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Review

Genetics of Transformed Follicular Lymphoma

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Abstract: Histological transformation (HT) to a more aggressive disease–mostly diffuse large B-cell lymphoma–is considered one of the most dismal events in the clinical course of follicular lymphoma (FL). Current knowledge has not found a single biological event specific for HT, although different studies have highlighted common genetic alterations, such as *TP53* and *CDKN2A/B* loss, and *MYC* translocations, among others. Together, they increase genomic complexity and mutational burden at HT. A better knowledge of HT pathogenesis would presumably help to find diagnostic biomarkers allowing the identification of patients at high-risk of transformation, as well as the discrimination from patients with FL recurrence, and those who remain in remission. This would also help to identify new drug targets and the design of clinical trials for the treatment of transformation. In the present review we provide a comprehensive overview of the genetic events frequently identified in transformed FL contributing to the switch towards aggressive behaviour, and we will discuss current open questions in the field of HT.

Keywords: transformed follicular lymphoma; genetics; histological transformation

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1. Introduction

Follicular lymphoma (FL) is a B-cell lymphoid neoplasm whose origin is the germinal centre cells present in the lymphoid follicle of the lymph nodes. It constitutes the second most frequent non-Hodgkin's lymphoma (NHL), with an estimated incidence of 20–30% of all lymphomas in western countries, and approximately 2.2 new cases per 100,000 inhabitants per year [1–4]. In a prospective epidemiological registry of lymphoid neoplasms (RELINF) initiated in 2014 by the Spanish GELTAMO group (Grupo Español de Linfoma y Trasplante de Médula Ósea), 23.1% (n = 2099) of B-cell lymphomas were FL [5]. The median age of presentation is ~60 years, being infrequent in young patients.

The number of centroblasts (enlarged activated B-cells) visualised by light microscopy distinguishes the histological grades of FL: grade 1 (0–5 centroblasts per high-power–40×magnification, 0.159 mm^2–microscopic field–HPF), grade 2 (6–15 centroblasts per HPF), and grade 3, further differentiated into 3A (>15 centroblasts per HPF, with centrocytes -B-cells with irregular or cleaved nucleus-still present) and 3B (extensive and diffuse infiltration by centroblasts or immunoblasts). In the clinical practice, grade 3B FL management is similar to that of diffuse large B-cell lymphoma (DLBCL), due to its more aggressive clinical behaviour. In the recent updates of the classification of lymphoid neoplasms [6,7], in addition to classical nodal FL, there are other types of FL recognised, including the in situ follicular B-cell neoplasm, duodenal type FL, paediatric FL, as well as the provisional

entity BCL2-rearrangement negative, CD23-positive follicle centre lymphoma, which will not be the subject of the present review.

The prognosis of patients with nodal FL is relatively favourable, reflecting their generally indolent behaviour, with median survival over 15 years, thanks in part to the introduction of immunotherapy both at induction and relapse [8–10]. However, continuous relapses, decreases in the response duration, and the gradual acquisition of drug resistance defines the clinical pattern of this lymphoma, often leading to the death of the patients [2,11]. Additionally ~20% of patients progress within 24 months of treatment and half of them die within five years [12,13]; on the other hand, those who remain in complete remission within 24 months of treatment have a similar overall survival (OS) as the general population [14].

Historically, approximately 3% of FL patients per year transform into an aggressive lymphoma, commonly DLBCL, as a first or a later event, even in the absence of treatment. More recently, the cumulative incidence of histological transformation (HT) is lower since the incorporation of rituximab. In a European series with more than 5000 patients studied, the cumulative incidence of HT as a first event at five years was 7% in patients who had not received rituximab, while it was 5% in those who had received rituximab only at induction, and 3% in patients who received rituximab not only at induction but also at maintenance [15]. HT has been considered one of the most unfavourable events in FL's natural history, with a five-year survival from transformation (SFT) of ~20–30% both prior to and in the rituximab era [16–22], although this survival increases up to 40–50% when considering only transformation as a first event [15]. Those cases experiencing early histological transformation show a reduced five-year SFT compared to late histological transformation, although the time point to define early/late HT has to be validated [15,19,23]. Therefore, the prediction of histological transformation at diagnosis remains a challenge [24].

In the present work we will review the most frequent genetic events described in transformed FL and discuss current open questions in this field.

2. Definition of FL Transformation

The gold standard for determining FL transformation is based on the histologically confirmed progression of grade 1, 2, or 3A FL to a high-grade lymphoma, consisting of a predominance of large cells and the loss of the follicular architecture [23,25]. Most of the transformed cases have a DLBCL histology (>80% of the cases) according to the current WHO classification, although other histologies have been described, such as high-grade B-cell lymphoma, FL grade 3B, Burkitt lymphoma, B lymphoblastic leukemia/lymphoma, and plasmablastic lymphoma [25–28]. There are other atypical forms suggestive of histological transformation, such as the presence at diagnosis of both FL and DLBCL cells, at the same site, referred to as composite lymphoma, or at different sites such as DLBCL in the lymph node and FL in bone marrow, as well as DLBCL cases that undergo a process of reverse transformation, relapsing as a lower grade lymphoma. These forms are not addressed in the present review.

