**Lymphoma Microenvironment in DLBCL and PTCL-NOS: the key to uncovering heterogeneity and the potential for stratification**

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Diffuse large B-cell lymphoma (DLBCL) and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) are the most common subtypes of mature B cell neoplasm and T/NK cell lymphoma, respectively. They share a commonality in that they are, by definition, highly heterogeneous populations. Recent studies are revealing more about the heterogeneity of these diseases, and at the same time, there is an active debate on how to stratify these heterogeneous diseases and make them useful in clinical practice. The various immune cells and non-cellular components surrounding lymphoma cells, i.e., the lymphoma microenvironment, have been the subject of intense research since the late 2000s, and much knowledge has been accumulated over the past decade. As a result, it has become clear that the lymphoma microenvironment, despite its paucity in tissues, significantly impacts the lymphoma pathogenesis and clinical behavior, such as its prognosis and response to therapy. In this article, we review the role of the lymphoma microenvironment in DLBCL and PTCL-NOS, with particular attention given to its impact on the prognosis and stratification.

**Keywords:** Lymphoma microenvironment, DLBCL, PTCL, NOS, immune microenvironment

**INTRODUCTION**

Diffuse large B-cell lymphoma (DLBCL) and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) are the most common subtypes of B-cell lymphoma and T-cell lymphoma, respectively. The histopathological definition of DLBCL is the diffuse proliferation of medium to large-sized B cells. Therefore, DLBCL is a mixture of clinically and biologically relevant disease entities and is heterogeneous in terms of the involved organs, the response to standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy, and pathological findings. Recent advances in high-throughput sequencing shed light on the genetic landscape of DLBCL, while, ironically, it seems that these studies further emphasized the genetic complexity of this disease, highlighting not only the inter-tumor heterogeneity but also the intra-tumor heterogeneity (i.e., multiple mutations were detected at various frequencies in a single tissue). Researchers have been trying to establish therapeutic strategies by dissecting the heterogeneity of DLBCL using a stratification model based on the characteristics of tumor cells such as cell-of-origin (COO) or oncogenic mutations. The diagnostic criteria of PTCL-NOS, analogous to DLBCL, NOS, include excluding other mature T-cell lymphomas. For this reason, PTCL-NOS is sometimes called “wastebasket” entities, implying their heterogeneity. As in DLBCL, the biology of PTCL-NOS has been uncovered mainly by the aspect of the characteristics of tumor cells. However, with the advent of immune therapy, including immune checkpoint inhibitors (ICPIs) and CAR-T cell therapy in the oncology field, the interaction between tumor cells and microenvironment components is becoming a focus of scientific attention. More and more knowledge on this field has been accumulated in this decade especially regarding DLBCL, as seen in the number of PubMed search results (Figure 1). On the other hand, the lymphoma microenvironment (LME) of PTCL-NOS has not been studied well (Figure 1). In recent years we have been analyzing clinical samples to try stratifying these large and heterogeneous disease entities of B-cell and T-cell lymphoma. By exploiting comprehensive gene expression profiling (GEP), we explored the possibility that the LME might contribute to biologically and clinically meaningful stratification in association with the molecular characteristics of tumor cells. Here, we review current knowledge about the LME in DLBCL and PTCL-NOS, mainly focusing on its clinical impact.
MICROENVIRONMENT OF DLBCL

It is widely recognized that DLBCL occurs as a result of the malignant transformation of mature B cells in the germinal center (GC) light zone or more differentiated B cells in the secondary lymphoid organs (SLO). The comprehensive GEP using cDNA microarray first identified major subtypes of DLBCL based on the COO of tumor cells. The heterogeneous DLBCL cases could be subdivided into two major groups, germinal center B-cell-like (GCB) and activated B-cell-like (ABC) DLBCL, representing the global gene expression signatures of the normal germinal center (GC) B cells and post-GC B cells, respectively. More importantly, this landmark study revealed that the COO-based stratification predicted clinical outcomes, as ABC-DLBCL showed an unfavorable prognosis, providing the gold-standard prognostication in DLBCL. It should be noted that GC is where immature B cells are challenged by a foreign antigen and represents the primary site for clonal expansion and antibody affinity maturation. In this GC reaction, the microenvironment components, includingstromal components, macrophages, dendritic cells (DC), granulocytes, and T cells, tightly regulated these processes. The disruption or malfunction of GC microenvironment cells resulted in susceptibility to infection, auto-immune diseases, or even lymphoid neoplasms. Given the tight interaction between B cells and microenvironment immune cells in normal GC reactions, we need a different perspective in understanding the LME from the tumor microenvironment of other solid cancers, where most immune cells, including tumor-killing T cells (known as tumor-infiltrating lymphocytes (TIL)), are recruited from outside the tissue sites.

