Institute of DNA Medicine
Department of Oncology

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General Summary

The aim of our research is to develop and establish novel cancer therapies. Concepts for new anticancer therapies, generated from the unique ideas of our researchers, would be verified by basic and clinical studies so that they could be applied clinically. Most of our research has been based on antitumor immunity.

Research Activities

A phase I clinical study of immunotherapy against advanced pancreatic cancer using dendritic cells pulsed with WT1 class I and II peptides
Wilms' tumor 1 (WT1) is a tumor antigen recognized by specific T cells. Vaccination with dendritic cells (DCs) pulsed with WT1 class I and II peptides would stimulate WT1-specific cytotoxic T cells, as well as helper T cells, leading to the induction of potent WT1-specifc antitumor immunity. In 2013, 7 patients with advanced pancreatic cancer were treated with this DC therapy combined with gemcitabine. Four of these patients have been followed up in good condition as outpatients. All 4 patients showed positive skin reaction tests for WT1.

Immunotherapy against glioblastoma using a DC vaccine
Patients with glioblastoma treated with the combination of temozolomide and DC therapy have survived significantly longer than those treated with temozolomide alone. Analyses by tetramer assay indicated that 3 of 6 patients treated with both temozolomide and DC therapy showed induction of cytotoxic T cell responses specific for WT1, glycoprotein 100, and melanoma-associated antigen family A, 2.

Generation of artificial protein vaccine inducing potent cellular immunity
Artificial proteins composed of cytotoxic T-lymphocyte (CTL) epitopes, helper epitopes, and intercalated peptides of ovalbumin were generated using the MolCraft system for protein evolution. Uptake of the artificial protein via the scavenger receptor on antigen-presenting cells might be closely associated with the induction of cellular immunity. An artificial WT1 protein for use in cancer vaccines is now being generated on the basis of the specific protein structure inducing cellular immune responses.

Exploitation of antigenic peptides for T-cell responses generated from mutated gene products of cancer
Immunogenic proteins might be generated from gene mutations of cancer cells, and such

gene products might serve as tumor antigens for immunological tumor rejection. Structures of proteins generated by gene mutation were determined in human prostate and pancreatic cancer cells, and antigenic peptides for specific T-cell responses derived from the mutated proteins are now exploited by liquid chromatography/tandem mass spectrometry analysis.

Intensified antibody therapy by enhancement of target molecular expression

Antibody therapy targeting human epidermal growth factor receptor 2 (HER2) was not effective against pancreatic cancer because of low HER2 expression. We found that treatment with gemcitabine enhanced HER2 expression on pancreatic cancer cells. Gemcitabine-treated pancreatic cancer cells were more sensitive to trastuzumab-emtansine, a conjugate of an anti-HER2 monoclonal antibody and a chemotherapeutic agent, through gemcitabine-induced enhancement of HER2 expression. Gemcitabine also increased CD20 expression on human diffuse large B cell lymphoma cells. Complement-dependent cytotoxicity mediated by rituximab was enhanced by pretreatment of human diffuse large B cell lymphoma cells with gemcitabine.

Nafamostat mesylate inhibits interferon-gamma-induced expression of programmed cell death ligand 1 on cancer cells

As the interaction between programmed cell death (PD) 1 on CTLs and PD ligand (PD-L) 1 on cancer cells induces apoptosis of CTLs, PD-1/PD-L1 plays an important role in cancer-related immune suppression. The expression of PD-L1 on cancer cells is generally induced by interferon-gamma produced by CTLs attacking cancer cells. We found that treatment of cancer cells with nafamostat mesylate significantly suppressed interferon-gamma-induced PD-L1 expression. Nafamostat mesylate might contribute to the inhibition of cancer-related immune suppression and enhance the antitumor effect of anti-PD-L1 antibody therapy.

Publications

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