Challenges in defining the immune microenvironment in T-cell lymphoma

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In this issue of *Haematologica*, Stephan *et al.* report a detailed single-cell immune profiling of T cells in peripheral T-cell lymphomas (TCL).[1] Immuno-oncology approaches including immune checkpoint blockade,[2] chimeric antigen receptor (CAR) T cells,[3] and bi-specific therapeutic antibodies[4] have been effectively employed in the management of B-cell lineage lymphomas (BCL). For many BCL subtypes, these therapies have altered the standard of care. The success of these treatments is partly attributed to a deep understanding of the underlying immunobiology of B-cell lineage lymphomas.[5-8] Although there is growing interest in applying similar therapeutic strategies to TCL, progress has been limited. This is due in part to the rarity and the biological complexity of these disorders, but the primary obstacle remains our inadequate understanding of the immune microenvironment. In this respect, TCL offer unique challenges. The effector cells for all immuno-oncology applications in B-cell lineage lymphomas are the T cells which can be analyzed in the context of their normal physiology. In contrast, in TCL, the microenvironment contains not only physiological reactive T cells but also neoplastic T cells which show functional and partial phenotypic overlaps with their benign counterparts. Therefore, analysis of the immune microenvironment requires techniques distinguishing the signals from the benign T cells and the neoplastic T cells. A small number of sophisticated studies have attempted to address this question by a variety of approaches.[9-13] These are summarized and discussed in Table 1.

Table 1. Studies analyzing the immune microenvironment.

Study	Tumor-type (N)	Controls (N)	Method	Conclusions	Comment
Ham *et al.*, 2017[9]	AITL (21)	None	IHC	CD68-CD163$^+$ M2 macrophage adverse OS.	Limited phenotyping, small clinical cohort.
Sugio *et al.*, 2018[10]	PTCL-NOS (68)	None	nCounter GEP	B-cell and DC signatures showed favorable clinical outcomes.	Whole tissue analysis. No single cell resolution or spatial analysis.
Zhu *et al.*, 2021[11]	AITL (50)	None	FC	High B cells and high CD4:CD8 gave favorable prognosis.	Limited diagnostic FC panel. No spatial analysis.
Pritchett *et al.*, 2022[12]	AITL (25)	LN, TL, SPL (105)	CyTOF	Distinct CD8$^+$ T cells with an exhausted phenotype. Changes in B cells.	True single cell analysis focused on lymphoid cells. No spatial analysis, no clinical correlates.
Suma *et al.*, 2024[13]	TFHL (9)	LN (7)	scRNAseq IMC	Oligoclonal exhausted CD8$^+$ T cells adjacent to tumor cells.	Single cells scRNA seq. Spatial analysis, clinical correlates.
Stephan *et al.*, 2024[1]	TFHL (11) PTCL (7)	TL (5)	FC	Impaired function of cytotoxic T cells, CD39 expression, and adverse outcome.	Single cell analysis, limited spatial information, weak clinical associations.

AITL: follicular helper T-cell lymphoma-angioimmunoblastic type; CyTOF: cytometry by time of flight; DC: dendritic cells; FC: flow cytometry; GEP: gene expression profiling; IHC: immunohistochemistry; IMC: imaging mass cytometry; LN: lymph nodes; N: number; OS: overall survival; PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified; scRNAseq: single cell RNA sequencing; SPL: spleen; TFHL: follicular helper T-cell lymphoma; TL: tonsil.

Stephan and colleagues approach this question by harnessing the power of spectral flow cytometry (FC) to perform an extensive analysis of the immune background in TCL. The approach allows for a detailed analysis of T-cell phenotypes with a relatively limited analysis of additional subsets including B cells, macrophages, and dendritic cells. The data illustrate the ability of spectral FC to quickly and relatively inexpensively facilitate the analysis of hundreds of thousands of cells per case. As the study requires viable tumor cell suspensions, the number of cases that could be studied was quite limited but the study was nevertheless informative. One of the most striking findings is the significant difference in the TCL microenvironment compared to normal lymphoid tissue. This is primarily driven by remarkable heterogeneity in the so-called $CD4^+$ 'conventional' T cells (Tconv). The authors attempted to explicitly clarify whether the signal was derived from neoplastic or benign T cells using both automated and manual gating approaches. Unfortunately, they were not fully successful. The antibody panels were primarily designed to assess physiological T-cell subsets but not necessarily to define the neoplastic T cells. This ambiguity of the signal derivation remains the main limitation of the study. More precise information can be obtained for T-cell subsets such as T-regulatory cells (Tregs) and $CD8^+$ T-cell subsets as these can be readily distinguished from neoplastic T cells. As seen in most other lymphoid neoplasms, the study reports that in TCL there is a marked increase in Tregs and an exhausted phenotype in $CD8^+$ cytotoxic T cells raising the possibility of novel therapeutic approaches. In addition, the analysis identifies heterogeneity of CD39 expression, an important immune checkpoint in cancer biology. The authors also explore the potential value of high CD39 expression as an adverse prognostic factor in a separate cohort of angioimmunoblastic TCL.

The study by Stephan *et al*. demonstrates the feasibility of deep and relatively inexpensive phenotypic analysis of the immune microenvironment in TCL at the single-cell level, while also highlighting the numerous challenges in this field. To address these challenges and develop effective immuno-oncology therapies for TCL, a major shift in approach is required. This shift should include the acquisition of well-annotated, viable biospecimens and the implementation of analytical methods that can be scaled up within the context of clinical trials. These methods must enable not only the unequivocal identification of neoplastic and benign T cells, but also the characterization of other immune components, such as B cells, macrophages, and dendritic cells, as well as the elucidation of the spatial relationships between different components of the immune system.

Disclosures

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Contributions

AD and MR both developed and wrote the manuscript.

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