

Review

Molecular Pathogenesis of Follicular Lymphoma: From Genetics to Clinical Practice

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Abstract: Follicular lymphoma (FL), a generally indolent disease that derives from germinal center (GC) B cells, represents around 20–25% of all new lymphomas diagnosed in Western countries. The characteristic t(14;18)(q32;q21) translocation that places the *BCL2* oncogene under control of the immunoglobulin heavy-chain enhancer occurs in pro- or pre-B cells. However, additional secondary alterations are required for the development of overt FL, which mainly affects genes involved in epigenetic and transcriptional regulation, signaling and B cell differentiation, the BCR/NF-κB pathway, and proliferation/apoptosis. On the other hand, new insights into the FL pathogenesis suggest that FL lacking the *BCL2* translocation might be a distinct biological entity with genomic features different from the classical FL. Although FL is considered an indolent disease, around 10–20% of cases eventually transform to an aggressive lymphoma, usually a diffuse large B cell lymphoma, generally by a divergent evolution process from a common altered precursor cell acquiring genomic alterations involved in the cell cycle and DNA damage responses. Importantly, FL tumor cells require interaction with the microenvironment, which sustains cell survival and proliferation. Although the use of rituximab has improved the outlook of most FL patients, further genomic studies are needed to identify those of high risk who can benefit from innovative therapies. This review provides an updated synopsis of FL, including the molecular and cellular pathogenesis, key events of transformation, and targeted treatments.

Keywords: follicular lymphoma; *BCL2* rearrangement; genetic alterations; histological transformation; tumor microenvironment; targeted therapies



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1. Introduction

Follicular lymphoma (FL), the most common indolent B cell lymphoma, is histologically characterized by a follicular or nodular pattern of tumor cell growth [1,2]. Its molecular and cellular features make FL the paradigm of a germinal center (GC)-derived neoplasm, with expression of *BCL6*, *CD10*, and activation-induced cytidine deaminase (*AID*), which is critical for immunoglobulin somatic hypermutation. More than 85% of FL cases harbor the characteristic t(14;18)(q32;q21), which occurs in pro- or pre-B cells of the bone marrow [3,4].

The disease generally presents with lymphadenopathy, with eventual dissemination to the bone marrow or other organs [5]. For diagnosis, a tissue biopsy showing the typical histological and immunohistochemical pattern is required, which will also allow histological grading (proportion of centrocytes and centroblasts). FL is characterized by a pattern of continuous relapses, with a progressively shorter duration of response [6]. For this reason, most patients with low tumor burden, non-localized disease are amenable to a watchful waiting strategy without active therapy [5]. In turn, high tumor burden patients

require treatment, in the form of immunochemotherapy (ICT) or immunotherapy alone (rituximab). In the event of a relapse, although no standard exists, high-dose therapy and autologous stem cell transplantation (ASCT) are still considered appropriate for a subset of patients, while newer drugs such as bispecific T cell engagers and CAR-T cells will soon be the cornerstone of management for non-transplant-eligible patients and in the event of subsequent relapses.

Although the median overall survival (OS) for FL patients now approaches 20 years [7], specific subsets of patients exhibit a markedly worse prognosis, namely those experiencing an early relapse (progression of disease within 24 months of frontline ICT, POD24) [8] or developing histological transformation (HT) to an aggressive lymphoma [9]. A myriad of prognostic scores have been developed with the aim of identifying individuals with poor outcomes, and eventually tailoring therapy accordingly [10]. However, their success has been limited and most patients receive similar regimens irrespective of prognostic scores, with the exception of obinutuzumab instead of rituximab as part of ICT for high-risk patients in some countries [11].

In the past years, molecular analyses have expanded our knowledge on the mutational landscape of FL, highlighting the importance of epigenetic modifiers, survival pathways, and the tumor microenvironment. However, elucidating the biological mechanisms that underlie the clinical heterogeneity remains a research priority. This review describes the current knowledge regarding the role of the *BCL2* rearrangement in FL, the genomic landscape of these tumors, clonal dynamics of transformation, as well as the contribution of the microenvironment. Finally, available and upcoming targeted therapies are summarized.

2. *BCL2* Rearrangement in FL

The genetic hallmark of FL is the t(14;18)(q32;q21) translocation, present in 80–85% of patients, which occurs in pro- or pre-B cells in the bone marrow as an error of V(D)J recombination mediated by RAG1 and 2 enzymes [3,4,12]. As a consequence, the *BCL2* oncogene is placed under control of the immunoglobulin heavy-chain enhancer, leading to the overexpression of the BCL2 protein, which confers a survival advantage to B cells. The 18q21 breakpoints are mainly clustered within a 2.8 kb major breakpoint region (MBR) located in the 3'UTR of the *BCL2* gene [3,12–14] (Figure 1). Breakpoints located within the intermediate cluster region (ICR) and the minor cluster region (MCR), just downstream and far downstream of *BCL2*, respectively, are less common. The breakpoint in the *IGH* locus (14q32) occurs in the J and D segments, close to the recombination sequence signal (RSS) site of a J_H gene segment or the 5'RSS of a D_HJ_H joint, suggesting that the translocation took place as the cell attempted a D_H to J_H or V_H to D_HJ_H rearrangement [4,13–15] (Figure 1). Variant translocations t(2;18)(p12;q21) and t(18;22)(q21;q11) are less frequent and juxtapose the *BCL2* gene to the *IGK* and *IGL* loci, respectively. In these variants, the breakpoints are located in the 5' end of *BCL2* locus [14]. Remarkably, breakpoints in the 5' end of the *BCL2* gene have also been described in t(14;18), leading to a higher BCL2 expression compared to that of t(14;18)-positive cells affecting the 3'UTR region of *BCL2* [16].

