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Progress Against Follicular Lymphoma

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Abstract

Purpose of review—We wish to share recent progress in research and new therapies against follicular lymphoma (FL) and highlight exciting opportunities to improve the treatment of FL.

Recent findings—Follicular lymphoma has been somewhat neglected by the research community, but recent genomic studies have identified key genetic lesions in FL. In addition, a new murine model is available to explore the function of these lesions in development, progression, and treatment of FL. Moreover, new small molecule inhibitors are now available that target key pathways in FL including B-cell receptor signaling and histone modifiers.

Summary—FL is a very common and still incurable form of lymphoma. However recent genomic and in vivo biological studies are beginning to unveil the molecular drivers of FL. This coincides with the development of effective small molecule inhibitors against key targets. Together these developments suggest that we are at a long overdue watershed moment in the treatment of FL.

Keywords

Follicular lymphoma; pathogenesis; genomics; therapy; experimental models

Introduction

Follicular lymphoma (FL) is the most common indolent nodal lymphoma and is diagnosed in ~ 20,000 Americans per year with a median age of 55 years [1]. Despite much progress over the last two decades, including the advent of the anti-CD20 antibody (Rituximab), a cure for FL has remained elusive[2]. More recently, genomic sequencing studies, novel experimental models, and extrapolation of findings in aggressive lymphomas have begun to shape a new understanding of FL pathogenesis. We will discuss these new insights, ongoing and future research directions, and emerging changes in FL diagnosis and treatment. This article cannot be comprehensive and for example tumor environment, immunotherapy, and transplantation are not discussed.

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Conflicts of Interest

The authors declare no conflict of interest.

The status quo

The cytogenetic hallmark of FL, present in 85% of patients, is the translocation t(14;18) (q32;q21) that places the *BCL2* gene under control of the immunoglobulin heavy chain promoter. Constitutive expression of the anti-apoptotic BCL2 protein likely promotes survival of germinal center B-cells. However, the translocation t(14; 18) is also detectable in up 50% of healthy individuals[3,4]. Clearly, it is not sufficient for FL development and identifying and targeting pathogenic drivers is an active area of research. Clinically, FL typically presents as disseminated, asymptomatic lymphadenopathy and runs an indolent course marked by initial response to treatment followed by relentless relapses.

Approximately, 45% eventually transform (progress) towards an aggressive disease that resembles diffuse large B-cell lymphoma (DLBCL)[5]. The FL International Prognostic Index (FLIPI), a scoring system of clinical factors is used to anticipate patient outcomes [6,7]. Nevertheless, the optimum initial management of patients with asymptomatic low-burden disseminated disease remains controversial, and many favor “watch and wait” while others advocate early chemotherapy with Rituximab or Rituximab alone when comorbidities are a concern [2]. These approaches achieve high response rates and overall survival times exceed 10 years[8]. However, relapse remains inevitable and the effects of chemotherapy complicate long-term management[5,8,9]. The benefit of autologous transplantation is not established, and while allogeneic transplantation offers a chance of cure in younger and otherwise healthy patients it remains a risky procedure [2]. Transformation of FL (tFL) into a DLBCL-like disease is a major complication and occurs in 3% of FL patients per year. Transformation reflects outgrowth of a proliferative clone and requires rapid initiation of aggressive combination chemotherapy. The molecular causes are not yet established, and clinical factors summarized in the FLIPI point to high-risk patients [9,10]. Transformation severely worsens outcomes and 10-year survival drops from 75% to 36% for tFL patients [5]. Looking forward and based on emerging new data on FL, the authors expect that potential avenues to improve FL outcomes include: 1) Improved upfront therapy with extended initial remissions will benefit the often elderly FL patients; 2) Improved prediction of transformation will enable better risk-benefit assessment and treatment decisions; 3) New therapeutics that target specific pathogenic mechanisms provide effective and less toxic additions and alternatives to current therapy.

