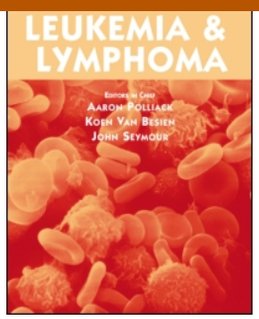

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REVIEW

Follicular lymphoma genomics

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ABSTRACT

Although outcomes for follicular lymphoma (FL) continue to improve, it remains incurable for the majority of patients. Through next generation sequencing (NGS) studies, we now recognize that the genomic landscape of FL is skewed toward highly recurrent mutations in genes that encode epigenetic regulators co-occurring with the pathognomonic t(14;18) translocation. Adopting these technologies to study longitudinal and spatially-derived lymphomas has provided unique insights into the tumoral heterogeneity, clonal evolution of the disease and supports the existence of a tumor-repopulating population, considered the Achilles' heel of this lymphoma. An in-depth understanding of the genomics and its contribution to the disease pathogenesis is identifying new biomarkers and therapeutic targets that can be translated into clinical practice and, in the not too distant future, enable us to start considering precision-based approaches to the management of FL.

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Introduction

Follicular lymphoma (FL) is a malignancy derived from germinal center (GC) B-cells and the most common indolent B-cell lymphoma with an estimated 3–4 new cases per 100,000 persons per year [1]. The median overall survival for FL now extends to 15–20 years [2], however it is still referred to as an incurable malignancy. The natural history of FL is characterized by a protracted, relapse remitting course, with each disease-free period becoming progressively shorter leading to eventual treatment refractoriness. Importantly, significant clinical heterogeneity exists amongst patients, which poses dilemmas for treatment decision-making. A group of patients can be managed expectantly for many years without requiring treatment whereas approximately 15–20% display high risk features by progressing or being refractory to initial conventional treatment within the first few years or undergoing histological transformation to an aggressive high grade lymphoma, typically diffuse large B cell lymphoma (DLBCL) [3]. These high risk patients have significantly poorer prognosis [4,5]. Elucidating the biological processes that underpin the clinical heterogeneity remains a major research focus. This is particularly pressing as our current induction treatments still underserve the high risk FL population and may indeed over-treat those with low risk disease.

Our understanding of the genetic basis of FL has changed significantly in the last decade and continues to evolve, firstly due to the development of next generation sequencing (NGS) technologies and, more recently, single cell multi-modal approaches allow features of the cancer to be studied at a single cell resolution. This review summarizes recent insights into FL genetics, both at diagnosis and relapse, its contribution to pathogenesis and perturbed biological pathways and how this is beginning to be translated into clinical practice.

Genomic landscape of follicular lymphoma

A key hallmark of FL biology is the t(14;18)(q32.3, q21.3) reciprocal translocation, present in 80–85% of patients and considered the first hit in the oncogenic cascade [6,7]. The translocation juxtaposes the proto-oncogene *BCL2* in close vicinity to the Ig heavy chain loci *IGH*, resulting in constitutive BCL2 overexpression. The t(14;18) break occurs during an early stage of B-cell development within the bone marrow [8]. Ectopic overexpression of BCL2 confers a survival advantage to the t(14;18)-bearing B cells, however, multiple lines of evidence support the insufficiency of *BCL2* deregulation alone in propagating tumorigenesis. Firstly, the translocation can be detected at very low levels in the

