blood® Editorial



# Introduction to a review series on the influence of the tumor microenvironment on the pathogenesis of B-cell lymphomas

The tumor microenvironment (TME) has emerged as a critical component of the oncogenic process, influencing therapeutic targeting and treatment resistance. An increasing understanding of the role of the TME now touches virtually every lymphoid cancer type. The overall prominence and relative abundance of nonmalignant cellular compartments in the TME can vary significantly, and it is postulated that the composition and functional state are major determinants of disease behavior. However, the cellular ecosystem of malignant and nonmalignant cells is dynamic, evolving during disease duration and treatment. To date, the most insight into TME biology in lymphoma has been gleaned from studies in classic Hodgkin lymphoma, follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL). However, the literature is rapidly expanding across the full disease spectrum. Although disease boundaries are important to provide the context of understanding pathogenesis related to a specific cell-of-origin and tumor niche, cellular cross talk and immune escape mechanisms often have broader relevance. Thus, lessons learned in a particular type of lymphoid cancer are valuable and applicable to other types, and likely all cancers. This is evidenced, for example, by the commonly observed abundance of stromal cells, macrophage polarization, T-cell exhaustion phenotypes, and shared somatic gene mutations across entities.

A strong rationale for this review series on TME biology in lymphoid cancer was the exploding amount of genetic and phenotypic characterizations of the TME in the context of clinical outcome data, as well as the availability of targeted immunotherapies interfering with TME cellular cross talk, such as immune checkpoint inhibitors, bispecific antibodies, chimeric antigen receptor T cells, and now, other modulatory or blocking agents. The significance and future-oriented value of the 4 individual reviews is further elevated by the recent technology breakthroughs that enable the description of comprehensive mutational and phenotypic landscapes, deployment of single-cell transcriptome technologies, spatial histology imaging, and single molecule tracking, as well as the development of appropriate model systems to study cellular cross talk.

The reviews in this series include:

- Andrea J. Radtke and Mark Roschewski, "The follicular lymphoma tumor microenvironment at single-cell and spatial resolution"
- Camille Laurent, Sascha Dietrich, and Karin Tarte, "Cell cross talk within the lymphoma tumor microenvironment: follicular lymphoma as a paradigm"
- Freda K. Stevenson and Francesco Forconi, "The essential microenvironmental role of oligomannoses specifically inserted into the antigen-binding sites of lymphoma cells"
- Leandro Cerchietti, "Genetic mechanisms underlying tumor microenvironment composition and function in diffuse large B-cell lymphoma"

FL pathogenesis can be considered a paradigm for a dynamically changing TME, characterized by effacement of normal lymph node architecture and immune cell 're-education' in the TME. The first review by Radtke and Roschewski highlights the emerging evidence that these dynamic interactions underlie varying clinical outcomes including transformation to aggressive disease. They also highlight the developing technologies capable of capturing transcriptomes and multiparametric proteome information at single-cell resolution. Given the importance of careful subtyping of T effector and follicular helper cell populations, as well as lymph node stromal cells for a comprehensive description of progressive exhaustion and immune evasion, the authors make a compelling case that single-cell technologies will be pivotal for future progress in TME-based subtyping and clinical decision-making.

In the second review of the series, Laurent, Dietrich, and Tarte review the specific cellular cross talk mechanisms in FL with an emphasis on the bidirectional, dynamic, and therapeutically targetable interplay between malignant cells and the TME, for example, with T follicular helper cell and stromal cell compartments. The latter focus on lymphoid stromal cells (LSCs) is a unique feature of this review highlighting LSCs as key players for tumor growth and tissue remodeling. The authors summarize the dynamic changes in expression features between normal LSCs and FL-associated LSCs, with the prominent examples of CXCL12, CCL19, and CCL21 as major mediators of immune cell recruitment and niche transformation. Moreover, in this review, the diverse cross talk axes are explored as biomarkers and potential targets in the context of ongoing and future clinical trials.

The third review in the series, from Stevenson and Forconi, leads into the accelerating field of posttranslational B-cell

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receptor (BCR) modifications in B-cell lymphomas. Introduction of specific sequence motifs in the immunoglobulin variable region during somatic hypermutation in germinal center reactions renders the BCR available for addition of oligomannoses. This modification then facilitates a tumor cell–specific interaction with dendritic cell–specific ICAM-3–grabbing nonintegrin (DC-SIGN)–expressing cells in the TME, such as follicular dendritic cells and M2-polarized macrophages. The authors lead through the early evidence in FL and extend their insights to DLBCL and Burkitt lymphoma. Although this oncogenic mechanism is now described for >20 years, the pathogenic importance is still underappreciated in the field, and characterization of BCR modification and DC-SIGN is lacking in most biomarker studies in FL and DLBCL. As a main oncogenic property, DC-SIGN–dependent interaction can be considered a hallmark in FL alongside other features such as t(14;18) and somatic mutation of epigenetic modifier genes (eg, *CREBBP* and *EZH2*). Beyond classic oncogenic signaling affecting proliferation and survival, the review also highlights changes in adhesion properties through upregulation of integrins and actin cytoskeleton remodeling. Novel therapeutic options via simple blockade of this essential interaction are also emerging.

TME cellular composition in tissue biopsies is highly variable from patient to patient. The fourth article in the series puts the spotlight on this interpatient heterogeneity using the example of DLBCL. Cerchietti reviews the various intrinsic (cancer cell–specific) and extrinsic (host-specific) factors underlying and orchestrating TME composition and function. Main mechanisms shaping the TME include (1) mutations that directly target interactor molecules, (2) mutations that reprogram lymphoma cells changing the expression of membrane receptors, and (3) mutations leading to changes in the extracellular release of metabolites and cytokines. Although correlates between gene mutations and TME composition have produced unprecedented insight into somatically acquired mechanisms of immune modulation and evasion, the insufficient prediction of TME types by mutation status emphasizes the complexity of cellular interactions, importance of host-specific biology, and independent biomarker value of TME characteristics.

In summary, the individual reviews highlight the synergistic conceptual approaches across technology fields and lymphoma entities with a common focus on cellular ecosystems as a reflection of the broader oncogenic process involving both malignant and host cells of the microenvironment. The cross-referencing between the individual reviews helps to provide a consensus of our current understanding of the lymphoma/TME interactions. From the perspective of clinical translation, this review series can serve as a foundation to inform future biomarker strategies to capture TME biology and to identify cross talk axes as molecular targets of immunotherapy.

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