Since lymphoma lesions are not isolated, other tumour areas might have a FL component at the same time in addition to the transformation area [23,29,30]. Positron emission tomography and computerized tomography (PET/CT) could help by selecting the biopsy site according to the highest standardized uptake value (SUV) of 18[F] fluorodeoxyglucose, since a high value (generally > 14) is correlated with more aggressive histology [31]. However, only ~50% of patients are biopsied, with inaccessibility of the tumour, the patient's clinical situation or refusal among the main reasons [32]. Based on the clinical behaviour of transformed patients, several clinical criteria of transformation suspicion could be of utility in these cases, including an increase in lactate dehydrogenase (LDH) levels or hypercalcemia, rapid lymphadenopathy growth or the appearance of lymphoma masses or conglomerates, and the novel involvement of extranodal sites and new B symptoms. However, these criteria vary between studies and are not standardised [16,18,19]. Moreover, these clinical criteria are also present in patients who progress without transformation [32].

3. Clonal Evolution

Clonality analysis to test the relationship between the transformation and diagnosis samples is essential to distinguish true transformed cases from a secondary de novo DLBCL, and is especially recommended when the transformation occurs years later after the FL biopsy [25,33]. It is well known in transformation from chronic lymphocytic leukaemia (CLL), namely Richter syndrome (RS), that clonally unrelated cases can represent up to 20% of all histological transformations in this setting. This fact can have clinical implications, because clonally unrelated cases have a superior survival rate compared to clonally related cases [3,34]. Studies in FL suggest that up to 5% of the transformed cases are clonally unrelated to their FL counterpart at diagnosis [35,36]. Due to the lack of clonality testing in several studies, the availability of paired low-grade and transformed samples and the relatively low incidence of clonally unrelated cases, it is currently unknown whether these cases could have a different clinical outcome compared to clonally related cases.

The pattern of clonal evolution in transformed FLs follows two main models: (i) the linear model, a direct evolution of the transformed clone from the indolent lymphoma by the acquisition of new lesions, and therefore retaining the genetic aberrations of the indolent phase; (ii) the divergent/branching model, in which both the FL and the clonal related transformed samples presumably derived from a common progenitor clone (CPC), which independently acquired some genetic events at each phase. Both indolent and aggressive clones will share the genetic events present in the CPC, such as t(14;18), and mutations in *KMT2D*, and *CREBBP,* which drives lymphomagenesis (Figure 1).

Few studies have analysed paired clonally related FL and transformed FL samples with next-generation sequencing (NGS), mainly due to the difficulties in case recruitment, or in obtaining DNA with good quality and quantity at both events. Previous work using karyotype, SNP-arrays or custom NGS panels to analyse a limited set of mutations have observed a slightly higher incidence of the divergent evolution model (>50%) [37–40]. However, accurate classification of transformed cases on each model highly depends on the number of genetic alterations studied and the inclusion of other samples of the FL evolution. Indeed, up to 70% of transformations were classified as divergent when FL relapse samples were added to the analysis [39,41]. In addition, when we consider studies using whole-genome (WGS) or whole-exome sequencing (WES), most cases (~90%) present a divergent evolution [28,41,42]. This predominance of the divergent model contrasts with other transformed B-cell lymphoproliferative disorders, such as in RS-CLL, in which the evolution usually follows a linear model [43]. In addition, two patterns of evolution from the CPC have been identified. The most frequent (~80%) is the 'rich' CPC pattern, in which there is high similarity of genetic events shared in FL and transformed samples. The other one is the 'sparse' CPC pattern, in which only a few genetic alterations are shared between both samples [41].

Despite the use of different treatments, the CPC is difficult to eradicate and can persist over time. The development of a donor-derived FL several years after an allogeneic stem-cell transplantation (allo-SCT), sharing identical t(14;18) breakpoint, immunoglobulin heavy chain (IGHV) usage, and different genetic events between recipient and donor, further support the existence of this CPC and its persistence over time [44,45].

In FL progression, the responsible progression-contributing clones are already present at diagnosis. In contrast, the dominant clone(s) at transformation were very rarely detected (<1%) or absent at diagnosis even after analyses with ultra-sensitive variant detection methods [28]. Several possibilities can explain why the responsible clone at transformation was not seen at diagnosis: (1) very low numbers, which would have required even more sensitive detection methods to identify the original clone at diagnosis; (2) the presence of the responsible subclone at a different site compared to the primary site, perhaps requiring the analyses of several lymphoma biopsies or liquid biopsy [46]; or (3) the emergence of new clones being responsible for the transformation after the diagnosis.

