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REVIEW ARTICLE

Follicular lymphoma and its transformation to diffuse large B-cell lymphoma - a brief introduction to disease biology

Ivan Negara[1*], Oleg Arnaut[1,2,3], Sanda Buruiana[4]

[1]National Cancer Registry, Oncology Institute, Chisinau, Republic of Moldova
[2]Department of Human Physiology and Biophysics, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[3]Bioinformatics and Computational Medicine Laboratory, National Institute for Health and Medical Research, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[4]Discipline of Hematology, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

ABSTRACT

Introduction. Follicular lymphoma (FL) is a slow-growing B-cell lymphoma with a generally favorable prognosis. Nevertheless, its clinical course is heterogeneous, with a significant subset of patients experiencing early progression or histological transformation into diffuse large B-cell lymphoma (DLBCL), both considered to be high-risk events associated with treatment resistance and markedly inferior outcomes. Importantly, clinical risk factors have limited value in predicting these complications. This review outlines the key biologic features of FL, discussing how the novel molecular biology approaches can explain the clinical heterogeneity and high-risk disease evolution of FL.

Materials and methods. A focused literature review was conducted using the PubMed/MEDLINE database to identify studies on follicular lymphoma and its histological transformation to diffuse large B-cell lymphoma. Priority was given to original research or review articles investigating genetic, epigenetic, transcriptional, or microenvironmental determinants of FL.

Results. Evidence from early cytogenetic and DNA sequencing studies established BCL2 deregulation as an initiating lesion in FL, with further genetic alterations in epigenetic regulators like *KMT2D, EZH2, CREBBP/EP300* occurring early on and persisting throughout the disease course. Studies of transformed FL samples indicate that aggressive evolution is associated with acquisition of additional genetic lesions, such as those affecting the cell cycle regulators *CDKN2A/2B* and *TP53*. More recently, integrated genomic, transcriptomic and spatial resolved techniques have demonstrated substantial transcriptional heterogeneity within individual genetic subclones, suggesting that the genotype alone does not determine the phenotype of the malignant cells and supporting a pathogenetic model in which clinical trajectories reflect the combined effects of genomic evolution, transcriptional cell state, and tumor-microenvironment crosstalk. Important findings, including greater infiltration with $LAG3^{+}CD8^{+}$ T cells in cases of histological transformation to DLBCL and upregulation of transcriptional programs that promote stromal expansion and B-cell receptor signaling in cases of early FL relapse, indicate that integrated profiling represents a promising avenue for identifying the biomarkers and treatment targets that are specific to high-risk disease.

Conclusions. Continued research concentrated on multiomic profiling of both malignant and non-malignant tumor compartments is essential in order to reveal the mechanisms of FL heterogeneity and translate these data into practical biomarkers and therapeutic strategies.

Keywords: follicular lymphoma, diffuse large B-cell lymphoma, molecular biology, multiomics.

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***Corresponding author:** Ivan Negara, MD
National Cancer Registry
Oncology Institute

Key messages

What is not yet known on the issue addressed in the submitted manuscript

Follicular lymphoma is a malignancy characterized by substantial heterogeneity in terms of clinical trajectories. Early progression and histological transformation to diffuse large B-cell lymphoma,

30 Nicolae Testemițanu str., MD-2025, Chisinau, Republic of Moldova
e-mail: ivan.negara07@gmail.com

Authors' ORCID IDs
Ivan Negara – https://orcid.org/0000-0002-1901-5187
Oleg Arnaut – https://orcid.org/0000-0002-5483-8672
Sanda Buruiana – https://orcid.org/0000-0003-2341-0099

both events characterized by poor prognosis and incompletely understood biology, cannot be reliably predicted, limiting the possibility of personalized upfront treatment decisions.

The research hypothesis

Recent studies have demonstrated that the clinical heterogeneity inherent to follicular lymphoma arises from the combined effects of multiple biological determinants that are currently being resolved using novel molecular biology approaches.

The novelty added by the manuscript to the already published scientific literature

Herein, a clinician-oriented synthesis is provided of how these techniques are shaping the current pathogenetic models of de novo and transformed follicular lymphoma, and how they may contribute to the identification of practical biomarkers and therapeutic vulnerabilities.