The Newly Emerging Genetic Basis of Follicular Lymphoma

Until recently FL has not received much scientific attention compared with aggressive lymphomas. However, new experimental tools including genomic sequencing, genetic screens, and accurate murine models are now shedding light on FL pathogenesis (Figure 1). For example, previous cytogenetic studies had identified the hallmark translocation t(14;18) along with recurrent alterations including gains of the c-MYC locus, and losses affecting p53 or large deletions of chromosome 6q. These lesions were shown to impact patient outcomes and hence represent important changes in tumor biology [11,12]. For some cytogenetic lesions the key molecular target was established, but for others the genetic target(s) of these genomic rearrangements had remained elusive. Functional genetic screens provide a powerful tool to simultaneously test the biological activity of large numbers of candidate genes. For example, we used an RNAi screening approach to dissect the common 6q deletions and identified several candidate targets including the ephrin receptor A7 (EPHA7). Intriguingly, EPHA7 encodes a soluble protein that acts as a dominant inhibitor of other ephrin receptors and ultimately intersects with B-cell receptor mediated activation of oncogenic kinases including Erk and Src. This also implies that exogenous administration of EPHA7 – for example using the anti-CD20 as a vehicle - is a strategy to selectively restore a tumor suppressor in lymphoma and block the activation of downstream signaling molecules

[13]. We are currently developing antibody-directed delivery of EPHA7 as a targeted therapy for FL and other B-cell malignancies.

Direct sequencing of lymphoma genomes has identified biological processes and pathways that are targets of recurrent mutations. For example, epigenetic regulators are frequently mutated. Notably, the histone-methyl transferase MLL2 is mutated in ~ 90% of FLs, less frequent targets of mutations are enzymes involved in protein and histone acetylation (e.g. CREBBP, EP300, and MEF2B), or the polycomb factor EZH2 [14,15]. The exact biological consequences of these lesions are not yet established. Their pleiotropic effects reflect changes in DNA accessibility or modulation of key transcription factors (like p53 or Bcl6). At this point, we can speculate that they impact B-cell differentiation and may counter signals that promote plasmacytic differentiation. However, it is likely that tumor cells coopt additional effects for their benefit.

Other recurrent mutations affect genes involved in tumor cell immune recognition including the MHC class I molecule B2M, the NK-cell receptor CD58, TNFSR14 which can interact with light and BTCLAL ligands on T-cells, and the CIITA factor involved in MHC class II gene expression [14–17]. In aggregate these mutations likely contribute to the low immunogenicity of lymphoma cells and dampen NK and T-cell activation. How these lesions affect immune-therapeutic approaches is not clear. Clearly, immunological defenses pose a significant obstacle to lymphoma development that could be utilized for treatment.

Additional lesions affect the B-cell receptor (BCR) signaling pathway (e.g. CARD11 or CD79B). There is also functional evidence of BCR signal activation in FL[18], however these lesions are more abundant in aggressive DBCL and represent one mechanism whereby downstream growth, survival and differentiation signals are activated (reviewed in [19]). Surprisingly, a sizeable portion of FLs harbor genetic lesions that affect cell cycle control loci including RB, p16 and CDK14. These growth stimuli are clearly exciting opportunities for targeted therapeutics that block either signal molecules in BCR pathway of the cell cycle kinases. Together, these lesions provide a window on the biological programs and processes that either hinder or promote FL and they indicate increasingly realistic therapeutic targets.

Relapse and transformation are the two events most likely to lead to death in FL patients. Attempts to determine the origin of the transformed FL (tFL) clone have been aided by persistent activation induced cytidine deaminase (AID) mutagenic action that enablestracing back the origins of the tFL clone and relate it to the original FL clone [20–22]. AID-generated mutations may also directly promote transformation, although in some instances ongoing AID activity can be deleterious to rapidly proliferating tumors [23]. Several proto-oncogenes have been implicated in transformation and these include c-MYC, p53, CDKN2A, and BCL6 [20,24]. Most likely ongoing deep sequencing studies on tFLs will soon provide more definite insight into FL transformation.

Modeling The Pathogenesis and Progression of Follicular Lymphoma In Vivo

Genetic studies are rapidly cataloguing recurrent genetic lesions in FL. Next we need to understand the biological effects of these changes. Previously, functional studies on FL have been limited by a paucity of good experimental models and most human FL cell lines are derived from tFL. This implies that these lines cannot inform us about early, non-transformed FL or the process of transformation. A pathologically and genetically accurate mouse model of FL based on the vavP-Bcl2 transgene provides a first opportunity to study non-transformed FL and its progression in vivo [13,25,26] (Figure 2). The lymphomas arising in these animals recapitulate many aspects of human FL including T-cell infiltration,

