Research Center for Medical Sciences
Division of Oncology

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General Summary

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

Research Activities

High blood levels of soluble OX40, an immune costimulatory molecule, indicate reduced survival in patients with advanced colorectal cancer

The interaction between OX40 (CD134) on T cells and the OX40 ligand (OX40L) on antigen presenting cells (APCs) is a pivotal step for activating T cells and promoting antitumor immunity. However, soluble OX40 (sOX40) in blood is thought to suppress T cell activation by blocking OX40/OX40L interaction. Here, we investigated the association between blood sOX40 levels and the clinical characteristics of patients with advanced colorectal cancer. Blood was collected from 22 patients with advanced colorectal cancer. Blood sOX40 levels were determined with enzyme-linked immunosorbent assay. Blood sOX40 levels were positively correlated with the blood levels of carbohydrate antigen 19-9, carcinoembryonic antigen, C-reactive protein, and soluble programmed cell death ligand-1 but were negatively correlated with the blood levels of albumin. Importantly, according to both univariate and multivariate analyses, high blood sOX40 levels were significantly correlated with a reduced survival time. High blood levels of sOX40 were possibly associated with the suppression of antitumor immunity by sOX40.

Induction of Wilms tumor 1-specific cytotoxic lymphocytes by the artificial antigen vaccine

From a functional viewpoint, vaccine adjuvants are classified into 2 types: “physical adjuvants” increase the efficacy of antigen presentation in APCs, and “signal adjuvants” induce the maturation of APCs. By using ovalbumin as a model antigen, we have previously demonstrated that a physical adjuvant can be encrypted into proteinous antigens (F37A) by creating artificial proteins with motif-programming (Ito M et al, PLOS ONE 2014, 2017). In the present study, we replaced the MHC class I and class II epitope peptide motifs of ovalbumin in F37A with those of the Wilms tumor 1 (WT1) epitopes to construct a WT1 artificial antigen, WT1-C2. When WT1-C2 was incubated with human peripheral blood mononuclear cells, the antigen was endocytosed to dendritic cells (con-

firmed by flow cytometry) to induce WT1-specific cytotoxic lymphocytes (CTLs) (confirmed by tetramer assay). The induced CTLs were cytotoxic to T2-A24 lymphoblastoid cells pulsed with WT1 epitope peptide. Therefore, F37A can be used as a framework protein to construct a physical adjuvant free-artificial antigen by substituting the ovalbumin epitopes in F37A with another peptide motif, which induces CTLs against target cells.

Search for the immunogenic mutation-derived antigens of human malignant brain tumors
Dendritic/tumor fusion cell vaccine therapy has been performed for the treatment of patients with glioma at The Jikei University Hospital. Variant peptides generated by the gene mutation of glioma cells might be functioning as target tumor antigens in fusion cell vaccine therapy. We have performed whole exome and whole transcriptome analysis of gliomas from adult patients treated with the fusion cell vaccine and have identified several candidates for a novel mutation-derived antigen. A clinical trial of the fusion cell vaccine to pediatric brain tumors was start this year. Several candidate mutation-derived antigens were identified by the analyses in pediatric brain tumors. Furthermore, glioma stem-like cells induced from original glioma cells *in vitro* are often available in generation of the fusion cell vaccine. The use of glioma stem-like cells as a fusion partner of dendritic cells might make the fusion cell vaccine more effective. Glioma stem-like cell-specific mutated antigens were searched for, and several candidates were found.

Publications

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