



Tumor microenvironment of follicular lymphoma

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Abstract: Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma and accounts for approximately 20% of all new non-Hodgkin lymphomas in western countries. Although FL generally has an indolent natural history, a subset can transform into high-grade lymphomas such as diffuse large B-cell lymphoma (DLBCL) or progress rapidly with associated poor clinical outcomes. The development of more effective means of FL control prior to transformation or progression is likely to be key to improving results. Over the past 10–15 years there has been a rapid accumulation in studies focusing on the FL tumor microenvironment, leading to an expansion in our understanding of this complex and complicated neighbourhood. The FL microenvironment is distinct from other B cell lymphomas, with a complex interplay of cellular and non-cellular components, and plays a critical role in the pathogenesis of this disease. As part of this special series on FL, this Review covers our current knowledge of the FL tumor microenvironment with a focus on the cellular composition, key genetic aberrations, disturbances in the cytokine milieu and the neoantigen landscape of FL. We then explore the impact of the FL tumor microenvironment on risk stratification strategies and role of novel therapeutics targeting the microenvironment. Given the critical role of the microenvironment in the pathogenesis of FL, and the exciting possibility of novel therapeutic avenues, the objective of this review is to provide the reader with a summary to understand the key literature and highlight gaps in knowledge that should be prioritised in the pursuit of more effective therapies.

Keywords: Follicular lymphoma (FL); tumor microenvironment; non-Hodgkin lymphoma; immunotherapy

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Introduction

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma and develops from precursor B cells in the germinal centre (GC) of lymphoid tissues (1,2). Understanding the pathogenesis of FL is critical to optimize therapeutic interventions and build upon prognostic models. A key component of FL pathogenesis is its microenvironment, which is the cellular and molecular environment in which the tumor resides, and includes immune cells, stromal cells, blood vessels and the extra-

cellular matrix (3,4). Specific genetic aberrations within the tumor act to re-educate these neighbouring cells and there is ultimately an essential dependence on the microenvironment for tumor cell survival and proliferation (4). In this way, the FL tumor microenvironment is a critical mediator of lymphomagenesis with a fine balance between the promotion of a tumor permissive immune niche and suppression of antitumoral immune surveillance.

It is established that the FL immune milieu is a major contributor to patient outcome. Dave *et al.* first demonstrated that features of the non-malignant cells of the

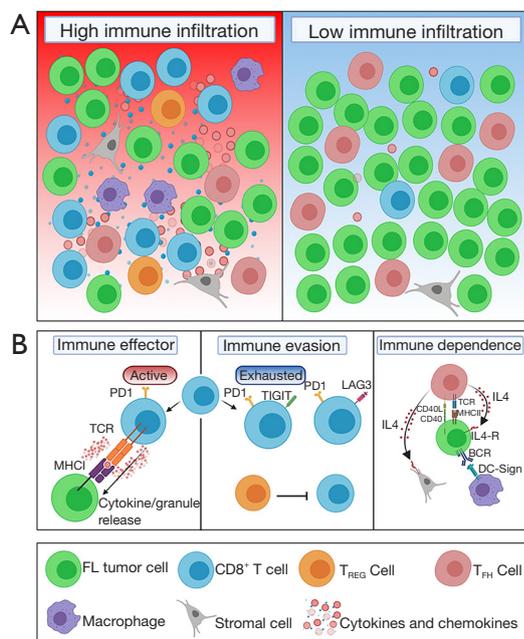


Figure 1 Key components of the FL immune microenvironment, and immune effector, evasion and dependence mechanisms. (A) High immune infiltration of the FL tumor microenvironment is associated with favourable outcomes. The increased presence of the primary immune effector, CD8⁺ T cells, are thought to control the growth of the FL tumor cell which is related to successful disease control. The recruitment of CD8⁺ T cells requires a complex interplay between various immune-stimulating and immune-dampening cells, cytokines and chemokines. Therapies to boost immune infiltration are currently in development. (B) The possible modalities of immune response to the FL tumor cell. In the immune effector phase, active CD8⁺ T cells recognize FL tumor specific antigens and cause apoptosis of the FL tumor cell. During immune evasion, CD8⁺ T cells express an exhausted phenotype, and T_{REG} cells start to dampen the immune response as a natural mechanism to prevent autoimmunity. The FL tumor cell reprograms cells of the tumor microenvironment and depends on reciprocal signalling for survival in the immune dependence phase.

immune microenvironment correlated better with patient prognosis than the gene expression within the FL tumor cells themselves (5). An intratumoral T cell gene signature was associated with increased survival in FL whereas genes expressed by macrophages and follicular dendritic cells were associated with inferior outcomes (5). In subsequent work, the magnitude of intratumoral immune infiltration in FL was shown to form an independent positive prognostic

marker in the rituximab era and identified the lymphoma microenvironment as a key determinant of early treatment failure (6). There was distinct clustering of immune molecules regardless of their categorization as immune effector, checkpoint or macrophage molecules, and having a low overall immune infiltrative state predicted for early progression of disease (6).

Recent technological advances have allowed for a more in-depth analysis of the FL microenvironment and revealed the marked heterogeneity of intratumoral immune cells. Further insights into this heterogeneity and complexity of the microenvironment is likely to offer new possibilities for patient risk stratification and therapeutic intervention.

To enable an understanding of the contribution of the FL microenvironment to disease, we start by characterizing the cellular components that comprise the FL microenvironment and the complex interplay of these cells are summarized. Next, key genetic aberrations that influences the FL microenvironment are explored. We then focus on the contribution of important non-cellular components, such as the cytokine milieu that further facilitate pathology via disturbances in homeostasis. Finally, we discuss the novel therapies that exploit pathways and mechanisms of the FL microenvironment to halt and or reverse disease progression.

Composition of the tumor microenvironment

The composition of the FL microenvironment is partially reflective of the physiological GC that it effaces, with neoplastic cells invading existing lymphoid follicles. By re-educating neighbouring microenvironmental cells toward a pro-tumoral state, FL tumor cells become highly dependent on them to survive and proliferate (4). The following section reviews the key cellular components of the FL microenvironment and includes immunocompetent lymphoid cells, macrophages and stromal cells, and should be read in reference to *Figure 1*.