Stromal cells

Lenz et al. first extensively revealed the prognostic impact of stromal components using global gene expression analysis. They identified two types of stromal signatures: the prognostically favorable “stromal-1” signature reflected extracellular matrix (ECM) deposition and monocytic cell infiltration, and the prognostically unfavorable “stromal-2” signature reflected the abundance of angiogenesis. The immunohistochemistry (IHC) analysis of representative “stromal-1” components revealed prominent fibronectin deposition between lymphoma cells. An earlier study with different technology (quantitative RT-PCR) found that fibronectin (FN) was among the most significant predictors in DLBCL, which was validated in an independent international cohort, confirming the favorable prognostic impact of the “stromal-1” gene. Other “stromal-1” signature components, connective-tissue growth factor (CTGF, also known as cellular communication network factor 2, CCN2) and secreted protein acidic and rich in cysteine (SPARC), were colocalized with CD68 protein in DLBCL tissues, suggesting their expression in monocyte-lineage cells. The abundance of SPARC protein and combination with fibronectin by IHC was associated with a favorable prognosis. However, the prognostic impact of the macrophage itself is still controversial and will be discussed in the following section. More recently, global gene expression profiling using a public cancer-wide atlas of prognostic genes, PRECOG, confirmed that the representative “stromal-1” signature genes (50 genes) were associated with a favorable prognosis not only in DLBCL but also in other B-cell malignancies such as follicular lymphoma and multiple myeloma. Interestingly, the “stromal-1” signature was associated with a poor prognosis in various types of solid tumors, including brain tumors, colon cancer, head and neck cancer, and ovarian cancer, suggesting different roles of the tumor microenvironment in lymphoma. On the other hand, fewer studies have validated the clinical impact of the “stromal-2” signature. Marinaccio et al. reported that the density of CD31+ microvasculature in DLBCL tissue was associated with the response to R-CHOP therapy. In addition, a recent study reported that the vessel density defined by ERG expression was not associated with clinical outcomes in a controlled cohort (n=455).

Although it has not been fully elucidated, several studies provided insights into underlying mechanisms in the prognostic impact of stromal cells. One study where DLBCL cell lines were co-cultured with human bone marrow stromal cells demonstrated that stromal cells might confer survival and chemoresistant capacity by activating relevant pathways such as the NF-kB and hedgehog signaling pathways. Furthermore, an in vivo mouse model of DLBCL, where the A20 murine DLBCL line was transplanted into SPARC-deficient mice, showed new evidence that the stromal microenvironment might affect key transcriptional pathways such as MYC expression, damage response programs, and immune checkpoints. Altogether, the stromal components are widely accepted to have a prognostic impact in DLBCL, yet there is some ambiguity remaining to be solved.
Macrophages

Macrophages are one of the important microenvironment components in SLO. In the primary follicles, the initial stage of GC, macrophages serve as antigen-presenting cells to immature IgD- B cells along with follicular dendritic cells (FDCs). In the mature GC, macrophages are widely recognized as tingible body macrophages (TBMs) with peculiar morphology. TBMs phagocytose apoptotic B cells in the dark zone, which are negatively selected through the GC reaction, eliminate “unwanted” B cells, and thus prevent excessive inflammation or autoimmunity. Given their critical roles in SLO, there is a good chance that macrophages might affect the clinical characteristics of GC-derived DLBCL, but there has been considerable controversy, as follows.