Introduction

Follicular lymphoma (FL) represents the most prevalent indolent B-cell lymphoma, comprising up to 25% of all non-Hodgkin lymphoma cases [1]. A combination of anti-CD20 agents with chemotherapy in the frontline setting results in favorable initial treatment responses in the majority of patients [2-6]0 to 54.5, leading to overall survival rates rivaling normal life expectancy [7]. Importantly, a significant number of patients follow clinical trajectories that are distinct from the otherwise prolonged and indolent course. In particular, approximately 20% experience early disease progression (commonly referred to as progression of disease within 24 months; POD24), which is associated with markedly inferior clinical outcomes [8-11]588 patients with stage 2 to 4 FL received first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP. A sizeable minority also undergoes histological transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL), a complication likewise linked to rapid progression and inferior survival [12-14]some patients experience early disease progression, including progression of disease within 24 months (POD24.

Technological breakthroughs in the fields of genomics, transcriptomics, and epigenomics have advanced the understanding of FL from being a single entity primarily driven by the t(14;18) translocation to a highly heterogeneous group of tumors with diverse molecular features [15]epigenetic, microenvironmental, and clinical features. It is the most prevalent indolent non-Hodgkin lymphoma, characterized by a relapsing course and risk of transformation to aggressive diffuse large B-cell lymphoma. Recent advances in high-throughput sequencing, spatial transcriptomics, and imaging technologies uncovered genetic, epigenetic, and immunogenetic features underpinning FL, offering insights into its biology and potential therapeutic vulnerabilities. Although FL is primarily driven by the hallmark t(14;18. These advances have also provided a rationale for the introduction of multiple novel therapeutic agents which target the various pathways related to the underlying disease pathogenesis, including epigenetic regulators [16, 17], the B-cell receptor (BCR) pathway [18, 19]randomized study that assessed the efficacy and safety of ZO versus obinutuzumab in patients with relapsed/refractory (R/R, E3 ubiquitin ligase complexes [20, 21] and the tumor microenvironment (TME) - via T-cell engagers such as bispecific antibodies [22-25]a novel CD3 × CD20 bispecific antibody, in the third-line and later setting of follicular lymphoma.\nMETHODS: EPCORE NHL-1 is a multicohort, single-arm, phase 1-2 trial conducted at 88 sites across 15 countries. Here, we report the primary analysis of patients with relapsed or refractory follicular lymphoma in the phase 2 part of the trial, which included the pivotal (dose expansion, chimeric antigen receptor (CAR) T cells [26-28], or via promoting tumor cell phagocytosis [29].

In view of the expanding range of novel treatment options, it is essential to reliably identify the high-risk patients who are unlikely to benefit from conventional chemoimmunotherapy, such as those predisposed to early progression or transformation. Although a number of clinical predictors were shown to be associated with these poor outcomes, including advanced stage, elevated LDH, poor performance status, presence of B symptoms, extranodal site involvement, and high overall Follicular Lymphoma International Prognostic Index (FLIPI) score [9, 30-33]such as progression of disease within 24 months (POD24, none of these risk factors have sufficient pre-treatment predictive capacity. Moreover, the biologic events that shape a particular disease trajectory in FL, and, therefore, have the potential to serve as candidate biomarkers for poor clinical outcomes, are still incompletely understood. Although genomic studies have provided a foundation for the mechanisms of FL lymphomagenesis, it has become increasingly evident that the disease cannot be fully explained at the DNA level alone, highlighting the need to investigate additional layers of tumor biology. These challenges are currently being addressed through the use of novel techniques such as single-cell profiling and multiomics, which allow for a more comprehensive interrogation of both the malignant and non-malignant tumor compartments. In this review, a brief clinician-oriented

overview is provided of how these and other techniques are reshaping our understanding of de novo and transformed FL, presents a rationale for how this knowledge may eventually translate into clinically meaningful risk assessment and therapy development.

Materials and methods

The PubMed/MEDLINE database was searched using combinations of terms including "follicular lymphoma", "transformation", "diffuse large B-cell lymphoma", "POD24", "early progression", "tumor microenvironment", "single-cell", "spatial", "integrated profiling" and "multiomics." Reference lists of publications were manually searched to identify additional relevant studies. Titles and abstracts were screened for relevance, followed by full-text review of potentially eligible articles. This review considered peer-reviewed original research, reviews and conference abstracts addressing FL and its histological transformation to DLBCL. Non–peer-reviewed sources and isolated case reports were excluded.