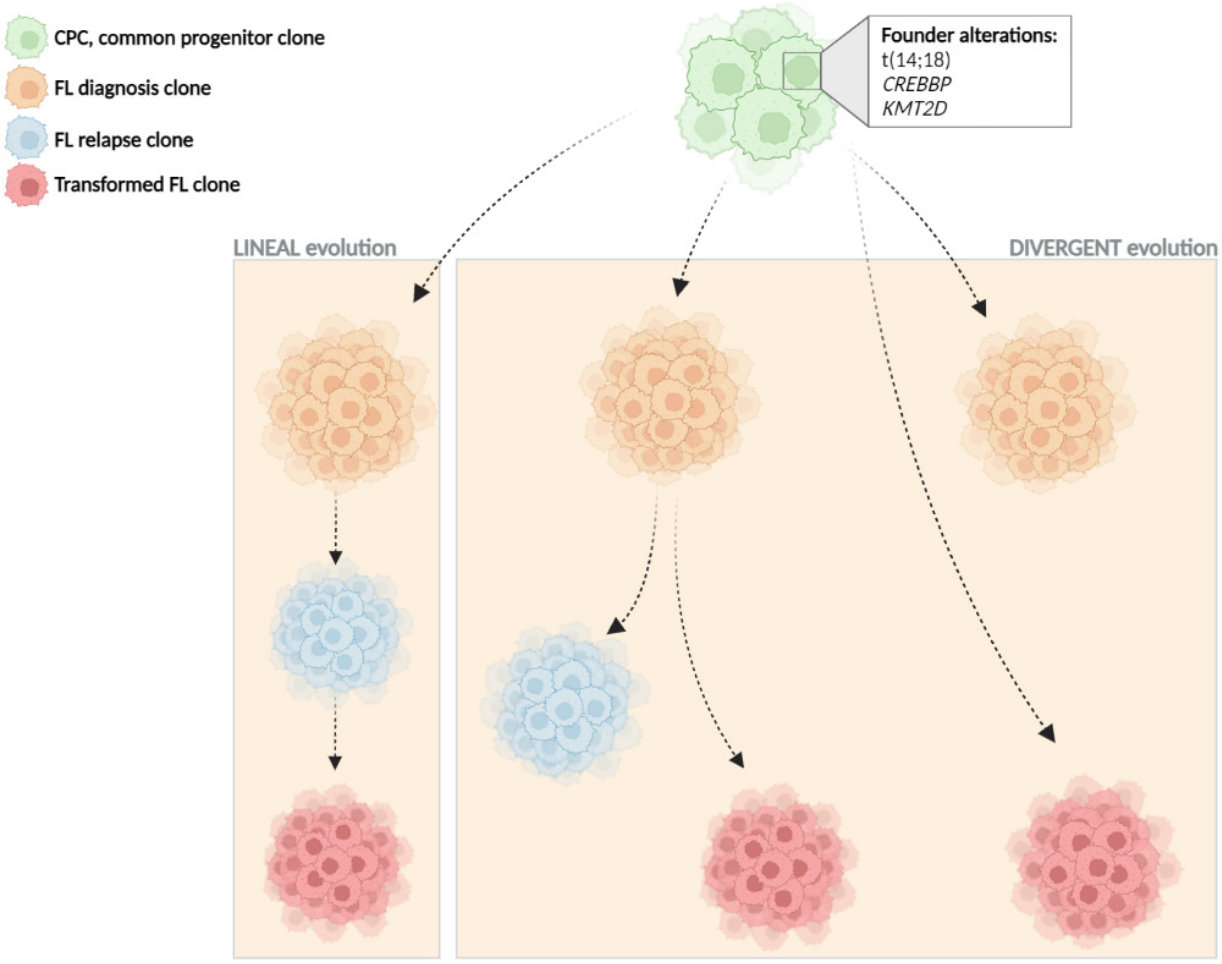

Figure 1. Models of clonal evolution in histological transformation.

Similarly, three evolution models have been proposed by analysing the somatic hypermutation of IGHV. In one, CPCs could coexist in FL and HT in the same lymph node. In the second, CPCs could be present only in the pre-lymphoma germinal centre, with the FL and HT arising independently of these CPCs. The third model proposes that the CPCs are maintained in bone marrow niches before acquiring new lesions and migrating to cause HT [44]; the last model is also supported by the development of FL in healthy individuals in whom a t(14;18) was detectable years before the diagnosis, as well as by the two transformed FL cases of donor origin after an allo-SCT [44,45,47]. It is plausible that the three models occur in different patients or even coexist in some cases.

These data, together with the predominance of the divergent model, implies that the predominant tumour clone at FL diagnosis is not the direct precursor of the transformed clone in most of the cases, and therefore the genetic events identified at diagnosis probably would not help to predict transformation.