Inspired by the accumulated findings of tumor-associated macrophages (TAM) in solid cancers, Hasselblom et al. evaluated TAM by the number of CD68+ cells in 176 tissues from de novo DLBCL patients diagnosed during 1995-2000 (probably treated without rituximab). However, they found no correlation between the abundance of CD68+ cells with clinical characteristics, including the International Prognostic Index (IPI), COO, or survival. On the other hand, a subsequent study showed CD68 expression was related to unfavorable outcomes in 112 DLBCL patients treated by CHOP. In the rituximab era, Meyer could not find any prognostic impact of CD68+ macrophages by IHC in a larger cohort of 262 patients. To overcome the methodological bias related to manual quantification in IHC, which is a potential reason for these discrepancies, Coutinho utilized a semi-automated counting system and evaluated CD68 expression, concluding that there was no evidence for the predictive power of CD68 expression. One study from a Nordic group even reported that mRNA levels, as well as the protein levels of CD68, have a positive prognostic impact in R-CHOP patients. Thus, there has been longstanding controversy in this issue, and the results from major studies with larger cohorts in the rituximab era could not prove the clinical impact of pan-macrophage marker CD68 in DLBCL. These discrepancies may be attributed to the heterogeneity in the subsets or the roles of macrophages in DLBCL.

It should be noted that the expression of CD163, a representative marker for tumor-promoting “M2 macrophage,” was associated with adverse outcomes in a series of studies except in one study where no prognostic impact of CD163 was found. In focusing on the unfavorable prognostic impact of M2 macrophage, Staiger et al. constructed a “lymphoma-associated macrophage interaction signature” (LAMIS) on pooled GEP datasets and showed that high expression of the LAMIS signature was associated with a dismal prognosis, independently of the COO and IPI status. The latest study revealed that the enrichment of macrophages with SPARC expression in IHC, the representative favorable “stromal-1” marker in Lenz et al., is a powerful prognostic marker in a very large cohort while showing the enrichment of CD68 alone conferred a favorable prognosis. As shown above, there is still room for discussion, and thus, we could not conclude about the prognostic implication of macrophages in DLBCL. Given the phenotypic or functional plasticity and multifaceted roles of macrophages, further research with a novel approach will be required for a comprehensive understanding of their functions within the DLBCL milieu.

T cells

The T-B cell interaction is essential for the normal GC reaction. This suggests that T cells or the T cell-mediated immune response should play a critical role in the pathogenesis of B-cell lymphoma. In fact, as many as 30% of SAP-deficient patients, who harbor hemizygous mutations in SH2D1A (the signaling lymphocyte activation molecule (SLAM)-associated protein, also known as SAP), develop lymphoma. There seem to be fewer controversies on the prognostic impact of infiltrating T cells in DLBCL tissues compared with macrophages.

Prior to the “stromal signature” study by Lenz et al., Monti et al. used a comprehensive gene expression analysis to identify a DLBCL subset, the “host response (HR)" group, characterized by the LME signatures such as T/NK cell-, complement-, monocyte/macrophage-, and ECM/adhesion-related gene expression. A subsequent study by Chang et al. noted that the presence of a CD45RO+ effector or memory T cells and DCs as a reflection of the anti-tumor effector and immune initiator, respectively, was correlated with a favorable prognosis; although the sample size was small and the patients were treated by CHOP without rituximab. The prognostic impact of T cells was studied more vigorously in the 2010s. The infiltration of overall T cells (CD3+ lymphocytes) detected by flow cytometry was favorably prognostic, validated by the IHC method in larger cohorts. In terms of T cell subsets, CD4+ T cells but not CD8+ or TIA-1+ T cells predicted favorable clinical outcomes treated by R-CHOP, in keeping with the data in the pre-rituximab era. Immunosuppressive regulatory T cell (Treg) is one of the most studied T cell subsets in immune-oncology, especially in solid cancer, and is known to be associated with a poor prognosis as the consequence of the suppressive effect on tumor immunity by Treg. Contrary to the findings in solid cancer, Treg infiltration, identified by the expression of hallmark transcription factor FOXP3, was the predictor of a favorable prognosis in follicular lymphoma and Hodgkin lymphoma, suggesting, again, the opposite roles of microenvironment Tregs in lymphoid malignancies. In keeping with this, the enrichment of FOXP3+ Tregs in DLBCL tissues was reported to be a favorable prognostic factor in a series of studies, whereas the prognostic impact of FOXP3 was not validated in a recent large-scale IHC study.

