Immunology Letters 263 (2023) 46–59

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Immune dysregulation as a leading principle for lymphoma development in diverse immunological backgrounds

P. Martijn Kolijn, Anton W. Langerak *

Laboratory Medical Immunology, Department of Immunology, Erasmus Medical Center, Rotterdam, the Netherlands

ARTICLE INFO

Keywords:
Lymphoma
Lymphoma predisposition
Immune dysregulation
autoimmunity
Chronic infection
Inborn errors of immunity

ABSTRACT

Lymphoma is a heterogeneous group of malignancies arising from lymphocytes, which poses a significant challenge in terms of diagnosis and treatment due to its diverse subtypes and underlying mechanisms. This review aims to explore the shared and distinct features of various forms of lymphoma predisposing conditions, with a focus on genetic, immunological and molecular aspects. While diseases such as autoimmune disorders, inborn errors of immunity and iatrogenic immunodeficiencies are biologically and immunologically distinct, each of these diseases results in profound immune dysregulation and a predisposition to lymphoma development. Interestingly, the increased risk is often skewed towards a particular subtype of lymphoma. Patients with inborn errors of immunity in particular present with extreme forms of lymphoma predisposition, providing a unique opportunity to study the underlying mechanisms. External factors such as chronic infections and environmental exposures further modulate the risk of lymphoma development. Common features of conditions predisposing to lymphoma include: persistent inflammation, recurrent DNA damage or malfunctioning DNA repair, impaired tumor surveillance and viral clearance, and dysregulation of fundamental cellular processes such as activation, proliferation and apoptosis. Our growing understanding of the underlying mechanisms of lymphomagenesis provides opportunities for early detection, prevention and tailored treatment of lymphoma development.

1. Introduction

The capacity of the adaptive immune system to rapidly proliferate in response to foreign invaders is an invaluable asset for all vertebrate species. [1] However, this capacity comes with an inherent weakness, the strong proliferative potential of immune cells also results in a vulnerability to develop into malignant cells. The resulting malignancies reflect the diversity of the immune system, showing strong heterogeneity, even after grouping by putative cell of origin according to WHO classification. [2,3,4] Lymphocytes in particular undergo many rounds of differentiation and maturation, with each step having the potential to spawn a malignancy with unique traits. [3] The focus of this review will be on lymphoma, classically defined as a malignancy of the cells of the lymphatic system. Contemporary evidence adds some nuance to that definition: while lymphoma often develops in the lymph nodes, the malignancy can occur in almost any tissue and even in the circulation, blurring the distinction between leukemia and lymphoma. [3,5] Historically, lymphomas are divided into Hodgkin (HL, 10 %) and non-Hodgkin lymphoma (NHL, 90 %), based on distinct clinical and histological features. [6] The relevant lymphocytes in the context of malignant transformation to NHL are B-cells, T-cells and natural killer (NK) cells. While lymphocytes normally play crucial roles in the adaptive (B- and T-cells) or innate (NK cells) immune response, malignant transformation to lymphoma results in a highly heterogeneous group of malignancies. [3] Clinically, distinction is made between indolent and aggressive subtypes, with indolent lymphomas being less dangerous if left untreated.

1.1. Epidemiology of lymphoma

The incidence of lymphoma in Europe is approximately 16 in 100,000 people, representing around 4 % of total malignancies. [7] The most frequently diagnosed subtypes of NHL are of B-cell origin, namely: diffuse large B-cell lymphoma (DLBCL, 30 %), follicular lymphoma (FL, 20 %), extranodal marginal zone lymphoma (EMZL, 7 %) of the mucosa-associated lymphoid tissue (MALT), and chronic lymphocytic leukemia (CLL, 7 %). [6] In contrast, T- and NK-cell NHL subtypes are far less common, encompassing around 9 % of all lymphoma diagnoses

* Corresponding author.
E-mail address: a.langerak@erasmusmc.nl (A.W. Langerak).

https://doi.org/10.1016/j.imlet.2023.08.007
Received 22 May 2023; Received in revised form 28 July 2023; Accepted 10 August 2023
Available online 27 September 2023

together. [6] Among the common subtypes of NHL, DLBCL is considered the most aggressive, with a median 10-year survival of 30-40 %,[8] while FL, CLL and EMZL are considered more indolent lymphomas, with median 10-year survival >80 %. [9,10,11] The T- and NK-cell NHL subgroups are similarly heterogeneous, encompassing both aggressive and indolent subtypes. [3]