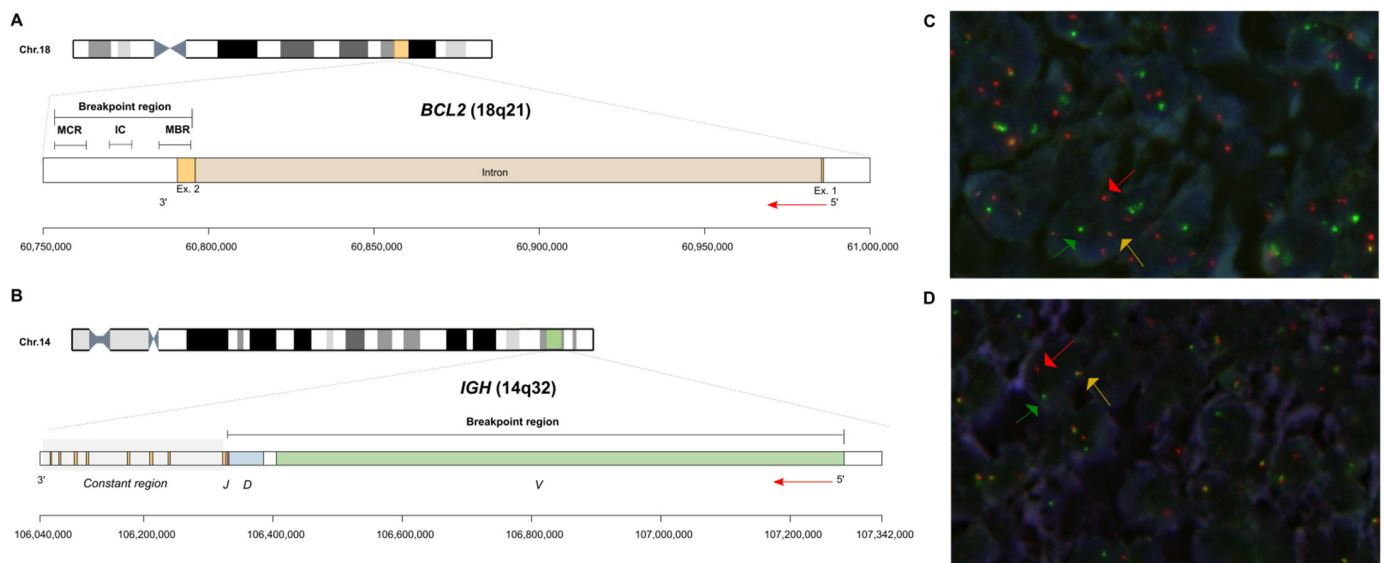


Figure 1. Schematic representation of the *IGH::BCL2* translocation breakpoints in follicular lymphoma. **(A)** The figure shows the *BCL2* locus, containing two exons and one intron located in 18q21 and annotated based on ENST00000398117.1 (hg19). The arrow indicates the direction of *BCL2* transcription. The breakpoints cluster in three main regions located at 3' of *BCL2*, namely major breakpoint region (MBR), intermediate cluster region (ICR), and minor cluster region (MCR). Breakpoints located at 5' of *BCL2* locus have also been described, mainly when *BCL2* is rearranged with the light chain loci on 2p12 and 22q11. **(B)** The panel illustrates the *IGH* locus, representing the constant region (yellow color and highlighted in light gray), the V (green), D (blue), and J (red) regions. The arrow shows the direction of *IGH* transcription. The distribution of the various breakpoints regions is displayed in the upper part, involving V(D)J region. **(C,D)** Fluorescence in situ hybridization of paraffin-embedded tumor sections using the dual color, dual fusion *IGH::BCL2* **(C)** and dual color, break-apart *BCL2* **(D)** probes. **(C)** FISH analysis shows two yellow signals (yellow arrow), indicating an *IGH::BCL2* fusion and one green (green arrow) and one red signal (red arrow) corresponding to unarranged *IGH* and *BCL2*, respectively. Normal cells display two green signals and two red signals. **(D)** Signal constellation shows a break in the *BCL2* locus indicated by a split of the yellow signal into one green and one red and unarranged *BCL2* labeled with a yellow signal. Normal cells have two yellow signals.

Using sensitive techniques, the t(14;18) may be detected in B cells from peripheral blood and/or lymphoid tissues of a large proportion (up to 70%) of healthy individuals [17–19], although the vast majority of them will never develop FL, indicating that *BCL2* deregulation alone is insufficient for tumorigenesis. Follow-up studies of epidemiological cohorts of healthy individuals have identified t(14;18)+ B cells in the blood for many years [20], with a frequency that increases with age [18,19], and change in the body's immune system due to certain infectious conditions (such as hepatitis C virus) [21]. t(14;18)+ cells, defined as “FL-like cells” (FLLCs), are a clonal population of atypical memory B cells displaying a GC-experienced phenotype that is characteristic of FL [22] and usually display more than one *IGH::BCL2* breakpoint, with a similar molecular structure to that seen in follicular lymphoma [23].

3. Genetic and Epigenetic Landscape of FL

In addition to t(14;18), FL has a characteristic genomic profile, with frequent losses of 1p (15–20%), 6q (20–30%), 10q (20%), and 13q (15%), and gains of 1q (25%), 2p (25%), 8q (10%), 12q (20%), and 18q (30%), and trisomies 7 (20%), 18 (20–30%), and chromosome X (20%) [24–26]. Furthermore, recurrent copy-neutral losses of heterozygosity (CN-LOH) involving 1p (30%), 6p (20%), and 16p (20–25%) have been identified [24–26].

Next generation sequencing (NGS) studies have unraveled secondary genomic alterations in FL mainly affecting genes involved in epigenetic and transcriptional regulation, signaling and B cell differentiation, the BCR/NF- κ B pathway, and proliferation/apoptosis (Figure 2).