4. Cell of Origin and Pathogenesis of FL Transformation

Transformed cases may have changes in their immunophenotype, with an antigenic drift including CD10 loss or positivity of MUM1/IRF4. Although most transformed FLs are of germinal B-cell DLBCL subtype (GCB), up to 15–20% of the cases change to an activated B-cell (ABC) without differences in survival between both subtypes [27,48,49]. This contrasts with transformation in other B-cell lymphoproliferative disorders, such as CLL, Waldenström macroglobulinemia or marginal zone lymphoma, in which transformed cases are mostly ABC/non-GCB [50–52].

Recurrent rearranged genes in DLBCL include *BCL2*, *BCL6* and *MYC*. There are no major changes in the frequency of *BCL2* or *BCL6* translocations in transformed samples compared to FL diagnosis, however, *MYC* translocations are commonly acquired and are present in 25% of transformed cases [27,42]. The acquisition of *MYC* translocations implies an increase in the proportion of double-hit lymphomas (presence of both *BCL2* and *MYC* translocations) in transformed patients, which is associated with a shorter SFT [27], although differences were not statistically significant likely due to the low number of cases analysed.

High-resolution genome wide analysis using SNP-array, WGS or WES, and targeted next-generation sequencing studies in transformed FL identify increased genomic complexity and mutational burden at transformation in comparison to FL [28,39,41,42,53–56]. The most recurrent genetic lesions acquired in transformed FL cases are summarized in Table 1 and Figure 2, and include alterations (mainly mutations and/or deletions) in *TP53* in approximately 15–30% transformed cases, *CDKN2A/B* deletions in 20–30% of cases, and *B2M* mutations and/or deletions in 20–25% of cases, together with the previously mentioned *MYC* translocations [28,39,41,42,54,55,57]. Of note, although these lesions are commonly acquired in transformation, they are not specific, as they could also be present at diagnosis or acquired during disease recurrence, representing markers of more aggressive disease [25,28,39,41,42,54,55,58]. In fact, these are also common acquired lesions in refractoriness and/or transformation in other haematological disorders [43,59].

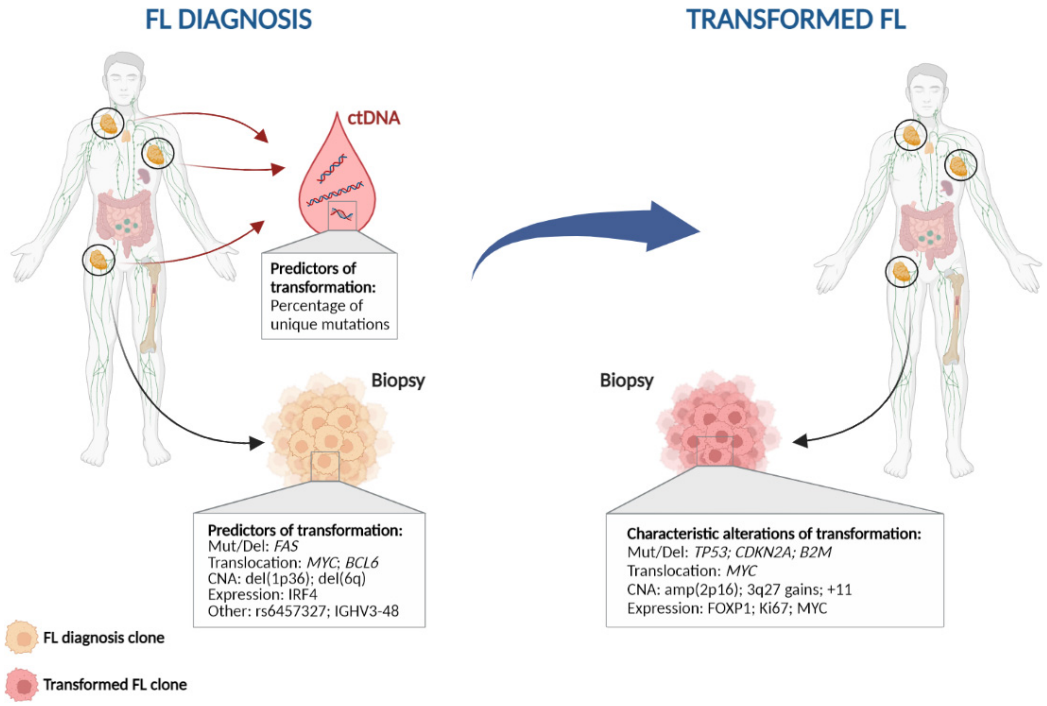

Figure 2. Characteristic genetic events in follicular lymphoma histological transformation. Left: Potential predictors of transformation; Right: Genetic alterations commonly found at histological transformation. CNA: copy number alteration; ctDNA: circulating tumour DNA; Mut/Del: mutation and/or deletion.