IgH class recombination, V-gene hypermutations, Bcl2 expression, low Ki67, follicular morphology, and germinal center origin by PNA staining. Most likely there are also differences, but for now they provide the only in vivo model of this cancer. To facilitate genetic studies on lymphomagenesis and transformation in vivo, we use an adoptive transfer approach that involves transplantation of virally transduced hematopoietic progenitor cells (HPCs)[13]. The recipients of these HPCs are mosaic and their hematopoietic system is derived, at least in part, from vavPBcl2 transgenic HPCs that are engineered to harbor defined genetic lesions. This mosaic mouse model enables genetic studies of FL development and progression and provides genetically defined tumors for downstream studies of tumor phenotypes and molecular analyses. The murine model is also ideally suited to treatment studies that compare drug action against tumors harboring defined genetic lesions. Notably, at the moment FL drug development relies on preclinical studies in other diseases, sometimes complemented by DLBCL cell lines that contain the translocation t(14; 18) and may be derived from tFL. We advocate that a defined murine model of FL will improve preclinical testing, provide detailed genotype-response data, and improve the design of clinical trials.

Emerging targeted therapeutics against follicular lymphoma

As outlined above we do not yet understand the detailed biological consequences of the recently identified genetic lesions in FL. However, they already pinpoint potential drug targets, and in some cases new compounds are available and testing is already underway (Table 1). For example BCL2 is a rational target in FL, and drugs that mimic the BCL2 homology 3 (BH3) domain found on pro-apoptotic BCL2 family proteins can act as BCL2 inhibitors[27]. Obatoclax was the first purported BH3 mimetic tested in trials, although its true mechanism is somewhat controversial and clinical activity has not been impressive[28]. Results from a trial in treatment-naïve FL are not yet available. ABT263 (Navitoclax) is an orally bioavailable BH3 mimetic showing high affinity for BCL2 plus similar family members including BCL-XL, and causes cell death in a BAX/BAK dependent manner[29]. In a phase I dose escalation study in relapsed NHL, measurable tumor reduction was observed in 6/16 FL patients and the main toxicity was thrombocytopenia that was at least in part due to BCL-XL inhibition. ABT199 is more selective for BCL2 and should avoid thrombocytopenia, and both ABT263 and ABT199 are now in clinical development for FL as single agents and in combination with rituximab.

The nearly ubiquitous mutations in chromatin-modifying enzymes in FL implicate them as drivers of FL and important drug targets. For example, the *MLL2* gene is mutated in 89% of FLs [30]. Its function in lymphomagenesis is not clear. A recent study in an *MLL2* knockout carcinoma cell line implicates transcriptional effects on p53, cAMP, and retinoic acid receptor signaling[31], but today no drug to revert the effects of its loss is available. Better understood though less frequently altered in FL is the polycomb repressive complex-2 (PRC2), whose enzymatic core protein EZH2 acquires activating mutations in 7.2% of FLs (compared with 21.7% of germinal center-derived DLBCLs)[14]. Mutant EZH2 results in increased H3K27 trimethylation, a repressive chromatin mark[15,32,33]. Chromatin immunoprecipitation sequencing suggested EZH2 participation in a germinal center B-cell proliferative program, and RNAi knockdown of its expression halted growth of many GC-derived lymphoma cell lines[34]. Targeting mutant EZH2 clinically may soon be possible and companies including Novartis, Epizyme, and Glaxo-Smith Kline are all developing inhibitors. For example, GSK126 was the lead compound identified in a biochemical screen for inhibition of PRC2 complex activity[35]. It binds to EZH2's catalytic SET domain, reduces H3K27 trimethylation, and kills EZH2-mutant lymphoma cell lines in vitro and in vivo without major toxicities. No information about human dosing and formulation is available at this time. A key question will be whether the drug is active only against EZH2-

mutant disease or whether the rare mutations are an indicator of a broader EZH2 dependence in FL. A recent genetic study shows a synthetic lethal relation between SWI/SNF complex alterations and EZH2 inhibition and might argue for a broader activity of EZH inhibitors[36]. Murine models are one way in which we can assess these genotyperesponse relations to optimize patient treatment.