Cytotoxic CD8⁺ T cells

Tumor recognition by cytotoxic CD8⁺ T cells is a requirement for T cell mediated tumor control and may explain the spontaneous regressions that have been reported in FL (7). The FL microenvironment contains variable numbers of CD8⁺ T cells, but they are consistently lower than their CD4⁺ T cell counterpart, and are predominantly localised to peri-follicular regions (8,9). The immunological

synapse between cytotoxic T cells and FL tumor cells has been demonstrated by confocal microscopy and is suggestive of tumor-specific antigen recognition (8). Upon activation, CD8⁺ T cells mediate their antitumoral function by cytokine production and granule release.

Identification of CD8⁺ T cells has mostly relied on immunohistochemistry (IHC), and to a lesser extent, flow cytometry. These studies have consistently shown favourable outcomes in patients with increased numbers of infiltrating CD8⁺ T cells (8,10-12) and more recently, transcriptional upregulation of T effector genes was shown to correlate with chemioimmunotherapy response in FL (13). Intriguingly, patients with an inflamed T effector phenotype had high tumor mutational loads (which may represent a proxy for neoantigen burden) compared to their non-inflamed counterparts (13). High throughput profiling techniques such as T cell receptor (TCR) repertoire sequencing has also allowed the field to move beyond relatively crude IHC studies to profile CD8⁺ T cells at considerable depth. TCR repertoire sequencing demonstrated clonal T cell expansions amongst high immune infiltrated FL subsets (6), with more detailed analysis of sorted T cell subsets revealing that these large clonal expansions resided within the cytotoxic T cell compartment (Nath *et al.*, *Blood Advances*, in press). Further characterization of the neo-antigenic targets that these clones recognize is required.

The intratumoral CD8⁺ T cell population can be functionally subdivided into active, resting or exhausted (dysfunctional) states. Surprisingly, the high cell surface expression of the inhibitory receptor PD-1 (programmed cell death protein-1) is associated with an activated T cell state in FL, and it is the co-expression of both PD-1 and LAG3 (lymphocyte activation gene 3 protein) that define dysfunctional T cells with reduced capacity to perform classic effector functions (14). Increased PD-1/LAG3 co-expressing T cells adversely affected patient outcomes in a small series, and pending validation, warrant consideration as a predictive biomarker (14). Of note, these findings may explain the minimal response to anti-PD-1 therapy in FL (15) and a more suitable approach may be dual checkpoint blockade of both PD-1 and LAG3 to reinvigorate the exhausted CD8⁺ T cell subset. More recently, co-expression of the coinhibitory receptors TIGIT (T cell immunoglobulin and ITIM domain) and PD-1 was also shown to indicate an exhausted T cell phenotype, suggesting a role for TIGIT and PD-1 co-blockade (16). The factors (tumor and microenvironmental) driving the

functional heterogeneity of intratumoral CD8⁺ T cells in FL requires further investigation.

Kiaii and colleagues demonstrated a marked dysregulation in the gene expression of highly purified CD8⁺ (and CD4⁺) intratumoral T cells in FL compared to healthy controls (17). One such example was the downregulation of *ACTN1*, which is involved in actin-based motility and cytoskeletal signalling, and contributed toward an impairment in the motility of FL tumor infiltrating lymphocytes (17). Interestingly, the coculture of healthy T cells with FL tumor cells induced similar defects in T cell protein expression (17). Collectively, these findings are strongly suggestive that FL tumor cells evade the immune microenvironment by directly altering the gene expression of neighbouring CD8⁺ and CD4⁺ T cells.

CD4⁺ T Cell populations

The dependency of FL tumor cells on surrounding CD4⁺ T cells to survive and expand has been demonstrated in patient-derived xenograft and *in vitro* culture models (18,19). Recent in-depth analysis using mass cytometry established the marked heterogeneity within the intratumoral CD4⁺ T cell population with the identification of at least 12 distinct subsets (20). In this study, the lack of co-stimulatory receptors (CD27 and CD28) on CD4⁺ T cells (consistent with a suppressive microenvironment) predicted for inferior outcomes, whereas the prognostic implications of PD-1 immune checkpoint expression varied between distinct subpopulations (20). In addition to the heterogeneity, the topographical distribution of CD4⁺ T cells may also play an independent role in prognostication and warrants integration into prognostic scores to improve risk stratification (21,22).

The following section describes the most well described CD4⁺ T cell subsets in FL and includes T Follicular Helper (T_{FH}) cells, T Regulatory (T_{REG}) cells and T Follicular Regulatory (T_{FR}) cells.

T follicular helper cells

Under normal immune reactions T follicular helper (T_{FH}) cells interact with antigen-activated GC B cells within the light zone of lymphoid follicles to support GC B cell selection and differentiation (23). GC T_{FH} cells are characterized by a high expression of PD-1, ICOS and CXCR5, which is responsible for their follicular localization (24).

In FL, the malignant B cell retains its dependency on

T_{FH} cells and re-educates them towards a creating a tumor permissive immune niche. FL tumors are enriched with T_{FH} cells and these highly express CD40L and IL4 compared to T_{FH} cells from healthy nodes (25). The CD40L⁺ T_{FH} cells interact with CD40⁺ neoplastic B cells, and together with the secretion of IL4 and IL21, appear to support tumor cell growth and survival (26). IL4 has further downstream effects including skewing of tumor associated macrophages (TAMs) towards cancer promotion (27) and secretion of CXCL12 by stromal cells to increase FL tumor cell recruitment and migration (28). It has also been demonstrated that both CD40L and IL4 have direct anti-apoptotic activity on FL B cells (25). Taken together, these observations suggest that FL tumor cells subvert the T_{FH} population to their own advantage and a high T_{FH} infiltrate has been shown to translate to inferior clinical outcomes (29).

