

Risk factors, etiology, and pathogenesis

Anastasios Stathis and Colette Owens

Lymphomas are a heterogeneous group of neoplastic disorders that originate from lymphatic cells. Clinical and epidemiological studies have revealed some risk factors that are associated with the development of lymphomas while molecular biology studies have elucidated mechanisms that drive the malignant transformation of lymphatic cells. In this chapter we review current knowledge of the risk factors and of the molecular pathogenesis of the most common lymphomas.

Risk factors and causes

Immune deregulation plays a major role in the pathogenesis of lymphomas. In this context, some infectious agents, autoimmune diseases, and immunosuppression represent well-established risk factors for the development of specific lymphoma subtypes.

Infection

Growing epidemiological and biological evidence has linked infections to the development of lymphomas (Table 2.1). A strong association between human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and several B-cell lymphoma subtypes has been reported by several studies. The risk is higher for non-Hodgkin lymphoma (NHL)

Infectious agent	Lymphoid malignancy
EBV	Burkitt lymphoma
	Post organ transplant lymphoma
	Primary CNS DLBCL
	Hodgkin's disease
	Extranodal NK/T-cell lymphoma, nasal type
HTLV-1	Adult T-cell leukemia/lymphoma
Helicobacter pylori	Gastric MALT lymphoma
Human herpesvirus 8	Primary effusion lymphoma
	Castleman's disease
HIV	Diffuse large B cell lymphoma
	Burkitt lymphoma
Hepatitis C	Lymphoplasmacytic lymphoma
Chlamydia psittaci	Orbital adnexal lymphoma
Campylobacter jejuni	Immunoproliferative small bowel disease
Borrelia burgdorferi	Cutaneous MALT lymphoma

Table 2.1 Infectious agents associated with lymphoma. CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HTLV-1, Human T-cell lymphotropic virus; MALT, mucosa-associated lymphoma tissue; NK, natural killer.

with a 60–200 times increased risk for all subtypes of NHL in HIV-positive patients [1,2]. The most common HIV-associated lymphomas include diffuse large B cell lymphoma (DLBCL; with up to one third of cases presenting as primary central nervous system lymphomas), Burkitt lymphoma, primary effusion lymphoma, and plasmablastic lymphoma. Hodgkin lymphoma (HL) is also increased in the setting of HIV. The pathogenesis of HIV-associated lymphomas includes several mechanisms, among them chronic antigen stimulation, genetic abnormalities, cytokine deregulation and infections by Epstein-Barr virus (EBV) and human herpes virus 8 (HHV8) [3]. The incidence of HIV-associated lymphomas has significantly decreased with the advent of highly active antiretroviral therapy (HAART).

Other viruses can have impact on lymphoma risk. The human retrovirus T-cell leukemia virus type 1 (HTLV-1) is an established cause for the development of adult T-cell leukemia/lymphoma (ATLL), a peripheral T-cell neoplasm that is endemic in Japan, the Caribbean, and parts of Central Africa. The distribution of the disease is linked to the prevalence of HTLV-1 in the population. The cumulative incidence of ATLL

is estimated to be approximately 3% in HTLV-1 carriers [4]. EBV was initially identified in cases of endemic Burkitt's lymphoma from Africa. Subsequently EBV was detected in cases of sporadic BL, HIV-associated lymphomas, and post-transplant lymphoproliferative disorders. In contrast to endemic BL where EBV is invariably associated, EBV is associated to approximately one third of sporadic BL cases [5,6]. In HIV-associated lymphomas, EBV is detected in approximately 40% of all cases (80–100% of primary central nervous system [CNS] lymphoma and primary effusion lymphoma, 80% of DLBCL with immunoblastic features, and 30–50% of BL and nearly all cases of HL) [6,7]. The HHV8, known also as Kaposi's sarcoma herpesvirus was initially identified in tissues of patients with AIDS-related Kaposi's sarcoma and was subsequently linked to the development of a peculiar type of lymphoma known as primary effusion lymphoma [8]. HHV-8 has been also linked to a significant fraction of multicentric Castleman's disease.