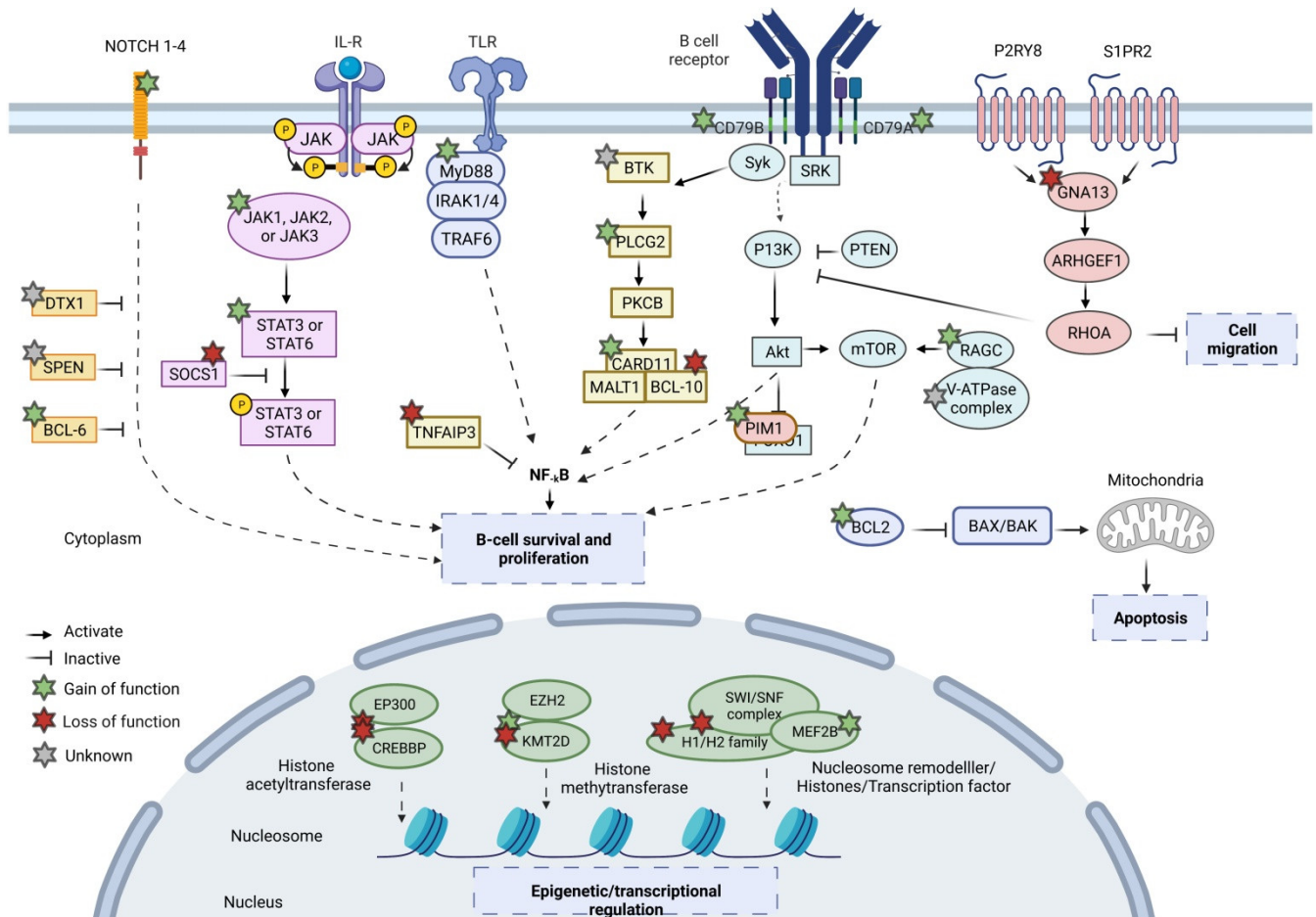


Figure 2. Molecular pathways involved in follicular lymphoma. The figure shows the several pathways dysregulated in follicular lymphoma. Gain-of-function alterations are labeled with a green star, loss-of-function with a red star, and unknown functions with a grey star. BCL2 overexpression leads to apoptosis inhibition. Genomic alterations affecting Janus Kinase (JAK) signal, B cell receptor (BCR) pathways, MYD88, and NOTCH pathway directly stimulate B cell survival and proliferation. Alterations in sphingosine 1-phosphatase receptor 2 (S1PR2) and guanine nucleotide binding protein subunit (GNA13) enhance dissemination outside the germinal centers. Figure created with [BioRender.com](https://www.biorender.com) (accessed on 13 July 2022).

3.1. Epigenetic and Transcriptional Regulation

Genomic alterations in histone-modifying enzymes, including *KMT2D*, *CREBBP*, *EP300*, and *EZH2*, are detected in virtually all FL patients [27–31]. The *KMT2D* gene encodes a H3K4 methyltransferase and is the most frequently altered gene in FL (70–80% of cases) [32–34]. The majority of these alterations are nonsense or frameshift somatic mutations leading to a loss of function and, consequently, a loss of active transcription marks (H3 lysine 4 methylation, H3K4me) [35]. Studies using mouse models have shown that the ablation of *Kmt2d* in B cells leads to GC expansion and impaired terminal differentiation promoting lymphomagenesis [35,36]. The *CREBBP* gene encodes a lysine acetyltransferase that acetylates histone 3 at lysines 18 (H3K18Ac) and 27 (H3K27Ac) [37] and is altered in 70% of FL cases [29,31,33,35,38]. Around 80% of somatic mutations cluster within the KAT domain, reducing its acetyltransferase activity [29,30,38,39]. Murine studies reported that

loss of *Crebbp* promotes B cell lymphoma, especially in cooperation with *BCL2* overexpression [38], and that the regions of decreased histone acetylation were primarily located at distal enhancer elements, including MHC class II genes [38,40–42]. Moreover, *CREBBP* mutations have been previously associated with a reduction of acetylation of nonhistone proteins such as TP53 and BCL6, highlighting the crucial role of alterations in this gene in lymphomagenesis [30]. In addition, the alteration of *EP300*, also encoding for a histone acetyltransferase, occurs in 15% of FL cases [29,31,33]. *EP300* regulates different GC transcriptional programs and cooperates with *CREBBP* in the GC reaction [43]. The *EZH2* gene encodes a lysine methyltransferase that catalyzes the trimethylation of H3K27 (H3K27me3) as part of the polycomb repressive complex 2 (PRC2). *EZH2* mutations, present in 25–30% of FL cases, were the first recurrent chromatin modifying gene mutations described [27,44–46]. The majority of the mutations are located in the catalytic SET domain, mostly involving tyrosine 646 (Y646). These mutations result in a gain of function, increasing the transcriptional repressive H3K27me3 mark [47,48]. Altered *EZH2* regulates the GC phenotype by repressing specific cell cycle genes (e.g., *CDKN1A* and *CDKN1B*) and abrogates GC formation [44]. In addition, mutations in linker histones (*HIST1H1B-E*) [28,49] and core histone genes and in genes encoding members of SWI/SNF (e.g., *ARID1A*, *ARID1B*, *BCL7A*, and *SMARCA4*) are also frequently found in FL [29,31,33,35,50].

The transcriptional regulator *BCL6* is altered by somatic mutations or translocation in 5–10% of FL cases [50–53]. Rearrangements involving *BCL6*, mainly t(3;14)(q27;q32), leading to the *IGH::BCL6* fusion, are commonly found in grade 3B cases [54]. On the other hand, mutations in the transcriptional activator *MEF2B* involved in the recruitment of demethylases and deacetylases to promoters and enhancers, are present in 12–15% of FL patients [32,55]. *MEF2B* mutations modify the ability of *MEF2B* to bind to DNA or to the co-repressor *CABIN1*, leading to increased transcriptional activity [55,56].

