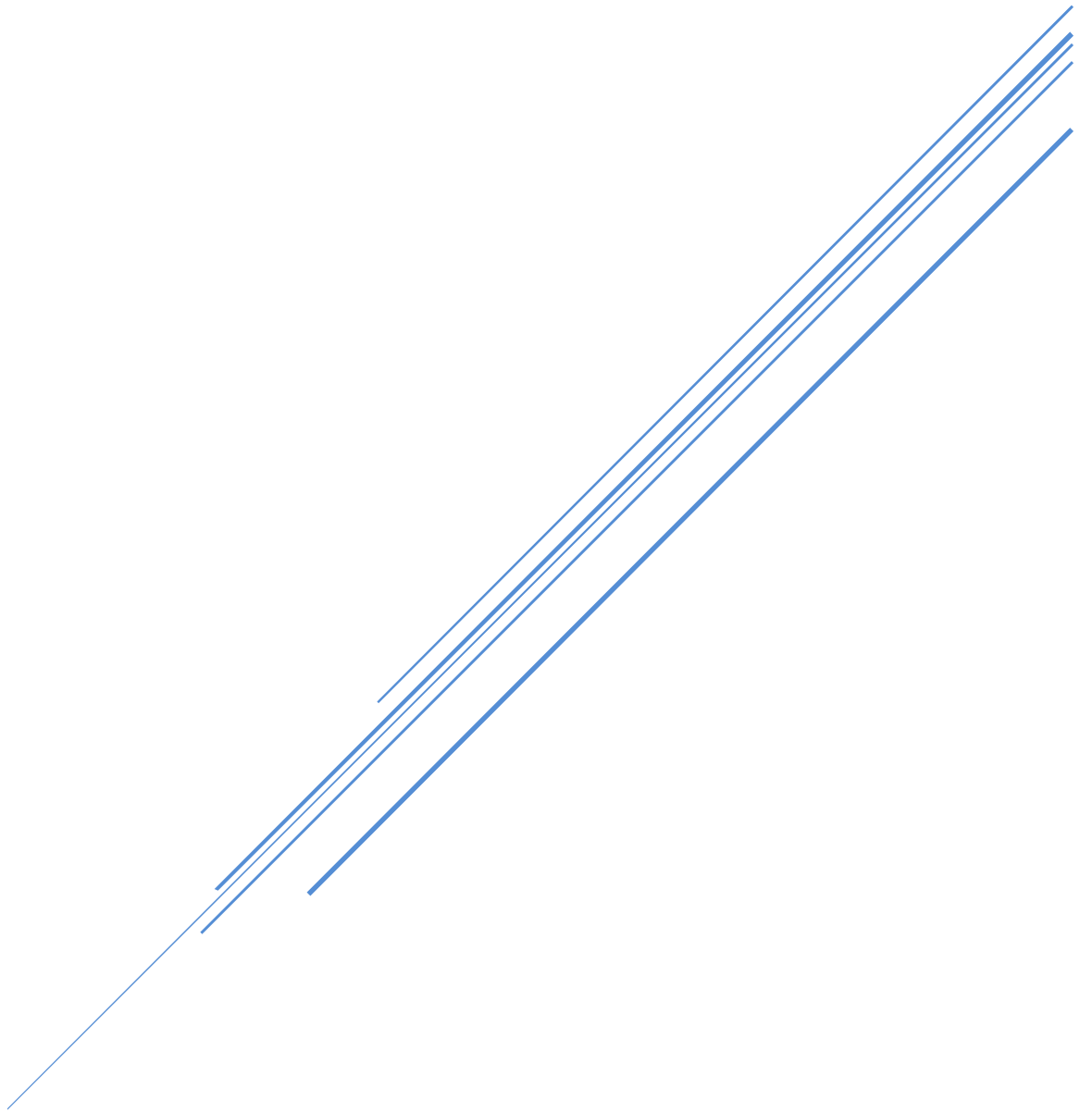# INSIGHT INTO THE PATHOGENESIS OF FOLLICULAR LYMPHOMA

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Review article

Insight into the pathogenesis of follicular lymphoma

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Abstract

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL). FL is clinically designated as an indolent with a long median survival of 8-10 years. However, the clinical and biological behavior of FL shows considerable variability, with some patients showing aggressive disease progression and very short survival. A hallmark of FL is the Bcl-2 translocation t(14;18), This translocation is not sufficient to drive FL development and subsequent molecular defect appears to lead to FL progression. The microenvironment plays an important role. The disease is diagnosed in an advanced clinical stage. The outcome improvement caused by the introduction of the targeted immunotherapy rituximab, both in inductions as well as in maintenance therapy. However, notwithstanding this improvement, subsequent relapses occur, they can be managed by a variety of approaches based on many factors. One most events is the histological transformation. The present review briefly summarizes understanding of biology, pathological clinical course and management.