T regulatory cells

FOXP3⁺CD4⁺CD25⁺ T Regulatory (T_{REG}) cells are actively recruited and expanded within the FL microenvironment and FL tumor cells are able to convert conventional CD4⁺ T cells into CD4⁺ T_{REG} cells (30-32). Yang and colleagues have shown that intratumoral FL T_{REG} cells suppress the proliferation and cytokine production of neighbouring tumor infiltrating helper and cytotoxic T cells (33,34). Indeed, the diversity of the T_{REG} TCR repertoire inversely correlated with intratumoral CD8⁺ TCR diversity in a small series, raising speculation that antigen-specific T_{REG} cells suppress neighbouring FL-specific cytotoxic T cells (9).

A more comprehensive understanding of T_{REG} cells is now possible with the emergence of mass cytometry. This has demonstrated that FL T_{REG} cells are indeed a heterogeneous population. PD-1 expression discriminated an activated subset (also co-expressing the activation-related molecules CD27, CD28, CD69, TIGIT) of intratumoral T_{REG} cells (20). The increased PD-1 expression on FL T_{REG} cells (in contrast to the Hodgkin lymphoma microenvironment where T_{REG} cells are polarized toward a CXCR3⁺Tbet⁺ T helper-1 phenotype) has also been described by other groups (35). TIGIT expression on T_{REG} cells in FL has also been shown to further enhance their suppressive properties (36).

As the T_{REG} population appears to be driven at least in part by FL tumor cells, characteristics of this cell population deserves consideration as potential predictive biomarkers. In previous work, a high number of intra-tumoral T_{REG} cells was surprisingly reported to be predictive of a favourable

response to various chemotherapy regimens and one explanation for this may be direct T_{REG} cell suppression of the tumor cells (37). However, in a more recent and uniformly treated FL cohort, the pre-treatment presence of high follicular or perifollicular T_{REG} cells was associated with an inferior outcome (38). Moreover, the total T_{REG} cell count had no impact on outcome (38). de Jong *et al.* showed that the density of T_{REG} cells had opposite effects depending on what chemotherapy patients received, with a negative impact seen with fludarabine treated patients and a good prognostic impact reported with CVP (39). A simple explanation for these discrepancies may be the methodological differences between studies, which includes variations in treatment regimens. Indeed, the prognostic impact of FL T_{REG} cells is circumvented with the addition of rituximab (40), suggesting that treatment may be the prime determinant for prognostic implications of T_{REG} cells. Conceptually, the heterogeneity within T_{REG} cells along with its differentiation state into the T_{FR} subset might also be crucial to understanding its role as a predictive biomarker. Strategies that can recognize the T_{REG} population at greater depth and studying its prognostic effects in a uniformly treated cohort in the rituximab era are required.

T follicular regulatory cells

Another T cell subset important to FL tumor cell growth and survival is the T_{FR} cell. T_{FR} cells make up a minor component of the FL immune microenvironment (~3% of CD4⁺ T cells) (25), and have functional similarities to both T_{FH} and T_{REG} cells. Though the precise role of FL T_{FR} cells remains unclear, these FOXP3/CXCR5/ICOS co-expressing T cells are located within neoplastic follicles and thought to regulate T_{FH} and B cell interactions, ultimately maintaining GC B cell proliferation (41). Though speculative, FL T_{FR} cells may help explain the finding that a follicular distribution of FOXP3 T cells was associated with inferior clinical outcomes in the pre-rituximab era (38).

Natural killer (NK) cells

Although intratumoral NK cells only contribute toward a small percentage of the non-malignant cells in the FL microenvironment, the mature and cytotoxicity active (CD56^{dim}) NK cell subset is enriched in FL compared to healthy controls (42). This is relevant given the routine incorporation of rituximab into FL treatment algorithms

and the significant role of NK cells in mediating rituximab's antibody-dependent-cell-mediated cytotoxic (ADCC) activity against FL tumor cells (43). Using sequential FL tissue samples, it has been shown that rituximab induces a rapid and proliferative NK cell response (42), which may be attributed to the role of NK cells as key effectors of ADCC activity.

Given as ADCC tumor-cell killing is likely dependent on effector to target cell ratios, NK cell counts can be considered a potential biomarker in predicting response to therapeutic monoclonal antibodies. This was confirmed in a *post-boc* analysis of the phase III GALLIUM trial where a low baseline peripheral blood NK cell count in FL patients treated with rituximab or obinutuzumab plus chemotherapy was independently associated with inferior survival outcomes (44).

Tumor-associated macrophages

Tissue macrophages are the end cells of the mononuclear phagocytic lineage and are derived from circulating monocytes that originate in the bone marrow (45). In a somewhat simplistic binary model, such macrophages can be further categorized based on their inflammatory states into antitumoral M1 (activated) or pro-tumoral M2 (alternatively activated) subtypes (46). It has been shown that an over-expression CCL2 (secreted by stromal cells) and IL4 in the FL microenvironment contributes toward monocyte recruitment and their subsequent polarization into M2 tumor-associated macrophages (TAMs) (47,48). FL TAMs favor malignant B cell growth via the downstream effects of dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN) engagement with mannose regions on the FL B cell receptor (48), and also through their angiogenic and immunosuppressive properties (49,50).

Perhaps not surprisingly, a high expression of FL TAMs was originally identified to indicate a poor prognosis (5,51). However, this initial observation has conflicted with more recent studies that incorporated rituximab into FL treatment regimens (52,53). A possible explanation is that TAMs act as effector cells in rituximab's ADCC activity against FL tumor cells (43,54). Kridel and colleagues highlighted that prognostication by macrophage infiltration is dependent on patient treatment by showing that M2 macrophages favourably modulated the efficacy of rituximab in those who received doxorubicin-containing chemotherapy (55). Indeed, it has been previously demonstrated that the efficacy of doxorubicin is enhanced by macrophage activation (56) and that the ADCC activity of rituximab

is more profound in macrophages polarized toward a M2 phenotype (57). And in support of this, a low M2 macrophage infiltration was associated with early treatment failure in a recent, comprehensive investigation of uniformly immunochemotherapy-treated FL patients (58).