Other commonly acquired events include mutations in *MYC*, *CCND3*, *CD58*, *EBF1*, *GNA13*, *P2RY8*, and *S1PR2*, as well as gains of 3q27.3-q28 (*BCL6*), amplification of 2p16 (*REL*), and gains in chromosomes 2, 5, and 11 [28,35,41,42,54,55,60,61]. All of these alterations together indicate that different pathways may be involved in transformation, including both cell cycle and DNA damage dysregulation, immune escape, JAK-STAT or NF-κB pathways, increased proliferation, and lymphoma cell migration.

When transformed cases are classified according to their cell-of-origin, different patterns of mutations are observed in each group. *MYD88*, *CD79B*, and *BCL10* mutations are more frequently (~15–25%) identified in ABC transformed cases, while amplification of 2p16 (*REL*) are more common in GCB, consistent with what is observed in DLBCL [28,54,55,61]. This suggests that there could be at least two different subgroups of transformed FLs. Moreover, recent studies have classified de novo DLBCL into different molecular clusters according to their mutation, copy-number and structural variation profile, and these clusters are associated with different outcomes [62,63]. There is no information regarding the distribution of these clusters in transformed FL, although some of the most common alterations in HT such as *TP53* mutations/deletions, *CDKN2A/B* deletions and *REL* amplification are present in cluster C2, while C5 and MCD comprised mostly ABC-DLBCL, with mutations in *CD79B* and *MYD88* [62,63]. This suggests that different clusters of transformed FL could be present, possibly with different pathways leading to transformation, and perhaps a distinct outcome. In line with this, a previous study showed an increased proliferation rate by gene expression analysis at transformation in a subgroup of HT, which was enriched with aberrations in *TP53*, *CDKN2A/B*, and *REL* in contrast to other HT, suggesting different mechanisms of transformation [48]. Similarly, previous studies in CLL have suggested three groups of RS, one of them with alterations in *TP53* and deletions in *CDKN2A/B* with poorer prognosis than other RS [64]

Table 1. Biological and genetic factors enriched at follicular lymphoma histological transformation in the literature.

Category	Variable	Biological Effect	Effect on Transformation
IHQ and microenvironment	IRF4 expression	-	Increased at HT [27]
	MYC expression	-	Increased at HT [65]
	FOXP1 expression	-	Increased at HT [66]
Genomic variants	*TP53* mutation and deletion	Cell cycle	Increased at HT [28,39,41,42,55]
	B2microglobulin mutation and deletion	Immune surveillance	Increased at HT [28,42]
	FAS mutation and deletion	Apoptosis	Enriched in transformed cases [42]
	MYC mutation and translocation	Cell cycle	Increased at HT [27,42]
	CCND3 mutation	Cell cycle, JAK-STAT signalling	Increased at HT [28,39]
	EBF1 mutation	B-cell development	Increased at HT [28,41]
	GNA13 mutation	NF-kB/BCR signalling	Increased at HT [28]
	P2RY8 mutation	B-cell migration	Increased at HT [28]
	S1PR2 mutation	Proliferation	Increased at HT [28]
	CD58 mutation	Immune surveillance	Increased at HT [42]
	MYD88 mutation	NF-kB/BCR signalling	Increased at HT, ABC-HT related [28,39,41,55]
	CD79B mutation	NF-kB/BCR signalling	Increased at HT, ABC-HT related [28,39,55]
	BCL10 mutation	NF-kB/BCR signalling	Increased at HT, ABC-HT related [28,55]
	CDKN2A/B deletion	Cell cycle	Increased at HT [28,41,42,54,57,61]
	BCL6 translocation	B-cell differentiation	Increased at HT [27,67]
	2p16 (*REL*) amplification	NF-kB/BCR signalling	Increased at HT, GCB-HT related [35,42,54,60,61]
	3q27.3-q28 (*BCL6*) gains	B-cell differentiation	Increased at HT [35,42,54,60]
	Chromosomes 2, 5 and 11 gains	-	Increased at HT [35,54]
	Genomic complexity -copy-number changes-	-	Increased at HT [28,41,42,53–56]
	Genetic complexity -mutations-	-	Increased at HT [28,39,41,42,55,68]

HT: Histological transformation.

5. Can We Predict Transformation at Diagnosis?

5.1. Clinical, Biological and Immunohistochemical Factors

Several retrospective and prospective studies analysing clinical variables in the rituximab era have suggested that a higher Follicular Lymphoma International Prognostic Index (FLIPI) at diagnosis as well as some of their individual factors (elevated serum LDH, advanced stage or low haemoglobin) associates with a higher risk of transformation [18–22,32]. Other clinical indexes evaluated, including FLIPI-2 and PRIMA-PI, are of limited value in predicting HT [69]. Moreover, an association with higher risk of transformation is also observed in patients experiencing a poor response to first-line treatment, especially in those cases which are refractory [22,70]. The FLIPI index is prognostic of OS and therefore it could be a poor tool to specifically predict transformation. Overall, lymphoma-related death is the main cause of mortality in FL [71]. However, lymphoma-related death is prominent in patients who experience transformation in contrast to patients who do not, thus indicating that transformation in FL is the major cause of lymphoma-related death. In line with this, a higher cumulative incidence of lymphoma-related death has also been observed in patients with a higher FLIPI, as well as those who do not achieve event-free survival at 24 months [71]. Thus, FLIPI will potentially play a role in predicting transformation, probably as part of an integrated clinical and biological score.