Introduction

Lymphoma- an overview

Malignant lymphoma is a very diverse group of neoplasms arising from lymphoid cells [1]. Typically, lymphoma is present as a solid tumour of lymphoid cells. More than seventy different disease entities currently comprise the lymphomas. Each lymphoma type has distinct clinical features, treatment, prognosis, genetic events and immunophenotype, and is diagnosed using multiple parameters, including histology, immunophenotyping, cytogenetics, and clinical behavior [1]. The classification of lymphomas has undergone revolutionary changes and recent insights into lymphocyte biology have revealed even more complexity. Based on the World Health Organization (WHO) classification of tumours of the haematopoietic and lymphoid tissues, lymphomas are classified into three main groups: mature B-cell lymphoma, T/NK cell lymphoma and Hodgkin lymphoma [1]. Lymphomas also can be divided into two main groups: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). NHL is significantly more common than HL. In the United States, NHL accounts for approximately 70,000 new cases diagnosed every year, compared to 9,000 cases of HL. Additionally, NHL is the fifth most common cancer in the United States [2]. Similarly, in Canada NHL is the fifth most commonly diagnosed cancer and the sixth leading cause of cancer death. According to the recent Canadian Cancer Statistic report, about 7800 new NHL cases are diagnosed annually and with 2800 deaths each year from NHL [3].

The majority of lymphomas are B-cell malignancies, whereas a minority of are T-cell lineage [1]. Most lymphoid malignancies arise at various stages of B-lymphopoiesis. Throughout their formation, differentiation, activation and antigenic stimulation, B-cells

may undergo genomic alterations that may disrupt the molecular pathways that regulate B-cell differentiation, proliferation and apoptosis and turn normal B-cells or progenitors into neoplastic cells [4]. A common genetic mechanism in B-cell lymphomas involves the occurrence of a chromosomal translocation during genetic rearrangement throughout B-cell differentiation [5]. Reciprocal chromosomal translocations involving the immunoglobulin heavy chain (IGH) loci are a hallmark of most B-cell lymphoma subtypes and usually result in dysregulated expression of oncogenes brought under the control of the IGH enhancers. Prominent examples include the t(11;14) in mantle cell lymphoma (MCL), which leads to CCND1 overexpression, t(8;14) in Burkitt lymphoma (BL), which leads to c-MYC overexpression, and the t(14;18) in follicular lymphoma (FL) that leads to overexpression of BCL-2 [6, 7]. B-cell lymphomas are also can be distinguished according to their cellular origin, such as pre-germinal center, which is the normal counterpart of MCL. The germinal center, which is the counterpart of FL, BL and the germinal center B cell-like (GCB) in subtype of diffuse large B-cell lymphoma (DLBCL). The post-germinal center of the activated B cell–like (ABC) subtype of DLBCL cells for FL and the GC- B cell–like subtype for diffuse large B-cell lymphoma (GCB-DLBCL) and marginal zone of marginal zone lymphoma (MZL) [6, 8]

Follicular lymphoma- an overview

Follicular lymphoma (FL) is the second most common NHL subtype after diffuse large B-cell lymphoma (DLBCL). As illustrated in Figure 1.1, FL accounts for 20-30% of all NHL cases and is the most common indolent or "slow-growing" NHL [9]. FL affects mostly older adults, with a median age at diagnosis of 60 years, and a nearly equal male-to-female ratio [10]. Although FL typically exhibits an indolent clinical course, it has been considered incurable. Follicular lymphoma is characterized by a variable clinical course associated with frequent relapses and increasing resistance to conventional therapy regimens over time. Most patients present with asymptomatic widespread disease at diagnosis with lymph node, spleen, and bone marrow involvement [11]. The median survival after diagnosis ranges from 8 to 10 years [1]. Approximately 30% of patients experience transformation of FL to a more aggressive lymphoma type, most commonly DLBCL [12, 13].