Mesenchymal stromal cells (MSCs)

Within secondary lymphoid organs, there is a heterogeneous population of non-haematopoietic cells of stromal origin collectively known as MSCs. FL tumor cells require MSCs for their *in vitro* expansion (59) and stromal cell generated cytokines such as CXCL12 has been shown to cause FL B cell activation, migration and adhesion (28,60).

MSCs can be further distinguished based on their morphology and function into subtypes that include fibroblastic reticular cells (FRCs) and follicular dendritic cells (FDCs). FL tumor cells upregulate the differentiation of MSCs into FRCs, which in turn support malignant cell survival via an immune escape phenomenon (61-63). Under normal conditions, FDCs present native antigens to B cells and contribute towards an efficient GC response (64). In FL, FDCs provide co-stimulatory signals that promote angiogenesis, cell adhesion, migration and ultimately favour lymphoma growth and dissemination (65). FDCs have been shown to communicate with neoplastic B cells via their expression of B cell activating factor (BAFF), and this appears to have an anti-apoptotic effect on FL tumor cells (66). It has also been recently shown that the *EZH2* gain-of-function mutation in FL (~25-30% FL patients) reprograms the GC to generate an increased FDC-dependent aberrant proliferation of B cells (67).

Non-cellular components of the tumor microenvironment

Cytokines and chemokines are signalling proteins used by cells for chemotaxis and modulation of responses such as inflammation. Collectively termed the "cytokine milieu", this milieu underlies the complex crosstalk of the various cells of the TME. FL cells both modulate and are modulated by the cytokine milieu, establishing a tumor promoting niche that is both immune privileged and growth factor rich. The cytokine milieu within the TME in FL is widely altered, and cytokine modulation has been advocated in FL as a therapeutic intervention. Most notably, interferon-alpha administered alone or in combination with chemotherapy has been shown to have anti-FL activity, but

is also a cause of clinically significant adverse effects (68). A key lesson is that cytokines have pleiotropic effects within different immune cellular contexts, meaning that a highly targeted and sophisticated approach is required before the beneficial effects of cytokine modulation can be fully realised.

Interleukin-2 (IL2)

In vitro, IL2 or IL2-soluble IL2R (sIL2R) complexes diverts the maturation of CD4⁺ T cells towards the immunosuppressive T_{REG} subtype (69), which may explain the observation in several studies that high levels of sIL2R is associated with progression and transformation in FL (69-72). Hence, IL2-receptor inhibition is currently being investigated as a therapeutic option in FL (73,74).

Interleukin-4 (IL4) and CXCL12

IL4 and CXCL12 are overexpressed in the FL TME, including T_{FH} and stromal cells respectively (28). Experimentally, only IL4 high FL- T_{FH} cells increased CXCL12 expression in committed stromal cells. Bearing this in mind, CXCL12 and its receptors CXCR4/CXCR7 have emerged as a key mechanism which allows communication between cancer and cells in the TME (75). CXCL12 directly promotes cell growth, metastasis and angiogenesis, whilst attracting even more CXCR4 bearing and CXCL12 producing cells, such as the aforementioned stromal cells to the tumor site, in an amplifying loop (75). Supporting this mechanism in FL, decreased levels of CXCR4 were associated with good prognosis in NHL (76).

Interleukin-12 (IL12)

Pre-clinically, IL12 was shown to have anti-tumor effects (77). However, a phase II clinical trial showed that a combination of IL12 and rituximab had reduced responses when compared to rituximab alone in NHLs (77). To determine the cause of experimental treatment failure, Yang *et al.* showed that *in vitro* exposure of CD4⁺ T cells to IL12 induced an exhausted phenotype via increased TIM-3 expression (78). IL12 expression was confirmed in FL samples. Building on this, elevated CXCL9, a downstream inflammatory chemokine of IL12 signalling, was associated with poor outcomes in FL (79). A lymphomagenesis mechanism involving CXCL9 has been described in the associated disease diffuse large B-cell lymphoma (DLBCL) (80). These lines

of evidence show that more experimental work should be done to illicit the underlying mechanisms of the IL12/TIM3/CXCL9 pathway and uncover a potential therapeutic target.

Prognostic value of serum cytokines

Serum cytokine levels have been linked to prognostication in FL, suggesting that a clinically validated serum-based test might have potential utility as a functional minimally invasive sequential biomarker (79). Eight cytokines (IL-1Ra, IL-6, IL-7, IL-10, IL-13, TNF- α , VEGF, and PDGF) were elevated in FL with high levels of TGF- β associated with superior overall survival and high levels of VEGF associated with poor progression free survival independent of lactate dehydrogenase (81). TGF- β has been variously described as having inhibitory roles in B-cell maturation whilst inducing exhaustion of effector memory T cells in NHLs (82,83). Finally, VEGF expression is upregulated and correlated to poor prognosis in FL as it mediates angiogenesis by stimulating the growth of vascular endothelial cells (84).

Genetic aberrations as determinants of the immune microenvironment

Several mutations in DNA repair, methylation and cell cycle control steps have been identified in FL. The t(14;18) (q32;q21) (*IGH/BCL2*) translocation, first reported in 1988, underlies over 90% of FL cases and is thought to be a founding genetic event (85). Unlike other oncogenes known to that point, BCL-2 did not regulate proliferation but rather it regulated apoptosis. The translocation of *BCL2* to the promoter region of *IGH* causes overexpression of the anti-apoptotic protein BCL2. However, this translocation alone is insufficient to trigger lymphomagenesis as approximately 70% of healthy individuals bear this translocation without ever developing FL (86).

Besides genetic aberrations increasing the intrinsic fitness of the FL cell, the FL cell has been shown to influence and modulate the TME (4). This section focuses on the key mechanisms behind the genetic aberrations that allows FL to modulate and influence the TME (summarized in *Figure 2*). Of the large catalogue of mutations, the chromatin modifying genes (CMGs), *EZH2* and *CREBBP* are the most commonly mutated genes in FL which have been implicated in TME modulation (87).