3.2. BCR/NF- κ B Pathway

Genomic alterations in genes encoding proteins in the BCR/NF- κ B signaling pathway (*CARD11*, *TNFAIP3*, *CD79A*, *CD79B*, and *MYD88*) are present in approximately 30% of FL patients [28,57]. *CARD11* gain of function mutations occur in 10% of the cases and affect mainly the coiled-coil domain [58]. Less prevalent are *TNFAIP3* somatic mutations, occurring in 5% of patients [29,59,60], although *TNFAIP3* deletions have a prevalence of 20% [25,26]. On the other hand, mutations in other components such as *CD79A*, *CD79B*, and *MYD88* are less frequent in FL as compared to other germinal center-derived B cell lymphomas [57]. The molecular consequence of the genomic alterations described above is the activation of the NF- κ B signaling pathway via tonic BCR (e.g., *CD79A* and *CD79B*), chronic BCR (e.g., *CARD11*), and toll receptor and interleukin-1 receptor signaling (e.g., *MYD88*) [61]. *BTK* and *FOXO1* somatic mutations are found in about 5–10% of FL cases [29,33,62]. *FOXO1* is a transcription factor activated downstream of BCR and the molecular consequence of the mutations described in FL is a gain of function [50]. Nonetheless, the functional consequences of *BTK* mutations warrant further investigations. Somatic mutations in the variable regions of the immunoglobulin heavy and light chain loci, which promote *N*-glycosylation, occur in up to 80% of FL cases [59,63,64].

3.3. Signaling Pathways

Genes involved in JAK-STAT (*SOCS1*, *STAT6*, *STAT3*) and NOTCH signaling (*NOTCH1*, *NOTCH2*, *NOTCH3*, *NOTCH4*, *DTX1*, and *SPEN*) are frequently altered in FL, promoting proliferation and survival of tumor cells [26,29,63,65,66]. *SOCS1* or *STAT6* mutations are found in around 10% of FL cases [60,67]. Somatic mutations involving the C-terminal PEST domain of the *NOTCH1* and *NOTCH2* proteins are similar to those observed in other B cell lymphomas [57,62], as well as alterations in the *NOTCH3* and *NOTCH4* loci and signaling regulators such as *DTX1* and *SPEN* [57,62]. Overall, the NOTCH pathway is altered in 18% of FL patients.

Recurrent mutations in genes encoding components of the mTOR complex 1 (mTORC1) pathway have been identified in FL. mTORC1 promotes protein synthesis in response to growth factors and nutrient signals. Intracellular amino acid levels are detected via a supercomplex that includes Rag GTPases, the Regulator complex, the v-ATPase complex, and SLC38A9 that cooperate to activate mTORC1 signaling in the presence of sufficient amino acids [68–70]. In the context of an acid-rich medium, active RAG GTPase heterodimers recruit mTORC1 to the lysosomal membrane [65,66,71]. Activating mutations in *RRAGC* enhance mTORC1 even after amino acid depletion and are found in 17% of FL patients. In addition, mutations in components of the V-ATPase complex have also been observed in FL [65,66]. Finally, inactivating mutations of the *S1PR2*-guanine nucleotide-binding protein subunit ($G\alpha 13$) pathway, responsible for retaining B cells into the GC niche, are present in around 10% of FL patients, promoting both dissemination and survival of FL cells [35,62,72].

3.4. Immune Regulation/Evasion

The *TNFRSF14* gene encodes the herpes virus entry mediator A (HVEM) which is the most recurrently altered gene via inactivating mutations, deletions, and CN-LOH [27,29,73], besides the epigenetic family members. HVEM induces activation or inactivation of B and T cells depending on its interaction with different ligands, including B and T-lymphocyte (BTLA) and LIGHT [74,75]. In BCL2 mouse models, HVEM or BTLA knockdown promoted the development of FL [76]. Remarkably, B cells lacking HVEM produce increased tumor necrosis factor (TNF)-associated cytokines, promoting an abnormal stroma activation, which induces a supportive tumor microenvironment and recruitment of T follicular helper cells which, in turn, support the survival of tumor cells.

3.5. Apoptosis and Proliferation

BCL2 mutations have been described together with the *BCL2* rearrangement in around half of FL cases [77]. Furthermore, *PIM1* mutations have been reported in around 10% of FL patients [57]. *PIM1* is a kinase which promotes NF- κ B signaling [78].

3.6. DNA Damage Response

Although *TP53* mutations are identified in a low proportion of FL patients at diagnosis (6%), they are enriched in subgroups of patients with an older age, higher-risk scores, and a shorter progression-free survival [79].

4. Follicular Lymphoma Lacking BCL2 Rearrangement: A Different Entity?

FL lacking the *BCL2* translocation (*BCL2* – FL) comprises 10–15% of all FL patients [1,72]. Several studies have investigated whether this subset of patients is biologically and clinically different to classical FL with *BCL2* rearrangement (*BCL2* + FL). Katzenberger and colleagues [73] identified that *BCL2* – FL were characterized by a diffuse growth pattern, frequent inguinal presentation, and 1p36 deletions. Subsequent studies trying to define the molecular profile of *BCL2* – FL cases revealed: (i) somatic hypermutation, aberrant somatic hypermutation and expression of activation-induced cytidine deaminase at similar levels compared to the *BCL2* + FL cases [72,80]; (ii) frequent gains of 2p16 involving *REL* [72]; (iii) absence of molecular features resembling marginal zone lymphoma [72]; and (iv) enrichment in late GC B cell and NF- κ B and proliferation signatures and significant downregulation of miR16 expression [72,81]. Intriguingly, the vast majority of *BCL2* – FL cases express *BCL2*, suggesting an alternative molecular mechanism to induce *BCL2* expression in this subset of cases [51].

Similar clinical features have been identified in *BCL2* + and *BCL2* – FL [51]. However, diffuse and pediatric forms of FL, which often lack *BCL2* translocation, exhibit a better clinical prognosis compared to *BCL2* + FL cases [73,82]. On the other hand, some studies have compared the clinical features of *BCL2* – FL with and without *BCL6* rearrangements and, although most studies point towards a similar clinical presentation, some differences have

been identified, e.g., advanced clinical stages, higher histological grades, and less frequent expression of the CD10 marker in *BCL2* – FL cases with *BCL6* rearrangement [54,83,84].

Katzenberger and colleagues [73] were the first authors to delineate a subgroup of FL patients with a diffuse growth pattern, characterized by CD23 expression, lack of *BCL2* rearrangement, and 1p36 deletion. Later on, Siddiqi confirmed these findings in 2016 [85], proposed the *TNFRSF14* locus as the candidate gene of 1p36 deletion, and identified recurrent mutations in the *STAT6* and *TNFRSF14* loci. In addition, current NGS studies of *BCL2* – FL cases have identified recurrent mutations in *CREBBP* [85–89], an enrichment in immune response and N-glycosylation signatures and less frequent N-glycosylation sites [88].