Results

The role of genomic sequencing in follicular lymphoma BCL2 dysregulation. Before the advent of next-generation sequencing (NGS) technologies, the knowledge of specific events leading to FL development was largely limited to a single genetic lesion (Fig. 1). Early cytogenetic studies from the mid-1980s revealed that 85-90% of FL patients carry a hallmark reciprocal translocation involving the *B-cell lymphoma 2* (*BCL2)* oncogene on chromosome 18 and the immunoglobulin heavy chain (*IgH*) gene locus on chromosome 14 [34-36]hybrid bcl-2/immunoglobulin heavy chain transcripts are produced that consist of the 5′ half of the bcl-2 mRNA fused to a "decapitated" immunoglobulin heavy chain mRNA. Nucleotide sequence analyses confirmed that the hybrid transcripts continue to encode a normal bcl-2 protein. Our results suggest that t(14;18. As a consequence, the *BCL2* gene is placed under the control of strong *IgH* gene enhancer elements, resulting in constitutive *BCL2* overexpression [37]. The *BCL2* gene product then acts as its role as an anti-apoptotic protein, providing a selective survival advantage to the FL precursors carrying the t(14;18) translocation [38] and allowing them to accumulate secondary genetic lesions without undergoing apoptosis [39]the structure in which B cells undergo somatic hypermutation (SHM).

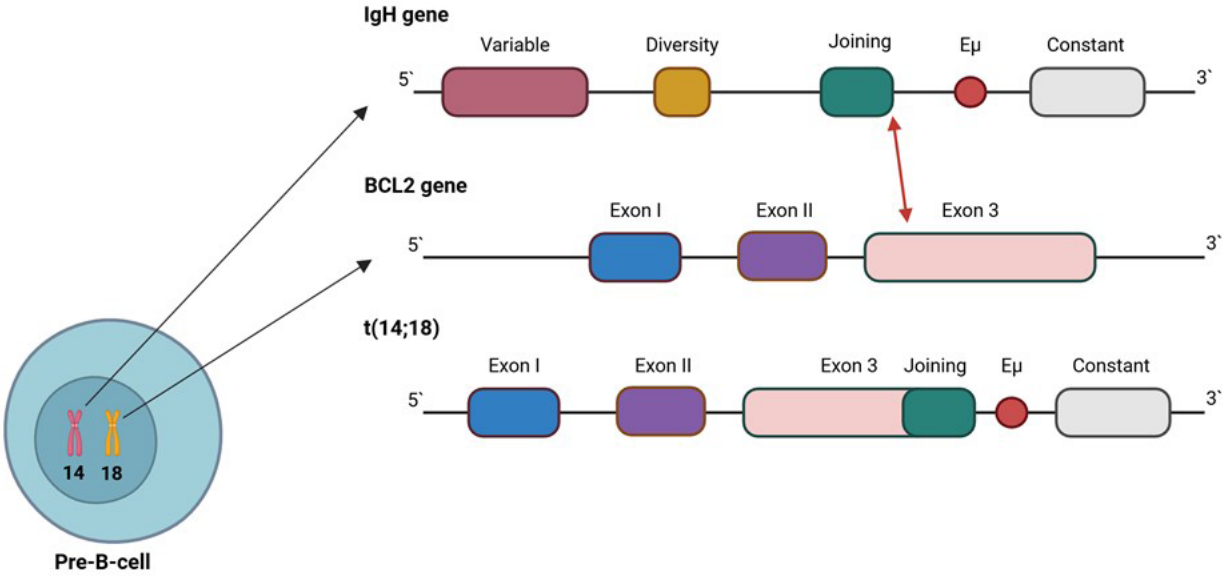

Fig. 1 A simplified schematic depiction of the hallmark t(14;18) rearrangement.

Note: *The reciprocal translocation, arising during the physiological V(D)J recombination process in developing B cells, juxtaposes BCL2 (chromosome 18, typically involving the region adjacent to exon 3) to the IgH (chromosome 14) Joining (J) region (red arrow), resulting in constitutive BCL2 expression driven by IgH regulatory sequences (such as Eμ) and promoting apoptosis resistance in B cells carrying the rearrangement.*

More recently, a role for somatic mutations in the *BCL2* gene has also been demonstrated. Correia *et al.* used Sanger sequencing to characterize *BCL2* mutations in FL and reported that such mutations, identified in 12% of patients, represent an independent risk factor for transformation and death from lymphoma [40]Follicular lymphoma (FL. However, the reliance on conventional Sanger sequencing likely underestimated the true prevalence and spectrum of *BCL2* alterations. Because Sanger sequencing produces only a single continuous read per DNA fragment, it is not sensitive enough to reliably detect mutations present below a variant allele frequency (VAF) of 15-20% [41]Sanger sequencing, single-strand conformation polymorphism (SSCP. This limitation is particularly important in the context of heterogeneous tumor samples, where a high background of DNA coming from normal cells within the tumor could mask mutations of the malignant clone. In contrast, NGS allows detection of less common variants through redundant sequencing of the same genomic regions. In line with the above, in a subsequent study by the same group