With the advent of ICPIs, the clinical relevance of immune checkpoint molecules, such as programmed cell death-1 (PD-1) and its ligands, PD-L1, TIM-3 (T cell immunoglobulin and mucin domain-containing protein-3), and LAG-3 (lymphocyte activation gene-3, CD223), has been studied in the last few years. Most notably, the PD-1/PD-L1 interaction is known to attenuate T cell-mediated tumor suppression, which is known to be associated with favorable outcomes.
immunity and thus is a potential therapeutic target in many solid cancers including hematologic malignancies. In fact, PD-L1 expression was observed on tumor B cells in a small proportion of DLBCL cases (10-16%), and was associated with an inferior prognosis. McCord et al. analyzed the expression status and the origin of PD-L1 in DLBCL patients from two controlled clinical trials (n = 552 and 225) and observed that PD-L1 was primarily expressed on myeloid cells (macrophages/hiosciytes cells) in around 90% of patients. In this study, the overall PD-L1 expression did not predict an inferior prognosis, and even correlated with improved outcomes in a subset of patients, reflecting a macrophage gene expression signature. Taken together, these studies suggest that although the prognosis for patients with PD-L1 expression on tumor cells is poor, it is only in a small number of cases, and in most other cases, PD-L1 is expressed in the microenvironment, such as macrophages, and does not necessarily have a negative impact on the prognosis. Recent advances in computational imaging analysis revealed that, in addition to the existence of immune checkpoint proteins, the interaction between PD-1+ T cells and PD-L1+ cells determined by proximity in the tissues was associated with the prognosis. They found that the interaction between PD-1+ T cells and PD-L1+ cells was associated with adverse outcomes. Therefore, the prognostic impact of immune checkpoint molecules in DLBCL is not straightforward, since the cell types expressed and cell-cell interactions must be considered. It is of importance to understand the biological meanings of this pathway and delineate disease subsets who serve as an inhibitory receptor that suppresses both the cytotoxic and helper T cell function. This molecule appears to affect the DLBCL prognosis in a bimodal fashion: both high expression of TIM-3 on lymphoma cells and the enrichment of TIM-3-positive cytotoxic T cells correlated with inferior survival.

Mast cells

Mast cells have highlighted multifaceted functions in the inflammatory response and tumor immunity, however, their roles as the LME subset in DLBCL have been poorly understood. In the pre-rituximab era, one study demonstrated that mast cell infiltration is a favorable prognostic factor. On the contrary, a subsequent study showed mast cell enrichment was found in a non-responder to R-CHOP, although the sample size was small (n = 29). Thus, there is insufficient evidence to conclude the prognostic impact of mast cells in DLBCL.

The lymphoma microenvironment based on integrative analysis

Whereas follicular lymphoma patients share common genetic alterations in a large number of patients; t(14;18), (q32;q21) (~90%), KMT2D (~72%), CREBBP (~65%), and EZH2 (25%) mutations, DLBCL is a far more heterogeneous disease, as most genetic events are shared by ~10% of patients. The above studies primarily focused on specific LME components or immune subsets. However, recent advancements in computational techniques and genome-wide analysis enable us to capture a comprehensive picture of the LME, including all microenvironment components or even tumor cells, in a more unbiased manner.

For example, Newman et al. proposed a powerful computational tool called CIBERSORT, the cell-type deconvolution method, which enables us to extract the frequencies of various immune cells in the tissues from GEP data. By exploiting CIBERSORT, Ciavarella et al. analyzed GEP datasets from 482 DLBCL patients and identified the prognostic microenvironment components, such as fibroblasts, DCs, and CD4+ T cells, among 17 immune and stromal cell types. Interestingly, the activated NK signature most correlated with a poor prognosis. They further validated the prognostic significance of the LME using a customized microenvironment-related gene panel with the Nanostring platform.

To dissect the biological roles of the LME in DLBCL, Kotlov et al. analyzed large-scale GEP data based on 25 Functional Gene Expression Signatures (FGES), which represent microenvironment cellular subtypes, ECM, biological process, and pathways. By the enrichment of each FGES, 4,565 DLBCLs (4,580 of publicly available GEP data and 75 of their RNA sequencing (RNA-seq) data) were classified into lymphoma microenvironment subgroups: “GC-like,” “mesenchymal,” “inflammatory,” and “depleted,” that are biologically and clinically distinct. “GC-like” was the most favorable, while “depleted,” characterized by a lack of microenvironment-derived FGES, had the most unfavorable prognosis. Notably, the study went further to provide the sheds of biological evidence for the use of DNA hypomethylating agents in the specific microenvironment category, thus implying a novel potential strategy for achieving precision medicine in DLBCL. A subsequent study by Steen et al. developed a novel machine-learning platform, which enables the integration of large-scale transcriptome deconvolution data and single-cell RNA-seq, based on CIBERSORTx. This innovative computational approach uncovered a clinically relevant DLBCL ecosystem consisting of both tumor cells and the LME component signature.