According to the histological grade, FL grade 3A patients have a higher risk of transformation according to some studies [27,32] but not in others [19–22]. MUM1/IRF4 expression is significantly higher in FL grade 3A than in FL grades 1–2 [72,73], and the positive MUM1/IRF4 expression at diagnosis has been associated with transformation [27], as well as lower progression-free (PFS) survival and OS in FL [74,75].

Different individual protein expressions have been associated with unfavourable outcomes in FL. For example, FOXP1 protein levels have been previously associated with failure-free survival and shorter OS in immunochemotherapy-treated patients [66,76], although no impact on progression of disease within 24 months (POD24) was observed in clinical trials [77]. FOXP1 regulates germinal centre differentiation and promotes B-cell survival [78–80]. FOXP1 protein levels were higher in non-GCB DLBCL, and have also been associated with shorter PFS and OS in DLBCL [81]. Although higher FOXP1 protein levels at transformation were observed [66], their role at diagnosis in transformation prediction have not been assessed. Similarly, higher MYC expression has been identified in HT as compared to diagnosis [65], although its role at diagnosis is unknown.

5.2. Genetic Aberrations

All FL cells harbour a clonal rearrangement of the immunoglobulin heavy chain gene (*IGH*). Previous reports showed a biased repertoire in FL in comparison with normal CD5 negative lymphocytes, with *IGHV3-23*, and *IGHV3-48* genes the commonest in FLs [36,82,83]. We have recently reported that patients carrying the *IGHV3-48* gene have a higher risk of transformation (Figure 2) [36]. IGHV gene usage was previously associated with higher risk of transformation in CLL bearing the *IGHV4-39* gene [84]. These findings require further validation in prospective series.

At diagnosis, the role in transformation of the frequent individual genetic alterations is controversial. Although *TP53* alterations (mutations or deletions) are rare at diagnosis (~5%), they have been associated with high POD24, shorter PFS and shorter OS, but not with risk of transformation [56,68,85–88]. *MYC* translocations at diagnosis are also an infrequent event (<3%), and most of these cases would therefore be double-hit lymphomas with *BCL2* and *MYC* translocations [89,90]. These cases usually have a shorter PFS, OS and SFT [91], although the very low number of *MYC* translocated cases precludes drawing definitive conclusions. *CDKN2A/B* deletions (<10%) have also been correlated with inferior PFS and OS [56,58]. Interestingly, methylation of *CDKN2A* is a more frequent event (~20%) and is also correlated with shorter OS [58]. Together, these genetic alterations are rare events

at diagnosis (<5%), but they have not been generally studied in large cohorts, especially analysing their role in transformation.

Other genetic events are present at similar frequency at diagnosis and at transformation, however a potential role in transformation has been suggested. *FAS* mutations (~5–10%) and deletions (~20%) are predominant in patients who will transform, suggesting that *FAS* alterations could be an early biomarker in transformation, although these findings require further validation [42]. *FAS* mutations have also been observed in GCB-DLBCL associated with an inferior outcome [92]. *BCL6* translocations at diagnosis are associated with a high risk of transformation [27,67], with a slightly increased frequency at transformation (25% at HT and 10% at diagnosis). *BCL6* translocations were similarly found in GCB or ABC HT [27], in contrast to DLBCL, in which they are more frequent in ABC cases [93].

At diagnosis, chromosomal imbalances have been recurrently identified in FL, including gains of 1q, 2p, +7, 12, 18, X, and losses in 1p36, 6q, 10q, and a copy-neutral loss of heterozygosity (CNN-LOH) in 1p, 6p and 16p, some of them correlated with a worse prognosis [53,54,56,94–98]. Losses in 1p36, 6q and CNN-LOH in 16p were also associated with high risk of transformation (Figure 2 and Table 2) [53,94,97]. although most of these studies included patients treated prior to the rituximab era and require validation.

Some genetic mutations alter FL B-cell interaction with the microenvironment. HVEM, encoded by the *TNFRSF14* gene, regulates T-cell response, delivering costimulatory or coinhibitory signals, depending on the ligand [99,100]. The BTLA ligand is expressed by B-cells and its interaction with HVEM inhibits T-cell response [99]. The *TNFRSF14* gene is disrupted by mutations (~30–40%), deletions, (~20–30%) and/or CNN-LOHs (~10%) in FL patients [41,53,54,68,97]. This would lead to reduced HVEM expression [101,102] and higher BTLA signalling [102]. Therefore, the inhibitory signalling of the HVEM-BTLA axis is disrupted by *TNFRSF14* aberrations modifying the microenvironment and inducing B-cell expansion, activated lymphoid stroma and increased number of follicular T helper cells [102]. Other genetic mutations altering the microenvironment include *CREBBP* mutations, which are involved in FL immune evasion by both decreasing the proliferation of T-cells and antigen presentation via downregulating the major histocompatibility complex (MHC) class II [103], and mutations in *CTSS* or *RRAGC*, which alter CD4+ T-cell interactions [104,105].