employing NGS, *BCL2* mutations were found in 52% of newly diagnosed FL [42]we examined 11 AICDA mutational targets, including BCL2, BCL6, PAX5, PIM1, RHOH, SOCS, and MYC, in 199 newly diagnosed grade 1 and 2 FLs. BCL2 mutations with VAF ≥20% occurred in 52% of cases. Among 97 FL patients who did not initially receive rituximab-containing therapy, nonsynonymous BCL2 mutations at VAF ≥20% were associated with increased transformation risk (HR 3.01, 95% CI 1.04–8.78, p = 0.043, in stark contrast to the 12% prevalence reported using Sanger sequencing [40]Follicular lymphoma (FL. Beyond sensitivity, Sanger sequencing approaches are also inherently targeted, focusing on preselected genes or regions, and therefore may miss pathogenic alterations outside the interrogated targets. Importantly, the observation that the t(14;18) translocation can be detected in a fraction of B cells in the majority of healthy individuals [43]chromosomal translocations are considered to be an early oncogenic hit. We investigated whether the lymphoma-associated t(14;18 further supports the notion that BCL2 deregulation alone is insufficient for malignant transformation, and that additional oncogenic events are required for FL development.

Epigenetic modifiers. Early NGS studies were foundational in defining the recurrent mutational landscape of FL. In a seminal study, Morin et al. conducted whole genome sequencing (WGS) of FL and DLBCL tumor samples, identifying recurrent mutations in EZH2, a gene encoding a H3K27 histone methyltransferase [44]. In a subsequent study by the same group, the authors discovered frequent inactivating mutations in the *KMT2D* (*MLL2*) gene, encoding for another histone methyltransferase [45], in 89% of FL patients [46]. In parallel, Pasqualucci et al. reported frequent mutations in the functionally related histone/protein lysine acetyltransferases *CREBBP* and *EP300*, detected in 32.6% and 8.7% of FL samples, respectively [47]. Building on these observations, Okosun et al. conducted WGS or whole exome sequencing (WES) of multiple samples that were collected from 10 patients at different time points during the course of their disease [48]. This sequential approach enabled the construction of phylogenetic trees, reflecting the clonal evolution of FL for each patient. The analysis demonstrated a branching evolution pattern in each of the trees, with the "trunk" representing the putative driver lesions that are shared between the initially identified and the subsequent clones in the FL tumors, thus supporting the existence of a common precursor and divergent subclones. In all patients, the precursor populations demonstrated an enrichment for mutations in the above-mentioned epigenetic modifiers, including *KMT2D, CREBBP, EP300*, and *EZH2*, and these findings were validated in an additional cohort of over 100 FL biopsies, where concurrent mutations in at least 2 epigenetic modifiers were found in more than 70% of cases. Interestingly, a small number of patients showed distinct mutations between diagnostic and subsequent biopsies that occurred within the same genes, a finding that was recently also observed in DLBCL [49], suggesting that certain driver lesions may be indispensable for lymphomagenesis and determine the commitment of the tumor towards a particular genetic phenotype.

Genetic determinants of FL transformation to DLBCL. The above data established epigenetic dysregulation as a central driving mechanism in the pathogenesis of de novo FL, with oncogenic effects that include immune evasion, cell cycle dysregulation, and alteration of multiple signaling pathways, including BCR, JAK-STAT, and NF-κB [15]. Importantly, analysis of sequential patient biopsies in the study of Okosun et al. reported that other genetic events, particularly abnormalities affecting cell cycle regulation and apoptosis (e.g., *MDM2*, *MYC*), as well as NF-κB signaling (*REL*, *MYD88*, *TNFAIP3*), appeared by the time of histological transformation of FL into DLBCL, and were not detectable in the initial FL biopsies [48]. Consistent with this, subsequent studies have demonstrated an association between transformation and increased mutational burden, in addition to recurrent genetic lesions affecting immune escape (B2M), confinement of B cells to the germinal center (*GNA13, S1PR2, P2RY8*), and cell cycle regulation and apoptosis (C*DKN2A, CDKN2B, TP53, MYC*) [50-53]. Notably, such abnormalities, in particular those affecting CDKN2A/2B, TP53 and MYC have also been implicated in transformation of chronic lymphocytic leukemia into DLBCL [54-56], and represent defining features of several prognostically inferior genetic subtypes of de novo DLBCL [53, 57-59]. Collectively, these findings support the notion that acquisition of specific genetic events contributes to the transformation of FL (Fig. 2)