Histological and pathological characteristics of FL

Follicular lymphoma is a malignancy of follicle center B-lymphocytes that has at least a partially follicular growth pattern (Figure 1.2). FL cells express markers associated with GC B-lymphocytes, including CD19, CD20, CD22, CD10 and CD79a. Typically, the majority of FL cases are BCL-2, BCL-6 and CD10 positive and CD5 and CD43 negative [1]. The neoplastic follicles in FL resemble the normal GC of secondary lymphoid follicles and comprise components of the normal GC. Histologically, FL neoplastic follicles contain two major types of B-cells normally found in the GC centrocytes and centroblasts with varying ratio (Figure 1.2).

Although in the majority of FL cases some residual follicularity will be seen, in a small proportion of FL cases the follicular growth pattern is lost and the proliferation adopts a diffuse growth pattern; residual follicles might only be discernible by staining for follicular dendritic cells (FDCs).

Typically, cases are diagnosed as FL if there is >75% follicular growth, follicular and diffuse when follicular growth is in the range 75–25, minimally follicular if it is less than 25% or diffuse if no follicular growth seen [1]. FL also is graded histologically as 1, 2 or 3 according to the number of large cells (centroblasts) in the neoplastic follicles per high-power field (hpf). Follicular lymphoma grade 3 is further subdivided into 3a if centrocytes are still present and 3b if sheets of centroblasts only are present. Currently, FL grade 3b is recognized as a separate subgroup of FL with aggressive behavior both histologically and clinically [14]. At a variable time from diagnosis, about 30% of FL patients with repeated biopsy eventually show evidence of histologic transformation (HT) to DLBCL [12].

Molecular pathogenesis of FL

The 14; 18 chromosomal translocation

The primary genetic event in the pathogenesis of FL is the t(14;18) translocation. This occurs during the random recombination of variable (V), diversity (D) and joining (J) regions (VHDHJH) of the immunoglobulin heavy chain (IGH) locus in precursor B-cells in the bone marrow. During this stage, a reciprocal translocation involving one of the immunoglobulin heavy chain gene IGH loci and the proto-oncogene BCL-2 may occur, which puts BCL-2 under the transcriptional influence of the IHG gene enhancer. This

illegitimate recombination event leads to constitutive expression of BCL-2 (Figure 1.3 A) [15, 16]. Normally, in the GC, unless stimulated by a specific antigen to become a plasma or memory B-cell, B-cell undergoes programmed cell death or apoptosis. Nevertheless, due to the t(14;18) translocation, FL B-cells expressing BCL-2, which prevents cells in from undergoing apoptosis, this, in turn, makes these cells more susceptible to the acquisition of additional genetic alterations (Figure 1.4). In normal reactive lymph nodes, BCL-2 protein is not expressed in the GC, which makes BCL-2 protein a very useful criterion in distinguishing FL from reactive follicular hyperplasia (Figure 1.3 B) [17].

Although BCL-2 overexpression plays a central role in the development of FL, the presence of this translocation alone is insufficient for the initiation of FL lymphomagenesis; additional genetic hits are necessary [17]. Transgenic mouse models with t(14;18) indicate that enforced expression of BCL-2 is insufficient to produce FL neoplastic phenotypes [18, 19]. However, after long latency (of 10-20 months), about 75% of these mice develop follicular hyperplasia and only a small subset (10-15%) of these mice develop lymphomas (mostly DLBCL). Approximately half of these lymphomas are associated with additional c-MYC rearrangement (18, 16). Further speaking to the insufficiency of t(14;18) in FL lymphomagenesis, a small number of t(14;18)-positive lymphocytes are detectable in a substantial proportion of healthy people [20].

Secondary genetic events

Other genetic events that have been associated with the pathogenesis of FL include: amplification of oncogenes such as, c-REL and c-MYC, genetic and epigenetic

inactivation of tumour suppressor genes (TSGs) including the TP53 gene by mutations and inactivation of the CDKN2A and CDKN2B genes by deletion or methylation [21]. In addition, several reported recurrent copy number alterations detected by either comparative genomic hybridization or array-CGH (aCGH) include chromosomal losses of 1p, 6q, 9p, 10q, and 17p, and gains of 1q, 2p, 7, 12, 18q, and X [22]. The histologic transformation (HT) of FL to DLBCL seems to be associated with certain recurring genetic aberrations, such as inactivation of TP53 or CDKN2A or amplification of oncogenes such as c-REL and c-MYC [23]. A study by Horsman et al. investigated the secondary cytogenetic changes in a large cohort of diagnostic FL samples (n = 165) with t(14;18). In this study, most of the cases (97%) had additional cytogenetic changes; losses in 6q and 1p were the most common changes detected (30% and 20%, respectively) [24].