A recent comprehensive study conducted in the largest cohort of *BCL2* – FL cases identified that this subtype is genetically heterogeneous. Patients were more commonly women, presented in early clinical stages at diagnosis, and had a favorable clinical behavior [86]. Two molecular clusters were identified: cluster A, characterized by *TNFRSF14* alterations and frequent mutations in epigenetic regulators, with recurrent losses of 6q21–q24, resembling *BCL2* + FL cases; and cluster B, showing few genetic alterations, namely *STAT6* mutations concurrent with *CREBBP* alterations, lacking *TNFRSF14* and *EZH2* mutations [86]. Furthermore, an association between *STAT6* mutations and CD23 expression, an uncommon marker in *BCL2* + FL, was identified, especially in cases with a diffuse growth pattern. Importantly, the study concludes that *BCL2* – FL cases are mainly characterized by a follicular growth pattern and only a few cases have a diffuse component [86].

Recently, the International Consensus Classification (ICC) proposed the *BCL2*-R-negative (here described as *BCL2* – FL), CD23-positive follicle center lymphoma subtype as a new provisional entity [2]. Besides, pediatric-type and testicular FL are also proposed as distinct entities [2]. Pediatric-type FL is characterized by recurrent mutations in the MAPK pathway, lack of *BCL2* rearrangement, and an excellent prognosis FL [90–92], and has also been included as a new subtype in the 5th edition of the WHO Classification [83]. Furthermore, testicular FL, identified as a new FL entity in young boys, which confers good prognosis, is also characterized by the lack of *BCL2* translocations [84,93].

5. Molecular Mechanisms of Transformation

Histological transformation of FL (tFL) into an aggressive lymphoma (mainly diffuse large B cell lymphoma—DLBCL) [94–98] can occur during the course of the disease and affects approximately 10–20% of patients [9,99–101]. Several studies have been conducted to describe the genetic landscape of tFL and compare it to baseline biopsy samples. The studies of paired diagnostic and tFL cases identified that tFL arises mainly through a divergent or branching evolution from a common altered precursor cell (CPC) [29,73,102,103] (Figure 3). Remarkably, none of these studies identified a single genetic event driving transformation.

Initial studies described an increased number of copy-number alterations (CNA), including gains of oncogenes *REL/BCL11A* (2p16), *BCL6* (3q27), and *MYC* (8q24), and losses of tumor suppressor genes like *TP53* (17p13) and *CDKN2A/B* (9p21) in transformed compared to diagnostic samples [104–107]. Somatic mutations enriched at transformation involve signaling pathways (e.g., *PIM1*, *SOCS1*, *STAT6*, *MYD88*, *TNFAIP3*, and *ITPKB*), the cell cycle (e.g., *CCND3*), sphingosine-1-phosphate signaling (*GNA13*, *S1PR2*, and *P2RY8*), B cell development (*EBF1*), and immune evasion (*B2M* and *CD58*) [29,73,102]. The majority of tFL cases fall into the germinal center B (GCB) molecular subtype of DLBCL, although 20% of cases are of the activated B cell (ABC) subtype. The genomic profile differs between the GCB and ABC subtypes of tFL, indicating that the different biological backgrounds modulate the transformation process, mainly concerning the activation of the BCR and NF-κB pathways associated with the ABC subtype [25,108].

Transcriptomic analysis of tFL suggests the implication of an embryonic stem cell signature maintained by MYC activation, or the role of the NF-κB pathway in the transformation event [99,109]. On the other hand, transformation in FL is also modulated by the interaction of tumor cells with the immune system. Consequently, the composition and

distribution of the immune cells infiltrating the tumor, such as CD4⁺ T helper cells, have been identified as a predictor of transformation [100].

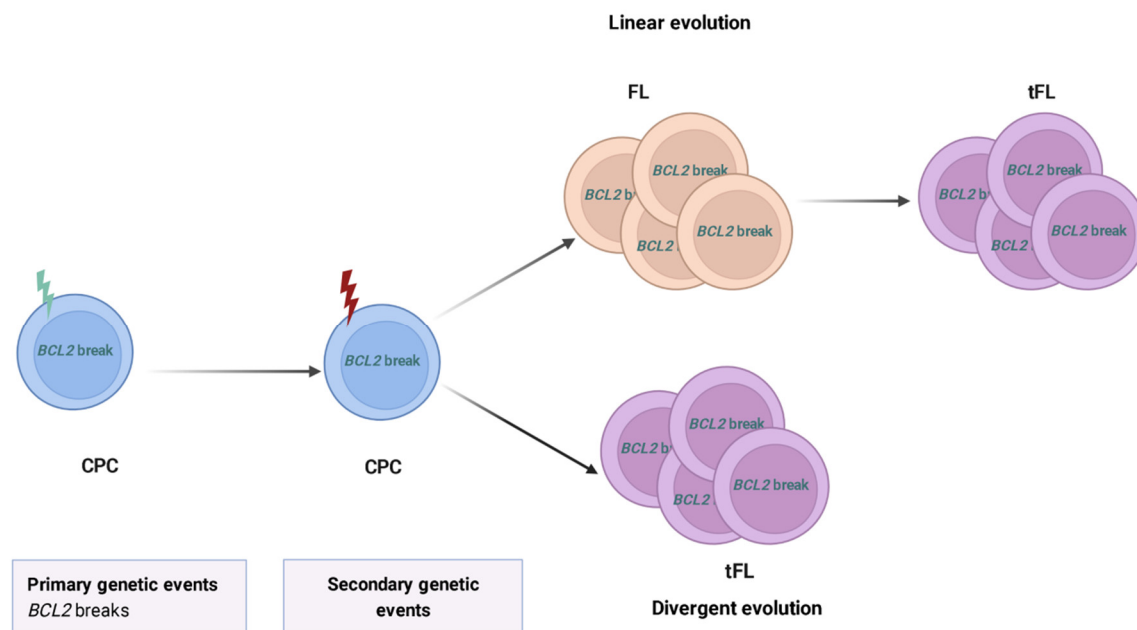


Figure 3. Clonal dynamics of transformed follicular lymphoma. Models of clonal evolution during FL transformation. FL tumors derived from a common progenitor cell (CPC), that has acquired the primary genetic events, e.g., *BCL2* rearrangements (green thunderbolt). The CPC subsequently harbors additional secondary alterations leading to the neoplasm (red thunderbolt). The transformed FL (tFL) clone might originate from the FL clone after the acquisition of additional alterations corresponding to a linear evolution, or derive from a CPC through an independent acquisition of distinct mutations suggesting a divergent evolution. Figure created with [BioRender.com](https://www.biorender.com) (accessed on 13 July 2022).

