlation between elevated serum levels of ANA and anti-tumor immune response?

Sadamu Homma: It was found that patients who showed positive with serum ANA after dendritic/tumor-fusion vaccination showed good clinical responses (19). No clinical symptoms compatible with autoimmune diseases have not been observed so far. It is conceivable that nucleoprotein of tumor cells of dendritic/tumor-fusion vac-

cine might be recognized by host immune system, resulting in positive with serum ANA. However, ANA might be induced in association with anti-tumor activity induced by the vaccination, because elevation of serum ANA level was also seen in immunotherapy using DCs pulsed with Carcino-Embryonic Antigen (CEA) peptide (20).

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