The microenvironment also seems to be particularly significant in the development and progression of FL, such as the interaction between the neoplastic B-cells with neighboring immune cells. More specifically, T-cells, macrophages and FDCs may provide additional oncogenic stimulation signals, which promote FL development and proliferation [25]. Finally, the exact molecular mechanism responsible for the clinical heterogeneity of FL remains unclear.

Clinical characteristics of FL

The clinical course of FL is generally indolent [26]. Patients often manifest asymptomatic lymphadenopathy involving the cervical, axillary, inguinal, or femoral regions. Some patients report a history of recurrent "waxing and waning" of lymph node size before diagnosis. Patients also in most cases present with low tumour grade (Grades

1 and 2) [27]. FL clinical staging is usually done according to the Ann Arbor classification system, which divides patients into four stages (I to IV) based on disease localization in one or multiple sites [28]. Approximately 80-85% of FL patients present at the clinic for the first time with advanced stage (Ann Arbor stage III and IV). Patients with low stage (Ann Arbor I and II) disease are seen uncommonly at diagnosis; only 15–20% of all patients present with stage I or II disease [29, 30]. The median age at diagnosis is approximately 60 years; the disease is diagnosed rarely in the young [26]. The clinical presentation and behavior of follicular lymphoma differ according to both histologic grade and clinical stage [31].

The diagnosis of FL requires histological examination of lymph node biopsies by a hematopathologist with experience in lymphoma pathology. The pathologist plays a crucial role in the diagnosis and grading of FL. This work generally involves immunohistochemistry (IHC) and/or flow cytometry evaluations. Clinical investigations for disease staging that are usually performed at diagnosis include computed tomography (CT) scanning, bone marrow biopsy, blood counting, and biochemical evaluation including lactate dehydrogenase (LDH), hemoglobin (Hgb), ESR and β2-microglobulin to determine patient's disease stage [32, 33]. This initial clinical and pathological evaluation for FL patients is important for determining the treatment strategy and for predicting outcome

Clinical outcome and prognosis

The clinical outcome of FL shows considerable variability. Whereas some patients have an indolent and slowly progressive disease over a period of many years, in others

disease progresses rapidly, sometimes with transformation to aggressive lymphoma and subsequent death [34]. Still, in most cases, FL manifests indolent clinical behavior such that most FL patients will enjoy extended survival after diagnosis, with an estimated median OS time of 8-10 years. Follicular lymphoma also is characterized by cycles of disease relapses and remissions, with the frequency varying from one patient to another [11, 26, 35].

Clinical management and current treatment options

Despite the significant improvements in treatment and survival of FL, it remains substantially an incurable disease [36]. Furthermore, the heterogeneous clinical course of FL makes decisions as to which patient needs urgent treatment and when such treatment should be implemented complicated and controversial. Although there are good initial responses to treatment, relapse usually occurs after a period of time and some lymphomas may acquire resistance to therapies that were effective initially [36]. The goal of treatment is to keep the patient symptom-free and maintain a good quality of life for as long as possible. Resistance of the disease to the treatments, tumour progression and/or transformation or the side effects of therapy are the usual causes of death among FL patients [26].

A large population-based study of 14,564 patients diagnosed with FL between 1978 and 1999 has shown a significant improvement in the overall outcomes and survival of patients over these 20 years. This improvement in survival may be a result of the progressive improvement in supportive care, which may include early diagnosis, better health care delivery and different combinations of effective therapeutic regimens [37].

Currently, available treatment options for patients with FL include: chemotherapy regimens such as CVP (cyclophosphamide, vincristine, prednisone), fludarabine and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), with or without the addition of rituximab (R-CVP and R-CHOP). Autologous stem cell transplantation (ASCT) and radioimmunotherapy (RIT) are also used for treating patients with advanced disease stage [11, 36]. The introduction of the anti-CD20 monoclonal antibody rituximab) into clinical practice substantially improved the clinical management of FL and patients' outcomes (34). Although a number of clinical trials have shown that maintenance therapy using rituximab with or without chemotherapy improves progression-free survival (PFS), especially in patients with relapsed disease, no treatment regimen has yet produced a significant improvement in OS [38]. Nonetheless, recent randomized trials have demonstrated that rituximab maintenance can improve patients' response rates and duration if used as a front-line treatment [39].