Table 2. Biological, genetic and clinical risk factors at follicular lymphoma diagnosis associated with histological transformation in the literature.

Category	Variable	Effect on Transformation
Clinical	High FLIPI (≥3)	Higher risk of HT [18–22,32]
IHQ and microenvironment	FL Grade 3A	Higher risk of HT (controversial) [27,32]
	High IRF4 expression	Higher risk of HT [27]
	High levels of lymphoma-associated macrophages	Shorter time to HT [106]
	High density of CD21 Follicular dendritic cells	Shorter time to HT, absent at HT [106]
	High levels of CD4+, CD8+, CD57+, PD1+, and FOXP3+	Higher risk of HT [106]
	Follicular pattern of FOXP3+ T-cells	Higher risk of HT [107]
	Low tumour distance to blood vessels	Higher risk of HT [108]
Genomic variants	1p36, 6q deletions	Higher risk of HT [94,97]
	BCL6, *MYC* translocations	Higher risk of HT [27,42,67]
	16p CNN-LOH	Higher risk of HT [53]
	IGHV3-48 gene usage	Higher risk of HT [36]
	SNP rs6457327 (6p region)	Higher risk of HT [109]
	Circulating tumour DNA mutations	Higher risk of HT [46]

CNN-LOH: copy number neutral loss of heterozygosity; HT: Histological transformation; SNP: single nucleotide polymorphism.

In summary, no single factor has been shown to accurately predict transformation, but the combination of several genomic aberrations could be a good predictor of transformation. The m7-FLIPI index, which integrates the FLIPI clinical variables and performance status with the mutational status of 7 genes—*ARID1A*, *CARD11*, *CREBBP*, *EP300*, *EZH2*, *FOXO1*, and *MEF2B*—better classified patients with treatment failure, POD24 and OS than FLIPI [86,87]. The POD24-PI, which includes FLIPI and the mutational status of 3 genes—*EZH2*, *EP300*, and *FOXO1*, demonstrated superiority to identify POD24 patients in comparison with FLIPI and m7-FLIPI [87]. However, none of these scores has been used to assess the risk of transformation. The same can be said for genomic (copy-number aberrations -CNAs- or CNN-LOH) or genetic (mutations) complexity, which is associated with POD24, and inferior PFS, and OS when they are present at diagnosis [56,68]. Although their frequencies are increased at transformation, their role in prediction is still unknown.

In addition, several genetic expression signatures have been associated with higher risk of transformation in FL in the pre-rituximab era, which includes a pluripotency signature composed of embryonic stem cell genes [110], and a six NF-kβ target signature scores [111], being the BTK score later validated in a series of patients receiving immunotherapy [112].

5.3. Tumour Microenvironment

Several components of the tumour microenvironment, including lymphoma-associated macrophages (LAMs), follicular dendritic cells (FDCs), and different T-cell subsets, may play a key role in FL outcome [113–116].

A higher level of LAMs has been associated with a worse PFS and OS in the pre-rituximab era [113,114,117], although the unfavourable prognosis of LAMs has been reversed in the rituximab era [74,115,116], possibly due to the binding of the macrophages to the rituximab-opsonized lymphoma cells and its phagocytosis [118]. The number of LAMs at diagnosis is not related to a higher risk of transformation, although this cohort was heterogeneously treated including pre-rituximab and rituximab patients [106]. However, within FL patients who transform, the number of LAMs at diagnosis is associated with shorter time to transformation [106].

Similarly, the high density of CD21+ FDCs at diagnosis have been correlated with inferior PFS, OS and, in those who transform, shorter time to transformation [106,119,120], although not with higher risk of transformation at diagnosis [106]. At transformation, most cases showed the absence of CD21+ FDCs [106].

CD8+ tumour-infiltrating T-cells (TIL) have been correlated with better outcomes in FLs, presumably due to their cytotoxic effect, and this association was stronger when high expression of granzyme B is present [121–123]. Conversely, CD4+ cells are associated with poor outcome, presumably due to B-cell stimulation [122].

Some studies have identified a higher risk of transformation in patients with high levels of CD4+, CD8+, CD57+, PD1+, and FOXP3+ T-cells at diagnosis, as well as a FOXP3+ follicular pattern, a low tumour distance to blood vessels (TDV) or the high expression of vimentin [106–108,124]. Interestingly, both the FOXP3 pattern and TDV are correlated with the higher number of LAMs, although these studies included patients not treated with an anti-CD20 monoclonal antibody [107,108].

