Lymphoma Microenvironment and Immunotherapy

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KEYWORDS

• Immune surveillance • Tumor microenvironment • Immunomodulatory drugs • Immune checkpoint • Tumor-associated macrophages

ABSTRACT

Understanding of the lymphoma tumor microenvironment is poised to expand in the era of next-generation sequencing studies of the tumor cells themselves. Successful therapies of the future will rely on deeper appreciation of the interactions between elements of the microenvironment. Although the phenotypic, cytogenetic, and molecular characterization of tumor cells in lymphomas has progressed faster than most other solid organ tumors, concrete advancements in understanding the lymphoma microenvironment have been fewer. This article explores the composition of the lymphoma tumor microenvironment; its role in immune surveillance, evasion, and drug resistance; and its potential role in the development of targeted therapies.

Key Features

- Understanding of the lymphoma tumor microenvironment is poised to expand in the era of next-generation sequencing studies of the tumor cells themselves.
- Successful therapies of the future will rely on deeper appreciation of the interactions between elements of the microenvironment.

OVERVIEW

Tumor microenvironment was initially addressed in the context of carcinoma metastases by Stephen Paget in 1889.[1] In examining the pattern of breast cancer metastases at autopsy, he found that some organs demonstrated a preponderance of metastases and generated the hypothesis that "seeds," or neoplastic cells, could only land and flourish in appropriate "soil," or microenvironment. Decades later, scientists discovered that lung-homing melanoma cells, when implanted in mice, selectively metastasize to lung and ectopically placed lung but not other tissues.[2]

Novel drugs targeting the tumor microenvironment in carcinomas have been primarily concentrated in the inhibition of tumor-related angiogenesis. Compounds include inhibitors of vascular endothelial growth factor (bevacizumab) and vascular endothelial growth factor receptor–2 tyrosine kinase (sorafenib and sunitinib). In patients with non–small cell lung cancer and colon cancer, bevacizumab, used in the conjunction with standard chemotherapy, demonstrated prolonged progression-free survival and overall survival.[3,4]

Although the phenotypic, cytogenetic, and molecular characterizations of tumor cells in lymphomas have progressed faster than for most other solid organ tumors, concrete advancements in understanding the lymphoma microenvironment have been fewer. This article explores the composition of the lymphoma tumor microenvironment; its role in immune surveillance, evasion, and drug resistance; and its potential role in the development of targeted therapies. In the context of morphologic and prognostic tumor evaluation, pathologists can provide insights critical for cutting-edge clinical care.

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TUMOR MICROENVIRONMENT IN LYMPHOMA

The key constituents of the lymphoma microenvironment and their pattern of distribution within tissue vary widely between tumors depending on the host inflammatory response as well as the genetics and proliferation rate of malignant cells (**Box 1**). For example, in tumors such as classic Hodgkin Lymphoma, polymorphic post-transplant lymphoproliferative disorders, and angioimmunoblastic T-cell lymphoma, the background non-neoplastic inflammatory components are prominent and often display typical morphologic features identifiable to the tumor type. In contrast, extranodal marginal zone lymphomas of mucosa-associated lymphoid tissues, follicular lymphomas, and some mantle cell lymphomas in the early stage retain or recapitulate normal lymphoid architecture. Further on the spectrum, many diffuse large B-cell lymphomas and virtually all Burkitt lymphomas show effacement of the underlying architecture. Often, the more aggressive lymphomas seem to demonstrate independence from the signals and supporting network provided by the microenvironment.

SIGNALS TO AND FROM THE TUMOR MICROENVIRONMENT

Lymphoma B cells have been shown to secrete CC-chemokine ligand 22 (CCL22), recruiting intratumoral regulatory T cells (Tregs) to suppress antitumor response. Substantially higher numbers of $CD4^+$ $CD25^+$ Tregs have been found in B-cell NHL biopsies than in non-neoplastic lymph nodes and normal peripheral blood mononuclear cells. These T cells have been shown to inhibit production of interferon γ and interleukin (IL)-4 by $CD4^+$ $CD25^-$ T cells.[5] In studying the attraction of Tregs for the tumor sites, it has been found that lymphoma B cells expressed significantly higher levels of CCL22. This chemokine may be responsible for chemotaxis and migration of intratumoral Tregs to sites of tumor.[6] In turn, the $CD4^+$ $CD25^+$ Tregs can directly down-regulate normal B-cell activation and humoral immune responses.[7,8]

Increased Tregs in B-cell lymphomas have been shown to be associated with down-regulation of T_H17 cells. T_H17 cells seem to abundantly secrete IL-17, a proinflammatory cytokine critical for host protection against a wide variety of pathogens. Although the exact mechanism for this process is not clear, costimulatory molecules CD70, CD80, and CD86 are involved in generation of Tregs; their blockade with targeted antibodies increases the number of IL-17–producing cells.[9]

EVASION FROM IMMUNE SYSTEM

In recent years, improved understanding of the tumor microenvironment highlighted the ways in which neoplastic cells escape from immune surveillance using its interactions with non-neoplastic neighboring cells.

A variety of lymphomas show decreased major histocompatibility complex (MHC) II expression, which may be a primary mode of evasion. In classic Hodgkin lymphoma and primary mediastinal (thymic) large B-cell lymphoma, genomic breaks in MHC class II transactivator CIITA are highly recurrent. These CIITA fusions lead to down-regulation of surface HLA class II expression as well as up-regulation of programmed cell death 1 ligands, CD274/PD-L1 and CD273/PD-L2.[10] Intriguing data also show homozygous deletions of HLA class II genes in testicular and central nervous system diffuse large B-cell lymphomas, likely contributing to the immune privilege of those sites.[11]

The function of PD-L1 and PD-L2 expression by malignant B cells is thought to cause T-cell exhaustion on contact with PD-1–bearing $CD4^+$ T cells. A subset of aggressive B-cell lymphomas and virus-associated and immunodeficiency-associated lymphoproliferative disorders have demonstrated overexpression of PD-L1 by tumor cells and infiltrating macrophages, identifying a group of tumors that could be rationally targeted with PD-1/PD-L1 therapies.[12] Primary non-Hodgkin lymphoma cells show increased numbers of functionally exhausted $CD70^+$ T cells that express PD-1 and Tim-3, a phenotype shown to be induced by transforming growth factor (TGF)-β.[13]

In addition, copy number analysis of classic Hodgkin lymphoma, nodular sclerosis subtype, and primary mediastinal (thymic) large B-cell lymphoma showed amplification at 9p24.1/PD-1 ligand as well as induction by JAK2. These findings suggest that consideration toward targeting PD-1 and JAK2 pathways may be warranted in these tumors.[14]

CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia cells disrupt the normal lymphoid architecture and show a distinctive morphology, often composed of pseudofollicles or proliferation centers that contain numerous prolymphocytes. This complete disruption of the normal microenvironment could explain the often associated immune deficiency and hypogammaglobulinemia seen in CLL patients.[15]

The tumor cells themselves express high levels of CXCR4 (the receptor for CXCL12) and tumor necrosis factor (TNF)-α to inhibit normal hematopoiesis.