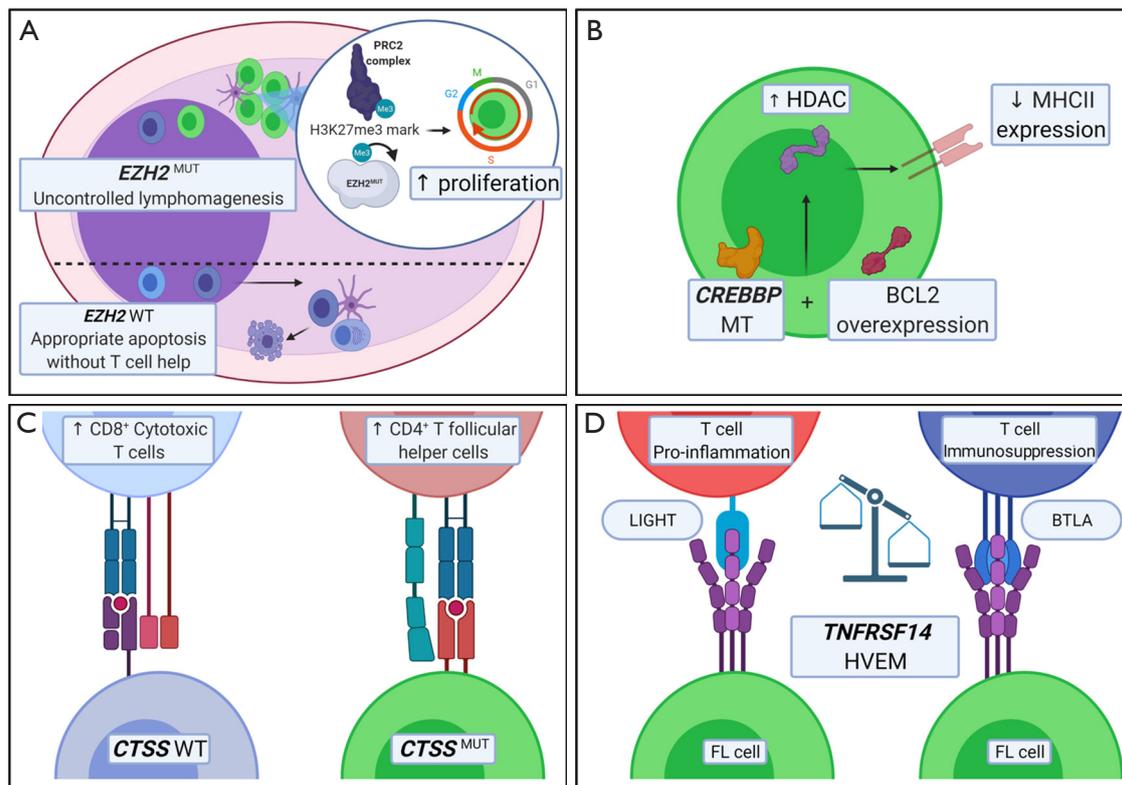


Figure 2 Key genetic aberrations that modulate the FL tumor microenvironment. (A) *EZH2* mutations lead to independence from the TME and uncontrolled lymphomagenesis by avoiding physiological apoptosis induced by the lack of T cell help. (B) *CREBBP* mutations lead to decreased MHC-II expression and increased immune evasion. (C) *CTSS* mutations shifts the TME from a majority CD8⁺ cytotoxic T cell to a CD4⁺ T_{FH} enriched TME. (D) The balance of proinflammatory versus immunosuppressive TME are influenced by the ligand (LIGHT or BTLA) that TNFRSF14 interacts with and are perturbed in FL.

EZH2

EZH2 catalyses trimethylation of the polycomb repressive complex 2 which has downstream effects on transcriptional silencing (87,88). In FL, gain-of-function mutations of *EZH2* recurrently occur at three sites, Y646 (also known as *EZH2*^{Y641F}), A682 and A692 in approximately 25% of FLs with variant allele frequencies ranging from 2–61% (89–92). Mutations affecting Tyr 646 (Y646) in the SET domain of *EZH2* increases the affinity for methylating the histone mark, H3K27me₂ to H3K27me₃ compared to wild-type protein (67). A copy of a wild-type *EZH2* and mutant Y646 is required for lymphomagenesis as the wild-type enzyme favours the mono- and di- methylation steps, whilst the mutant enzyme is only hyperactive in the third trimethylation step (92). These gain-of-function mutations in *EZH2* result in the perturbation of another gene, *SESTRIN1*, leading to downstream disruption of P53

mediated control over the mammalian target of rapamycin complex 1 (mTORC1) (93), allowing B cells to proliferate and accumulate.

Recently, *EZH2* mutations were shown to initiate lymphomagenesis by reprogramming the immune response (94). Normally, as part of the GC reaction, GC B-cells requires a T_{FH} cell of the correct affinity to prevent apoptosis, whilst in *EZH2* bearing mutants the apoptotic signal is evaded (95). When a CD40 blocking ligand is administered to inhibit the activity of T_{FH}, the GC reaction was impaired in wild-type cells (67). However, no such impairment of the GC reaction was seen in *EZH2* bearing mutants. In contrast, when lymphotoxin β was administered to block FDC activity, *EZH2*^{MUT} cells had reduced fitness compared to wild-type cells. Taken together, this study shows how FL cells bearing *EZH2*^{Y641F} mutations evades normal physiological control and requires an altered TME in the form of FDCs. Hence, inhibiting *EZH2* activity is a promising potential therapy

for FL (96).

MHC-I/II-deficient tumors, characterized by reduced levels of tumor-infiltrating lymphocytes, demonstrate a strong enrichment of *EZH2* mutations (97). Importantly, *EZH2* inhibitors restored MHC expression in *EZH2*-mutated human lymphoma cell-lines, suggesting a role for the way for development of complementary therapeutic approaches combining immunotherapy with epigenetic reprogramming.

CREBBP/EP300

CREBBP is another recurrently mutated CMG that modulates the TME in FL. *CREBBP* encodes a lysine acetyltransferase (KAT) which acetylates histone 3 and enables access to DNA by transcription factors (98). *EP300* is an associated homolog of *CREBBP* with over 90% sequence homology and is thought to be functionally similar to *CREBBP*. Mutations in *EP300* occur in approximately 20% of FL whereas *CREBBP* is mutated in 41–65% with either truncating mutations or inactivating mutations in the HAT domain that are functionally more severe (99,100).