Epidemiological studies have associated hepatitis C chronic infection with some B-cell NHL subtypes including marginal zone lymphomas (MZLs), in particular splenic MZLs (SMZLs), extranodal (mainly non-gastric) MZL of mucosa-associated lymphoid tissue (MALT), lymphoplasmacytic lymphoma (LPL), and DLBCL. While a causal relationship remains controversial, the most convincing proof is the observation, mainly limited to some indolent subtypes, of B-cell lymphoma regressions after hepatitis C virus (HCV) eradication with interferon (IFN) and ribavirin [9]. Bacterial infections have also been associated in the context of chronic inflammation to the development of certain lymphoma subtypes.

Extranodal marginal zone B-cell lymphomas of the MALT arise from lymphoid populations that are induced by chronic inflammation in extranodal sites. The most frequently affected organ is the stomach, where MALT lymphoma is incontrovertibly associated with a chronic gastritis induced by *Helicobacter pylori* (Hp). The initial observation in a few cases that this lymphoma can regress following Hp eradication was subsequently confirmed by a large number of clinical trials and Hp eradication therapy represents today the standard first line of treatment for Hp-positive localized gastric MALT lymphoma. Other bacterial infections have since been found to be implicated in the pathogenesis

of MZL arising in the skin (*Borrelia burgdorferi*), in the ocular adnexa (*Chlamydophila psittaci*), in the small intestine (*Campylobacter jejuni*), and possibly in the lung (*Achromobacter xylosoxidans*) [10].

Immune deficiency

Some rare inherited genetic syndromes that cause primary immune disorders are associated with an increased risk of serious infections and a higher risk of developing NHLs. The primary immune disorders that are most frequently associated with lymphoproliferative diseases are ataxia telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, severe combined immunodeficiency, X-linked lymphoproliferative disorder, Nijmegen breakage syndrome, hyper-IgM syndrome, and autoimmune lymphoproliferative disorder. With the exception of common variable immunodeficiency these diseases present primarily in the pediatric age [11].

Additionally, it is now well established that lymphoproliferative disorders can arise as a consequence of immunosuppression in recipients of solid organ, bone marrow, or stem cell allograft. Post-transplant lymphoproliferative disorders (PTLD) can develop with different frequency among patients receiving solid organ transplant, the higher being in those receiving heart-lung/lung, or intestinal allografts (5% of patients) and lower in those receiving renal, hepatic, and cardiac allografts (approximately 1% of patients) [12]. Stem cell and bone marrow allografts have a risk of approximately 1% [13]. The majority of PTLD are associated with EBV infection.

Autoimmune disease

Some autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE or lupus), Sjögren disease, celiac sprue (gluten-sensitive enteropathy), and others have been linked with an increased rate of NHL. The frequency of these lymphomas is not well known and it is difficult to determine if they are related to the underlying condition or to the treatment. Indeed, methotrexate, and some anti-tumor necrosis factor (TNF) therapies used for some of these diseases may cause an increased risk for the development of a lymphoma [14].

Other risk factors

Increased age, familiarity, previous treatment for cancer, and exposure to some chemicals and to radiation have all been proposed as possible risk factors but their exact link with the development of lymphoma is not clearly defined.

Pathogenesis of non-Hodgkin lymphoma

NHLs are a heterogeneous group of lymphatic tumors with distinct histological, immunophenotypic, genetic, and clinical features that originate from B lymphocytes, less commonly from T lymphocytes, while extremely rare are those originating from natural killer (NK) cells.

Over the past years, there has been significant improvement in our knowledge of the molecular pathogenesis of NHL as a clonal expansion of lymphatic cells. B and T lymphocytes, undergo under physiological circumstances, profound DNA rearrangements that permit expression of the functional B- and T-cell receptors, which determine the specificity of the immune response. This process involves multiple DNA double-strand breaks, which can form the basis for genomic lesions that contribute to lymphomagenesis.

Most mature lymphoid tumors present recurrent genetic lesions including non-random chromosomal translocations, somatic mutations, DNA gains, or losses. Some of these genetic changes can be preferentially observed in individual lymphoma entities but the vast majority are shared by different lymphoma subtypes. At the molecular level, these genetic lesions can result in activation of oncogenes by chromosomal translocations, as well as inactivation of tumor suppressor genes by chromosomal deletion and mutation. In addition, it is now known that the genome of certain lymphoma subtypes can be altered by the introduction of exogenous genes by oncogenic viruses and in particular the most studied for the development of some NHL are represented by EBV, HHV8, and HTLV-1.

