In T-follicular helper lymphomas, 'one lymphoma can hide another': beginning to explain

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Received: October 11, 2024.
Accepted: October 31, 2024.

Citation: François Lemonnier and Philippe Gaulard.
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Haematologica. 2024 Nov 14. doi: 10.3324/haematol.2024.286173 [Epub ahead of print]

"In T-follicular helper lymphomas, 'one lymphoma can hide another': beginning to explain"

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Conflicts of interest

FL reports receiving honoraria from Kiowa, Miltenyi, and BMS; research funding from Roche and BMS; and travel support from Roche and Gilead. PG.. reports receiving honoraria from Takeda, and Gilead; research funding from Innate Pharma, Takeda and Sanofi and travel support from Roche.

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Follicular helper T-cell lymphomas (TFHL) encompass three subtypes - angioimmunoblastic-type (AITL), follicular-type (TFHL-F) and NOS (TFHL-NOS), sharing a common TFH-phenotype and genetic landscape(1,2). Angioimmunoblastic T-cell lymphoma is the prototype and most common form of TFHL. As reflected in its denomination, AITL is characterized by a prominent microenvironment including hyperplastic vessels and large B cells that are often, though inconstantly, infected by EBV. The number of immunoblasts is variable from case to case, ranging from a few scattered to numerous B-blasts, sometimes resulting in a B-cell lymphoproliferative disease (LPD) that may or may not be synchronous with TFHL and even may mask TFHL. The pathological spectrum of B-cell LPDs in TFHL is broad encompassing those mimicking large B-cell lymphoma, polymorphic LPD, follicular or marginal zone lymphoma, plasmocytoma or myeloma, or Hodgkin lymphoma(3).

The relationship between B cells and neoplastic TFH cells is not fully understood. Recent data from mouse models suggest that B cells are important in supporting lymphomagenesis(4,5) and that TFHL may support B cell LPDs, which occur more frequently than expected by chance. Several hypotheses may be proposed to explain the occurrence of these B-cell LPD (Figure): 1/ It has been demonstrated that TFHL arises from *TET2* and/or *DNMT3A* mutated clonal hematopoiesis (CH) in a large proportion of TFHL patients, with *TET2* and *DNMT3A* mutations detected not only in neoplastic T cells but also in B cells or myeloid cells in more than half of the cases(6–8). This implies that these “reactive” cells may show epigenetic dysregulation that could confer phenotypic changes and promote tumor transformation; 2/ EBV, a well known oncogenic agent for B-cells commonly detected in these B-cell

LPDs may provide genomic instability, cell transformation and B-cell proliferation, favoured by local immunosuppression; 3/ additional mutations specific to B-cells, may play a role in driving B-cell LPD. In a recent study, micro-dissected B-cells in AITL disclosed "private" mutations in *NOTCH1* which were not present in neoplastic TFH(8); 4/ CH may be complex in TFHL as multiple clones can coexist, perhaps favored by cytotoxic treatments, which could pave the way for clonally unrelated LPD(9); 5/ the function of normal TFH to provide help to B cells is likely preserved in neoplastic TFH, as suggested by the frequent hypergammaglobulinemia and autoimmune manifestations observed in AITL. In addition to the TFH function, the observation of clonal and transplantable B-cell LPDs in a mouse model by transplanting *Tet2* knockout (KO) T cells with or without an *Idh2* mutation into a TCR KO recipient *Tet2* wild-type B cells, suggests that abnormal *Tet2* KO T cells *per se* may favor B-cell transformation(10).