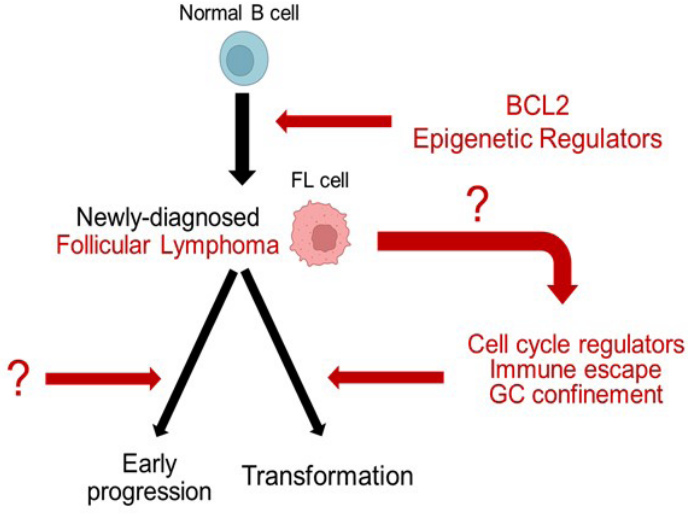

Fig. 2 Conceptual model of follicular lymphoma pathogenesis.

Note: *Early molecular events, including BCL2 deregulation and recurrent alterations in epigenetic regulators (upper right), contribute to malignant transformation of normal B cells into follicular lymphoma. Following diagnosis, FL may follow distinct evolutionary and clinical courses, including high-risk outcomes such as early progression and histological transformation to aggressive lymphoma. Transformation is accompanied by gain of additional genetic lesions, such as those affecting cell cycle regulators, immune escape, and germinal center confinement (lower right). Black arrows indicate established evolutionary relationships; red arrows indicate the mechanisms driving these relationships. Question marks denote biologic events that are incompletely understood: the determinants of early progression (lower left) and the events leading to acquisition of transformation-enabling genetic lesions (middle right).*

and raise the possibility that similar mechanisms play an important role in the development of more aggressive phenotypes across a spectrum of lymphoid malignancies [60].

The above findings indicate that transformation of FL into DLBCL is driven by an expansion of a tumor subclone with the propensity to acquire transformation-enabling genetic lesions [52, 61], a tendency that may arise as a functional consequence of pre-existing genetic abnormalities or other biologic events. In this context, it appears to be of more value to identify how the mutations at initial diagnosis influence the risk of FL transformation, rather than those acquired later during the course of disease progression, given that such an approach could eventually help guide up-front clinical decision-making. In a recent study that analyzed WGS data from 423 FL and de novo DLBCL patients, two genetically distinct FL subgroups were resolved using a machine learning classifier trained to discriminate between DLBCL and FL based on mutational profiles [62]. The first group, which included 53% of untransformed FL from the training cohort, was termed the constrained FL (cFL). Patients within this group were less likely to undergo transformation, and were distinguished by the presence of missense mutations in the lysine acetyltransferase domain of *CREBBP*, in addition to mutations in several genes involved in the *mTORC1* signaling pathway (*RRAGC*, *ATP6AP1*, and *ATP6V1B2*). The remaining 47% of untransformed FL were classified as DLBCL-like FL (*dFL*), a subgroup presenting with increased rates of aberrant somatic hypermutation (as demonstrated by a higher prevalence of mutations within the transcription start sites of commonly affected genes, such as *BCL6*, *BCL7A*, *RHOH*, and *ZFP36L1*), nonsense *CREBBP* mutations, and higher risk of transformation to *DLBCL*. These findings indicate that certain early genetic lesions may predispose FL to a commitment toward histological transformation, and thus serve as potential predictors for this clinical outcome. Whether these early genetic events contribute to transformation directly, or determine a state in which additional transformation-inducing genetic events accumulate, is currently unclear.

Genetic risk stratification models. Data from the aforementioned studies have laid the foundation for developing pretreatment prognostic scoring systems that incorporate somatic mutations for FL risk stratification. The most well-known of these models is the m7-FLIPI, a molecular prognostic tool created using a targeted NGS panel of 74 genes applied to pretreatment biopsies from 151 FL patients [63]. The score integrates several clinical parameters with the mutation status of 7 genes: *EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP*, and *CARD11*. In the initial trials, it was able to stratify patients into low- and high-risk subgroups based on failure-free survival [63], as well as identify those at highest risk for POD24 [9]. However, multiple follow-up studies attempting to validate the m7-FLIPI score have yielded inconsistent results in external patient cohorts [33, 64-67], suggesting that specific genetic lesions may be associated with distinct functional consequences in different clinical and biologic contexts. Given these challenges, no mutation-based prognostic score is currently adopted in clinical practice. As expanded upon below, the extensive inter- and intraclonal heterogeneity inherent to FL likely diminishes the ability of simplified models that are based on individual genes to consistently identify high-risk patients across different settings. At earlier time points, such as at diagnosis, the smaller, potentially prognostically relevant subclones may, at best, only be detectable using ultra-sensitive technologies [52, 61]. Moreover, none of the existing risk-stratification models were specifically trained for the most pertinent predictor of inferior survival, POD24 [68]. Finally, the risk of adverse clinical outcomes, such as transformation, may be associated with exposure to specific treatment regimens [69], further complicating our understanding of the predictive value of genetic lesions in FL. Collectively, these findings indicate that conventional, bulk DNA-level profiling alone is not sufficient to identify the core determinants underlying the clinical trajectories seen in FL.