All the above studies have in common that the original GEP data used to extract microenvironment components are obtained using microarray or RNA-seq. These methods are superior in that they can comprehensively analyze the expression levels of thousands of genes, but on the other hand, there is a problem with the reproducibility and accuracy of the data when analyzing low-quality RNA such as from FFPE tissues. The nCounter system solves this problem with its unique RNA detection mechanism, i.e., RNA molecules are directly captured and counted by barcode probes without reverse transcription or PCR reactions. This unique detection method allows nCounter to more faithfully reproduce the original (or fresh-frozen) sample information in the RNA quantification
of FFPE samples compared to existing methods such as RNA-seq, microarray, and qPCR. This advantage is expected to be more pronounced in the analysis of low-abundance genes, since correlation with the gene expression data from RNA-seq is diminished in low-abundance genes. In the differential expression analysis using FFPE specimens, nCounter detected more differentially expressed genes than targeted RNA-seq, which is superior in detection sensitivity and accuracy to conventional RNA-seq. These results suggest that nCounter is a suitable platform for the evaluation of low-frequency components in tissues such as the LME. In addition, nCounter is suitable for use in clinical settings because of its ability to perform multiplex gene expression assays quickly and easily, and because the process is largely automated, which enables high inter-sample, inter-user, and inter-facility data reproducibility. In fact, several clinical diagnostics have already been developed.

Recently, our group exploited the nCounter system to semi-comprehensively screen genes related to tumor cells and microenvironment-related genes, in combination with whole transcriptome screening by RNA-seq, to determine the prognostic genes in DLBCL. As a result, many microenvironment-related genes, especially those of follicular T cells (TFH), dendritic cells/macrophages (DC/Mφ), and stromal cell lineages, were extracted as prognostic genes rather than tumor cell-related genes. A simple prognostic score, which we called the DLBCL Microenvironment Signature (DMS) score, was generated using the most powerful prognostic genes among each LME component: ICOS (TF marker), CD11c/ITGAX (DC/Mφ marker), and FGFR1 (stromal marker). This prognostic model composed of microenvironment-related factors demonstrated strong prognostic stratification independent of COO and IPI. Interestingly, this prognostic model was inversely correlated with genomic alterations, gene expression, and phenotypes such as double-expressor lymphoma, which are known to be associated with a poor prognosis. Collectively, these data suggest that the LME signature reflects the multifaceted signatures of tumor cells themselves that explain the malignant activity of DLBCL. This opens up the possibility of developing a simple prognostic tool that reflects information that would be known through various omics tests such as IHC, FISH, genomic mutation, and gene expression profiling.

Furthermore, the advent of spatial transcriptome and proteome analysis has been providing the cellular location information in the tissue, which adds another layer of complexity, and also provides a deeper understanding of cellular interaction in DLBCL biology. Tripodo et al. showed that, by exploiting a digital spatial profiling method, Nanostring GeoMx, GC-related aggressive B-cell lymphoma can be subdivided based on the dark- and light-zone microenvironment signatures. These innovative technologies will shed light on the biological interaction and underlying mechanisms of clinical behavior in DLBCL.

Thus, recent advancements in research are revealing the full picture of the LME with a broader perspective that includes more components and finer resolution, which are expected to be applied to clinical practice. On the other hand, however, further studies are needed to elucidate the causal relationship between the microenvironment signatures and tumor cells and the underlying mechanisms.

