Cancer-mediated immunosuppression in the tumor microenvironment identified by immuno-genomic analyses

Hiroyoshi Nishikawa[1), 2), 3)]

[1)] *Division of Cancer Immune Multicellular System Regulation, Center for Cancer Immunotherapy and Immunobiology, Kyoto University Graduate School of Medicine,*
[2)] *Division of Cancer Immunology, Research Institute / EPOC, National Cancer Center Japan*
[3)] *Department of Immunology, Nagoya University Graduate School of Medicine*

Abstract

The clinical application of cancer immunotherapy has revealed that cancer tissues are heterogenous in humans. The heterogeneity in the tumor microenvironment (TME) influences the effect of cancer immunotherapy, thus, applying therapeutic strategies based on the TME of each patient is essential for successful cancer immunotherapy. We have developed a new method (immuno-genomic analyses) to comprehensively explore immunological phenotypes in the TME using small cacner specimens.

We found that the balance of PD-1 expression between tumor-infiltrating effector cells, particularly CD8+ T cells and regulatory T (Treg) cells correlated with the clinical outcome of PD-1 blockade therapy. Comprehensive genomic and immunologic analyses further clarified that PD-1-expressing Treg cells were highly detected in MYC-amplified tumors and liver metastatic lesions, in which glucose metabolism was markedly elevated. In fact, Treg cells harbored a specific pathway to metabolize lactic acid, and therefore, high lactic acid environment in the TME promoted proliferation and activation of Treg cells, resulting in the abundance of PD-1-expressing Treg cells.

In addition, some genetic alterations in cancer cells directly modulated infiltration/activation of immune cells; in Epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer, EGFR signaling changed the local chemokine milieu, which directly inhibited effector T cell infiltration and induced Treg cell infiltration in the TME. In Ras homolog family member A (RHOA)-mutated gastric cancer, alternation of RHOA signaling changed the metabolic environment, which induced Treg cell expansion by in the TME. Moreover, in renal cell carcinoma, in which CD8+ T-cell infiltration is a poor prognostic factor, Treg cells were proliferated/activated in the TME due to copy number gain of self-antigens, leading to the poor prognosis even in CD8+ T-cell abundant tumors. In these cancer types, a combination cancer immunotherapy containing Treg cell-targeted therapy should be necessary to gain optimal clinical efficacy.

Altogether, considering that genetic abnormalities in cancer cells directly affect the immune system, integrated analyses of immunological and genomic assays (immuno-genomic analyses) are crucial for immune-genomic precision medicine, which can maximize the effectiveness of cancer immunotherapy.

Biography

Hiroyoshi Nishikawa received his MD degree from School of Medicine, Mie University (Mie, Japan) in 1995 and a PhD degree from the Graduate School of Medicine, Mie University (Mie, Japan) in 2002. He studied the role of immune suppressive mechanisms, particularly regulatory T cells in tumor immunity working in Dr. Lloyd J Old's lab. at Memorial Sloan Kettering Cancer Center (New York, NY) and then in Dr. Shimon Sakaguchi's lab. at Osaka University (Osaka Japan). He is now the chief of the Division of Cancer Immunology, Research Institute at the National Cancer Center Japan and cross-appointed as the Professor of Division of Cancer Immune Multicellular System Regulation, Center for Cancer Immunotherapy and Immunobiology, Kyoto University Graduate School of Medicine and the Professor of Department of Immunology, Nagoya University Graduate School of Medicine. The major focus of his research is clarifying the control mechanism(s) of immune tolerance and immune surveillance focusing on tumor immunity. He also develops novel cancer immunotherapies targeting regulatory T cells.