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Department of Oncology

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General Summary

Establishing effective treatments for malignant tumors on the basis of antitumor immune responses is a goal of this department. For this purpose, several experimental and clinical studies of cancer immunotherapy and cancer vaccines have been performed. Promising results were obtained from clinical studies of cancer vaccines targeting advanced pancreatic cancer and glioblastoma. A unique artificial protein generated with motif-programming technology could become a next-generation cancer vaccine for inducing potent antitumor immunity. Novel cancer-specific antigens that might be ideal targets for antitumor immune responses were found with mass spectrometric analysis. Induced pluripotent stem (iPS) cells have been used to generate new cancer vaccines. For cancer vaccine therapy, antigenic peptides of known tumor antigens can be detected with mass spectrometric analysis of formalin-fixed tumor tissue.

Research Activities

Phase I and II clinical studies of Wilm's tumor protein 1-targeting immunotherapy against advanced pancreatic cancer

Because pancreatic cancer is a devastating disease with an extremely poor prognosis, establishing effective treatments for pancreatic cancer is an urgent issue. We have started a phase I clinical study of combined therapy with gemcitabine and dendritic cells pulsed with Wilm's tumor protein (WT) 1 class I and II peptides in collaboration with the Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kashiwa Hospital. To our knowledge, this study is the first of vaccination with dendritic cells pulsed with both WT1 class I and class II peptides for treating pancreatic cancer. However, a phase I clinical study of combination therapy with gemcitabine and a WT1 peptide vaccine has been completed, and its results are now being analyzed. Adverse effects associated with the therapy were caused by the toxicity of gemcitabine; thus, the safety and feasibility of this therapy were shown. The specific immune responses observed in patients with pancreatic cancer showing a good clinical response might be used as biomarkers to predict the efficacy of therapy. Five university hospitals, including The Jikei University, have collaboratively started a phase II clinical study of combination therapy with gemcitabine and a WT1 peptide vaccine to rapidly evaluate its therapeutic efficacy.

A clinical study of a dendritic/tumor fusion cell vaccine to prevent the recurrence of glioblastoma on postoperative status

Glioblastoma is a highly malignant brain tumor with an extremely poor prognosis. We

have reported that treatment with a dendritic/tumor fusion cell vaccine elicited a good response against glioblastoma. Although temozolomide has contributed to the improved prognosis of patients with glioblastoma, outcomes remain unsatisfactory. To prevent the recurrence of glioblastoma, we have provided postoperative combination treatment with fusion cell vaccine and temozolomide to patients with glioblastoma. This treatment has resulted in many cases of long-term survival without recurrence; 1 patient has survived more than 5 years. These results suggest that combination treatment with a fusion cell vaccine and temozolomide is superior to treatment with temozolomide alone for preventing the recurrence of glioblastoma. The mechanism of the possible synergistic effect of the fusion cell vaccine and temozolomide is now being investigated in in-vivo and in-vitro studies.

Generation of a novel cancer vaccine composed of artificially constructed protein
Using motif programming technology, we have constructed an artificial protein library by combining 4 peptide motifs associated with the MHC class I and class II epitopes of ovalbumin, an alpha-helical motif, and a randomized peptide sequence. Immunization with 2 artificial proteins, F37A and F182A, potently induced ovalbumin-specific cellular immunity in mice. Subcutaneous injection with the artificial proteins efficiently presented the ovalbumin-specific MHC class I epitope through the cross-presentation pathway in antigen-presenting cells. These results demonstrate that vaccination with the motif-programmed artificial proteins of tumor antigen might be able to induce cellular immunity to elicit antitumor activity.

Exploitation on novel tumor antigens by mass spectrometric analysis
We have searched for candidate peptides for a novel cancer vaccine using the technology of proteomics. Peptides presented on HLA class I molecules are recognized by cytotoxic T lymphocytes with specific T-cell receptors. Some candidate peptides were identified among HLA-binding peptides from human prostate cancer cells by means of mass spectrometric analysis. Cancer specificity and the potential to become a target antigen for antitumor immunity are now being evaluated. One candidate peptide from an unexploited protein showed high messenger RNA expression in some human cancer cell lines but extremely low expression in many noncancerous tissues. Promising novel cancer vaccines might be generated on the basis of the structures of HLA class I-binding peptides of tumor cells.

Cancer vaccine targeting tumor vessels generated from iPS cells
Vaccination of mice with dendritic cells pulsed with lysate of induced vascular progenitor (iVP) cells derived from iPS cells showed potent antitumor activity against tumor-cell challenge, although vaccination with undifferentiated iPS cells did not. Suppression of tumor vasculature was observed in tumors formed in iVP-vaccinated mice. Furthermore, $CD8^+$ T cells from iVP-vaccinated mice showed significant cytotoxic activity against endothelial cells in vitro, but those from iPS-vaccinated mice did not. These results suggest that the immune response to iVP cells might suppress the development of tumor vessels, possibly by attacking endothelial cells in tumor tissue. The target antigen

responsible for this immune response is being identified with microarray analysis focusing on genes expressed in common in up-regulated genes of iVP cells through differentiation and constitutively expressed genes in tumor endothelial cells.

Detection of antigenic peptides of tumor antigens from formalin-fixed tumor tissue
Presentation of antigenic peptides of tumor antigens of MHC class I molecules on the surfaces of tumor cells is essential for antitumor immune responses. Although tumor antigen expression in tumor cells has been proven with immunohistochemical analysis, tumor cells with impaired antigen-processing capacity cannot express antigenic peptides despite high expression of tumor antigens. Conversely, expression of an antigenic peptide might be sufficient for an immune response, despite negative staining for tumor antigens on immunohistochemical analysis, if antigen processing is extremely rapid. Accordingly, direct demonstration of antigenic peptides of tumor antigens in tumor tissue is important for predicting the immune response to a tumor site. For this purpose, detection of antigenic peptides of known tumor antigens in formalin-fixed tumor tissue by means of liquid chromatography/tandem mass spectrometry (LC/MS/MS) analysis has been studied. We have previously achieved the quantitative detection of WT1 antigenic peptide from fresh pancreatic cancer tissue. The optimal conditions for detecting antigenic peptides of tumor antigens in formalin-fixed tumor tissue with LC/MS/MS are now being investigated. The quantity of antigenic peptides in tumor tissues might become a future predictive marker of the efficacy of cancer vaccine therapy.

Publications

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