The role of single-cell sequencing and integrated multiomic approaches in follicular lymphoma

Single-cell profiling and tumor microenvironment as a driver of clinical behavior. Bulk DNA sequencing is readily accessible, and widely used across cancer studies for diagnosis and biomarker identification. However, every tumor cell can exhibit a unique genomic, epigenomic, and transcriptional profile. Modifications at the RNA level appear particularly important, given that genomic and epigenomic changes are ultimately reflected at the RNA level. With the development of the 10x Genomics Chromium systems, single-cell RNA sequencing has recently become more accessible to the scientific community, allowing for analysis of gene expression profiles from thousands of individual cells per run [70]splicing variants, mutations/indels in addition to differential gene expression, thus providing a more complete genetic picture than DNA sequencing. This most widely used technology in genomics tool box has evolved from classic bulk RNA sequencing (RNAseq, exposing subclones and cell states that would otherwise be invisible in bulk sequencing.

Multiple studies employing single-cell RNA sequencing have reaffirmed that FL tumors consist of several coexisting subclones, either at different anatomical sites, or within the same lesion. In a recent study, Haebe *et al.* used single-cell RNA, B- and T-cell receptor sequencing, as well as flow cytometry to profile synchronously acquired tumors from different sites in 10 patients with FL [71]FL can exhibit site-to-site genetic and phenotypic divergence as well as differential Tfh abundance and tumor-Tfh cross talk.In FL, biopsy of a single anatomical site may not capture the full scope of a patient's disease., Tumor heterogeneity complicates biomarker development and fosters drug resistance in solid malignancies. In lymphoma, our knowledge of site-to-site heterogeneity and its clinical implications is still limited. Here, we profiled 2 nodal, synchronously acquired tumor samples from 10 patients with follicular lymphoma (FL. Unexpectedly, the authors found that in many patients the disease evolved independently at different sites, exhibiting site-to-site divergence in BCR evolution, gene expression and surface protein profiles. Supporting these observations, bulk WES of samples obtained from multiple disease sites

within the same patients revealed spatially discordant genetic abnormalities, including alterations in several m7-FLIPI-related genes, such as *EZH2* and *EP300* [72]. These findings appear particularly relevant given that most FL patients manifest disseminated tumor involvement. They also support the notion that a diagnostic biopsy from a single anatomical site may be insufficient, and further add to the limited predictive ability of the approaches relying just on bulk genome sequencing and clinical data. Moving forward, the potential requirement for multiple biopsies may be circumvented by genomic profiling of circulating tumor DNA [73] yet the identification of poor-risk groups remains challenging. In addition, the biology underlying these differences is incompletely understood. We hypothesized that characterization of mutational heterogeneity and genomic evolution using circulating tumor DNA (ctDNA, although the utility of such an approach in FL remains to be validated.

In a study integrating single-cell RNA and bulk exome sequencing, Andor *et al.* also identified the presence of multiple subclones within individual FL tumors, each associated with transcriptional profiles that reflected their distinct genetic backgrounds [74]characterized by differential pathway activities.In CD4+ Tregs, known immune checkpoint genes are coexpressed with transcription factors and immune regulators, including CEBPA and B2M., Follicular lymphoma (FL. Notably, substantial transcriptional heterogeneity was also observed within individual genetic subclones, suggesting that phenotypic diversity is not solely determined by the genotype. Consistent with this, malignant B cells in FL were shown to cycle between different transcriptional states largely independently of their mutational profile, a process likely driven by extrinsic signals from the non-malignant components of the lymphoma microenvironment [75]the second most frequent lymphoma in adults, often presents as a disseminated disease at diagnosis. Despite a generally slow progression and a median overall survival of more than 15 years with current chemo-immunotherapies, FL patients often suffer from multiple relapses. Yet, the biological mechanisms promoting FL dissemination, progression and relapse are still poorly understood. FL, like most B-cell lymphomas, originates from germinal centers (GC.