1.2. Genetic predisposition and heritability of susceptibility

A familial predisposition to lymphoma has been established in large case-control and twin studies, with increased susceptibility often occurring across lymphoma subtypes and even extending to leukemia. [12] Nonetheless, the risk of lymphoma clusters by NHL subtype, with first-degree relatives of CLL patients having an 8.5 fold risk of CLL, first-degree relatives of DLBCL patients having a 9.8 fold increased risk of DLBCL and first-degree relatives of FL patients having a fourfold increased risk of FL. [12,13,14] In contrast, the increased risk of a subtype of NHL in individuals with a first-degree relative having a different NHL subtype is much lower at around 1.7 fold. [12,15]

1.3. Cellular origins of lymphoma development

Lymphoma development can only be understood in the context of normal lymphocyte development, as each step in the lymphoid development process may result in lymphomas with unique biological and clinical features (Fig. 1). [5] B-lymphocytes arise in the bone marrow, where semi-random recombination of a variety of V, D and J genes forms the immunoglobulin (IG) heavy chain (IGH) of the B-cell receptor (BCR), while the IG light chain is formed through recombination of V and J genes only. [16] T-lymphocytes initially arise in the bone marrow from hematopoietic stem cells as well, before migrating to the thymus to mature and undergo VDJ recombination of their T-cell receptor (TR) genes. VDJ recombination occurs through the introduction of controlled double strand breaks in the DNA by the recombination activating gene (RAG) enzymes. [17] While these DNA breaks are normally swiftly rejoined, errors in the DNA repair process can result in the chromosome translocations that are frequently observed in lymphomas. [18] Interestingly, many of these translocations involve the IG and/or TR gene loci, suggesting a potential role for antibody diversification processes in lymphomagenesis. [19] These translocations can alter proto-oncogene, tumor suppressor and miRNA expression, driving leukemia or lymphoma development. [19,20,21] After B-cell development, the naïve B-cells migrate into the peripheral lymphoid tissues (blood, spleen, lymph nodes or mucosa-associated). [22]

In the event that mature IgM$^+$ B-cells recognize an antigen and receive concurrent stimulation from T-helper cells, the B-cell becomes activated and proliferates rapidly. [23] Upon B-cell activation, germinal centers are formed in the primary lymphoid follicles in the secondary lymphoid tissue. [23] During the germinal center reaction, affinity maturation occurs through somatic hypermutation (SHM) and isotype class switching under the influence of stimulation by T- follicular helper cells and follicular dendritic cells. [23,24] While the mechanisms involved are crucial in generating additional BCR diversity and perform efficiently on a population level, SHM and isotype switching nonetheless play a crucial role in the pathogenesis of several subtypes of lymphoma, including DLBCL, FL and Burkitt lymphoma (BL), resulting in both characteristic translocations in the IGH switch region and oncogenic gene mutations through SHM in non-IG genes. [19,20]

While most lymphomas consist of malignantly transformed mature lymphocytes, the disease does not necessarily always originate from these cells, but might in some cases sprout from lymphoid precursor cells such as lymphoblasts, multi-lymphoid progenitor cells and hematopoietic stem cells as well. [25,26] This factor greatly complicates research into the pathogenesis of lymphoma, as lymphoid precursor cells are spread over many different locations in the body, including the bone marrow, blood, spleen, lymph nodes and thymus. Key driver events may occur at any stage during lymphocyte development, giving rise to highly diverse lymphoma subtypes (Fig. 1). Although reports of allogeneic bone

