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General Summary

Our research focuses on tumor immunology and leukemia cell biology. Experiments were performed to enhance the beneficial effects of immunotherapy, to clarify differentiation mechanisms, and to investigate the pathophysiology of hepatitis induced by autoimmune mechanisms. Two clinical studies of immunotherapy are in progress.

Research Activities

Combined treatment with dendritic cells and 5-fluorouracil elicits augmented natural killer cell-mediated antitumor activity via the tumor necrosis factor-alpha pathway

Inoculation of mice with dendritic cells (DCs) increased the number of natural killer (NK) cells in the spleen and up-regulated tumor necrosis factor (TNF)-alpha expression on NK cells. Pretreatment with 5-fluorouracil (5-FU) enhanced expression of procaspase 8 in mouse colon cancer cells and induced apoptosis by TNF- α through the caspase 8 pathway. These results indicate that combined therapy with a DC vaccine and 5-FU is a promising strategy for cancer treatment.

Mechanisms of synergistic effect of WT1 peptide vaccine and gemcitabine against pancreatic cancer

Treatment with gemcitabine increased expression of WT1 (Wilms' tumor gene) messenger RNA in pancreatic cancer cells. WT1-specific CD8⁺ cytotoxic T lymphocytes killed the gemcitabine-treated pancreatic cancer cells more efficiently. These experiments indicate that cytotoxic effects of WT1-specific cytotoxic T lymphocytes induced by a WT1 peptide vaccine would be enhanced by gemcitabine treatment in a patient with pancreatic cancer.

The identification of novel tumor-associated antigens from a mouse model of familial adenomatous polyposis

Immunization of mice with DCs fused with tumor cells established from the intestinal tumors of a familial adenomatous polyposis mouse induced antibody production. The antigen recognized by this antibody showed homology with melanoma inhibitory activity 3 and was present in both Paneth cell-like tumor cells and normal Paneth cells. This novel antigen might function as a modulator of commensal microbiota.

Phase I clinical trial of combination therapy with WT1 peptide vaccine and gemcitabine against advanced pancreatic cancer

The modified 9-mer WT1 peptide (235–243AA, CYTWNQMNL for HLA-A*2402) has been used as a cancer vaccine. A phase I clinical trial of combination therapy with WT1 peptide vaccine and gemcitabine against advanced pancreatic cancer was performed in collaboration with Osaka University. In 2008, 2 patients were enrolled in the study, and no severe adverse effects were observed. One patient showed marked tumor regression (final tumor regression rate, 82%) with disappearance of symptoms.

Clinical immunotherapy for brain tumor

The combination of fusion-cell therapy with the chemotherapy has been on-going. Fusion cells have been produced in the Good Manufacturing Practice cell-processing system.

Adhesion-induced differentiation toward megakaryocytes

Adhesion to fibronectin and collagen induces megakaryocytic differentiation through activation of the FLI-1 gene, a member of the ets-family of transcription factors, in human leukemia JAS-R cells. We elucidated the mechanisms of the activation of this gene and found that FLI-1 functions in an autoaugmentation fashion once it is activated by adhesion.

Accumulation of functional regulatory T cells in actively inflamed liver in mouse DC-based autoimmune hepatic inflammation

Regulatory T cells accumulated in the liver through interaction of chemokine (C-X-C motif) receptor 3 and chemokine (C-X-C motif) ligand 9 and expanded locally by stimulation of transforming growth factor-beta and interleukin-2 in autoimmune hepatic inflammation. An increase in the number of functional regulatory T cells might be a protective reaction and might play a role in the severity and persistence of autoimmune hepatic inflammation.

Publications

Homma S, Koido S, Sagawa Y, Suzuki H, Komita H, Nagasaki E, Takahara A, Horiguchi-Yamada J, Tajiri H, Zeldin D, Obata T. Antigenic stimulation with cytochrome P450 2J expression in mouse hepatocellular carcinoma cells regulates host antitumor immunity. *Clin Exp Immunol* 2009; **156**: 344–52.

Koido S, Homma S, Hara E (Saitama Cancer Center), Mitsunaga M, Namiki Y, Takahara A, Nagasaki E, Komita H, Sagawa Y, Ohkusa T, Fujise K, Gong J (Boston Univ), Tajiri H. *In vitro* generation of cytotoxic and regulatory T cells by fusions of human dendritic and hepatocellular carcinoma cells. *J Transl Med* 2008; **6**: 51–70.

Reviews and Books

Horiguchi-Yamada J, Suzuki H, Takeda N, Yamada H. Sequential alterations in cell cycle and survival after X-ray irradiation in p53-deficient leukemia cells. *Cytomet Res* 2009; **19**: 53–60.

Homma S, Koido S, Obata T. Proteomics-based exploration of T-cell epitopes from tumor associated antigens for generation of new cancer vaccine (in Japanese). *Biotherapy* 2008; **22**: 385–8.