In this *issue of Haematologica*, Lewis, Petrova-Drus et al. (11) examined 25 TFHL samples enriched in cases with monoclonal LPD. They isolated by cell sorting and sequenced the T, B, and myeloid populations from involved lymph nodes, bone marrow, or peripheral blood of these TFHL patients. They first sequenced polyclonal/polytypic B cells of 11 patients without monoclonal/monotypic B-cell LPD (MBLs), and detected *TET2* and/or *DNMT3A* mutations associated with CH in 7/11 (64%) patients, with a median *TET2* variant allele frequency (VAF) of 0.11, suggesting that the median number of B cells derived from the CH was approximately 20%. They then studied 14 TFHL patients with monoclonal B-cell LPD and identified Identical *TET2/DNMT3A* mutations both in neoplastic TFHL cells and in B cells of 9/14 (64%) patients. Two additional MBLs patients carried a *TET2* mutation in the B cells that was not detected in neoplastic TFH, resulting in a total of 11/14 (79%) MBLs with *TET2* and/or *DNMT3A* mutations, with a median VAF of 0.42, which was higher than in polyclonal/polytypic B cells, suggesting a more pronounced expansion of *TET2*-mutated B cells in TFHL accompanied with MBLs. Interestingly, all but 2 (12/14, 86%) B-cell LPD samples showed mutations specific to B-cells, referred as "private", affecting signal transduction (N=22), epigenetic/translational regulation (N=14), and DNA damage response (N=3), indicating that CH-related mutations are unlikely to be sufficient to drive oncogenic transformation and require the cooperation of additional mutations. In contrast to a previous study, *NOTCH1* mutationwas not found in this series(8). The authors paid special attention to EBV but did not found any difference between EBV-positive and EBV-negative samples in terms of frequency of CH, VAF and number of B-cell private mutations. However, a limitation is that the authors in the current study did not search for genetic differences between EBV-positive and EBV-negative B cells at the single cell level.

Despite some limitations, this paper provides significant advances in the genetic of B cells in TFHL. Based on the availability of isolated B-, T-, and myeloid cells in a large cohort of TFHL samples with B-cell LPD, the authors expand the high frequency of *TET2* and/or *DNMT3A* mutations not only in neoplastic TFH cells, but also in polyclonal/polytypic or monoclonal B cells seen in the background of TFHL. Most of them originated from a common progenitor, but 2 B-cell LPDs had a private *TET2* mutation not detected in T cells, which could support the presence of oligoclonal hematopoiesis. This study also provides original data on the mutational landscape of these B-cell LPDs. However, B-cell LPD also occur in some cases without detectable CH or EBV infection, and additional work is warranted to better understand the factors contributing to B-cell expansion and transformation in TFHL in such cases.

References:

1. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229–1253.

2. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720–1748.

3. Ondrejka SL, Amador C, Climent F, et al. Follicular helper T-cell lymphomas: disease spectrum, relationship with clonal hematopoiesis, and mimics. A report of the 2022 EA4HP/SH lymphoma workshop. Virchows Arch. 2023;483(3):349–365.

4. Witalis M, Chang J, Zhong MC, et al. Progression of AITL-like tumors in mice is driven by Tfh signature proteins and T-B cross talk. Blood Adv. 2020;4(5):868–879.

5. Fujisawa M, Nguyen TB, Abe Y, et al. Clonal germinal center B cells function as a niche for T-cell lymphoma. Blood. 2022;140(18):1937–1950.

6. Lewis NE, Petrova-Drus K, Huet S, et al. Clonal hematopoiesis in angioimmunoblastic T-cell lymphoma with divergent evolution to myeloid neoplasms. Blood Adv. 2020;4(10):2261–2271.

7. Schwartz FH, Cai Q, Fellmann E, et al. TET2 mutations in B cells of patients affected by angioimmunoblastic T-cell lymphoma. J Pathol. 2017;242(2):129–133.