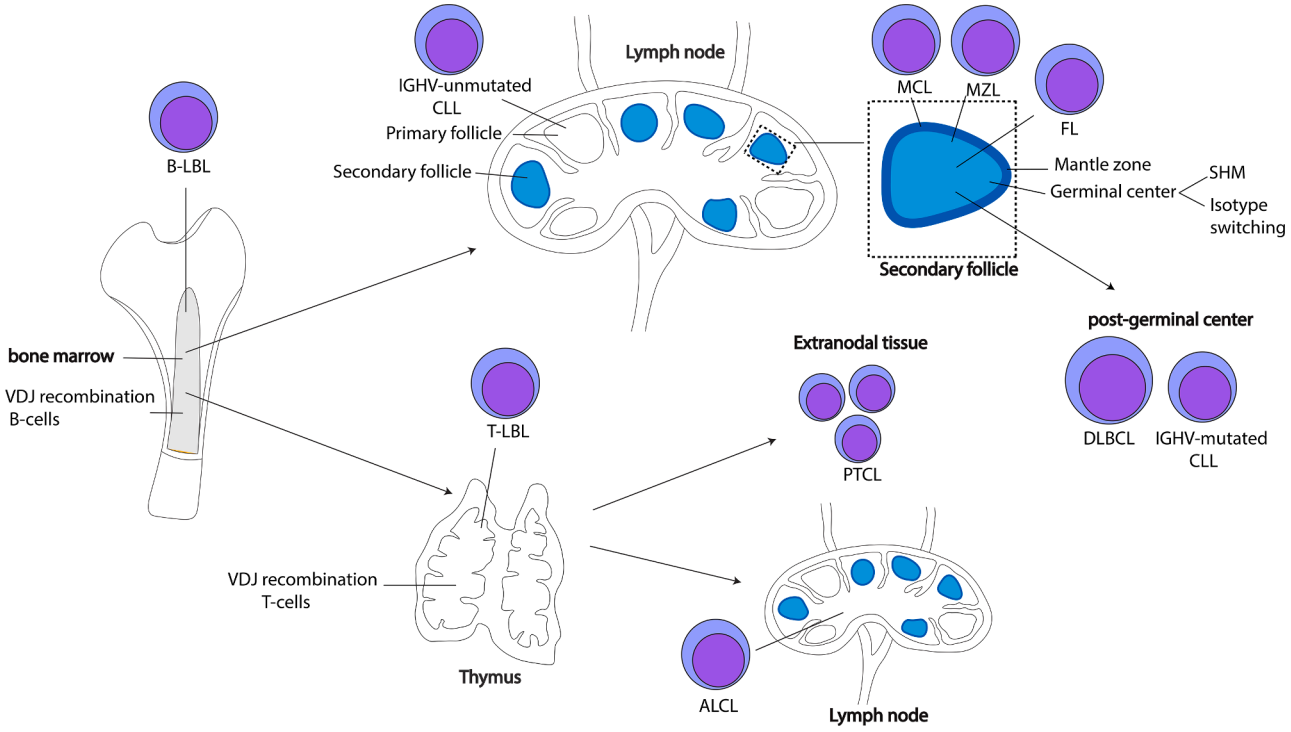

Fig. 1. Schematic overview of lymphocyte development and development of common NHL subtypes. LBL: lymphoblastic lymphoma, CLL: chronic lymphocytic leukemia, DLBCL: diffuse large B-cell lymphoma, MCL: mantle cell lymphoma, MZL: marginal zone lymphoma, FL: follicular lymphoma, ALCL: anaplastic large-cell lymphoma, PTCL: peripheral T-cell lymphoma. Mantle cell lymphoma consists of malignant B-lymphocytes pre-germinal center reaction, while the B-cells in MZL are post-germinal center reaction derived. Figure inspired by Shankland et al. 2012 [5].

marrow transplant donors and recipients developing identical mature lymphoid malignancies support the concept of stem cells harboring lymphoma-predisposing variants, their existence remains controversial. [25,27]

1.4. Shared molecular features among lymphoproliferative disorders

A variety of biologically and clinically distinct factors may contribute to lymphoma development/onset, including chronic viral and bacterial infections, autoimmune disorders and immune dysregulation. [12,14,28,29,30,31] Usually, this development is skewed towards a particular subtype of lymphoma. [31,32,33,34,35,36,37,38,39,40] Our understanding of the shared underlying mechanisms among such heterogeneous conditions is extremely limited. However, similarities too striking to be the result of mere coincidence have been observed among seemingly unconnected lymphoma-predisposing conditions. As an example, patients with chronic HCV infections develop nodal MZL utilizing the typical immunogenetics features of rheumatoid factor (RF) (so-called RF-like stereotypic features). [41,42,43,44,45,46,47] Highly similar RF-like stereotypic features were observed among primary Sjögren's syndrome (pSS)-associated eMZLs and are associated with pSS pathogenesis in general. [46,47] Furthermore, patients with ocular adnexal MZL after *Chlamydophila psittaci* infection also present with RF-like stereotypic features. [48] BCR stereotypy is a broadly reported phenomenon among CLL patients and a subset of these patients even present with BCR stereotypy with RF-like features. [49,50,51,52] What biological mechanism would result in similar BCR stereotypy in clinically and biologically unique backgrounds like chronic viral infection, chronic bacterial infection and autoimmunity? Interestingly, biological similarities between these conditions are not restricted to immunogenetic features. B-cell activation marker levels are also significantly elevated during lymphoma development, although they have also been observed to be elevated in absence of lymphoma development among HCV-infected patients, pSS and SLE patients and EBV-infected patients. [53,54,55] These shared phenomena provide an interesting opportunity to explore shared or homologous underlying mechanisms for lymphoma predisposition among clinically unique conditions and provide exciting perspectives for novel methods of early detection with impact across lymphoma subtypes.