For instance, a large cohort study of 2728 FL patients enrolled across the United States at 265 sites between 2004 and 2007 was undertaken to monitor the effect of different treatment approaches. The different therapeutic strategies were: observation alone, rituximab monotherapy, radiation therapy alone, chemotherapy alone and chemotherapy plus rituximab (R-CHOP or R-CVP). The results of this study support the notion that there is no single standard of care of FL patients [39]. Yet, more recently, the PRIMA (Primary Rituximab and Maintenance) study evaluated the benefit of rituximab maintenance as front-line treatment for FL. In this study, rituximab maintenance therapy significantly improves the PFS and was beneficial for patients regardless of their age

group or their follicular lymphoma international prognostic index (FLIPI) [40]. However,

longer follow-up is needed to evaluate the effect on OS.

Clinical and biological prognostic indicators in FL

The aim of identifying prognostic indicators is to stratify a group of patients into

different risk groups. Patients who are known to have a poor prognosis could be

candidates for more aggressive treatments and might be advised to enroll for

experimental treatments through clinical trials while those with better-prognosis disease

might benefit from less toxic treatments. Predicting clinical outcomes and prognosis in

FL may be accomplished using clinical and biological factors.

Clinical prognostic factors

Follicular lymphoma international prognostic index (FLIPI)

In FL the most commonly used approach to prognostication is the follicular

lymphoma international prognostic index (FLIPI), which was derived from the earlier

international prognostic index (IPI). FLIPI was specifically designed to be more effective

in predicting FL patients' outcomes than IPI [41, 42]. FLIPI substitutes the "performance

status" and "extranodal sites" of the IPI system, with low hemoglobin (Hgb) and the

number of nodal sites [41, 42]. The FLIPI score is based on the following factors: age

greater than 60 years, Ann Arbor stage III-IV, Hgb level less than 12g/dL, more than 4

nodal sites and elevated LDH level. FL patients' risk and OS are stratified based on the

presence and or absence of these risk factors into three risk groups: low, intermediate or

high [42]. Patients with one factor are classified as low-risk patients and have 5- and 10-

year survivals of 90% and 71%, respectively. Patients with two factors are classified as intermediate risk and they have 5- and 10-year survivals of 78% and 51%, respectively. Patients with three or more factors have high risk and 5- and 10-year survivals of 53% and 36%, respectively (38). Using the FLIPI system to stratify patients based on their risk groups can be applied clinically as an effective predictor of OS for patients with FL (Figure 2.1). However, there remains a considerable heterogeneity of outcome between patients within same risk group, which makes FLIPI alone as yet to impact on routine clinical management and treatment decisions of FL patients [43].

Pathological and biological prognostic factors

Although, using FLIPI as a clinical prognostic indicator has been widely used in FL risk-stratification, the power of FLIPI is limited, as shown by the persistent heterogeneity of the clinical behavior of FL patients within FLIPI-risk groups (39). Thus, markers related to the distinct biology of FL are necessary. Several studies have found different secondary genetic events associated with FL lymphomagenesis and transformation [44, 45].

Histologic transformation

The aggressive transformation of FL represents one of the most significant factors that impact upon patients' outcomes. In a study conducted by Al-Tourah et al. at the British Columbia Cancer Agency, based on a large cohort of 600 patients with FL diagnosed between 1986 and 2001, the median follow-up time was 9 years (range, <1 to 20.3 years). During the follow-up period in this study, 170 (28%) FL patients developed

transformation with an annual risk of (3%). Clinically, transformation was associated with aggressive clinical behavior and shorter OS; the median OS of patients with t-FL was 1.7 years [12]. Higher FLIPI scores, advanced stage and FL histology-grade 3b are associated with increased risk of transformation [45, 46].

Tumour microenvironment

An outcome prediction model in FL proposed by Dave et al. based on gene expression profiling [47] on biopsy specimens from untreated FL patients revealed two different tumour microenvironment signatures that correlated with survival [25]. In this study, the gene expression profiling [47] approach was used to study tumour biopsy samples obtained at the time of diagnosis from 191 patients. Data from GEP were used to assigned patients into two different clusters based on GEP signatures, one associated with better prognosis and the other associated with poor prognosis, and hierarchical clustering was applied separately to genes associated with longer survival (good prognosis) and shorter survival (poor prognosis). The gene expression signatures were called immune response 1 (IR-1) and immune response 2 (IR-2). The IR-1 signature includes some genes that are expressed in T-cells and macrophages, while the IR-2 signature includes genes known to be expressed in FDCs. IR-1 was found to be a good predictor for favorable prognosis and IR-2 for poor prognosis. The median survivals of patients were 3.9 and 13.6 years when patients were risk stratified based on these signatures [25].

