Research Center for Medical Sciences
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General Summary

Tumor immunology
We are conducting research to develop novel cancer immunotherapies; an adjuvant-free artificial antigen vaccine that induces tumor immunity using synthetic biological techniques; bispecific antibodies that bind cancer cells, and $CD8^+$ T cells to exert strong cytotoxicity.

Cancer genomics
Many gene mutations occur in tumor cells, and the mutant peptides resulting from the gene mutations are believed to act as neoantigens and to induce tumor-specific immune responses. In collaboration with clinical departments, we are searching for new target molecules, including neoantigens, for tumor immunity by gene mutations and expression analyses.

Research Activities

Possibility of augmentation of responses by anti-programmed cell death 1 antibodies against pancreatic cancer using Patched 1-interacting peptide (Mutsunori Murahashi)
Pancreatic ductal adenocarcinoma (PDAC) is resistant to immunotherapy. As a factor of resistance, the dense fibrosis of this cancer acts as a barrier to inhibit immune cell infiltration into a tumor. We examined the influence of a Hedgehog signal inhibitor, Patched 1-interacting peptide, on fibrosis, infiltration of immune cells, and the immunotherapeutic effects on PDAC. We found that this peptide inhibited proliferation and migration of cancer-associated fibroblasts and cancer cells. Furthermore, this peptide reduced the production of extracellular matrix and transforming growth factor β1 in cancer-associated fibroblasts and induced expression of HLA-ABC in PDAC cells and interferon-γ in lymphocytes. *In vivo*, the peptide suppressed fibrosis of PDAC and increased immune cell infiltration into tumors. The combination of this peptide and an antibody against programmed death 1 augmented the antitumor effect and showed the same effect in experiments with cancer cells and autologous lymphocytes. These results indicate that, in addition to the direct effect of tumor suppression, the Patched 1-interacting peptide increases the infiltration of immune cells by reducing fibrosis of PDAC and consequently enhances the effects of immunotherapy. Therefore, treatment with this peptide might be a novel therapy with 2 different mechanisms: direct tumor suppression and enhancing the immune response against PDAC.

Functional analysis of endogenous antigen presentation in cancer cells (Masaki Ito)
Cancer cells presenting somatically mutated peptides (neoepitope) on major histocompatibility complex I (MHC-I), known as human leucocyte antigen (HLA), are eliminated by the immune surveillance system in the early stage of tumor development. However, some cancer cells acquire the capability of immune evasion and subsequently develop malignant cancers. To investigate the mechanism of immune evasion of cancer, we have functionally analyzed the ability of endogenous antigen presenting in cancer cells using reporter T cells that recognize the Wilms Tumor 1 (WT1) peptide epitope on HLA-A*24. The ACC-MESO-4 (malignant mesothelioma) cells, which strongly express both WT1 and MHC-I, showed high endogenous antigen-presenting activity. By treatment with interferon gamma, the endogenous antigen presentation was induced in SW480 cells (colon cancer) and MIA Paca-2 cells (pancreatic cancer) with low WT1 expression. Despite expressing both WT1 and MHC-I, NCI-H460 cells (lung cancer) and Hep G2 cells (liver cancer) showed no antigen presentation. However, antigen presentation was observed when these cells were exogenously pulsed with the WT1 epitope peptide. This result suggests an abnormality in the process of endogenously processing the antigen in NCI-H460 cells and Hep G2 cells. Further analysis of the antigen processing pathway of endogenous antigens in cancer cells that do not show antigen presentation might improve the study of immune evasion mechanisms of cancer.

Search for neoantigens for malignant brain tumors (Yuko Kamata, Jun Takei)
Dendritic cell/tumor cell fusion vaccine therapy has been used for patients with malignant glioma. Variant peptides produced from tumor mutation are believed to play a role as tumor-specific antigens in cancer immunotherapy. To find novel mutation-derived antigens, we performed whole exome and whole transcriptome analysis of malignant glioma cells from 9 patients who have undergone dendritic cell/tumor cell fusion vaccine therapy and 1 type of glioma stem-like cell-induced malignant glioma cell. Because mutation-derived antigens differ by HLA, analysis of mutation-derived antigen was performed for HLA-A*24:02 and HLA-A*02:01, which are common HLA types in Japan. The number of candidate mutation-derived antigens detected in 5 or more samples was 46 for HLA-A*24:02 and 54 for HLA-A*02:01. Some candidate variants were validated with Sanger sequencing. The T2 cell assay showed that some candidate peptides had HLA-binding ability. For a more precise analysis, we have searched for mutation-derived antigens in an increasing number of patients with malignant glioma.

Publications

Sawada R, Arai Y, Sagawa Y, Nagata Y, Nishimura T, Noguchi M, Amano K, Arihiro S, Saruta M, Homma S. High blood levels of soluble OX40 (CD134), an immune costimulatory molecule, indicate reduced survival in patients with advanced colorectal cancer. *Oncol Rep.* 2019 Nov; **42**(5): 2057-2064. doi: 10.3892/or.2019.7304. Epub 2019 Sep 6. PMID: 31545443.

Honda M, Kimura T, Kamata Y, Tashiro K, Kimura S, Koike Y, Sato S, Yorozu T, Furusato B, Takahashi H, Kiyota H, Egawa S. Differential expression of androgen receptor variants in hormone-sensitive prostate cancer xenografts, castration- resistant sublines, and patient specimens according to the treatment sequence. *Prostate.* 2019 Jun; **79**(9): 1043-1052. doi: 10.1002/pros.23816. Epub 2019 Apr 18. PMID: 30998834.