All of these observations could be related to the therapy [119,125,126] and the presence of other cell populations such as mast cells [127,128]. Moreover, the differences between studies could also be due to small cohorts of patients, different cut-offs, and variability in the interpretation by distinct pathologists. Therefore, the role of the microenvironment immune cells in predicting FL transformation in the current scenario requires further research, without forgetting the treatment and the balance between immune cell subsets, to create a score/model for both prognosis and transformation with rituximab [117,121,122].

MHC (HLA in humans) is located in the 6p21.3 region, which is frequently disrupted by loss or CNN-LOH in FL as previously mentioned [53,54,97]. Genome-wide studies identify the 6p21.3 region as a susceptibility region for FL [129,130]. Previous studies have reported an association between certain HLA polymorphisms and the higher susceptibility

of B-cell lymphoproliferative disorders, including FL [131–134]. Studies analysing the role of HLA specificities in FL prognosis are scarce, and no studies have focused on the risk of HT [132]. Interestingly, the single-nucleotide polymorphism rs6457327, located in this region, has been associated with poor outcome and higher risk of transformation [109,135].

5.4. Liquid Biopsy

Liquid biopsy has emerged as a non-invasive method that allows the detection of tumour-associated alterations in circulating tumour DNA (ctDNA) in plasma, and has shown clinical utility in different lymphoproliferative disorders [136–139]. Since tumour ctDNA may arise from different clones, the ctDNA may better reflect the spatial and/or intra-tumour heterogeneity, a feature that is especially relevant in FL [30]. Focused on FL, the detection of high levels of ctDNA has been correlated with shorter PFS [137,140]. Interestingly, in one FL patient who transformed into DLBCL, mutations specific to the transformed clone were detected in the ctDNA at diagnosis but were not present in the FL lymph node biopsy, thus suggesting that the clone responsible for the transformation could be detected in the ctDNA at diagnosis at least in some cases [46]. The authors of this work described a predictive model only based on the mutations identified in plasma, which could be a promising biomarker for transformation prediction [46].

6. Discussion and Concluding Remarks

Histological transformation is an unfavourable event of FL course which clearly affects patient survival. In the last years, several works have increased the genetic knowledge of FL transformation, helping to dissect different possible mechanisms of transformation.

The predominance of the divergent model in transformed FL suggests the existence of an ancestral CPC driving FL recurrence and transformation. Whether this CPC (or the subclone responsible for transformation) was already present at diagnosis still remains unknown, and this could preclude prediction, at least in some transformed cases. The driver events that trigger HT from the CPC are still unknown. There is most probably not a single mechanism, but several distinct pathways driving HT from the CPC, as suggested by gene-expression analysis and the differences in genetic alterations between HT groups, for instance, according to the cell-of-origin of the HT, and these pathways could be different according to the CPC niche [27,28,54,61]. Moreover, the variable histologies observed at transformation also suggest different mechanisms, and this is highlighted by the different incidence of some alterations such as *TP53* mutations in DLBCL-HT compared to composite-HT [28].

There is still not an accurate predictor of transformation. This may in part result from the lack of biomarker validation, which, in turn, could be due to the heterogeneity of the series included in the different studies, for other reasons. Much research has focused on genetic aberrations, although some studies do not include FL relapse samples, or even do not distinguish FL samples at diagnosis or FL relapse, which could lead to missing or confounding information. The tumour microenvironment may play a key role in FL outcome and probably in transformation. As mentioned, this microenvironment is affected by the treatment and the presence of certain genetic alterations. Few studies have analysed the role of immune cell crosstalk together with genetic events, and this was performed in short and/or heterogeneous series. This emphasizes the need to perform comprehensive biological and clinical analysis in large-scale series of clonally related FL-HT, including at least genetic aberrations together with gene expression and microenvironment composition, in homogeneous cohorts, to better identify the different pathways triggering transformation. Moreover, emerging treatments, including EZH2 inhibitors, HDAC inhibitors, bispecific antibodies and CAR T-cells, would probably improve the survival of FL transformed patients, thus highlighting the need to perform these studies to help identify targets to personalize treatment approaches [141–143].

However, there are several challenges to address these studies in transformed FLs. First, not all cases can be biopsied at suspicion of transformation. There are limited available

biopsies, and these are stored in formalin-fixed paraffin-embedded which fragments and partially degrades DNA, limiting the availability of quality samples for the experiments. Therefore, it is difficult to have paired samples both at diagnosis and at transformation, and even more so when samples from different events, such as FL or transformation relapses, are included.

In summary, collaborative efforts are required to obtain high and robust FL-HT collections, to generate and collect genetic data of large-scale series of HT, and to identify the CPCs that if eradicated could potentially prevent both FL recurrence and transformation. We hope the increasing biological knowledge on FL transformation will enable personalized treatment strategies avoiding transformation.

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