The Stanford group demonstrated that mutations in *CREBBP* was associated with reduced MHC-II gene expression by microarray and flow-cytometry (98). Reduced MHC-II expression is associated with lymphomagenesis by interfering with the ability of T cells to detect aberrant cancer specific antigens (101). The normal function of *CREBBP* is antagonistic to that of the B-cell lymphoma 6 protein (BCL6)-Histone Deacetylase 3 (HDAC3) complexes (100,102). With *CREBBP* loss-of-function mutations, the deacetylation action of BCL6-HDAC3 complexes is perturbed but may be restored by inhibiting the action of HDAC3 (102). Building on these findings, Mondello *et al.* demonstrated that administration of HDAC3 inhibitors restored immune surveillance by the induction of interferon pathway and MHC-II genes (103).

CTSS

Besides CMGs, other genes also have been shown to be associated with TME modulation. One of these is *CTSS* that encodes for the lysosomal cysteine proteolytic enzyme Cathepsin S which has critical roles in MHC-II antigen presentation and GC maturation (104,105). Recently, two independent studies described recurrent *CTSS*^{Y132} gain-of-function mutations in FL and determined its subsequent impact on the TME in FL. They demonstrated that *CTSS*

is overexpressed and hyperactive in FL (106,107). This leads to enhanced MHC-II antigen presentation which promotes tumor growth by increasing the CD4⁺ T_{FH}: cytotoxic CD8⁺ T cell ratio (106,107). Conversely, when *CTSS* activity is inhibited, communication between the FL cell and CD4⁺ T_{FH} cells is reduced whilst CD8⁺ cytotoxic T cells increased their infiltration of the TME (106). In addition, *CTSS*^{Y132} was associated with favourable outcomes with R-CHOP chemoimmunotherapy that plausibly suppressed the CD4⁺ T_{FH} cell enriched TME (107). *CTSS* inhibitors are a potential novel therapeutic strategy that would be particularly applicable for *CTSS*-hyperactive FL.

TNFRSF14

Another gene involved in FL TME modulation is *TNFRSF14* which encodes for the herpes virus entry mediator (HVEM). Originally, binding of herpes simplex viral envelope glycoprotein D to this receptor was shown to be part of the viral entry mechanism. Two major families of ligands for HVEM may either activate or suppress T-cell activity (108). The ligands belonging to the TNF-related cytokine family: lymphotoxin-like inducible protein that competes with glycoprotein D for herpes virus entry on T cells (LIGHT), and lymphotoxin- α are both proinflammatory (108). Conversely, ligands from the immunoglobulin related membrane protein family, B and T lymphocyte attenuator (BTLA) and CD160 suppresses T-cell activity (109); 28–67% of FLs had recurrent alterations in the 1p36.32 region of *TNFRSF14* and are associated with poor prognosis (110,111). Loss-of-function *TNFRSF14* mutated lymphoma B cells induced a tumor supportive environment, with increased stromal activation and increased T_{FH} cell recruitment due to disruption of inhibitory cell-cell interactions between the HVEM and BTLA (112). In elegant experiments, these investigators restored tumor suppression by delivery of soluble HVEM via gene modified CD19⁺ chimeric antigen receptor (CAR)-T cells (112). Conversely, mutations resulting in a loss of *TNFRSF14* expression increased recognition of lymphoma B-cells by allogenic stem cell transplanted T cells resulting in increased eradication of lymphoma cells but may also result in undesirable graft versus host disease (113). In agreement, high expression of *TNFRSF14* and low *BTLA* was found to be associated with poor prognosis in FL (114). The complex bi-directional signalling nature of *TNFRSF14* clearly modulates the FL TME and awaits further characterization.

Novel therapies targeting the tumor microenvironment

The FL microenvironment can be therapeutically modulated to repress immune ‘ignorance’ and ‘evasion’ phenomena. Indeed, a high immune infiltrative state in FL predicted for improved responses to chemo-immunotherapy (6). As such, and with an improved understanding of the complex biology of the microenvironment, there is ongoing clinical development of an expanding number of immunotherapeutic targets in FL beyond anti-CD20 antibodies (*Table 1*), with several clinical trials demonstrating promising results. However, longer follow-up is required to determine treatment durability. There remains an ongoing need to determine predictive biomarkers of sensitivity to such agents and these biomarkers are likely to be treatment specific. The following section reviews the mechanistic evidence of novel therapies that directly or indirectly target the FL microenvironment. A more detailed review of novel immunotherapeutic agents is included elsewhere in this series by Khurana *et al.* entitled “Novel immunotherapy for FL”.

Immunomodulatory agents

Lenalidomide is a second-generation immunomodulatory agent that targets the ubiquitously expressed E3 ubiquitin-ligase cereblon protein and promotes the degradation of haematopoietic transcription factors Aiolos and Ikaros (132). This has a multitude of downstream effects on immune cells within the tumor microenvironment. Ramsay and colleagues have shown that formation of the T cell immune synapse is impaired in FL, and that this defect can be restored with lenalidomide (133). Additional antitumoral effects of lenalidomide includes stimulation of the proliferative and functional capacity of effector T cells (134) and the invigoration of NK cell activity (135). Enhancing NK cell-mediated ADCC with lenalidomide may contribute toward a synergistic action with anti-CD20 monoclonal antibodies (136,137). Indeed, lenalidomide in combination with rituximab has shown to be efficacious in large phase 3 clinical trials in both de-novo and relapsed FL (138,139), and avadomide (CC-122), a novel immunomodulatory agent, is also being investigated in combination with rituximab in relapsed and refractory FL (140). The synergistic activity of immunomodulatory agents with other drug classes is being actively tested using novel doublet and triplet combinations and a major focus of such approaches

should be to determine predictive microenvironmental markers. One such study revealed that combination therapy with lenalidomide and rituximab promoted the beneficial role of intratumoral GATA3⁺ T helper 2 cells, whilst counteracting the negative effect of PD-1⁺ T cells (141). These findings require validation in an independent cohort.