6. Role of the Tumor Microenvironment (TME)

Despite the crucial role of genomic alterations of lymphoma cells in the development, progression, and relapse of FL, their crosstalk with non-malignant tumor-infiltrating cells might be even more relevant [101,102] (Figure 4). While some other lymphomas, such as Burkitt's, are dependent on an intense proliferation of tumor cells, and others (Hodgkin's) recruit reactive cells, FL recapitulates the GC organization and uses the support of follicular dendritic cells and T follicular helper (T_{FH}) cells to build three-dimensional structures.

The tumor-promoting activity of the TME has been explained by the development of an ecosystem that sustains the growth and survival of lymphoma cells and by the induction of mechanisms of evasion of the host antitumor immunity. These effects are exerted by means of genetic modifications (e.g., mutations in epigenetic modifiers), a modulation of immune cell subsets (dampening of antitumor populations, stimulation of immune suppressive cells), and an induction of T cell exhaustion mechanisms. For the sake of practicality, cells of the TME can be categorized into T cells, tumor-associated macrophages (TAM), and stromal cells.

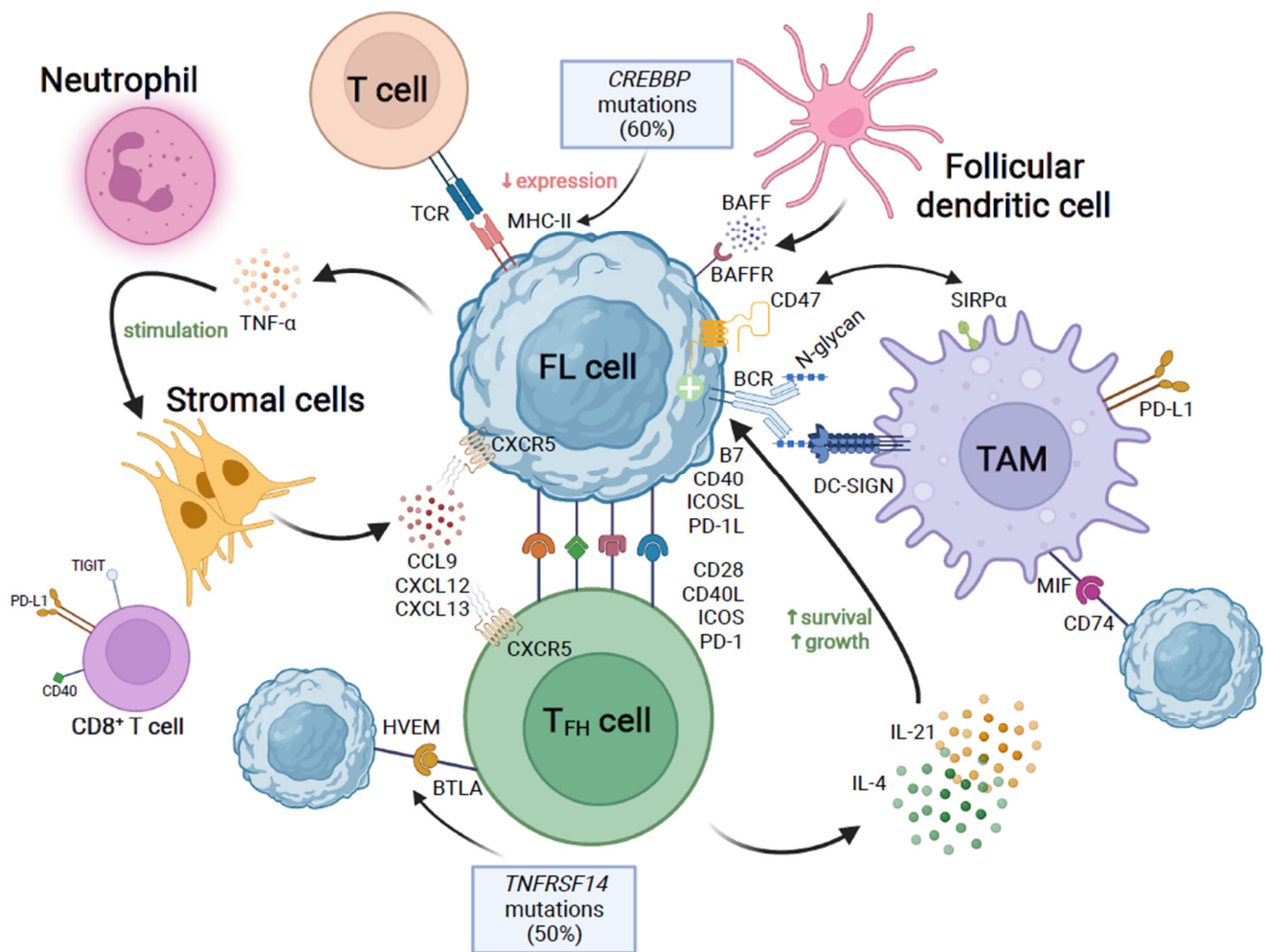


Figure 4. Schematic representation of the crosstalk between follicular lymphoma (FL) cells and the tumor microenvironment. From the upper right corner, clockwise: follicular dendritic cells secrete BAFF, which is sensed by BAFFR on FL cells. The “don’t eat me” signal CD47 expressed by FL cells interacts with SIRP α in tumor-associated macrophages (TAM), which induces immune tolerance towards tumor growth. N-glycan-modified residues of the B cell receptor (BCR) are recognized by DC-SIGN on the TAM. T_H cells secrete IL-4 and IL-21, which promote survival and growth of the FL cell. The immunological synapse is established, among others, between B7, CD40, ICOS, and PD-1L (FL cell) and CD28, CD40L, ICOS, and PD-1 (T_H cell). *TNFRSF14* mutations affect the HVEM–BTLA interaction between FL and T_H cells. Stromal cells secrete chemokines, which are sensed by CXCR5 on FL cells. In turn, tumor cells release TNF- α , which stimulates stromal cells. Mutations in *CREBBP* induce a decreased MHC-II expression on FL cells, which reduce the interaction with the T cell receptor (TCR), thus hampering the detection of tumor cells by the immune system. Figure created with [BioRender.com](https://www.biorender.com) (accessed on 13 July 2022).

