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Highlights: Lymphoma microenvironment

Commentary

Current progress of the tumor microenvironment in lymphoid malignancies

Kennosuke Karube

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Tumor tissue formation is based on the interaction between the tumor cells and the tumor microenvironment. Tumor biology has mainly focused on the tumor cells themselves, and many anticancer drugs and molecularly targeted therapies also target tumor cells. In recent years, however, the importance of the tumor microenvironment has been increasing, especially with the emergence of immune checkpoint inhibitors applicable for many types of cancer. In this review project, we asked hematologists and hematopathologists who are involved in the study of the tumor microenvironment of lymphoma for reviews summarizing our current knowledge about tumor cell-microenvironment interaction and future perspectives.

PD1 and PDL1 are direct targets of representative immune checkpoint inhibitors, and their expression in tumor cells or tissue macrophages is an important predictor of therapeutic response. Dr. Sakakibara and colleagues focused on clone SP142 among several PDL1 antibodies and reported that this clone is useful for differentiation of Hodgkin and Reed-Sternberg cells from their mimics associated with T-cell lymphoma.[1] In this review, they summarized the expression status of PD1/PDL1 in lymphomas detected by SP142, and found that PDL1 is highly expressed in several types, including classic Hodgkin lymphoma, intravascular lymphoma, and primary mediastinal large B-cell lymphoma.[2] PD-L1 is widely expressed in tumor cells and the tumor microenvironment. Genomic abnormalities of the PDL1 gene (*CD274*) have been representative mechanisms of the upregulation of PDL1. Dr. Kawashima, who identified trogocytosis as a new mechanism of the upregulation of PDL1,[3] summarized the mechanism of PDL1 expression along with the role of exosomes.[4] Dr. Ennishi, who identified the functional significance of *TMEM30A* alterations in DLBCL,[5] described the importance of CD47-mediated "don't eat me" signaling in DLBCL through the role of TMEM30A.[6] Dr. Miyawaki summarized how comprehensive gene expression profiling clarified the significance of the tumor microenvironment in diffuse large B cell lymphoma and peripheral T-cell lymphoma, not otherwise specified, the most frequent lymphomas of B-cell and T-cell lineage, respectively (in press). In addition, Dr. Takeuchi described the comprehensive expression status of immune evasion-related genes, including PD1 and PDL1, in tumor cells and the microenvironment of adult T-cell leukemia/lymphoma, a T-cell neoplasm associated with human T-cell leukemia virus type-1, which is endemic in Japan (in press).

As mentioned above, studies of tumor cell-microenvironment interaction mainly focusing on immune checkpoint molecules in malignant lymphoma have significantly progressed. This review series will serve as a foundation for future research, and lead to the development of new diagnostic and therapeutic methods for lymphoma.

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Department of Pathology and Cell Biology, Graduate School of Medicine, University of the Ryukyus, Nishihara, Japan
Corresponding author: Kennosuke Karube, Department of Pathology and Cell Biology, Graduate School of Medicine, University of the Ryukyus, Uehara 207, Nishihara, Japan.
E-mail: karube@med.u-ryukyu.ac.jp

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