Anti-CD47 monoclonal antibody

CD47 is upregulated on malignant cell surfaces and interacts with its receptors on macrophages to evade phagocytosis (142). Preventing this anti-phagocytic signal can be very effective as not only would macrophage mediated tumor-phagocytosis increase, but it would also allow for phagocytic cross-presentation of tumor antigens to trigger an anti-tumor cytotoxic T cell response (143). Hu5F9-G4 is an immune macrophage checkpoint inhibitor blocking CD47 and has shown promising synergistic activity with rituximab in relapsed FL in an early phase clinical trial (118). A phase II study of this combination is currently accruing patients (ClinicalTrials.gov number, NCT02953509) (117). A growing body of evidence suggests that other macrophage immune checkpoints may also serve as potentially clinically actionable targets in lymphoma (144).

Immune checkpoint blockade

Cancer immunotherapy targeting the PD-1 ligand (PD-L1) axis can elicit dramatic responses in a subset of hematologic malignancies. A key marker of responsiveness to anti-PD-1 or anti-PD-L1 therapy is PD-L1 overexpression. This can be driven by gene amplification, as reported in Hodgkin lymphoma and primary mediastinal large B cell lymphoma (145), or structural variants disrupting the 3' region of the PD-L1 gene, as reported in adult T cell leukemia and DLBCL (146). The absence of PD-L1 gene amplification or structural variants in FL may account for the modest clinical responses to single-agent PD-1 checkpoint blockade in this disease (15,147). However, combining the PD-1 inhibitor pembrolizumab with rituximab yielded promising results, with a high intratumoral CD8⁺ T effector score predicting for response in this small FL cohort (148). Dual-checkpoint blockade with anti-PD-1 and anti-LAG3 antibody therapy is also being actively investigated in FL (130), and such an approach may reinvigorate the exhausted intratumoral T cell population.

Table 1 Selected ongoing studies using novel agents to target the FL microenvironment

Class	Agent	Phase [Estimated Enrolment]	Population and study design
Immunomodulatory Agents	CC-122 (115)	Ib [n=75]	R/R DLBCL, indolent NHL CC-122 + Obinutuzumab
	Lenalidomide (116)	III [n=840]	Front-line, high tumor burden FL Post-induction PET positive patients randomized to anti-CD20 antibody maintenance +/- lenalidomide
Anti-CD47 Antibodies	Hu5F9-G4 (117)	Ib/II [n=422]	R/R B-cell NHL Hu5F9-G4 (magrolimab) + Rituximab Preliminary data: ORR 71% (CR 43%) in FL, n=7 (118)
BCL-2 Inhibitors	Venetoclax (119)	I/II [n=61]	Front-line, high tumor burden FL Lenalidomide + Venetoclax + Obinutuzumab
Bispecific Antibodies	Blinatumomab (120)	I [n=44]	R/R B cell NHL Blinatumomab + Lenalidomide
	Glofitamab (121)	I [n=207]	R/R B cell NHL Glofitamab + RO7227166 (CD19 targeted 41BB ligand), or obinutuzumab + RO7227166
	Mosunetuzumab (122)	I [n=746]	R/R B cell NHL and CLL Mosunetuzumab ± atezolizumab
CAR Therapy	CAR NK cell (123)	I/II [n=36]	R/R B cell lymphoid malignancies Umbilical Cord Blood-Derived CAR NK Cells Preliminary data: ORR 73% (CR 64%), n=11 (124)
	CAR T cell (125)	II [n=160]	R/R indolent NHL Axicabtagene Ciloleucel Preliminary data: ORR 94% (CR 80%) in FL, n=84 (126)
Cancer Vaccines	NeoVax (127)	I [n=20]	Front-line FL Front-line rituximab followed by personalised neoantigen vaccine
	Oncoquest-L-Vaccine (128)	II [n=30]	Front-line, non-bulky FL Autologous tumor-derived vaccine
	Tumour Vaccine (129)	I [n=20]	Relapsed FL Personalized tumor vaccine + Nivolumab
Immune Checkpoint Blockade	Pembrolizumab (130)	I/II [n=134]	R/R Lymphomas Pembrolizumab + MK-4280 (anti-LAG3 antibody)
	Atezolizumab (131)	II [n=138]	R/R B cell NHL Atezolizumab + Obinutuzumab + Venetoclax

Abbreviations: R/R, relapsed/refractory; DLBCL, diffuse large B cell lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; CR, complete response; n, number; FL, follicular lymphoma; CLL, chronic lymphocytic leukemia; NK, natural killer

CAR T cell therapy and bispecific antibodies

CD19 directed autologous CAR T cell therapy is effective and approved in patients with histologic transformation of FL (tFL) (149,150), and promising results have been reported with allogenic anti-CD19 CAR NK cells (124). CAR T cell therapy is being actively investigated in relapsed and refractory FL with early experience demonstrating an over 80% complete response rate (151). Strategies to increase the potency of CAR T cells by enhancing the antitumoral components of the microenvironment are also being explored. Boice and colleagues developed an innovative approach in the pre-clinical setting where CAR T cells were used as ‘micro-pharmacies’ to deliver anti-cancer proteins and restore host tumor suppression (112). They showed that loss of the HVEM (TNFRSF14) receptor gene, which is commonly mutated in FL, leads to a tumor-supportive microenvironment by exacerbating recruitment of T_{FH} cells and by activating the surrounding lymphoid stroma (112). Tumor suppression was successfully restored by administering a HVEM ectopic domain protein (soIHVEM) using modified CAR T cells that continually produced soIHVEM (112). Curran *et al.* enhanced the antitumoral effects of the microenvironment by modifying the CAR T cell construct to constitutively express CD40 ligand (152).

Mosunetuzumab, a T cell bispecific antibody (TCB) binding simultaneously to CD3 on cytotoxic T cells and CD20 on the malignant B cell results in the formation of an immunological synapse and subsequent T cell activation (153). Mosunetuzumab monotherapy showed modest clinical activity in heavily pre-treated FL patients in an early phase clinical trial, including a small subset with prior exposure to CAR T cell therapy (154). Another novel TCB with a ‘2:1’ configuration for increased tumor avidity (two fragment antigen binding regions for CD20, and one for CD3) is currently being investigated in relapsed FL (155).