6.1. T Cells

CD4⁺ cells: FL follicles show a higher proportion of some types of T cells compared to healthy germinal centers [103,110]. First, T_H cells are a subgroup of CD4⁺ T lymphocytes implicated in normal GC biology and antibody production. However, T_H cells of FL patients are not superimposable to those of healthy individuals [111,112]: they overexpress IL-2 and IL-4 and have activated STAT6 signaling, which increases proliferation and prevents apoptosis. Tumor immune evasion is also facilitated by T cell exhaustion and tolerance: dysfunctional CD4⁺ and CD8⁺ and functional T_H cells express PD-1, and some of them secrete IL-4, IL-21, and TNF- α , sustaining malignant development [113].

Second, regulatory T cells (T_{reg}), a $CD4^+$ immunosuppressive subset expressing CD25 and FOXP3, are crucial guarantors of peripheral immune tolerance [114]. However, their frequency is higher than in normal lymph nodes. By means of an increased number of immune checkpoint molecules (GITR, TIGIT, ICOS), they have a stronger suppressive capacity [115–117]. It has even been suggested that the T_{reg} population is oligoclonal [118], a fact that would explain their role in sustaining tumor growth. Finally, a recently described type of infiltrating lymphocytes are T_{FR} (follicular regulatory T cells) [110,119], which express FOXP3 and CXCR5. Indeed, the T_{FH}/T_{FR} ratio could be important for the biology of FL.

$CD8^+$ (cytotoxic) cells: This cell subset is key to antitumor immunity. Some studies have established that a higher proportion of $CD8^+$ cells is an independent favorable prognostic factor [120,121]. These cells build synaptic relationships with tumor cells and exert direct cytotoxicity by means of lytic granules containing granzyme B. However, their effector function can be lost with time, due to persistent antigen stimulation and the expression of inhibitory receptors (PD-1, LAG3, TIM3, TIGIT) [122,123]. A deeper understanding of these exhaustion mechanisms will be crucial for the development of novel immunotherapeutic strategies [102].

6.2. Tumor-Associated Macrophages (TAM)

Besides being part of the innate immune system, macrophages are professional antigen-presenting cells. Classically, two macrophage phenotypes were described: M1 (receiving activating signals in the form of lipopolysaccharide or $IFN-\gamma$) and M2 or activated (sensitive to IL-4 and IL-13) [124]. However, this dichotomic classification is now considered too simplistic and unable to grasp the plasticity of these cells [125].

Concerning the prognostic impact of macrophages, Dave and colleagues [126] demonstrated that FL cases with high expression of genes mainly related to macrophages and follicular dendritic cells (“immune response 2”) had shorter survival, while those of patients with high expression of T cell-related genes (“immune response 1”) were longer. The real importance of TAM in FL is yet to be determined, especially when evaluated using immunohistochemistry (CD68 and CD163). Although a higher proportion of $CD68^+$ cells was associated with a poorer prognosis in chemotherapy-treated FL patients, this effect was lost when rituximab was incorporated [127,128]. These apparently contradicting findings suggest that therapeutic strategies modulate the composition of the TME.

Macrophages are important players in antibody-dependent cellular phagocytosis and rituximab-induced cytotoxicity [129] and express SIRP α , which is part of the “don’t eat me” signaling pathway. A higher proportion of macrophages expressing this protein has been linked to poorer outcomes [130]. Furthermore, M2 macrophages enhance a dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN)-dependent adhesion via N-glycan-modified residues of the BCR and generate BCR-associated kinase activation [131].

6.3. Stromal Cells

Although initially viewed as not immunologically active, non-immune elements of the TME (endothelial cells, fibroblasts, mesenchymal stromal cells) are considered increasingly important in the pathogenesis of FL. Ongoing interesting studies are attempting to characterize the composition and cell organization of the lymph nodes, blood, and bone marrow. In this sense, the role of the crosstalk between the tumor and stromal cells needs to be highlighted [132]. Cancer-associated fibroblasts, emerging from the reprogramming of lymph node lymphoid stromal cells, directly support malignant B cell growth and orchestrate a permissive FL cell niche by recruiting and polarizing immune TME subsets.

7. Clinical Implications

7.1. Molecular Prognostic Scores

With the advent of NGS, attempts at incorporating molecular data to refine prognosis have been made. The first of such efforts was the m7-FLIPI, a clinicogenetic risk model encompassing clinical (FLIPI and ECOG performance status) and genetic data [133]. After applying a 74-gene deep sequencing panel to 151 lymph nodes from FL patients in need of treatment, the authors found that mutations in *EP300*, *FOXO1*, *CREBBP*, and *CARD11* (conferring poor prognosis), and in *MEF2B*, *ARID1A*, and *EZH2* (conferring good prognosis), enhanced the prognostic ability of the clinical parameters. The primary endpoint of the study was failure-free survival, but the score was similarly predictive of OS. Subsequent applications of the score to patients treated with different regimens have yielded diverse results, which, together with its unavailability in common practice, has limited its widespread use.

The same German and Canadian cohorts from the m7-FLIPI gave rise to the POD24 prognostic index (POD24-PI) [8], which was specifically designed to predict early treatment failure. Selecting only mutations in *EP300*, *EZH2*, and *FOXO1*, the sensitivity to predict POD24 was higher, at a cost of lower accuracy and specificity. Likewise, it has not reached clinical practice.

Finally, with the intention of capturing the complexity of FL biology and the crosstalk between tumor and accompanying cells, a gene expression profile score was devised, the 23-GEP [134]. After genes independently associated with PFS were selected, 23 of them were shown to have a strong correlation between the experimental platform and the standard Nanostring® technology. Those genes were finally included in a score that was predictive of PFS. The incorporation of a risk score using GEP is even more challenging than that of NGS-based indexes.

It must not be forgotten that molecular prognostic scores calculated using lymphoid tissue samples will always face the limitation of sampling bias: the mutational spectrum, akin to histological grading, might change according to the site of biopsy [135]. This drawback may be overcome by the incorporation of the circulating tumor DNA (ctDNA) technology [136], which could integrate/recapitulate the overall genomic landscape of a neoplasm.

7.2. Therapies Targeting the Molecular Pathogenesis of FL

Considering the importance of the t(14;18) and the *BCL2* oncogene in the pathogenesis of FL, its selective inhibitor, venetoclax, would be expected to have notable efficacy, akin to that seen in chronic lymphocytic leukemia. Results have been, however, underwhelming [137,138]. The phase 2 CONTRALTO study [138] compared venetoclax (V), bendamustine (B), and rituximab (R) with BR alone in the relapsed/refractory (RR) setting, with similar efficacy but higher toxicity in the VBR arm, leading to a high discontinuation rate of venetoclax. A chemotherapy-free arm with VR was also tested, with only 17% of complete responses. Several mechanisms explaining this insensitivity to BCL2 inhibitors have been postulated [102]: (i) the expression of BCL2 might be heterogeneous, (ii) other components of the anti-apoptotic BCL2 family might be active (MCL-1, BCL-XL), and (iii) a plethora of genetic and microenvironmental stimuli might make overt FL tumors less dependent on BCL2 expression.