The cellular proliferation index

The expression level of Ki-67 protein measures the cell proliferation index. In FL, high proliferation index is generally associated with higher histological grade (grade 3) [48, 49]. However, its prognostic significance on the survival of FL patients is disputable [50, 51]. FL patients with a low prevalence of Ki-67 expressing cells had a significantly prolonged PFS and OS compared to those with high Ki-67 [49]. Significant correlation has been found between the high Ki-67 counts and inferior response to treatment and prevalent Ki-67 expression in FL patients after (R-CHOP) treatment failure [52].

Cell-cycle regulators

Genes involved in cell cycle regulation have been implicated in FL progression. A proportion of FL cases and cases that have transformed from FL to DLBCL are associated with inactivation of TP53, CDKN2A and CDKN2B. TP53 mutations have been reported in FL at diagnosis and were associated with more aggressive clinical behavior and shorter survival [53]. O'Shea et al, reported mutations of TP53 in about (6%) of FLs at diagnosis, the presence of TP53 mutations in this study was significantly correlated with a shorter PFS and OS (51). In addition, there is a positive relationship between TP53 mutation and expression; studies showed that increased p53 levels are detected in TP53 mutated cases, mostly in cases with missense mutations [54, 55]. TP53 mutations and p53 overexpression were correlated with shorter OS in FL [56]. By IHC-based analysis for p53, in 127 diagnostic FL samples, we also found that increased abundance of p53 was significantly associated with reduced OS [57]. Alterations in CDKN2A and CDKN2B in FL are associated with increased risk of transformation to

DLBCL [21, 58]. Moreover, deletion of 9p21 was significantly associated with inferior OS in FL [59]. Additionally, two GEP studies compared GEPs between paired pre- and post- transformation specimens from 12 FL patients. A notable observation from this study was the association between increased levels of c-MYC and p38β MAPK and FL transformation to DLBCL and poor prognosis [22, 6].

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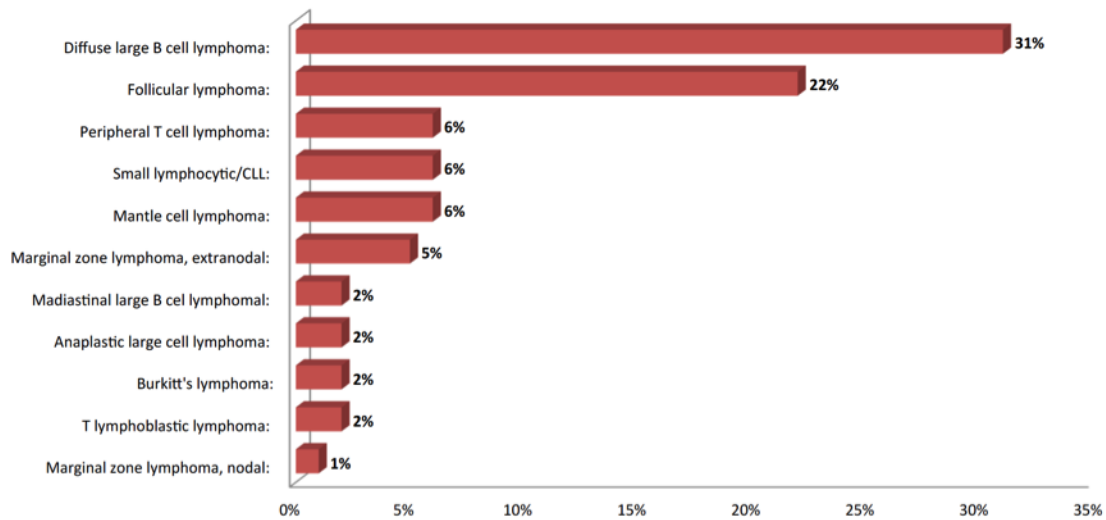
Figures:

