Division 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

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 cytotoxic T lymphocytes (CTLs) and PD ligand (PD-L) 1 on cancer cells induces the apoptosis of CTLs, PD-1/PD-L1 interaction plays an important role on the escape of cancer cells from antitumor immunity. The expression of PD-L1 on cancer cells is induced by interferon gamma produced by CTLs, which attack cancer cells. We found that treatment of cancer cells with nafamostat mesylate, a serine protease inhibitor, significantly suppressed interferon-gamma-induced PD-L1 expression on cancer cells in vitro at both messenger RNA and protein levels. Combined treatment of the cancer patients with anti-PD-1 antibodies and nafamostat mesylate might become promising for cancer.

Immunotherapy against glioblastoma with a dendritic cell vaccine

The clinical effect of the combination therapy with temozolomide and a dendritic cell (DC) vaccine against glioblastoma was examined. Patients with glioblastoma were assigned to 2 groups: a group with recurrent glioblastoma after failing temozolomide chemotherapy and a group with newly diagnosed glioblastoma. Autologous cultured glioma cells obtained from surgical specimens were fused with DCs using polyethylene glycol treatment. Progression-free survival and overall survival in patients with recurrent glioblastoma (n = 9) or newly diagnosed glioblastoma (n = 20) treated with the DC vaccine were significantly longer than those untreated with the DC vaccine. Up-regulation and cytoplasmic accumulation of chemoresistance-associated peptides were observed in recurrent gliomas in recurrent glioblastomas. Specific immune responses against chemoresistance-associated peptides were induced in both groups of patients.

Generation of artificial antigenic protein inducing potent cellular immunity

Invocation of cellular immunity by epitopic peptides remains largely dependent on empirically developed protocols, such as interfusion of aluminum salts and emulsification using terpenoids and surfactants. To explore novel vaccine formulation, epitopic peptide motifs

were co-programed with structural motifs to produce artificial antigens with our "motif-programming" approach. As a proof of concept, we used an ovalbumin system and prepared an artificial protein library with combinatorially polymerizing major histocompatibility complex (MHC) class I and II sequences from ovalbumin along with a sequence that tends to form secondary structures. The purified endotoxin-free proteins were then examined for their ability to activate ovalbumin-specific T-cell hybridoma cells after being processed within DCs. One clone, F37A (containing 3 MHC I and 2 MHC II ovalbumin epitopes), possessed a greater ability to evoke cellular immunity than did the native ovalbumin or the other artificial antigens. The sensitivity profiles of drugs that interfered with the F37A uptake differed from those of the other artificial proteins and ovalbumin, suggesting that alteration of the cross-presentation pathway is responsible for the enhanced immunogenicity. Moreover, F37A, but not an epitopic peptide, invoked cellular immunity when injected together with monophosphoryl lipid A and retarded tumor growth in mice. Thus, an artificially synthesized protein antigen induced cellular immunity in vivo in the absence of incomplete Freund's adjuvant or aluminum salts. The method described here might be used to develop vaccines for such intractable ailments as acquired immunodeficiency syndrome, malaria, and cancer, ailments in which cellular immunity likely plays crucial roles in prevention and treatment.

Whole exome-based search for cancer-specific antigens recognized by T-cell immunity
Cancer cells have many genetic alterations that generate amino acids changes of proteins. Antigenic peptides on the human leukocyte antigen (HLA) from these altered proteins are thought to be cancer-specific epitopes. Whole exome analysis of the cancer cell was performed, and the HLA-binding capacity of altered peptides was analyzed to investigate whether the altered peptide has high HLA-binding capacity. Variant peptides whose binding capacity to HLA was predicted to be stronger than that of original peptides were found in prostate cancer cell lines. These variant peptides might be more cancer-specific than the original peptide and possibly become targets of antitumor immunity. A whole exome-based search method for variant peptides with high HLA-binding capacity might provide the immune-responsive cancer-specific antigens of individual patients with cancer.

Intensified rituximab therapy against diffuse large B-cell lymphomas mediated by CD20 up-regulation by gemcitabine treatment
Treatment with gemcitabine increased CD20 expression by cells from human diffuse large B-cell lymphomas (DLBCLs) in vitro at messenger RNA and protein levels. This CD20 up-regulation is closely associated with activation of nuclear factor *k*B induced by gemcitabine. The rituximab-mediated complement-dependent cytotoxic activity against gemcitabine-pretreated DLBCL cells was enhanced by the increased binding of rituximab. Combined treatment with gemcitabine and rituximab might become a promising therapy against DLBCLs.

Soluble PD-L1 as an important mediator for immunosuppression in patients with pancreatic cancer

We found abundant soluble PD-L1 (sPD-L1) in the plasma of patients with advanced pancreatic cancer. The concentration of plasma sPD-L1 was decreased along with the decline of the lymphocyte number induced by chemotherapy. Furthermore, PD-L1 was highly expressed on CD4+T cells in patients with pancreatic cancer, suggesting that sPD-L1 was derived from CD4+T cells in blood. The CD4+T cells from the patients with pancreatic cancer release sPD-L1 into the medium in vitro. If the CD4+T cells in these patients could generate sPD-L1 that is functional enough for CTL suppression, antitumor immunity should be inhibited in the tumor microenvironment in which tumor PD-L1 inactivates PD-1 expressing CTLs and also in the peripheral blood in which sPD-L1 binds to PD-1 expressing CTLs.

Publications

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