1.5. Risk factors for lymphoma development

While the risk of malignant transformation during lymphoid development and maturation is relatively low under normal circumstances, individuals with a dysregulated immune system are at increased risk of lymphoma and leukemia development. [29,30,31,56,57,58] Risk factors include inborn errors of immunity, autoimmune disease, immunosuppressive treatment, environmental factors and chronic infections (Fig. 2). [30,31,59,60,61,62,63,64,65] The heterogeneous nature of the predisposed patient groups results in a highly context-dependent manifestation of lymphoma. To enhance the current standard for diagnosis and treatment of lymphoma, it is crucial to understand the differences in risk factors and underlying mechanisms between predisposed patient groups. Through precision medicine new developments can be applied in the right patient groups and adjusted according to specific needs.

In this review the commonalities and differences in predisposition for subtypes of lymphoma will be discussed, with a focus on informative underlying mechanisms. While lymphoma encompasses a heterogeneous group of malignancies, a bird's eye view reveals a pattern of disruptions with at its core immune dysregulation, DNA repair and genomic instability.

1.6. Populations predisposed to lymphoma development

1.6.1. Patients with inborn errors of immunity

Inborn errors of immunity (IEI), also referred to as primary immunodeficiencies, encompass a group of heterogeneous defects in cellular and humoral immunity. [30,57,66,67,68,69,70,71,72] Each deficiency or syndrome is characterized by its own unique mix of abnormalities in humoral and/or cellular immunity. [68] However, efforts to elucidate the pathogenesis of IEI quickly showed that the underlying genetic mutations had far-reaching implications for more than just the immune system's response to infectious diseases. [73] The severely dysregulated immune system of IEI patients additionally increases the risk of allergies, autoimmunity and malignancies (relative risk of 1.4). [73] More specifically, the relative risk of lymphoma in patients with IEI is 8-10 fold increased compared to the age-matched population. [69,70,72,73,74,75,76] Examples of IEIs associated with a marked predisposition to lymphoma include DNA repair defects (Ataxia telangiectasia [AT], Nijmegen breakage syndrome [NBS] and constitutional mismatch repair

