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

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Follicular helper T-cell lymphomas (TFHL) encompass three subtypes: angioimmunoblastic-type (angioimmunoblastic T-cell lymphoma, AITL), follicular-type (TFHL-F), and TFHL not otherwise specified (TFHL-NOS), sharing a common TFH-phenotype and genetic landscape.[1,2] AITL 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 not always, infected by Epstein-Barr virus (EBV). The number of immunoblasts varies 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 that may even mask the TFHL. There is a broad pathological spectrum of B-cell LPD in TFHL, 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 LPD, which occur more frequently than would be expected by chance. Several hypotheses may be proposed to explain the occurrence of these B-cell LPD (Figure 1). 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 LPD, may provide genomic instability, cell transformation, and B-cell proliferation, favored 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 so-called "private" mutations in *NOTCH1* which were not present in neoplastic TFH.[8] 4) CH may be complex in TFHL as multiple clones can co-exist, 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 LPD in a mouse model by transplanting *Tet2* knockout (KO) T cells with or without an *Idh2* mutation into 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 *et al*.[11] examined 25 TFHL samples, enriched in cases with monoclonal LPD. The T-cell, B-cell, and myeloid populations from involved lymph nodes, bone marrow, or peripheral blood of these TFHL patients were isolated by cell sorting and then sequenced. They first sequenced polyclonal / polytypic B cells of 11 patients without monoclonal / monotypic B-cell LPD (MBL), and detected *TET2* and/or *DNMT3A* mutations associated with CH in 7/11 (64%) of them, 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 MBL patients carried a *TET2* mutation in the B cells that was not detected in neoplastic TFH, resulting in a total of 11/14 (79%) MBL 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 with MBL. Interestingly, all but 2 (12/14, 86%) B-cell LPD samples showed mutations specific to B cells, referred

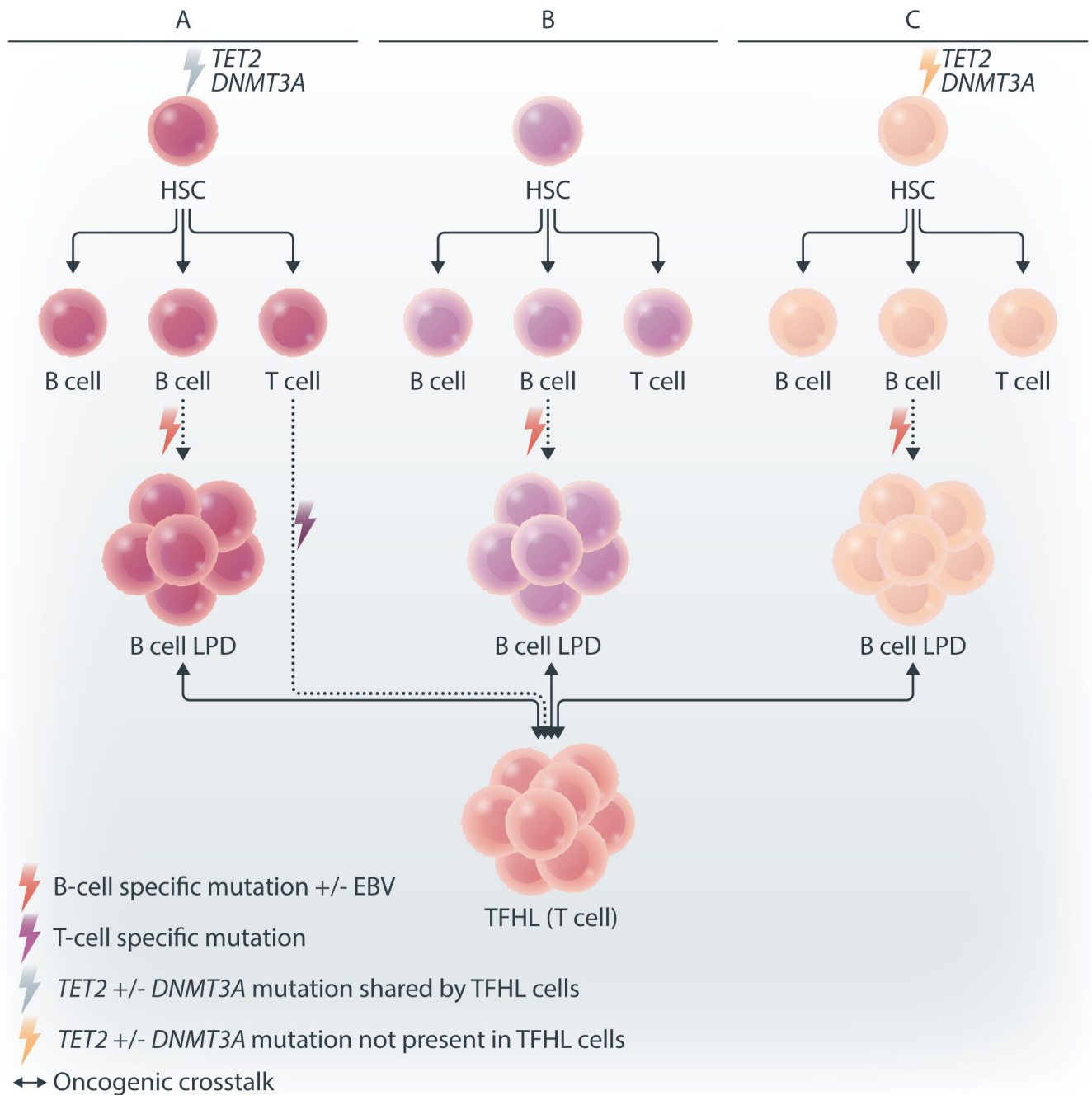

Figure 1. Schematic representation of different pathways of B-cell lymphoproliferative disease transformation. Clonal B-cell expansion can occur from a *TET2* (and/or *DNMT3A*) mutated hematopoietic stem cell (HSC) from which the follicular helper T-cell lymphoma (TFHL) cells are also derived (A), a 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, Epstein-Barr virus (EBV) infection, and crosstalk with neoplastic TFH cells. LPD: lymphoproliferative disease.

to 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 co-operation of additional mutations. In contrast to a previous study, *NOTCH1* mutation was not found in this series.[8] The authors paid special attention to EBV but did not find 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 of the study is that the authors did not search for genetic differences between EBV-positive and EBV-negative B cells at the single cell level.

Despite this limitation, this paper provides significant advances in the study of the genetics 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 show 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 LPD 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 LPD. 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.

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Contributions

Both authors contributed equally.

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