The structure of lymph nodes affected by FL retains features of normal lymphoid tissue, but the architecture is disorganized, with complete or partial effacement by the neoplastic follicles [76]primarily, within lymph nodes (LNs. It is enriched for T cells, including mostly $CD4^+$ subsets, such as T follicular helper cells, T regulatory cells, T follicular regulatory cells, and others, which were shown to contribute to tumor growth and treatment resistance via pro-survival signals (such as CD40L or IL-4), or by suppressing the normal anti-tumor immune response. Other cell types include the various macrophages and dendritic cells, which are frequently polarized into a tumor-supportive phenotype by the malignant cells, as well as a variety of stromal cells, which are able to promote tumor growth by altering the microenvironment or by interacting directly with the tumor cells and secreting tumor-promoting cytokines. Dave *et al.* were among the first to demonstrate the role of the FL TME in determining the patient clinical trajectory [77]. Using microarray-based gene-expression profiling, the authors resolved two survival-associated gene expression signatures, each reflecting the biologic characteristics of the non-malignant cells within the analyzed tumors. The first, termed immune-response 1, was associated with a favorable prognosis and enriched for expression of genes encoding T-cell and macrophage markers, whereas the second, termed immune-response 2, was associated with a poor prognosis and enriched only for genes preferentially expressed in macrophages and dendritic cells, thus suggesting a role for the TME-derived T cells in preventing tumor growth. These early bulk gene-expression data provided the first evidence that the FL microenvironment is a prognostically meaningful structure that could shape the disease trajectory. Single-cell technologies have since expanded this concept substantially. Han *et al.* used single-cell RNA sequencing to subdivide FL into four major subtypes based on the phenotype and relative abundance of the various T cell populations [78]and associations with characteristics of tumor-infiltrating T-cell subsets., Follicular lymphoma (FL. Importantly, the subtype characterized by T cell depletion was associated with poor survival, reinforcing the role of T cells in suppressing tumor growth and suggesting that immune evasion by the tumor cells is an important contributor to poor prognosis.

Integrated multiomic approaches in early relapse FL and transformation to DLBCL. A multiomic approach refers to the integrated analysis of two or more biologic data layers (e.g., genomics, transcriptomics, epigenomics, proteomics) to reconstruct a more complete view of tumor biology. In FL, where clonal heterogeneity and microenvironmental interactions appear to significantly influence disease behavior, multiomic profiling is particularly valuable for capturing the complexity that may otherwise be missed by single-modality methods. Using WES, bulk and single-cell RNA sequencing, and iterative bleaching extends multiplexity (IBEX) imaging (an immunofluorescence technique that allows visualization of more than 65 proteins in the same tissue section) [79]lacking a spatial context, and traditional immunofluorescence, capturing only two to six molecular features, cannot resolve these issues. Imaging technologies have been developed to address these problems, but each possesses limitations that constrain widespread use. Here we report a method that overcomes major impediments to highly multiplex tissue imaging. \"Iterative bleaching extends multiplexity\" (IBEX, Radtke *et al.* constructed a molecular and cellular atlas of lymph nodes affected by FL [80]. The authors demonstrated that malignant B cells in high-risk patients undergoing early relapse exhibited increased expression of genes related to BCR signaling and TME remodeling, unlike the malignant B cells derived from all other FL patients. The unique imaging technique enabled spatial resolution of the non-malignant cell populations within individual tumors, revealing that early-relapse cases were characterized by an expansion of specific stromal cell communities and desmoplasia. Notably, the tumor B cells were frequently found to be in close physi-

cal proximity to certain TME components (such as dendritic cells), a state that may facilitate sustained BCR signaling.

Additional insights were obtained from another integrative single-cell study by Sarkozy et al., who applied single-cell genome and transcriptome sequencing to investigate the co-evolution of the malignant B cells and the surrounding microenvironment during transformation of FL into DLBCL [61]. Transcriptomic profiling showed differential expression of MYC target genes, in addition to activation of oxidative phosphorylation and mTORC1 pathways during transformation. By integrating WGS and single-cell RNA sequencing data across sequential time points, the authors further identified an association between genomic evolution (i.e., emergence of additional genetic lesions) and acquisition of a transformation-related transcriptional phenotype. However, significant transcriptional diversity in the absence of detectable genomic evolution was also observed, reinforcing the notion that genotype alone does not fully determine the tumor cell state. Analysis of the non-B cell fraction revealed marked remodeling of the TME, with decreases in naive/memory-like and follicular helper-like T cells, accompanied by expansion of the exhausted/regulatory-like and effector T-cell clusters, findings that were further supported by immunofluorescence evidence of increased CD8+ T-cell exhaustion marker expression during transformation. Spatial profiling additionally showed that the exhausted T cells were more abundant in close proximity to the malignant B cells after transformation, suggesting that the malignant B cells engaging with the surrounding T cells may contribute to T-cell dysfunction, and, potentially, to transformation-associated transcriptional reprogramming in the tumor B cells. Importantly, expression of the exhaustion marker LAG3 on CD8+ T cells in two independent pre-treatment FL cohorts was significantly associated with shorter time to transformation, indicating that specific TME features could represent candidate biomarkers for histological transformation. Collectively, these studies support the notion that both transformation and early relapse are accompanied by a shift in the composition and spatial organization of the TME, thus indicating that the tumor-microenvironment crosstalk is a core component of the biologic process that drives the development of more aggressive disease phenotypes (Fig. 3).