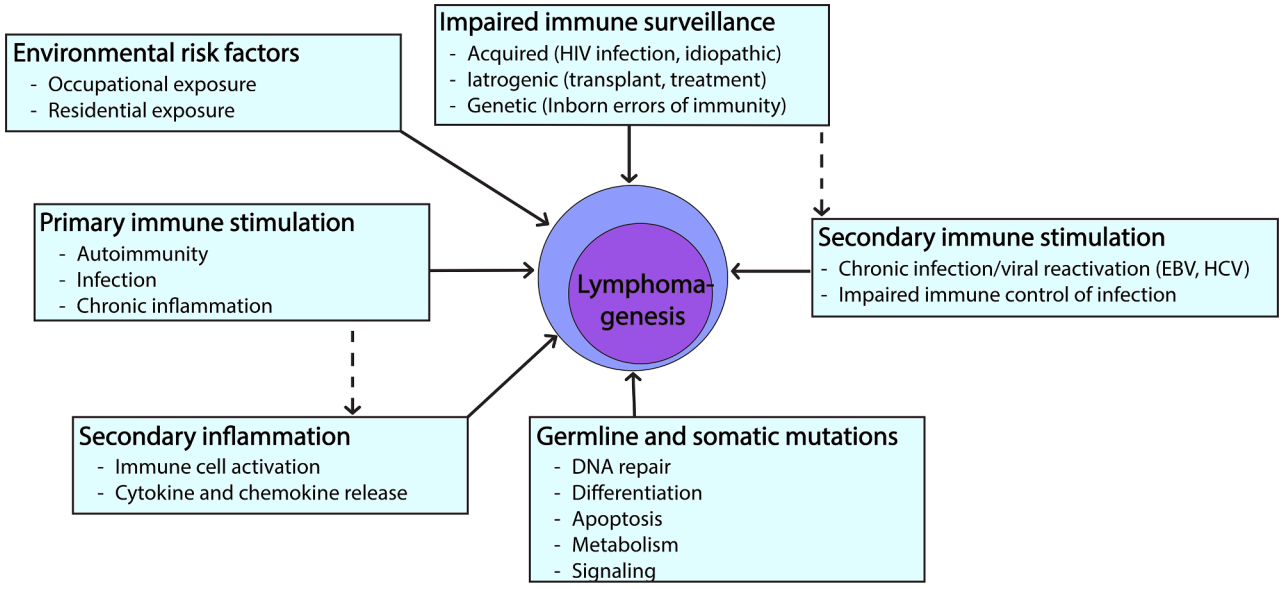

Fig. 2. Internal and external factors contributing to lymphomagenesis. EBV: Epstein-Barr virus, HCV: Hepatitis C virus. Figure adapted from Goldin and Landgren 2009 [101].

deficiency [CMMRD]), X-linked lymphoproliferative syndrome, Wiskott–Aldrich syndrome, common variable immunodeficiency (CVID), autoimmune lymphoproliferative syndrome (ALPS) and Bloom syndrome. [75] The relative risk of lymphoma in individual cancer-predisposing syndromes is rarely determined, perhaps partially because for many cancer predisposing syndromes the cancer diagnosis itself precedes the diagnosis of the underlying disorder. In this sense, calculation of a relative risk of cancer may be counterintuitive from a clinical perspective, while from a biological point of view the metric is highly relevant to understand the magnitude of the predisposition. Nonetheless, the available relative risk ratios for CVID (12.1 [6.03-21.6]) and AT (165 [4.19-922]) suggest lymphoma predisposition can be quite extreme, particularly since the overall prevalence of lymphoma in these patient groups is still relatively low compared to more overt cancer predisposition syndromes such as NBS and CMMRD (Table 1). [76] Interestingly, cancer-predisposing conditions can result in a more pronounced predisposition to leukemia or a more pronounced predisposition to lymphoma or may predispose to both. In most cases, the distinguishing factor is whether the predisposition is primarily lymphoid in origin or can extend to the myeloid compartment as well. In some conditions, there is an additional burden of solid tumors, often of a specific subtype, sometimes colocalizing with the site of lymphoma development.

While the exact NHL-predisposing mechanism in cancer-predisposing conditions remains largely elusive, several theories have been considered (Table 1). Generally, a combination of impaired cell maturation, chromosome instability and abnormalities in cell signaling creates an environment in which cells are primed for malignant transformation. This issue is further compounded by the presence of chronic infections, inflammation and weakened immune surveillance due to the inherent immune deficiency associated with the conditions. [75] ALPS is a particularly interesting example of a syndrome where impaired apoptotic regulation predisposes to both lymphoma development and autoimmunity. Infection of lymphocytes themselves by pathogens such as EBV can result in malignant transformation through several mechanisms. Initial insertion of the virus in the host genome already triggers initiation of the DNA damage response, resulting in genome instability, particularly in otherwise predisposed patients. Furthermore, increased production of radical oxygen species in response to chronic infection and inflammation may result in DNA damage and the expression of viral oncogenes may result in inhibition of tumor suppressor pathways or in chronic cellular activation. [40,59,77,78] Altogether, IEI syndromes create a unique stress on the immune system, impairing essential functions such as tumor surveillance, antigen receptor diversification, clonal expansion, immune response regulation and viral clearance. This stressed environment results in a multifactorial and context-dependent predisposition to cancer, including NHL subtypes.

1.6.2. Patients with autoimmune disorders

Consistent evidence linking particular forms of autoimmunity and an increased risk of lymphoma development has been reported for over three decades, especially for rheumatoid arthritis (RA), pSS, and systemic lupus erythematosus (SLE). [33,35,58,60,101,102,103,104] These associations are thought to arise from a combination of chronic immune stimulation, immunomodulatory treatment and shared underlying genetic or environmental factors resulting in immune dysregulation. [101] Processes specifically impaired in B-cells in systemic autoimmune diseases like RA, pSS and SLE include IG receptor editing,

Table 1
inborn errors of immunity associated with lymphoma predisposition. Lymphoma subtype distribution derived from Attarbaschi *et al.* 2016 and Seif *et al.* 2011. [75,79] Percentages of patients developing hematological malignancies are only provided for syndromes where more than 10 lymphoma cases were studied.