One of the few genetically-targeted therapies available in this disease is tazemetostat, an oral selective inhibitor of the epigenetic regulator *EZH2*, which has been recently approved by the Food and Drug Administration (FDA) for RR FL. A phase 2 study [139] tested tazemetostat in 99 RR FL patients (45 *EZH2*^{mut} and 54 *EZH2*^{wt}), and the overall response rate (ORR) was 69% and 35% in *EZH2*^{mut} and *EZH2*^{wt} patients, respectively. Median progression-free survival (PFS) was around one year, and toxicity was acceptable, mainly in the form of cytopenias. This makes tazemetostat an excellent candidate for drug combinations.

In contrast to *EZH2*, which is predominantly affected by activating mutations, the function of most epigenetic regulators, such as *CREBBP* and *KMT2D*, is disrupted by loss-of-function mutations, which are less easily amenable to pharmacological targeting. Acetyltransferase inactivating mutations are frequent in FL, which is why vorinostat, an oral histone deacetylase (HDAC) inhibitor, has been tested in this disease. By targeting HDAC, this drug would restore the epigenetic homeostasis of the tumor. In the phase 2 study including 39 FL patients [140], the ORR was 49% and median PFS was 20 months, with cytopenias as main adverse events. Vorinostat has later been combined with rituximab, with comparable results [141]. The pan-HDAC inhibitor panobinostat [142] has also been studied in FL, as well as newer-generation inhibitors, such as mocetinostat [143], albeit with limited efficacy. It remains to be seen whether genetically-targeted drugs and their combinations become relevant tools in the management of this neoplasm, in which epigenetic dysregulation is a hallmark.

Several immunomodulatory drugs targeting the TME have been tested, and some of them approved for both frontline and RR FL: lenalidomide [144,145] (a molecule unleashing pleiotropic antitumor effects), the anti-CD47 antibody Hu5F9-G4 [146] (inhibiting the “don’t eat me” signal on FL cells), as well as various CD20 × CD3 bispecific antibodies, such as mosunetuzumab [147]. Moreover, with the incorporation of CAR-T cells in earlier lines of therapy, prognosis for FL patients is likely to change significantly in the coming years.

8. Discussion

The t(14;18) is considered the primary genetic event in FL, juxtaposing the *BCL2* oncogene to the immunoglobulin heavy-chain enhancer, which promotes *BCL2* overexpression [3,4,12]. Important progress has been made to identify the additional genomic alterations cooperating with *BCL2* deregulation [28–31,33,35,77], although how these alterations interact with each other, and which specific alterations are maintained or emerge during the course of the disease remain unclear. Studies using more sensitive techniques (e.g., single cell whole genome sequencing/RNAseq) will be needed to understand the chronological evolution of single aberrations throughout the course of the disease. By comparison with other germinal center-derived B cell lymphomas, FL is addicted to epigenetic alterations [148], as over 90% of patients have mutations in genes encoding epigenetic modifiers [29,31,73,102], suggesting its potential as an attractive therapeutic target in this disease. Moreover, genomic alterations in signaling and B cell differentiation, the BCR/NF-κB pathway, and proliferation/apoptosis have been identified in FL, cooperating in tumorigenesis [29,31,33,38,73,77,102].

Although the *BCL2* rearrangement is the hallmark of FL, 10–15% of patients lack this translocation [1,72]. Several studies have suggested that this subset of patients is different to the classical *BCL2* + FL and consequently emerge as a new provisional entity in the ICC classification [51,72,73,80–82,85,86,88,149].

The identification of high-risk patient groups at diagnosis in FL is still challenging. New molecular prognostic scores have been developed during the last years, combining mutational (m7-FLIPI and POD24-PI) [8,133] or gene expression data (23-GEP) [134]. Nevertheless, their use in the clinical setting is limited, and the vast majority of patients are treated independently of prognostic scores.

The rate of transformation to a more aggressive lymphoma is estimated between 10% and 20% of all patients [101,150]. Studies conducted in paired diagnostic and tFL cases showed a divergent or branching evolution from a CPC, which is responsible for generating each new event (e.g., progression, transformation) of FL [29,73,102,103]. Genomic alterations in genes involving the cell cycle (*CDKN2A/B*), apoptosis (*TP53*), and signaling pathways and immune evasion (*B2M*, *CD58*) are more prevalent at transformation [73,110,111,113]. However, further studies using high resolution genomic techniques are needed to understand the evolution pattern and to identify whether these genomic alterations are acquired or present at low frequency at diagnosis. On the other hand, the com-

position of the TME is crucial for the development, progression, and relapse of FL [101,102]. A better understanding of the TME could help develop novel targeted therapies.

Reflecting the clinical and molecular heterogeneity of FL, not all high-risk patients (e.g., early relapse or primary refractory) are equal, and their clinical outcomes will differ based on the genetic tumor profile, patterns of clonal evolution, composition and interaction of tumor cells with the TME, and the timing and location of the relapse. Furthermore, a deeper knowledge of specific high-risk groups will be essential to understand the wide clinical spectrum of the disease.

Several therapies targeting key alterations in the pathogenesis of FL have been approved, highlighting the importance to expand our knowledge on the mutational profile of FL. Although the efficacy of venetoclax, targeting BCL2, is insufficient [137,138], tazemetostat, an EZH2 inhibitor, seems to be a good candidate for drug combinations [145]. Moreover, drugs targeting the TME, such as lenalidomide, have been investigated as new alternatives to modulate the interactions between tumor and non-tumor cells in FL [144,145].

9. Conclusions

FL, one of the most common lymphomas, is a heterogeneous disease, both genetically and clinically. Although the *IGH::BCL2* rearrangement and mutations in epigenetic modifiers are very common, the potential prognostic role of other genetic abnormalities remains to be consolidated. Since a majority of patients will have prolonged survival, tools to identify those at higher risk of early relapse, multiple relapses, or HT are eagerly sought. In this sense, refined molecular prognostic scores and ctDNA will most likely be of help. With the integration of those data, the practicing clinician will face the challenge of selecting the most appropriate management strategy for each patient, including watchful waiting, single-agent monoclonal antibodies, ICT, ASCT, immunomodulatory drugs, epigenetic therapies, bispecifics, and CAR-T cells

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