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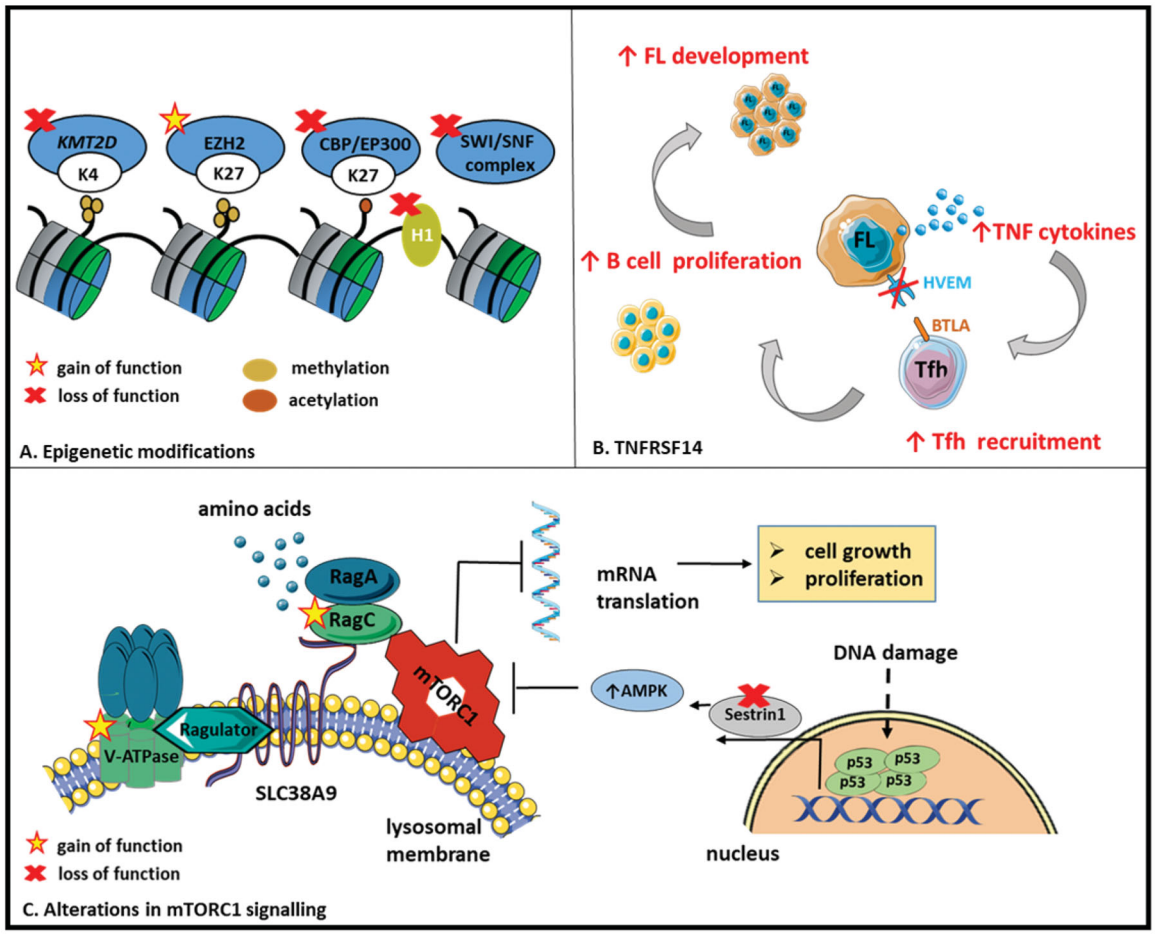

Figure 1. Key biological pathways affected in FL. (A) Mutations in histone-modifying genes in FL. Inactivating mutations in *KMT2D* lead to decreased methylation marks on lysine 4 of histone 3 (H3K4). *EZH2* gain of function mutations lead to accumulation of tri-methylated H3K27. Loss of function mutations in *CREBBP* and *EP300* impair H3K27 acetylation. Genes encoding linker histones (H1) are recurrently mutated in FL. (B) Loss of function mutations in *TNFRSF14* disrupt HVEM-BTLA signaling resulting in increased secretion of TNF associated cytokines and recruitment of Tfh cells, which support tumor B cell survival. (C) Genetic aberrations that converge on mTORC1 signaling. *RRAGC* mutations result in tethering of mTORC1 to the lysosomal surface and activation of mTORC1, even in amino acid deprived states. *Sestrin1*, an upstream negative regulator of mTORC1 is frequently deleted.

blood of healthy individuals [9–11]. Secondly, *BCL2* overexpression mouse models require additional genetic hits to promote overt tumor formation [12,13] and thirdly a subset of FL patients do not have the t(14;18) yet follow similar clinical trajectories [14]. Altogether, the acquisition of additional molecular events is necessary for the development of the overt malignant FL phenotype.