IEI condition (transmission mode, incidence)	Associated NHL subtype	Pathogenic mechanism	% of patients developing hematological malignancy	References
Constitutional mismatch repair deficiency (AR, <1:1,000,000)	T-LBL (81%), DLBCL (9.5%), BL (4.8%), BCP-LBL (4.8%)	Germline mutation in mismatch repair genes *MLH1, MSH2, MSH6* or *PMS2*. Accumulation of genetic mutations.	45/146 (30.8%)	[56,70,80, 81,82]
Ataxia telangiectasia (AR, 1:4000)	DLBCL (53%), BL (18.8%), B-NHL n. sp. (6%), ALCL (6%),BCP-LBL (6%), PTCL (3%), other (6%)	Germline mutation in the *ATM* gene, resulting in disruption of DNA double- and single-strand break repair and dysregulation of cell cycle checkpoints.	58/279 (20.8%)	[72,75,76, 83,84]
Nijmegen breakage syndrome (AR, 1:100,000)	DLBCL (30.8%), PTCL (23%), T-LBL (19%), B-NHL NOS (8%), BL (4%), other (11%)	Germline mutation of the *NBN* gene, disrupting DNA double- and single-strand break repair and regulation of cell cycle checkpoints through *ATM*.	136/226 (60.2%)	[57,85,86, 87,88,89]
X-linked lymphoproliferative syndrome (recessive, 1:1,000,000)	DLBCL (45.5%), BL (45.5%),B-NHL NOS (9%)	Germline mutations in *SH2D1A* resulting in impaired T-cell and NK-cell immunity, dysgamma-globulinaemia and increased susceptibility to primary EBV infection.	82/272 (30.1%)	[90,91]
Wiskott–Aldrich syndrome (X-linked recessive, ~1:250,000)	DLBCL, BL, ALCL	Germline mutation of *WAS* gene, resulting in extensive immune impairment across the innate and adaptive immune system. Impaired immunity against EBV contributes to lymphoma predisposition.	27/379 (7.1%)	[92,93]
Common variable immunodeficiency (unknown, ~1:50,000)	DLBCL, BL, MZL,ALCL, PTCL	A variety of mutations have been described in CVID patients, primarily associated with B-cell development, maturation and activation. Impaired immunity to EBV and *H.pylori* may contribute to lymphoma predisposition.	75/2212 (3.4%)	[94,95,96]
Autoimmune lymphoproliferative syndrome (AD, <1:1,000,000)	BL, FL, T-cell lymphoma (Primarily associated with HL.)	Heterozygous loss of function mutations in the *FAS* signaling pathway. Failure of apoptotic regulation to maintain lymphocyte homeostasis leads to both autoimmune phenomena and an increased risk of lymphoma development.	10/130 (7.7%)	[97,98,99]
Bloom syndrome (AR, 1:50.000)	B-NHL NOS	Loss of function mutation of the *BLM* gene. The *BLM* gene encodes a RecQ helicase essential in supporting chromosome stability. *BLM* mutations result in high levels of homologous chromosome recombination resulting in a high burden of somatic mutations.	77/145 (53%)	[66,79,100]

Abbreviations: IEI, inborn errors of immunity; AR, autosomal recessive; AD, autosomal dominant; NHL, non-Hodgkin lymphoma; T-LBL, T-cell lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; B-NHL NOS, B-cell non-Hodgkin lymphoma subtype not otherwise specified; BCP-LBL, B-cell lymphoblastic lymphoma; ALCL, anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma; MZL, marginal zone lymphoma; HL, Hodgkin's lymphoma; MLH1, MutL homolog 1; MSH2, mutS homolog 2; MSH6, mutS homolog 6; PMS2, PMS1 homolog 2, ATM, ataxia telangiectasia mutated; NBN, Nibrin; SH2D1A, SH2 domain containing 1A; WAS, WASP Actin Nucleation Promoting Factor; FAS, first apoptosis signal receptor; BLM, BLM RecQ like helicase.

peripheral selection, differentiation, and B-cell activation and proliferation. [102,105,106,107] These affected processes become clinically apparent in the form of hypergammaglobulinemia, circulating autoantibodies and immune complexes, altered B-cell subsets, ectopic lymphoid tissue formation, benign lymphoproliferation and an increased risk of B-NHL. [35,102,104,108] Nonetheless, conclusive evidence characterizing the putative link between autoimmunity and lymphoma is difficult to obtain, due to the rarity and heterogeneity of both conditions.