The cytogenetic abnormalities discovered and their subsequent molecular characterization have permitted the identification of specific genes that are altered in NHL. Currently, while not sufficient alone to pose a diagnosis of a specific lymphoma subtype, genetic features of lymphomas,

detected by cytogenetics or fluorescence in situ hybridization (FISH) are increasingly important in defining specific NHL subtypes, together with histopathology and clinical presentation of the disease (Table 2.2).

Diffuse large B-cell lymphoma

DLBCL has a high degree of genomic complexity with different somatic mutations and unbalanced genomic lesions as well as few chromosomal translocations. Two main biologically different DLBCL subtypes have been identified by gene-expression profiling (GEP) studies resembling two types of normal B cells, likely to represent the lymphoma cells of origin (COO): germinal center (GC) B-cell like (GCB) subtype and activated B-cell like (ABC) subtype [15].

These two different types of DLBCL have different outcomes with standard current treatments with the ABC type having the worst prognosis. Given the prognostic importance of the definition of the DLBCL type, and due to technical difficulties in applying GEP studies in the daily practice, surrogate immunohistochemistry algorithms using monoclonal antibodies against a limited number of molecules (CD10, BCL6, MUM1, GCET1, FOXP1) have been developed but a total overlap with GEP signature has not been reached yet [16].

Lymphoma subtype	Translocation	Genes involved	Main sites/frequency
MALT lymphoma	t(11;18)(q21;q21)	API2/MALT	Lung, stomach
	t(1;14)(p22;q32)	BCL-10/ IgH	
	t(14;18)(q32;q21)	IgH /MALT1	Ocular adnexae, salivary gland
	t(13;14)(p14.1;q32)	FOXP1/ IgH	Thyroid, ocular adnexae, skin
Mantle cell lymphoma	t(11;14)(q13;q32)	CCND1-IgH	90% of cases
Follicular lymphoma	t(14;18)(q32;q21)	IgH/BCL-2	90% of cases
Diffuse large B cell lymphoma	t(14;18)(q32;q21)	IgH/BCL-2	20–45% of cases
	t(3;-(q27;-)	BCL-6	25% of cases
	t(8;-(q24;-)	C-MYC	20% of cases
Burkitt's lymphoma	t(8;14)(q24;q32)	C-MYC/IgH	Most cases
	t(8;22)(q24;q11)	C-MYC/Igλ	Rare variant
	t(8;2)(q24;p12)	C-MYC/Igκ	Rare variant
Anaplastic large cell lymphoma, ALK positive	t(2;5)(p23;q35)	ALK/NPM	Virtually all cases

Table 2.2 Recurrent chromosomal translocations in lymphoma. MALT, mucosa-associated lymphoid tissue.

Genetic aberrations have been reported, which are associated with poor outcome in DLBCL patients. These lesions include BCL2 translocation, and TP53 inactivation (both apparently restricted to the GCB type), MYC translocations, gains at 3q, and losses at 8p and 9p21 (CDKN2A). A particularly poor prognosis seems to be associated with the concomitant involvement of MYC, BCL2, BCL6, or CCND1 (cyclin D1) in the so-called ‘double’ and ‘triple-hit’ lymphomas [17,18].

Follicular lymphoma

Follicular lymphoma (FL) is the most common indolent subtype of NHL and the second most common NHL. Up to 90% of FL cases have the t(14;18)(q32;q21) translocation, which juxtaposes the BCL2 gene to the IGHV locus resulting in the overexpression and accumulation of its transcript and protein. FISH is the best approach to detect the presence of the translocation [19].

Mantle cell lymphoma

The main genetic feature of mantle cell lymphoma (MCL) is the t(11;14)(q13;q32) chromosomal translocation with the deregulated ectopic expression of CCND1, coding for the cyclin D1, due to the juxtaposition to IGHV region. FISH is the technique of choice to demonstrate the presence of the translocation [20]. Approximately 10% of MCL lack the translocation. An indolent signature of MCL has been reported consisting in the lack or low levels of the transcriptional factor SOX11 [21].

Mucosa-associated lymphoid tissue lymphoma

The most common translocation is the t(11;18)(q21;q21), fusing BIRC3 (cIAP2) on 11q21 with MALT1 on 18q21. The presence of t(11;18) is associated with a low probability of response to antibiotics. The t(14;18)(q32;q21) translocation is cytogenetically virtual identical to the one involving BCL2 in FL or DLBCL, but in MALT lymphoma it brings MALT1 under the control of the promoter region of the IGHV genes with subsequent deregulation of MALT1 expression. The t(1;14)(p22;q32) translocation determines high levels of BCL10 expression due to its juxtaposition to

the IGHV promoter region. The presence of this translocation is associated with resistance to lymphoma eradication with antibiotics [22].