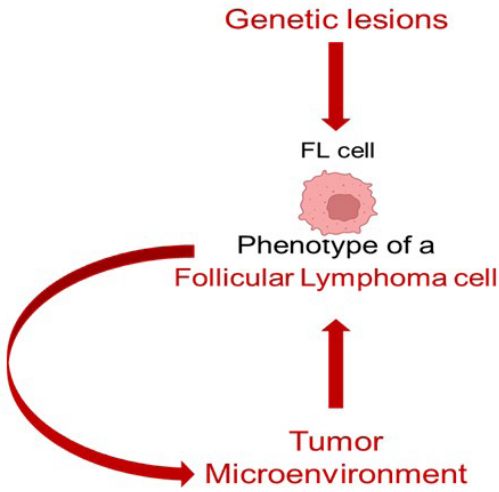

Fig. 3 Conceptual model for the determinants of a follicular lymphoma cell phenotype.

Note: *The phenotype of a malignant follicular lymphoma cell is shaped by both intrinsic genetic lesions (top arrow) and extrinsic signals from the tumor microenvironment (bottom arrow). The curved arrow denotes bidirectional crosstalk between tumor cells and surrounding non-malignant components, emphasizing the dynamic and reciprocal process determining the tumor cell phenotype.*

Discussion

Over the last few decades, the application of omics technologies has transformed the understanding of follicular lymphoma from a disease centered on BCL2 deregulation to a complex and heterogeneous entity shaped by multiple molecular mechanisms. Genomic sequencing has established epigenetic dysregulation as a core component of FL pathogenesis, with recurrent mutations in chromatin modifiers like *KMT2D*, *CREBBP*, *EP300* and *EZH2* occurring early and being maintained throughout disease evolution. In contrast, other genetic lesions, including those affecting cell cycle regulators, are more often acquired later on and are associated with more aggressive disease phenotypes such as transformation into DLBCL.

More recently, integrative approaches that combine genomics, transcriptomics, and spatial profiling have further shown that the mechanisms driving FL are multifaceted and cannot be explained by the genotype alone, instead reflecting the interplay between genetic lesions, transcriptional programs, and dynamic crosstalk with the lymphoma microenvironment. Collectively, the data presented in this review support a model of FL pathogenesis in which malignant cells undergo genetically driven phenotypic changes and engage in dynamic, bidirectional interactions with surrounding immune cells, thereby remodeling the immune microenvironment into a tumor-supporting framework that promotes further phenotypic changes in the malignant cells.

Despite these advances, FL continues to pose significant clinical challenges, with markedly inferior outcomes in patients with histological transformation or early progression. Recent discoveries, including the identification of $LAG3^{+}CD8^{+}$ T-cell infiltration as a candidate biomarker of histological transformation and the emergence of potential therapeutic vulnerabilities in early relapse, such as fibrosis-associated TME remodeling that may be targetable with antifibrotic agents and BCR pathway inhibitors, support the notion that multiomic profiling may continue to reveal clinically actionable biomarkers of high-risk disease and inform risk-adapted therapeutic strategies.

Conclusions

Follicular lymphoma is a biologically complex disease in which clinical outcomes are determined not only by the genetic background of the malignant cells, but also by their transcriptional states and interactions with the surrounding microenvironment. The data reviewed here indicate that continued research focused on multiomic profiling is essential to identify the distinct biologic determinants that drive

the various clinical trajectories in FL, thereby improving our ability to predict poor outcomes and facilitating therapeutic approaches that are focused on timely prevention of transformation and early progression.

Competing interests

None declared.

Authors' contributions

IN, OA and SB participated in conceptualization of the manuscript. IN conducted the literature review and drafted the manuscript. OA and SB critically revised the manuscript. All authors approved the final version of the manuscript.

Ethics approval

Not needed for this study.

Provenance and peer review

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The GPT-5.2 model was used during copy-editing of the finished manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of this publication.

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