Initially identification of these additional hits relied on lower resolution techniques including conventional cytogenetics, array comparative genomic hybridization (aCGH) and DNA microarrays. These primarily identified recurrent copy number alterations (CNAs) such as deletions in chromosome regions such as 1p36, 6q, 10q, 13p, 17p and gains of 1q, 2p, 7, 8, 12q, 18q and X [15–18]. These alterations span across many genes, proving difficult to pinpoint the exact genes within the regions that contributed to FL biology. The advent of NGS techniques including whole genome, exome and targeted gene sequencing in the last decade has enabled the identification of a near complete catalog of genetic lesions that occur alongside the t(14;18) translocation (Figure 1).

Role of epigenetic deregulation

Compared to other malignancies, FL tumors have an apparent 'addiction' to epigenetic alterations, as over 90% of patient tumors harbor mutations in genes encoding epigenetic modifiers ('epimutations') suggesting it is a pivotal pathogenic hallmark [19–22]. The majority of these epimutations center on genes involved in epigenetic regulation through histone modifications including *KMT2D*, *CREBBP* and *EZH2*,

highlighting the convergence on two specific amino acid residues along the histone tail, histone H3 lysine 4 (H3K4) and histone H3 lysine 27 (H3K27).

KMT2D encodes a H3K4 methyltransferase that facilitates gene transcription by marking gene promoters and enhancers [23]. It is the most frequently mutated gene in FL, with mutations occurring in approximately 70–80% of patients [19,20,22,24–26]. *KMT2D* aberrations are typically biallelic with copy neutral loss of heterozygosity (cnLOH) affecting one allele with the second allele targeted by mutations, usually truncating in nature thus leading to loss of its enzymatic activity or complete loss of protein expression [27]. Kmt2d-deficient mice have enhanced proliferation of germinal center (GC) B cells and reduced numbers of class-switched B cells, indicative of a block in B cell differentiation at the GC stage [23,27]. Genome-wide transcriptomic and epigenomic analysis of *KMT2D* mutated or deficient tumors showed reduced mono- and di- methylation of H3K4 enhancers of *KMT2D* target genes involved in CD40, JAK-STAT and BCR signaling suggesting these alterations contributed to the phenotype [23].

Aberrations in histone acetyltransferase (HATs) enzymes, *CREBBP* and *EP300*, occur in up to 70% and 15% of FL cases respectively [19–22,24–26]. *CREBBP* mutations are mostly clustered within the catalytic HAT domain and this locus is frequently affected by cnLOH therefore, rendering the mutations homozygous [20,28]. A recent study showed that different classes of *CREBBP* mutations conferred different functional severities, with HAT mutations associated with inferior clinical outcomes [29]. Global *CREBBP* knockdown preferentially depletes H3K27 acetylation at the enhancers of genes that are normally deactivated in GC B cells and linked with exiting the GC reaction implying that *CREBBP* mutations aberrantly maintain the GC phenotype [30–32]. These mutations also contribute to immune evasion by downregulation of antigen presentation genes including major histocompatibility class (MHC) II, with decreased frequencies of tumor infiltrating CD4 helper T cells and CD8 memory cytotoxic T cells in *CREBBP* mutant tumors [31,33]. The aberrations were associated with unopposed deacetylation by the BCL6-SMRT-HDAC3 transcriptional repressor complex [31]. Mechanistic studies exploring the relationship between *CREBBP* and *EP300* indicate that combined loss of *Crebbp* and *Ep300* in GC B-cells abrogated GC formation, suggesting these proteins partially compensate for each other through common transcriptional targets and *in vitro* *CREBBP* and *EP300* have a synthetic lethal relationship perhaps hinting at why mutations in these genes do not typically co-occur in patient tumors [34,35].