Burkitt lymphoma

BL is characterized by the t(8;14)(q24;q32) chromosomal translocation, juxtaposing the MYC to the IGHV genes. Rare variants are the t(2;8)(p12;q24) involving the Igk locus or the t(8;22)(q24;q11) involving the Igl locus. The differential diagnosis between BL and other aggressive lymphomas has important clinical consequences due to the specific regimes that can be given [23].

Pathogenesis of Hodgkin lymphoma

Hodgkin lymphoma (HL) is an uncommon B-cell lymphoma that accounts for ~10% of all lymphomas and comprises two disease entities: nodular lymphocyte-predominant HL (NLPHL) and classical HL (cHL), which is further divided into four subtypes: nodular sclerosis cHL, mixed cellularity cHL, lymphocyte-depleted cHL, and lymphocyte-rich cHL [24].

Classical HL accounts for 95% and NLPHL accounts for 5% of all HL. Studies of rearranged immunoglobulin variable-region heavy-chain (VH) genes from lymphoma cells isolated from patients with HL, have established that both lymphocyte-predominant cells (LP cells – the noplasic cells of NLPHL) as well as Hodgkin and Reed–Sternberg cells (HRS – the neoplastic cells of cHL) are of B-cell origin deriving from germinal centre B cells [25,26].

Despite their origin from germinal center B cells, HRS cells infrequently express B-cell genes, including CD20 antigen and the B-cell transcription factors OCT2, BOB1, and PU.1, presumably due to epigenetic reprogramming [27,28]. In cHL, deregulated transcription factors such as the nuclear factor kappa B (NFkB) and Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signaling pathway promote proliferation and abrogate apoptosis in HRS cells [29,30].

In contrast to some subtypes of NHL, no recurrent specific chromosomal translocations have been described in HL. Comparative genomic hybridization reveals recurrent gains of the chromosomal sub-regions on chromosomal arms 2p, 9p, and 12q and high-level amplifications on

4p16, 4q23-24 and 9p23-p24 [24]. Amplifications on 9p24.1 represent a recurrent genetic abnormality in the nodular sclerosis type of HL and have gained great interest in recent years with the development of monoclonal antibodies targeting programmed cell death 1 (PD-1) due to the fact that the genes encoding PD-1 ligands are key targets of chromosome 9p24.1 amplification [31].

cHL has been clearly associated with Epstein–Barr virus (EBV). In the Western World, HRS cells are infected with the EBV in ~40% of HL patients, and in 100% of HL patients who are infected with the human immunodeficiency virus (HIV) [32].

References

- 1 Beral V, Peterman T, Berkelman R, Jaffe H. AIDS-associated non-Hodgkin lymphoma. *Lancet*. 1991;337:805-809.
- 2 Levine AM. AIDS-related malignancies: the emerging epidemic. *J Natl Cancer Inst*. 1993;85:1382-1397.
- 3 Carbone A, Ghoghini A. AIDS-related lymphomas: from pathogenesis to pathology. *Br J Haematol*. 2005;130:662-670.
- 4 Tajima K, Hinuma Y. Epidemiology of HTLV-I/II in Japan and the world. In: Takatsuki K, Hinuma Y, Yoshida M, eds. *Advances in Adult T-cell Leukemia and HTLV-I Research (Gann Monograph on Cancer Research)*. Tokyo: Japan Scientific Societies Press; 1992. p. 129-149.
- 5 Tao Q, Robertson KD, Manns A, Hildesheim A, Ambinder RF. Epstein-Barr virus (EBV) in endemic Burkitt's lymphoma: molecular analysis of primary tumor tissue. *Blood*. 1998;91:1373-1381.
- 6 Hamilton-Dutoit SJ, Raphael M, Audouin J, et al. In situ demonstration of Epstein-Barr virus small RNAs (EBER 1) in acquired immunodeficiency syndrome-related lymphomas: correlation with tumor morphology and primary site. *Blood*. 1993;82:619-624.
- 7 Camilleri-Broët S, Davi F, Feuillard J, et al. AIDS-related primary brain lymphomas: histopathologic and immunohistochemical study of 51 cases. The French Study Group for HIV-Associated Tumors. *Hum Pathol*. 1997;28:367-374.
- 8 Teruya-Feldstein J, Zauber P, Setsuda JE, et al. Expression of human herpesvirus-8 oncogene and cytokine homologues in an HIV-seronegative patient with multicentric Castleman's disease and primary effusion lymphoma. *Lab Invest*. 1998;78:1637-1642.
- 9 Vannata B, Zucca E. Hepatitis C virus-associated B-cell non-Hodgkin lymphomas. *Hematology Am Soc Hematol Educ Program*. 2014;2014:590-598.
- 10 Zucca E, Bertoni F, Vannata B, Cavalli F. Emerging role of infectious etiologies in the pathogenesis of marginal zone B-cell lymphomas. *Clin Cancer Res*. 2014;20:5207-5216.
- 11 Jones AM, Gaspar HB. Immunogenetics: changing the face of immunodeficiency. *J Clin Pathol*. 2000;53:60-65.
- 12 Bakker NA, van Imhoff GW, Verschuuren EA, et al. Early onset post-transplant lymphoproliferative disease is associated with allograft localization. *Clin Transplant*. 2005;19:327-334.
- 13 Curtis RE, Travis LB, Rowlings PA, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. *Blood*. 1999;94:2208-2216.
- 14 Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. *Arthritis Rheum*. 2007;56:1433-1439.

