Research Center for Medical Sciences
Division of Oncology

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General Summary

The aim of our researches is to develop and establish novel cancer therapies. Concepts of new anti-cancer therapy generated from unique idea of the researchers would be verified by basic and clinical studies in order to apply such concepts to the clinical cancer treatment. Most of our researches have been based on antitumor immunity.

Research Activities

Comprehensive analyses on gene expression of human glioblastoma mutiforme (GM) for search of the predictive biomarkers for clinical effectiveness of dendritic cell (DC) therapy

DC vaccine for post-operative prevention or treatment against GM was generated by cell fusion of DCs and GM cells derived from the individual patients. The next generation sequencer for this investigation was TorrentSuite (ThermoFisher) and the transcripts of the GM cells used for the generation of DC vaccine were listed. The results demonstrated that neutrophil-associated genes such as chemokines or cytokines were highly expressed in GM cells from non-effective cases compared with those from effective cases. It has been known that neutrophils suppress the activity of cytotoxic T lymphocytes which play a central role in antitumor immunity. In non-effective case, antitumor T cells induced by DC therapy might have been inactivated by neutrophils recruited in tumor microenvironment by neutrophil-associated genes expressed in GM cells. Neutrophil-associated gene expression in GM cells could become biomarkers for prediction of the effectiveness of the DC therapy against GM.

Claudin 7 as a novel molecular target for treatment of pancreatic cancer

From a human pancreatic cancer cell line, MIA PaCa-2, MIA PaCa-2-A cells with epithelial morphology and MIA PaCa-2-R cells with non-epithelial morphology were clonogenically isolated by the limiting dilution method. Although the MIA PaCa-2-A and MIA PaCa-2-R cells displayed the same DNA short tandem repeat (STR) pattern identical to that of the parental MIA PaCa-2 cells, the MIA PaCa-2-A cells were more proliferative than the MIA PaCa-2-R cells both in culture and in xenografts generated in SCID mice. Furthermore, the MIA PaCa-2-A cells were more resistant to gemcitabine than the MIA PaCa-2-R cells. DNA microarray analysis demonstrated high expression of Claudin (CLDN) 7 in the MIA PaCa-2-A cells but not in the MIA PaCa-2-R cells. Knockdown of CLDN7 in the MIA PaCa-2-A cells using siRNA induced marked inhibition of proliferation without altering the cell morphology. The MIA PaCa-2-A cells with CLDN7 knock-

down showed G1 cell cycle arrest. CLDN7 might be expressed in the rapidly proliferating and dominant cell population in human pancreatic cancer tissues and might be a novel molecular target for the treatment of pancreatic cancer.

High PD-L1 expression indicates poor prognosis of HIV-infected non-small cell lung cancer patients

The status of antitumor immunity represented by the expression of programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) and the immune cell (IC) infiltration was unknown in HIV-infected non-small cell lung cancer (NSCLC) patients. Fifteen HIV-infected and 29 non-HIV-infected, or 13 of each propensity score matched NSCLC patients were analyzed. The expression of PD-1/PD-L1 and the infiltration of $CD4^+$, $CD8^+$ and $CD56^+$ ICs were examined by immunohistochemistry, and score ≥ 2 was defined as positive. In analysis of all the patients as well as the propensity matched cohort, high PD-L1 expression group showed shorter survival than low PD-L1 expression group in HIV-infected patients, whereas significant difference of survival was not observed between high and low PD-L1 expression groups of non-HIV cohort. High PD-L1 expression in tumor tissue clearly indicated poor prognosis in HIV-infected NSCLC patients but not in non-HIV-infected NSCLC patients. These results suggest that suppression of antitumor immunity by PD-1/PD-L1 axis might be stronger in HIV-infected NSCLC patients than in non-HIV-infected NSCLC patients.

Significance of functional soluble programmed cell death ligand-1 (sPD-L1) in blood of advanced cancer patients

We have previously reported that the plasma levels of sPD-L1 in patients with advanced pancreatic cancer (PC) were higher than those of healthy subjects. Although PD-L1 is expressed in PC tissues, PD-L1 expression in tumor tissue and plasma sPD-L1 level were not correlated. Furthermore, plasma sPD-L1 levels were not associated with serum CA19-9 levels or tumor sizes in PC patients, indicating that main source of sPD-L1 is not tumor tissue. Plasma sPD-L1 levels declined along with the decrease in blood lymphocyte count with progression of the disease. We found that monocyte derived dendritic cells (DCs) from PC patients released abundant sPD-L1 *in vitro* but not non-adherent cells in peripheral blood mononuclear cells. sPD-L1 from DCs could activate PD-1 signaling in the cell-based functional assay for PD-1/PD-L1 interaction, suggesting that sPD-L1 is functionally immunosuppressive. sPD-L1 in cancer patients should be involved in the suppression of antitumor immunity and become a novel target for the next generation cancer immunotherapy.

A functional cell-based assay for immune checkpoint molecules

Immune checkpoint inhibitors such as the antibodies targeting the programmed death 1 (PD-1) receptor have shown promising results in multiple cancers. However, it has been shown that the expression level of programmed death-1 ligand-1 (PD-L1) in tumor does not necessarily correlate with the therapeutic effect of anti-PD-1 antibody. PD-1 contains two immmunoreceptor tyrosine-based motifs (ITIM and ITAM) that are phosphorylated upon receptor engagement and recruit Src homology 2-domain-containinng tyrosine

phosphatase 2 (SHP2). We developed the functional cell-based assay system to detect the recruitment of SHP2 to PD-1 by the interaction of PD-1 and its ligands PD-L1 in the TCR-independent condition. Split bioluminescence reporters were used for detecting the interactions between PD-1 and SHP-2. Antigen presenting cells expressing PD-L1 and PD-L2 elicited strong PD-1 signaling in this assay system, but the PD-1 signal intensity induced by tumor cells did not correlate with the PD-L1 expression level of tumor cells. Our assay system representing a functional PD-1 signaling status may be useful in searching for factors influencing the PD-1 signaling pathway.

Publications

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Reviews and Books

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