EZH2 is a SET domain histone methyltransferase, a catalytic subunit of the polycomb repressive complex 2 (PRC2) [36], which silences gene transcription by trimethylating the lysine 27 residue of histone 3 (H3K27) [37]. *EZH2* mutations are present in up to 25% of FL cases, the majority are heterozygous single nucleotide variants centered on 3 amino acids within the catalytic SET domain, most notably affecting tyrosine 646 (Y646) [38,39]. These mutations result in a gain of function and a global increase in the H3K27 mark. Mutant *EZH2* regulates the GC phenotype through the repression of specific cell cycle checkpoint genes such as *CDKN1A* and genes responsible for exit from the GC and terminal differentiation (*IRF4* and *PRDM1)* [37,40,41]. *Ezh2* loss abrogated GC formation, however there is no evidence of overt tumor formation with the *Ezh2* mutation alone indicating additional oncogenic hits are required for overt tumorigenesis [37].

Other commonly altered genes in FL within the large epigenetic umbrella include mutations in genes involved in chromatin remodeling such as, *ARID1A* (typically nonsense mutations) and the linker histones (*HIST1H1B-E*), occurring in up to 10% and 30% of cases respectively [19,42]. *HIST1H1C* and *HIST1H1E* are the most frequently mutated linker histones. The majority of these aberrations are missense mutations, clustered in the highly conserved globular domain. Mutations in linker histones (H1) compromise chromatin compaction [19] and has recently been shown to induce primitive stem cell transcriptional programs suggesting they can enhance self-renewal [43].

Overall, these studies demonstrate that epigenetic aberrations promote a shift toward aberrant repression of gene transcription, block normal GC B cell exit and differentiation. The epimutations alone do not appear sufficient to initiate lymphoma, but require dysregulated expression of BCL2 to induce lymphomagenesis [23,27,28,32]. This is supported by studies in which individuals with germline mutations in *KMT2D, CREBBP* and *EZH2* do not have a predisposition to early onset, or a higher incidence of lymphoma [44–46]. Critically, the majority of FLs are affected by multiple co-occurring epimutations indicating that mechanistic cooperation is likely required for lymphomagenesis.

Genes impacting the tumor microenvironment

Herpes virus entry mediator A (HVEM), encoded by the gene *TNFRSF14,* is the most recurrently mutated gene outside of the epigenetic family [47,48]. Up to

40% of FL patients have loss of function mutations, deletions or cnLOH in *TNFRSF14* [48]. HVEM is a bidirectional signaling molecule involved in B and T cell activation or inhibition depending on its interaction with different ligands including B and T-lymphocyte attenuator (BTLA) and LIGHT [49]. Hvem or btla knockdown accelerated FL development in a BCL2 mouse model [50]. This was partially explained by disruption to HVEM-BTLA signaling, which inhibits BCR signaling and B cell proliferation. Interestingly, HVEM-deficient B cells produce increased tumor necrosis factor (TNF) associated cytokines resulting in abnormal stroma activation, thereby inducing a supportive tumor microenvironment (TME) milieu with increased recruitment of T follicular helper (Tfh) cells that support tumor B cell survival. Recently, HVEM engagement of BTLA on Tfh cells was shown to reduce the delivery of T helper signals to B cells, restraining B cell proliferation [51]. These studies highlight how genetic aberrations contribute to subverting the TME to their advantage promoting tumor cell survival *TNFRSF14* mutations were initially thought to confer adverse clinical outcomes [47], although this was not validated in a subsequent study [48].