- 15 Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:1937-1947.
- 16 Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103:275-282.
- 17 Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. *Blood*. 2009;114:2273-2279.
- 18 Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. *Blood*. 2009;114:3533-3537.
- 19 Belaud-Rotureau MA, Parrens M, Carrere N, et al. Interphase fluorescence in situ hybridization is more sensitive than BIOMED-2 polymerase chain reaction protocol in detecting IGH-BCL2 rearrangement in both fixed and frozen lymph node with follicular lymphoma. *Hum Pathol*. 2007;38:365-372.
- 20 Pérez-Galán P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. *Blood*. 2011;117:26-38.
- 21 Mozas A, Royo C, Hartmann E et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. *Haematologica*. 2009;94:1555-1562.
- 22 Kwee I, Rancoita PM, Rinaldi A, et al. Genomic profiles of MALT lymphomas: variability across anatomic sites. *Haematologica*. 2001;96:1064-1066.
- 23 Klapproth K, Wirth T. Advances in the understanding of MYC- induced lymphomagenesis. *Br J Haematol*. 2010;149:484-497.
- 24 Swerdlow S, Campo E, Harris NL et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC 2008.
- 25 Marafioti T, Hummel M, Anagnostopoulos I, et al. Origin of nodular lymphocyte-predominant Hodgkin's disease from a clonal expansion of highly mutated germinal-center B cells. *N Engl J Med*. 1997;337:453-458.
- 26 Hummel M, Ziemann K, Lammert H, Pileri S, Sabattini E, Stein H. Hodgkin's disease with monoclonal and polyclonal populations of Reed-Sternberg cells. *N Engl J Med*. 1995;333: 901-906.
- 27 Thomas RK, Re D, Wolf J, Diehl V. Part I: Hodgkin's lymphoma—molecular biology of Hodgkin and Reed-Sternberg cells. *Lancet Oncol*. 2004;5:11-18.
- 28 Kuppers R. The biology of Hodgkin's lymphoma. *Nat Rev Cancer*. 2009;9:15-27.
- 29 Hinz M, Lemke P, Anagnostopoulos I, et al. Nuclear factor kappaB-dependent gene expression profiling of Hodgkin's disease tumor cells, pathogenetic significance, and link to constitutive signal transducer and activator of transcription 5a activity. *J Exp Med*. 2002;196:605-617.
- 30 Skinnider BF, Elia AJ, Gascoyne RD, et al. Signal transducer and activator of transcription 6 is frequently activated in Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. *Blood*. 2002;99:618-626.
- 31 Ansell SM, Lesokhin AM, Borrello I, Halwani A, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372:311-319.
- 32 Hummel M, Anagnostopoulos I, Dallenbach F, Korbjuhn P, Dimmler C, Stein H. EBV infection patterns in Hodgkin's disease and normal lymphoid tissue: expression and cellular localization of EBV gene products. *Br J Haematol*. 1992;82:689-694.

Handbook of Lymphoma

Younes, A. (Ed.)

2016, XV, 112 p. 7 illus. in color., Softcover

ISBN: 978-3-319-08466-4