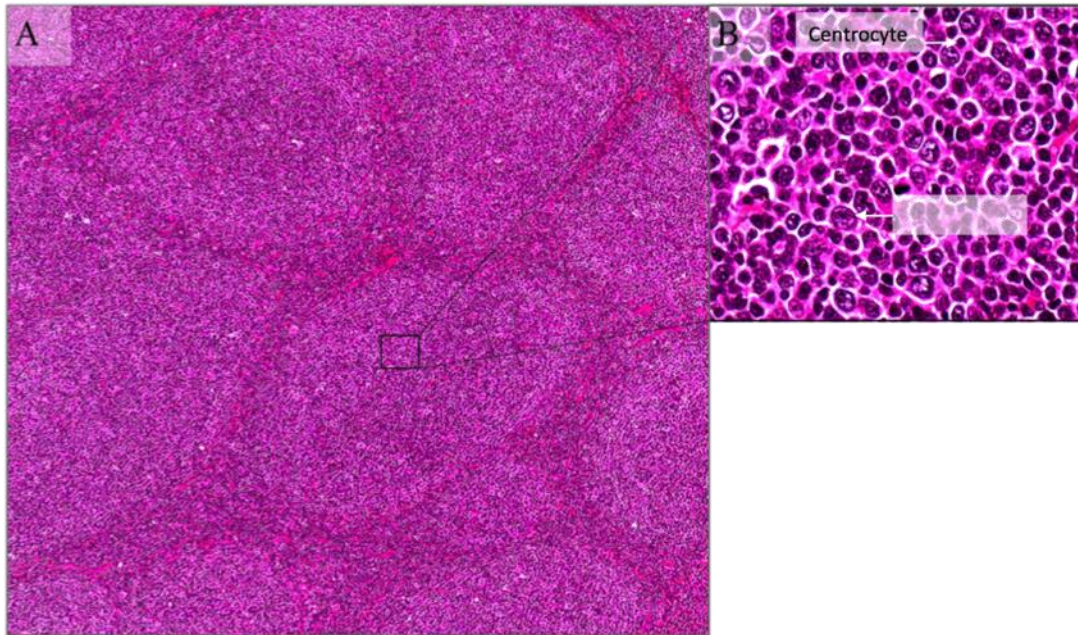Figure 1: Most common types of NHL. Adapted from Armitage JO, et al [8].

Figure 2: Illustration of follicular lymphoma histology. In most cases, the neoplastic

follicles are regular, back-to-back with relatively homogeneous follicle sizes and shapes, original magnification 20x. (A). Higher magnification shows a mixture of small lymphocytes (centrocytes) and large lymphocytes (centroblasts) within the neoplastic follicles, original magnification 40x (B).
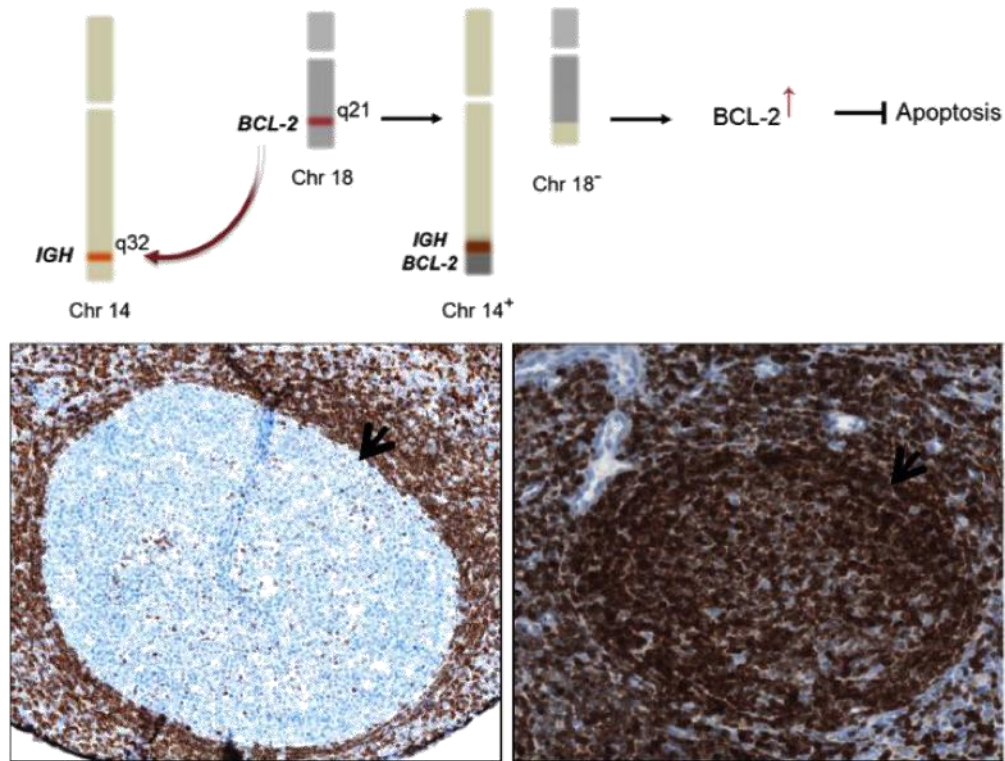