Neoantigens, abscopal effect and immunogenic cell death

FL Neoantigens

Neoantigens are peptides generated from somatically acquired tumor genetic mutations that are then presented to the microenvironment in the context of major histocompatibility complexes (MHCs) (156). There is compelling evidence that the intratumoral T cell repertoire recognizes and elicits an immune response to epitopes that arise from cancer neoantigens. In FL,

the malignant B lymphocytes undergo ongoing somatic hypermutation of V(D)J alleles of their immunoglobulin genes generating unique B cell receptor idiotypes (157). Khodadoust *et al.* used proteomics to demonstrate that it is these immunoglobulin-derived FL neoantigens that are presented by class II MHC to CD4⁺ T cells, whilst MHC presentation of non-immunoglobulin neoantigens was not seen (158). Nielsen and colleagues identified only small subsets of FL patients harbouring low frequency neoantigen-specific CD8⁺ T cells derived from mutant *CREBBP* and *MEF2B* genes (159). Interestingly, Bolen *et al.* used tumor mutational burden as a proxy for immunogenic neoantigen formation and showed that a high mutation load identified an ‘inflamed’ FL subset with a high effector T cell signature (13). A greater recognition of the immunogenic neoantigens in FL is critical to harness their anti-tumor effects via therapeutic manipulation with adoptive cell and vaccine therapy.

Abscopal effect and immunogenic cell death

The effect of local radiotherapy leading to regression of metastatic cancer at distant sites is known as the abscopal effect (160). The mechanism for this rare phenomenon is immune-mediated, whereby irradiation causes tumor cell apoptosis, and subsequent liberation of neoantigens (161). This increase in neoantigens can generate a cytotoxic tumor-specific immune response, resulting in both local and distant antitumor effects. In addition to this, tumor cell injury stimulates an immune response through the release of danger-associated molecular patterns (DAMPs), which in turn induces immunogenic cell death of malignant cells and acts as a catalyst to promote further immune activation (162) (*Figure 3*). Radiotherapy is used as part of the treatment armamentarium in FL. Although most studies of the abscopal effect have focused on solid tumors, FL has been shown to be the most common lymphoma subtype associated with abscopal regressions (163). Efforts to boost abscopal responses by combining radiotherapy with immunomodulation and thereby overcoming the suppressive features of the immune microenvironment need to be further explored in FL (164).

Conclusions

Immune evasion is a hallmark of cancer (165). Paradoxically, FL is a cancer of the immune system that originates from the GC of lymphoid tissues. Undoubtedly, developments in

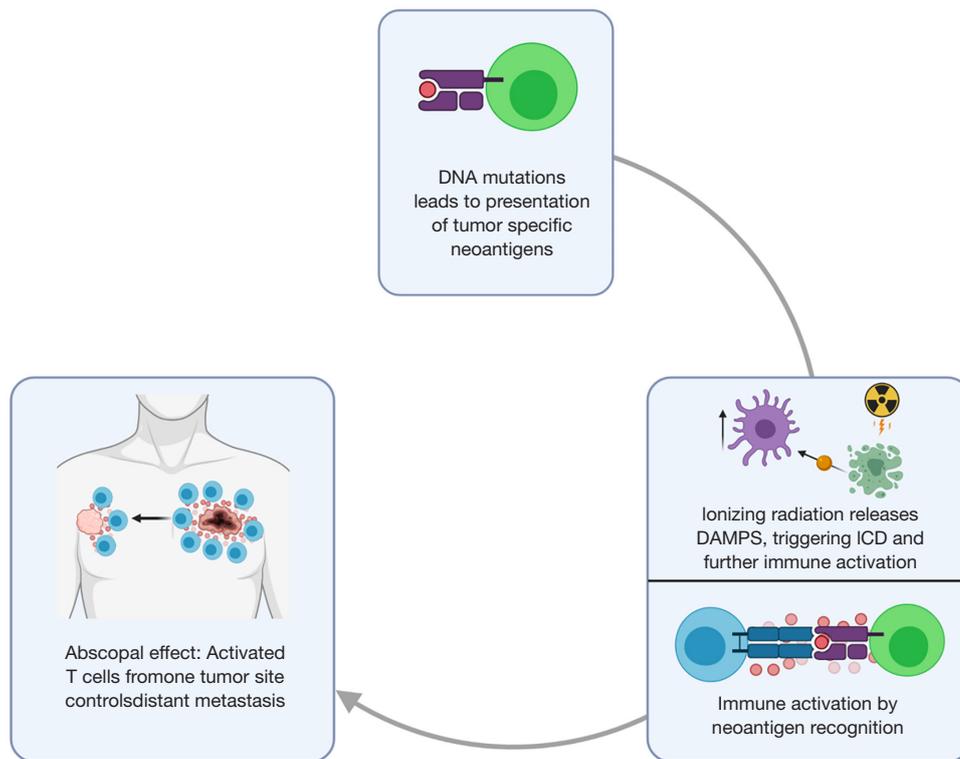


Figure 3 DNA mutations, a hallmark of cancer, results in the production of tumor specific neoantigens. Conventional treatments such as ionizing radiation releases damage-associated molecular patterns (DAMPs) which triggers immunogenic cell death and leads to further immune activation and neoantigen recognition. These activated T cells are believed to migrate to and control distant metastasis through the abscopal effect.

high-throughput genome sequencing, computer technology and transgenic animal models have led to unprecedented advances in our understanding of the genetic aberrations and down-stream signalling events that underpin the pathogenesis of the malignant B cell. However, our understanding of the bi-directional interplay between the FL B cell and the cellular, stromal and cytokine/chemokine components within which they reside remains at a relatively primitive stage. The field remains wide-open. Lack of cell-lines, relevant *in vitro* and humanised animal models, integrated biobanking and difficulty in obtaining sequential node biopsies during treatment remain obstacles to be overcome, if we are to fully harness the therapeutic potential of TME modulation.

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