Cancer Immunotherapy- from basic research to clinic

Yuka Maeda, Ph.D.
Division of Cancer Immunology, National Cancer Center Research Institute

< Cancer Immunology and Immune Checkpoint >

Human has the immune system to exclude a non-self-substance. In early 1900's, Paul Ehrlich proposed that cancer occurs spontaneously *in vivo* and that the immune system protects the host by killing it. This hypothesis was expanded by Burnet and Thomas as "Cancer Immunosurveilance". However, cancer acquires mechanism to escape from cancer immunosurveilance and proliferates and invades in the host. Old and Schreiber et al. integrated the process from carcinogenesis to cancer progression as "Cancer Immunoediting". The processes of cancer immunoediting are composed of three phases: elimination, equilibrium and escape. In tumor microenvironment, immunogenic cancer cells developed by stimuli such as UV and radiation are depleted by the immune system (cancer immunosurveilance = elimination). Low-immunogenic cancer cells which the immune system is difficult to recognize and attack are then selectively survived (equilibrium), though these cells cannot progress by the immune pressure. Cancer cells recruit immune suppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) and express immune suppressive molecules including immune checkpoint molecules to escape from the immune pressure and grow in the presence of normal immune system. Therefore, cancers in the clinic are selected by the immune pressure and harbor a various type of immune suppressive machineries.

<Immune Checkpoint Inhibitor>

Inhibitors against two major immune checkpoint molecules CTLA-4 and PD-1 are currently available for cancer therapy in the clinic. In 1987, a French group identified a protein called CTLA-4 (Cytotoxic T-lymphocyte-associated protein 4; CD152) expressed by T cells. While the role of CTLA-4 was a mystery until 1996, Prof. James Allison' group at University of California, Berkeley showed that it acts as a brake on T-cell responses, and T cells can be resurged and attack certain cancer cells by inhibiting the signal. The finding was confirmed by later studies and led to the development of ipilimumab, an antibody-based drug that targets CTLA-4.

PD-1 (Programmed cell death-1; CD279) is also an immune checkpoint molecule found

by Prof. Tasuku Honjo at Kyoto University in 1992 as a molecule expressed at T-cell apoptosis. The immune suppressive function of this molecules was revealed by the data showing that the lack of PD-1 is associated with autoimmune disorders. Additionally, inhibiting PD-1 signaling activated anti-tumor immune responses and resulted in the tumor regression, leading to the development of nivolumab, an antibody targeting PD-1.

<How it works? >

Recent success of cancer immunotherapy makes it a key component for cancer therapy, and a lot of clinical trials are under investigation to further develop new reagents. Upon the clinical introduction of cancer immunotherapy in which treatment efficacy is dependent on the immune system resulting in the partial window of clinical responses, comprehensive cancer research including genome and immunology are urgently required to identify biomarkers that can predict responders. I would like to share our studies to clarify the effective anti-tumor immune responses in cancer immunotherapies from basic research to identify predictive biomarkers.