Figure 3: The (14;18) chromosomal translocation in FL. This translocation juxtaposes the BCL2 locus at chromosome band 18q21.3 with the immunoglobulin heavy chain gene (IGH) locus at 14q32.3. This leads to the overexpression of BCL-2 (A). BCL-2 staining in a normal lymphoid follicle and in a neoplastic follicle of follicular lymphoma. In the normal follicle (left), BCL-2 is present in mantle zone cells but not in germinal center (arrowed). In contrast, most follicular lymphomas exhibit strong BCL-2 staining within neoplastic follicle canter (right) (B).
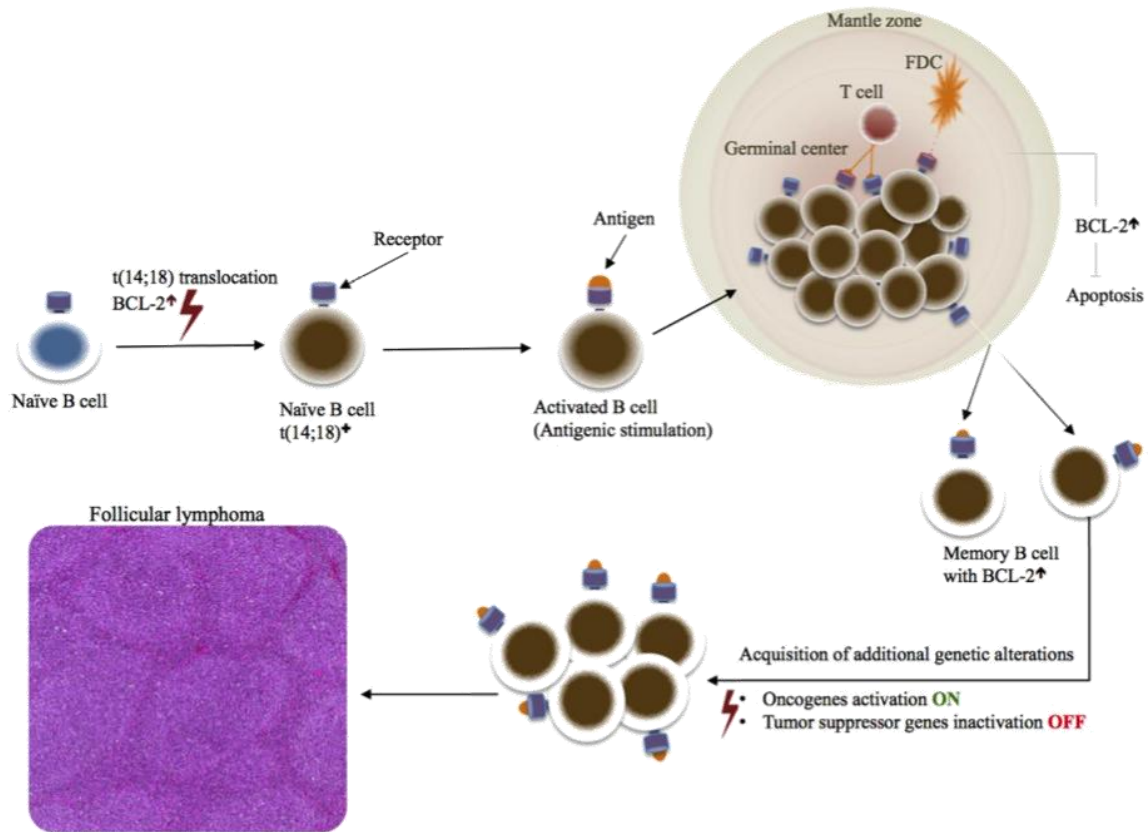
Figure 4: Steps in FL pathogenesis. The t(14;18) translocation is likely to occur in a naive B-cell and upon antigenic stimulation, this may enter into the germinal-center reaction. There, in response to further stimulation by an antigen on the surface of a follicular dendritic cell (FDC) together with T-cell help its progeny may differentiate into memory B-cells that can still be stimulated by antigen. One of these cells may then sustain further oncogenic lesions, leading to full transformation to follicular lymphoma, which may retain a degree of dependency on antigenic stimulation. Adapted and modified from Roulland, et al. [19].