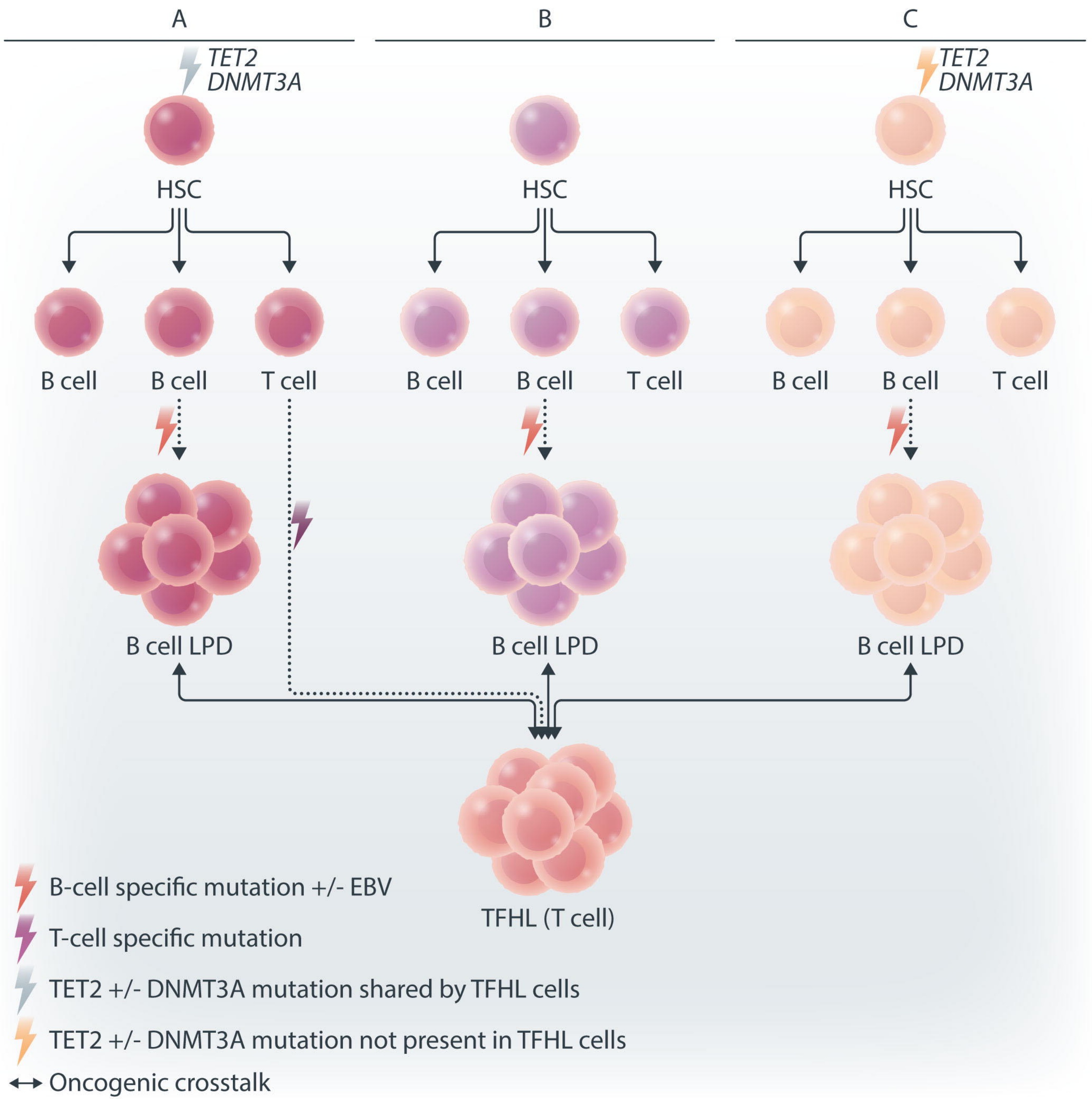
8. Nguyen TB, Sakata-Yanagimoto M, Asabe Y, et al. Identification of cell-type-specific mutations in nodal T-cell lymphomas. Blood Cancer J. 2017;7(1):e516.

9. Loyaux R, Sako N, Quang VT, et al. CLONAL ARCHITECTURE OF RELAPSED OR REFRACTORY FOLLICULAR HELPER T-CELL LYMPHOMA: AN ANCILLARY STUDY OF THE ORACLE TRIAL, A LYSA STUDY. Hematol Oncol. 2023;41(S2):108–110.

10. Leca J, Lemonnier F, Meydan C, et al. IDH2 and TET2 mutations synergize to modulate T Follicular Helper cell functional interaction with the AITL microenvironment. Cancer Cell. 2023;41(2):323-339.e10.

11. Lewis NE, Petrova-Drus K, Sardana R, et al. Polytypic B cells, monotypic/monoclonal B-cell proliferations, and neoplastic T cells diverge from TET2-/DNMT3A-mutant clonal hematopoiesis in follicular helper T-cell lymphomas. Haematologica. xxx

Figure legend: Schematic representation of different pathways of B-cell LPD transformation: clonal B-cell expansion can occur from a *TET2* (and/or *DNMT3A*) mutated hematopoietic stem cell (HSC) from which the TFH lymphoma (TFHL) cells are also derived (A), a wild type HSC (B), or an HSC bearing another *TET2* and/or *DNMT3A* mutation not present in the TFHL cells (C). B-cell LPD requires additional events, such as B-cell specific mutations, EBV infection, and crosstalk with neoplastic TFH cells.


A
B
C
TET2
DNMT3A
TET2
DNMT3A
HSC
HSC
HSC
B cell
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B cell
B cell
T cell
B cell LPD
B cell LPD
B cell LPD
TFHL (T cell)
B-cell specific mutation +/- EBV
T-cell specific mutation
TET2 +/- DNMT3A mutation shared by TFHL cells
TET2 +/- DNMT3A mutation not present in TFHL cells
Oncogenic crosstalk