Alterations in mTORC1 signaling

More recently, mutations in the nutrient-sensing arm of the metabolic checkpoint, mTORC1, were reported. In normal cells, intracellular amino acid levels are sensed through a supercomplex that includes Rag GTPases, the Ragulator complex, the v-ATPase complex and sodium-coupled neutral amino acid transporter 9 (SLC38A9) that in a concerted manner activate mTORC1 signaling but only in the presence of sufficient amino acids [52–54]. *RRAGC*, a Rag GTPase, is mutated in up to 17% of FL patients and particularly co-occur with mutations in subunits of the v-ATPase complex (*ATP6V1B2* and *ATP6AP1*). For reasons that are unclear, mutations in these genes appear unique to FL [55,56]. *RRAGC* mutations are predominantly missense mutations that confer a gain-of-function, by promoting the interaction with mTORC1, tethering mTORC1 to the lysosomal surface and subsequently activating mTORC1 even in states of amino acid deprivation [55–57]. *Rragc* mutant mice have expanded germinal centers but have reduced need for micro environmental signals, with resistance to apoptosis and a decrease of Tfh cell abundance [58]. Interestingly, the opposing reliance on Tfh support might explain why *RRAGC* and *TNFRSF14* mutations are mostly mutually exclusive indicating that FL tumors with different mutation profiles utilize different micro environmental mechanisms to support their growth. Recently, *ATP6V1B2* mutations (present in about 10% of FLs) were shown to activate autophagy even under nutrient deprived conditions [59]. Deletions and epigenetic silencing of *SESTRIN1*, an upstream negative regulator of mTORC1 *via* p53 occurs in 20% of FL patients and is mutually exclusive with *RRAGC* mutations [60]. Altogether, these show a convergence on mTORC1 signaling.

Other signaling pathways

Genes involved in BCR-NFκB and JAK-STAT signaling are frequently mutated in FL. Mutations in genes encoding proteins in the BCR-NFκB signaling pathway (*CARD11, TNFAIP3, CD79A, CD79B MYD88*) collectively occur in approximately one third of patients [19,26]. *CARD11* mutations are activating and occur in the coiled-coil domain whilst *TNFAIP3* mutations are inactivating [61,62]. They both occur in about 10% of FLs and lead to a constitutive activation of anti-apoptotic NFκB signaling [63,64]. The JAK/STAT pathway mediates signal transduction downstream of a variety of cytokines and growth factors and is essential for the GC reaction. Mutations in *SOCS1* and *STAT6* occur in approximately 10% and 12% of FL cases, respectively [19,21]. Activating *STAT6* mutations allow preferential localization to the nucleus and induction of *STAT6* target gene expression, promoting cell survival [65].

We now have a more complete picture of the genomic landscape of FL. However, the majority of these discovery efforts have come from typically single institution analyses. Larger scale genomic studies to determine specific patterns of mutual exclusivity and co-occurrences, how these relate to clinical phenotypes, both at diagnosis and progression, together with more detailed studies to elaborate the functional impact of these mutations are important next steps in realizing the full potential of which, if any, of these gene mutations can serve as predictive or prognostic biomarkers.

Tumor evolution and heterogeneity

A FL patient's disease journey is punctuated by episodes of relapse, progression and/or transformation. Analyzing sequential tumor samples provides unprecedented snapshots into the genetic evolution that occurs at specific disease episodes. Earlier studies showed that patterns of somatic hypermutation (SHM) within the variable regions of the *IGH* gene in sequential tumors could infer the clonal dynamics of tumor

evolution [66–68]. Through SHM, these regions also acquire sequence motifs that act as sites for N-glycosylation [69]. Shared SHM patterns between progression events and the preceding FL confirmed that sequential tumors were primarily clonally-related [70].

Analysis of sequential tumor samples, using WES and WGS, has added considerably to this understanding. Genomic and exomic analysis of paired diagnostic and relapsed or transformed FL (tFL) tumors demonstrate branching or divergent evolution as the most frequent pattern of evolution. Kridel *et al.* showed that early progression arises due to expansion of preexisting subclones already present at diagnosis, suggesting these subclones were resistant to conventional therapy [22]. Mutations in ten genes (*KMT2C, TP53, BTG1, MKI67, XBP1*, *SOCS1, IKZF3, B2M, FAS* and *MYD88)* were enriched in the diagnostic tumors of patients who experienced early progression.