Furthermore, the relative risk of lymphoma development in distinct autoimmune disorders such as RA (3.9), SLE (7.4) and pSS (18.8) differs substantially, suggesting distinct underlying mechanisms[33] (Table 2). Generally, the associated lymphomas develop during the antigen activation or affinity maturation stages of B-cell differentiation, an observation supported by the SHM load of the rearranged IGHV gene in these lymphomas. [109] Particular subtypes of NHL have been associated with specific autoimmune diseases. [102] For pSS in particular, MALT lymphoma is the most common NHL subtype diagnosed, with a 28-fold increased risk compared to the general population. [58,102,110] Interestingly, the degree of high-grade vs low-grade lymphomas varies between the autoimmune disorders, with a high incidence of low-grade extranodal MZL in pSS in comparison to a dominance of high-grade DLBCL cases for SLE and RA (Table 2). [102] Other autoimmune diseases previously associated with lymphoma include Crohn's disease, celiac disease, sarcoidosis, systemic sclerosis, psoriasis and discoid lupus erythematosus. [101]

In pSS, the produced autoantibodies cover a wide spectrum, including antinuclear antibodies, anti-Ro/SSA, anti-La/SSB and RF. [111] Strikingly, parotid MALT lymphomas in pSS frequently produce antibodies with RF activity, suggesting autoreactivity is an early driver during lymphoma development. [45,46,47,112,113] These RF clones are characterized by the usage of either IGHV4-59/IGHJ2, IGHV4-59/IGHJ5, IGHV1-69/IGHJ4 or IGHV3-7/IGHJ3 in combination with an IGKV3-15 or IGKV3-20 IG light chain rearrangement. [45,46,47,113] Therefore, a putative model for parotid MALT lymphomagenesis in pSS is that RF clones organize in ectopic germinal center-like structures in a salivary gland, stimulating SHM, proliferation and accumulation of driver mutations. [114,115,116] In fact, such clonal populations with RF stereotypy are already detectable in lip biopsies taken years before MALT lymphoma diagnosis in pSS patients. [112] In RA, lymphoma development has been associated with persistent inflammatory activity and disease severity, with a 9-fold increased risk of NHL in patients with persistent inflammation and a 70-fold increased lymphoma risk among patients with severe longstanding RA. [117,118] The role of immunosuppressive therapy in lymphoma development is a much studied topic in RA, with inconclusive results. Because the vast majority of RA patients are treated with immunosuppressive therapy, it is difficult to discern between the effect of the disease itself and the effect of the treatment given on lymphoma development. The results of most recent studies suggest there is no strong association between immunosuppressive therapy received and NHL. [117,118,119,120,121,122,123] In SLE, the risk factors for lymphoma development are more unclear, as associations with disease activity and EBV status have been explored, but no conclusive associations have been found. An association has been described between the expression of a proliferating-inducing ligand (APRIL), a cytokine, in DLBCL lymphoma. Interestingly, APRIL was highly expressed in DLBCL cases associated with SLE, while the association was not found for RA. This finding hints at disease-specific underlying mechanisms. [124,125]

Altogether, a link between autoimmune disease and lymphoma has been robustly established, but much remains to be discovered on the underlying pathobiological mechanisms and clinical features. As a general concept, autoimmunity appears to precede and facilitate lymphoma development through (auto)antigen stimulation, inflammation and immune modulation, though in some cases both diseases may result from the same predisposing condition, e.g. BAFF overexpression. [33,126]

1.6.3. Iatrogenic immunosuppression: solid organ and hematopoietic stem cell transplant recipients

Other individuals at increased risk of lymphoma development include hematopoietic or solid organ transplant recipients. [20] Post-transplant lymphoproliferative disease (PTLD) is a heterogeneous group of lymphoid disorders arising after solid or hematopoietic stem cell transplantation. [39,63,155,156] The cell of origin for most PTLDs is the B-cell, although ~5 % is derived from T- or NK-cells. [157] While PTLD can range from indolent polyclonal lymphoproliferations to aggressive lymphomas, PTLD is generally considered a serious complication of organ transplantation, with historical mortality rates reaching as high as 70 %. [157] More recently, outcomes have improved significantly after introduction of novel therapeutic agents such as rituximab, resulting in a 3 year overall survival of 73 %. [158] The incidence of PTLD varies based on the transplanted organ and is thought to correlate with the degree of immunosuppressive therapy required, ranging from 1-5 % in kidney and liver transplant recipients to 8-25 % in heart, lung, intestinal and multi-organ transplant recipients (Table 3). [159] Estimated incidence rates for PTLD can vary considerably between studies and between centers. This is partly the result of the relatively low rate at which solid organ transplants are performed, resulting in a relatively small sample size, especially for single-center studies. Additionally, the observed differences in incidence rates may partly depend on differences in follow up time between the studies, the type of immunosuppressive treatment given and EBV-serostatus of the participants. [160]