Mutations targeting key components of the B-cell receptor (BCR) pathway have been described in aggressive lymphoma and less frequently in FL[30,37]. However, BCR signaling is clearly activated in FL compared to normal B-cells, and BCR signaling is required for their survival [18] [38]. Together these data indicate a therapeutic opportunity, and drugs targeting BCR signaling through BTK and PI3K delta are now available[39,40]. Additional approaches include targeting the BCR subunit CD79B with an antibody-drug conjugate, or interception of the BCR signal with a dominant inhibitory ephrin receptor (EPHA7)[13,41].

Ibrutinib is an irreversible BTK inhibitor and may also affect additional targets[39]. Ibrutinib preliminarily has shown excellent activity against chronic lymphocytic leukemia (CLL). A Phase I ibrutinib dose-escalation study resulted in response in 11/14 (79 %) of CLL patients[42], and multiple larger CLL trials are now underway testing single-agent and combinations with rituximab or chemotherapy. The latest results from two ongoing trials were presented at ASH 2012, generating excitement about long progression free survivals in both treatment-naïve patients[43] and in pretreated patients with the highest-risk clinical features[44]. In FL, efficacy data for ibrutinib are lacking, though the original phase I trial included 16 relapsed FL patients, of whom six responded, including 3 CRs[42]. Phase II evaluation specifically in FL is underway, though results are not yet available.

Genetic studies indicate a B-cell specific function of the PI3K delta isoform [45]. Several small molecule inhibitors of this PI3K isoform are now available, and Cal-101 has received the most attention [46]. Isoform selectivity should provide a therapeutic window in B-cell malignancies. Early-phase clinical results of Cal-101, presented at meetings, show encouraging rates of response especially in indolent NHL subtypes but have not yet been published. For example, in CLL greater than 80 percent of patients obtained a nodal response when Cal-101 was combined with rituximab, bendamustine, or both[47]. Thirteen different open or planned trials of Cal-101 are now listed on clinicaltrials.gov, including single-agent and combinations with antibodies and chemoimmunotherapy. The focus is on CLL, but many trials are also open to FL. Neither ibrutinib or Cal-101 have won FDA approval yet, but BCR-targeted therapy for FL appears imminent.

Conclusion

These are exciting times to work on FL. Genomic studies have catalogued the most common mutations in this cancer and we now have experimental models to explore their biological effects. Moreover, small-molecule inhibitors of pathways and processes implicated in FL have become available and already show promise in related B-cell malignancies. How can we make the most of these opportunities for FL patients? Clearly inclusion of FL patients in ongoing trials with ibrutinib, Cal-101, and combinations is key. The reduced toxicity of these drugs likely will prompt earlier use, and they may extend initial treatment responses or delay transformation. In parallel, research needs to define what patients based on the genetics of the tumor are most likely to benefit. Combined with molecular studies into the biological effects of common lesions this also will identify molecular markers, potentially superior drug targets, or rational ways to combine existing drugs. Clearly, not all combinations of tumor genotype and drugs can be tested clinically, and adequate tumor models can play a key role in defining optimum strategies ahead of clinical trials. In summary, with new

genomic data, experimental models, and targeted inhibitors in hand we are likely at a watershed moment in the treatment of FL.

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Key points

1. Recent genomics studies have highlighted key pathways in follicular lymphoma.
2. Targeted inhibitors against important molecules (e.g. BTK, PI3K delta, EZH2) in these pathways are available.
3. New experimental models enable studies into FL pathogenesis, progression, and treatment.

Figure 1.
Graphic summary of common genetic lesions in follicular lymphoma

Figure 2. A versatile murine model of follicular lymphoma

A) Schematic of adoptive transfer strategy that enables studies of genetic interactions in lymphomagenesis and progression in vivo. B) Exemplary data indicating how distinct genetic lesions affect tumor latency in vivo (myc = c-Myc, shEpha7 = short hairpin RNA against Epha7, vector control). C) Representative histologies of murine lymphomas stained with HE (left) and for PNA (right).

Table 1

Simplified summary of current and emerging treatment options for follicular lymphoma.

Current Treatments		CHOP+Rituximab
New Therapies	Signalling	Ibrutinib, Cal101 EphA7-hCD20
	Apoptosis	ABT-737, ABT-199 Obatoclax
	Cell Cycle	PD---0332991
	Epigenetics	EZH2 inhibitors (GSK126, EI-1, EPZ005687)
	Immunotherapy	Anti-CTLA4 Anti-PD-1L CAR-anti-CD19