FL transformation (tFL) affects approximately 10–15% of patients but remains the leading cause of lymphoma-related mortality [71–73]. Somatic mutations present in nearly all tumor cells (clonal) represent early events and are likely driver mutations, the most frequent of which are the epimutations (*KMT2D* and *CREBBP*). These driver mutations are stable and remain clonally dominant from diagnosis to transformation, irrespective of therapy [19,21,22]. Unsurprisingly, in all of these studies, no single genetic event drives transformation. Instead, the genetic landscape of the transformed tumor becomes more complex with additional genetic events that are enriched at transformation including mutations in genes involved in NFκB signaling (*MYD88, TNFAIP3)*, B cell development (*EBF1*), cell cycle control (*CDKN2A/B)* and immune evasion (*B2M, CD58*) [19,21,22]. Additionally, tFL is characterized by increased CNAs including amplifications in regions that encompass genes such as *EZH2*, *MYC* and *REL* [15,19]. However, it is important to note that these genetic aberrations are imperfect predictors for transformation as they are also present in untransformed FL tumors, although at lower frequencies. Critically, the majority of these transformation-enriched genetic alterations did not exist in the precedent FL biopsy, suggesting they were gained during the clonal expansion event leading to transformation, perhaps underscoring the need for repeat biopsies at progression and transformation.

Most studies have focused on studying the temporal clonal dynamics of FL, however, we are becoming aware of the extent and clinical importance of spatial tumor heterogeneity within an individual FL patient who typically have multiple sites of tumor involvement. Genomic analyses of spatially-separated synchronous biopsies from FL patients showed variable levels of spatial heterogeneity [74]. The epimutations, *CREBBP* and *KMT2D* were spatially concordant in all the patients in the series reaffirming these are early driver events. Of relevance, the incidences of spatial discordance where gene mutations are present in one site of disease but absent in the other presents a challenge for accurately identifying predictive or prognostic biomarkers that rely on gene mutations. This spatial heterogeneity has been further illustrated by a recent study using single cell RNA sequencing (scRNA-seq) to interrogate the gene expression and microenvironment composition in spatially-separated fine needle lymph node aspirates from FL patients at diagnosis [75]. Recent single cell analyses also show that within an individual, FL cells exhibit a broad continuum of transcriptional states rather than being fixed at the GC stage as was once thought [76]. Collectively, the degree of clonal evolution and intra-patient heterogeneity in space and time in FL patients' tumors reinforces the notion that a single biopsy cannot capture such molecular diversity.

Evidence for a dormant reservoir population

There are increasing clues that FL tumors may be propagated from a reservoir population with 'stemness' hallmarks such as self-renewal capacity and ability to recapitulate the entire cell repertoire of the whole tumor. Initial data supporting the existence of a putative lymphoma-propagating population came from two unique cases of donor-derived FL following allogeneic stem cell transplantation [77,78]. In both cases, the donor and recipient tumors shared identical *BCL2-IGH* rearrangements in addition to other genetic alterations, suggesting that lymphoma precursor cells had been transferred from the donor to recipient at the time of transplantation, several years before clinical onset of the disease. Intriguingly, in one case, three somatic mutations shared between the donor and recipient were identified in both the mature $CD19^{+}$ B-cell population and the immature stem cell-progenitor enriched ($CD34^{+}CD10^{-}CD19^{-}$) populations of the donor lymphocyte infusion (collected 7 years before onset of symptomatic lymphoma), allowing one to hypothesize that lymphoma-associated mutations could occur early in the hematopoietic hierarchy.

Furthermore, the notion of FL-propagating populations is supported by genomic profiling of sequential FL biopsies that were discussed earlier. The evolutionary history of these tumors can be reconstructed with