## MICROENVIRONMENT OF PTCL-NOS

### Diagnostic and therapeutic difficulties of PTCL-NOS

PTCL-NOS is morphologically and immunophenotypically diagnosed as “mature T-cell lymphomas that do not correspond to any of the specifically defined entities of mature T-cell lymphoma.” Therefore, the diagnosis of PTCL-NOS has been changed with the advances in the biological understanding of T-cell lymphoma as seen in the rise of “nodal peripheral T-cell lymphoma with TFH phenotype,” which is characterized by expression of TFH-cell markers and is now excluded from this disease entity. In addition, the ambiguity and diagnostic difficulties should also be noted. The molecular signature, such as gene expression profiles and genetic alterations, have shed light on this ambiguity and new insights for the diagnosis of PTCLs. For example, the GEP-based molecular diagnosis revealed that 14% of pathologically diagnosed PTCL-NOS cases showed an identical GEP signature to angioimmunoblastic T-cell lymphoma (AITL). In this study, researchers showed that some cases of PTCL-NOS by pathological diagnosis were reclassified as anaplastic large cell lymphoma (ALCL) or extranodal NK/T-cell lymphoma, nasal type (ENKTL) by gene expression patterns. Furthermore, in a genomic analysis study of PTCL-NOS, a substantial amount of HTLV-1 proviral genome was detected in 18 of 142 cases (12.7%), and these cases were excluded from the analysis because they could be adult T-cell leukemia/lymphoma (ATLL). Thus, PTCL-NOS is a concept that overlaps with other T/NK cell lymphomas, and caution should be exercised in the interpretation of each study. This diagnostic ambiguity is being verified by gene expression analysis and genomic analysis, as described above, and it is expected that an integrated and more precise diagnosis will be formulated in the future.

Due to the ambiguity of the disease definition, there is currently no established standard of care for PTCL-NOS, and treatment is generally based on CHOP. However, its prognosis is extremely poor among T-cell lymphomas. Therefore, we believe that biologically and clinically meaningful stratification for this highly heterogeneous disease is crucial to improve the poor prognosis, and that the development of appropriate therapy for each stratified group is a reliable strategy.

### The current state of PTCL-NOS stratification

To date, stratification of PTCL-NOS or other PTCL subtypes has been attempted mainly by cellular origin and genomic alterations of tumor cells with great success. Tfh-related mutations, including TET2 and RHOA, were spread in PTCL subtypes, and these PTCLs were newly categorized as Tfh-lymphoma. Recently, Watatani et al.
formed a comprehensive genomic mutation analysis of 133 PTCL-NOS cases to identify new mutations and stratify them into groups with TFH phenotype, TP53 and/or CDKN2A mutations, and others. Importantly, these groups had different prognoses and different molecular signatures, such as immune evasion, suggesting a novel insight for the therapeutic strategy.

The cellular origin of PTCL-NOS has also been extensively analyzed. Rodriguez-Pinilla et al. revealed that 20-30% of PTCL-NOS expressed Th-specific surface markers, which was categorized into a new disease entity, nodal PTCL with Th phenotype, in the 2016 WHO classification. Several gene expression studies revealed that the remaining PTCL-NOS could be derived from cytotoxic T cells (Tc), T-BX21-expressing Th1, and GATA2-expressing Th2 cells. These studies showed that cases with a Tc and Th2 signature had a poorer prognosis, however, the prognostic impact of cell-of-origin in PTCL-NOS is still controversial.

Microenvironment of PTCL-NOS

Contrary to DLBCL, the LME of PTCL-NOS has not been researched so rigorously (Figure 1). However, the emergence of ICPIs in clinical oncology poses the importance of the interaction between tumor cells and microenvironment components. Actually, PD-1 and PD-L1 protein expression was confirmed in substantial numbers of PTCL-NOS tissues, although their frequency ranges widely from 10 to 70%, and both tumor cells and microenvironment cells (reactive immune cells) expressed PD-1/PD-L1 protein, which raises the complexity to understand the interaction between these cells. The results from the clinical trials of PD-1/PD-L1 signal blockade monotherapy in PTCL were not promising. There were even cases in which the PD-1/PD-L1 blockade worsened the disease, termed “hyperprogression.” On the other hand, there are some cases of PTCL that respond dramatically to ICPIs. Given that ICPIs have not been tested in enough patients to cover the heterogeneity of PTCL, the clinical benefit of ICPIs for PTCL-NOS still needs to be verified. To this end, stratification models or biomarkers that can reliably identify patients who are expected to respond and elucidation of the response mechanism that can provide a logical basis for treatment are required.

Our groups recently performed gene expression profiling using a similar approach to that of the DLBCL study described above. To identify the gene signatures which can determine whether these microenvironmental cell characteristics are useful in identifying ICPI responders (jRCT2071210101).

CONCLUSION

The importance of the microenvironment in lymphoma is gradually increasing, although it has not yet become a mainstay for understanding and stratifying the disease. In particular, it may be the key to stratification, understanding the pathogenesis, and developing novel therapy, especially in disease groups characterized by heterogeneity such as DLBCL and PTCL-NOS.

CONFLICT OF INTEREST

The authors declare no conflicts of interest associated with this manuscript.

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