Clinical significance of the tumor microenvironment in non-small cell lung cancer

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Abstract: Several biomarkers have been reported as predictors of survival and recurrence in non-small cell lung cancer. Recently, several groups have demonstrated that the immune microenvironment of the primary tumors is a prognostic factor. These "immunological biomarkers" in the tumor microenvironment are useful predictors of prognosis as well as promising targets for novel therapeutic approaches. Especially, tumor-infiltrating Treg cells are a powerful immunological biomarker, and possible mechanisms involved in the induction of tumor-infiltrating Treg cells are the expression of Cox-2, IL-12Rβ2 or the lack of IL7R on the tumor cells. These findings may pave the way for individualized immunomodulatory therapies to deplete tumor-infiltrating Treg cells from the tumor microenvironment.

Key Words: Non-small cell lung cancer (NSCLC); tumor microenvironment; tumor-infiltrating Treg

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This editorial refers to the 'Clinical Impact of Immune Microenvironment in Stage I Lung Adenocarcinoma: Tumor Interleukin-12 Receptor 2 (IL-12R2), IL-7R, and Stromal FoxP3/CD3 Ratio Are Independent Predictors of Recurrence' by K. Suzuki *et al.*, published in the *Journal of Clinical Oncology* (1).

Lung cancer is a major cause of death in many developed countries. Surgical resection continues to play an important role in the treatment of this disease, especially during the early stages of non-small cell lung cancer (NSCLC). Even in patients diagnosed at an early stage, however, the reported relapse rate is as high as 15-35% after surgical resection. Therefore, the prognostic factors of NSCLC patients following resection have been investigated. Until now, the anatomic extent of the tumor (TNM classification) has been the most powerful tool to predict the prognosis in NSCLC patients. Several biomarkers have been reported as predictors of survival and recurrence: (I) clinical factors (e.g., sex, age, or performance-status); (II) pathological factors (e.g., histological subtype, cell differentiation, or visceral pleural invasion; (III) many biological factors involved in cancer development and progression (e.g., *EGFR* mutation). Recently, several groups, including ours, have demonstrated that the immune microenvironment of the primary tumors is a prognostic factor for disease-free and overall survival. Thus, the tumor immune microenvironment has been increasingly considered as a biomarker of the prognosis, as well as a therapeutic target in patients with NSCLC.

Tumor-infiltrating immune cells

It is composed of two distinct compartments mediating the innate and adaptive immune responses. The innate immune system consists of phagocytes including neutrophils, mast cells/macrophages (CD68), dendritic cells (DC), NK cells (CD56+CD3-), and NK T cells (CD56+CD3+). The innate immune system mainly serves as the first-line defense against both foreign pathogens and transformed cells. The adaptive immune system is mediated by two major T lymphocyte subsets; cytotoxic T cells (CTL) (CD8) and helper T cells (Th) (CD4), and B cells (CD20). The adaptive immune system is the second-line of defense via

antigen-specific molecules which requires clonal expansion following the recognition of foreign antigens.

Of these, tumor-infiltrating DCs (2,3), NK cells (3), macrophages (4), mast cells (5), cytotoxic T cells (6), and helper T cells (7) have been reported as potential prognostic factors following resection in patients with NSCLC. In addition, we recently reported that the number of tumor infiltrating FOXP3+ Treg cells was associated with earlier recurrence, especially in patients with node-negative NSCLC, and positively correlated with Cox-2 expression on the tumor cells (8). Therefore, we suggested that Cox-2 expressed in tumors is a possible target for decreasing the number of tumor-infiltrating Treg cells.

Tumors expressing cytokine receptors

The interactions between cancer cells and the tumor microenvironment are bidirectional, and include activation of both tumor and accessory stromal cells. These interactions are crucial for cancer progression. In order to create a suitable tumor microenvironment, cancer cells communicate with the microenvironment via a complex network of many growth factors, chemokines, cytokines, and their own receptors.

Chemokines and chemokine receptors play important roles in tumor progression. Both cancer cells and stromal cells elaborate several chemokines and cytokines. Expressions of CXCR4 and its ligand CXCL12 have been reported in some solid tumors. Clinical data indicate that high CXCR4 expression is correlated with poor clinical outcome in several cancers. The proposed paracrine roles for the CXCR4/CXCL12 axis are to assist in facilitation of the development of distant metastasis, while the CCL21/CCR7 axis favors the development of lymph node metastasis. These two chemokine ligand-receptor interactions are reported as common key mediators of tumor cell metastasis in several types of cancers. Thus, both CXCR4 and CCR7 have been implicated in the process of metastasis; however, the potential prognostic values of these molecules in resected NSCLC are unknown. Previous studies have assessed the relationship between the concentrations of cytokines in the serum and the clinicopathological factors in NSCLC patients; however, there are few studies that have assessed the expressions of cytokine receptors on the tumor cells. The interleukin-7 receptor (IL-7R) provides critical survival signals to lymphocytes, while IL-12Rβ2 acts not only as a cytokine receptor component, but also as a gatekeeper gene, since lung adenocarcinoma develops spontaneously in IL-12Rβ2 deficient mice.

Of these, IL-7R expression on the tumor cells has been reported to be associated with a shorter overall survival in NSCLC patients (9), while *IL-12Rβ2* methylation has been shown to be correlated with a poor prognosis in lung adenocarcinoma patients (10).

A previous study showed that the type, density, and location of immune cells within the tumor microenvironment influence the risk of recurrence. Suzuki *et al.* additionally demonstrated that the expressions of the cytokine receptor IL-7R and IL-12Rβ2 on the tumor cells are also useful predictive prognostic factors following resection in patients with NSCLC. Taken together, "Immunological biomarkers" in the tumor microenvironment are useful predictors of prognosis as well as promising targets for novel therapeutic approaches. Tumor-infiltrating FOXP3+ Treg cells are a powerful immunological biomarker for the predicting prognosis following resection in patients with NSCLC. Recent studies have suggested possible mechanisms involved in the induction of tumor-infiltrating Treg cells are the expression of Cox-2, IL-12Rβ2 or the lack of IL7R on the tumor cells. These findings may pave the way for individualized immunomodulatory therapies using the Cox-2 inhibitor, IL-12Rβ2 stimulator, or the IL-7R inhibitor to deplete tumor-infiltrating Treg cells from the tumor microenvironment.

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