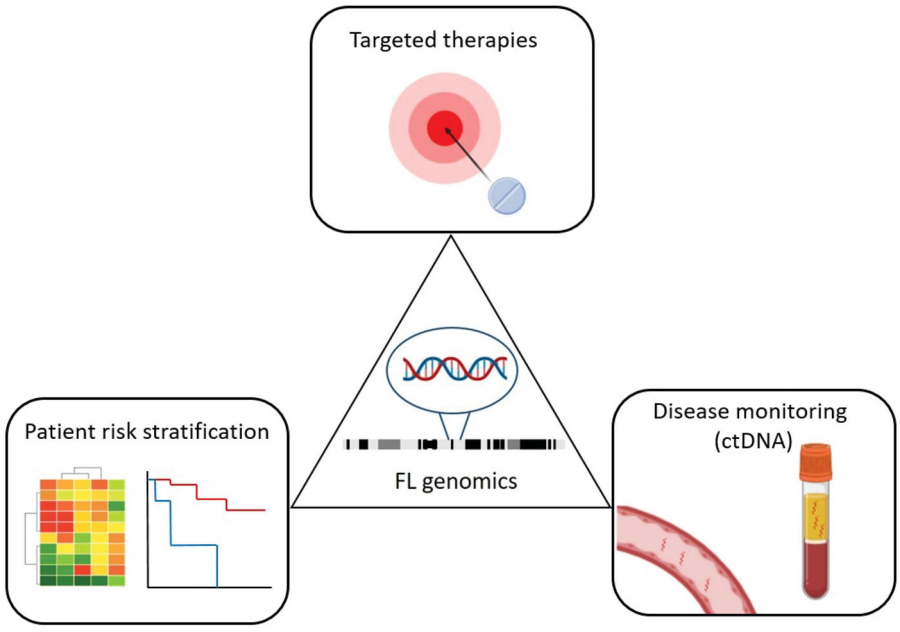

Figure 2. Potential clinical utility of molecular data. Biomarkers from the molecular information including genomics and transcriptomics can lead to improved prognostic tools, new targets and therapies and novel ways for disease monitoring.

phylogenetic trees and demonstrate that every disease episode arises from a 'trunk' of shared mutations that represents a common ancestral origin referred to in the literature as the common precursor or progenitor cell (CPC) [19,21,22,79].

The genetic aberrations within this putative lymphoma-propagating population has been inferred from deep sequencing of bulk tumor samples, with many cases harboring the *BCL2-IGH* translocation along with mutations in the histone-modifiers, *CREBBP* and *KMT2D* [19,21,25,69], and N-glycosylation sites [80]. There remains a lack of clarity of where exactly these early driver events occur within the stages of B cell development. Of note, mice with conditional *Kmt2d* deletions prior to the GC stage of development, but not after, were shown to have a profound magnitude of transcriptional change and B-cell proliferation [27] and analogous to these observations, loss of *Crebbp* in murine hematopoietic stem and progenitor cells results in increased incidence of B cell lymphomas compared to *Crebbp* wild-type mice [81]. Whilst this intimates that genotypes at different stages of differentiation confers different tumor phenotypes, the significance of these data in the context of human FL tumors remains unclear. Nevertheless, the sequential studies and prevalence of progression and transformation in FL suggests that current treatment do not sufficiently eradicate these CPC reservoirs and a better understanding of these dormant and elusive populations warrants further investigation.

Can this genomic information inform clinical practice?

With an increasing wealth of information, the next steps are finding avenues where these can be incorporated to improve patient prognostication, disease monitoring, identifying predictive biomarkers and ultimately refined treatment strategies, with particular emphasis given to high risk FL patients (Figure 2).

Patient risk stratification

Biology-based prognostic tools have been developed using molecular information from tumor biopsies, including the m7-FLIPI [82] and gene expression scores [83] that aims to dichotomize patients into low and high risk groups at diagnoses. The m7-FLIPI incorporates the mutation status of 7 genes (*EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, CARD11*) with clinical characteristics (performance status and FLIPI score) to compute a risk score for each patient. The validity of the m7-FLIPI score was proven in patients receiving rituximab together with either CHOP or CVP chemotherapy, however retrospective analysis of samples from the phase III GALLIUM trial (NCT01332968) [84] showed that the m7-FLIPI was not prognostic for patients receiving bendamustine in combination with immunotherapy [85]. Interestingly, this analysis also reported that *EZH2* mutation status could serve as a predictive biomarker to guide chemotherapy selection.

EZH2-mutated patients who received CHOP/CVP with immunotherapy had a superior progression free survival compared to those who received bendamustine with immunotherapy. Of note, the m7-FLIPI model was not prognostic for FL patients who received rituximab without chemotherapy [86], perhaps indicating that the validity of such tools occurs within the confines of specific treatment approaches. Huet and colleagues showed that a prognostic model derived from the expression profile of 23 genes can also risk stratify FL patients, although needs prospective validation [83]. The position of these prognostic tools in informing clinical decision making is uncertain especially as treatment algorithms continue to evolve. Presently, each of these tools rely on molecular information from the diagnostic tumors alone and may lack the true precision in predicting the continued tumor evolution and heterogeneity seen in progressing FL.

Disease monitoring

An emerging area is molecular subtyping and disease monitoring of circulating tumor DNA (ctDNA) from liquid biopsies. As ctDNA is released into the blood from multiple tumor sites, it may better reflect intrapatient tumoral heterogeneity [87], providing a better assessment of genomic landscape at diagnosis and enable early detection of progression [88]. Delfau–Larue *et al* demonstrated that ctDNA is prognostic in FL and correlated with total metabolic tumor volume [89]. Pretreatment and reduction of ctDNA levels after the first two cycles of treatment is prognostic in DLBCL [90]. As such, the value of ctDNA in lymphoma monitoring is currently under evaluation and will require standardization and prospective validation before incorporation into routine clinical practice.

New 'actionable' targets

Better understanding of the genomic basis of FL opens up the potential characteristics that are 'actionable' and therapeutically targeted. As epigenetic changes are reversible, drugs targeting the epigenome could be effective in patients carrying these mutations. Activating *EZH2* mutations are an attractive therapeutic target in *EZH2*-mutated lymphomas. Potent small-molecule EZH2 inhibitors have been developed which decrease the aberrant global H3K27me3 levels due to *EZH2* mutations [91–93]. In a phase II study, relapsed/refractory FL patients with *EZH2*-mutated tumors treated with the EZH2 inhibitor, tazemetostat (Tazverik) had superior overall response rates compared with wild-type *EZH2* patients (ORR: 69% vs 35% respectively) and was well tolerated with a low incidence of treatment-related adverse events [94]. Recently, Ennishi and colleagues demonstrated that *EZH2*-mutant GCB DLBCLs have significantly lower expression of antigen presentation molecules. Tazemetostat restored MHC expression and increased T-cell infiltration in *EZH2*-mutant cell lines suggesting that epigenetic therapies could also indirectly modulate antitumor immunity and exert an anti-lymphoma effect [95]. Pan-HDAC inhibitors have shown moderate activity in B-cell lymphomas like FL [96,97] but have not been explored beyond early phase studies. However, selective HDAC3 inhibitors are showing promise as a means of abrogating the effect of *CREBBP* mutations [29,31,98].

There is an increasing armory of drugs being evaluated in FL, especially in the relapsed- refractory setting, including PI3 kinase, BCL2 inhibitors and immunotherapies including checkpoint inhibitors and bispecific antibodies [99–102]. One of the current challenges in managing patients with FL is determining which patients will respond to these newer treatments. The next focus must be to identify molecular correlates that define why some patients respond to treatments and others do not, thereby enabling us to stratify who will benefit most from specific therapies. Pharmacologically targeting a single genetic aberration may ultimately lead to development of treatment-resistant clones, therefore combination therapies to target the multiple vulnerabilities of the tumor will be needed to stave off resistance. Finally, if it is believed that the CPC is the root of the disease events in FL, a hypothetical strategy would be to identify drugs that target the specific vulnerabilities of this reservoir population as a means of eradicating this tumor-replenishing reservoir.

Conclusion

Our understanding of FL genomics, heterogeneity and evolution continue to shed light on the pathogenesis of this lymphoma. These observations open up new questions: why do FL tumors appear so dependent on epigenetic dysregulation, can it be easily reversed, what are the characteristics of the reservoir populations, where do they reside, can they be targeted and can we learn lessons from early stage FL that seem mostly 'cured' with radiotherapy. Careful research is now required to understand the contributions of the various genetic events in FL and the interplay with other features such as host-tumor immunity and the

epigenetic landscape to determine how they shape these tumors. How best we deploy and maximize this new-found and evolving biological knowledge into clinical practice and move toward more precision-based approaches, especially for the underserved FL populations, will likely require a change in the status quo and more innovative biology-guided clinical trial designs.

Disclosure statement

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