Epstein–Barr virus (EBV) infection plays an essential role in the pathogenesis of most forms of PTLD and infection with EBV or reactivation of a latent infection following solid organ transplantation is a crucial risk factor for PTLD development. [155,161] Infection with EBV can occur prior or after transplantation through the normal transmission route in saliva or alternatively as a consequence of transplantation via a graft from an EBV-positive donor in an EBV-negative recipient. [160]

Table 2
Autoimmune disorders associated with lymphoma predisposition.

Autoimmune disorder	Associated NHL subtype	Pathogenic mechanism	Relative risk of lymphoma [95% CI]	References
Primary Sjögren's syndrome (pSS)	eMZL (75-80%), DLBCL (10-20%)	The leading theory is that autoreactive B-cells essential to the pathogenesis of pSS become malignant under the pressure of somatic hypermutation, proliferation and accumulation of driver mutations.	18.8 [9.5-37.3]	[33,127,128,129,130,131,132,133,134]
Systemic lupus erythematosus (SLE)	DLBCL(50-60%), MZL, MCL	Unclear, associations with disease activity and EBV status have been explored, but no conclusive associations have been found.	7.4 [3.3-17.0]	[124,125,135,136,137,138,139,140,141,142,143,144,145]
Rheumatoid arthritis (RA)	DLBCL (~67%)	Primarily EBV- NHL (83%), not associated with immunosuppressive therapy. Risk of lymphoma correlates with persistent inflammatory activity and disease severity.	3.9 [2.5-5.9]	[104,146,147,148,149,150,151,152,153,154]

Abbreviations: CI, confidence interval; eMZL, extranodal marginal zone lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma.

Table 3
Lymphoma predisposition in solid organ and hematopoietic stem cell transplant recipients.

Transplantation type	% of patients developing PTLD	References
Kidney transplant	Adult: 1–2.3% Pediatric: 1.2–10.1%	[189,190,191]
Heart transplant	Adult: 1–6.3% Pediatric: 6.4–19.5%	[189,192]
Liver transplant	Adult: 1–2.8% Pediatric: 4–15%	[193]
Intestinal transplant	Overall: 11-21%	[194,195,196]
Lung transplant	Adult: 4.2–10% Pediatric: 6.4–19.5%	[189,192]
Hematopoietic stem-cell transplant	Overall: 0.5-17%	[187,197,198,199,200]

Abbreviations: PTLD, post-transplant lymphoproliferative disorder.

Naturally, PTLD following EBV-reactivation is more common in adults, while children with PTLD are more likely to experience a primary EBV infection. Consequently, PTLD incidence is significantly increased in pediatric solid organ transplantation compared to adults (Table 3). [160] Additionally, the incidence of PTLD is increased among EBV-negative recipients, supporting the role for primary EBV infection in PTLD development. EBV-negative PTLD may constitute a distinct entity, representing around 30-45 % of all PTLD cases. EBV-negative PTLD is characterized by late development post-transplant compared to EBV-positive PTLD (62 months vs 11.5 months after solid organ transplantation). [157,162,163] Furthermore, EBV- PTLD is more frequently monomorphic than EBV+ PTLD (67 % vs. 42 %). [163] The incidence of EBV-negative PTLD increases with post-transplant follow up and is increased compared to lymphoma incidence rates in the healthy population, indicating other causal factors like the immunosuppressive treatment may be at play. [163]

Historically, reduction of immunosuppressive treatment has been the standard of care after diagnosis of early lesions and polymorphic PTLD, achieving response rates of 45 % for reduction of immunosuppressive treatment alone and 70 % when combined with surgical excision. [164] Whereas monomorphic PTLD can also respond to reduction of immunosuppressive treatment, remission rates are significantly improved by rituximab-based therapy. [158] Nonetheless, PTLD remains a serious complication after solid organ transplantation, prompting extensive study into potential biomarkers for PTLD development. [165] A key focus in these studies has been monitoring of molecular changes in B-cells upon EBV infection. Antibodies against latent and lytic cycle EBV proteins are used in combination with quantitative PCR of EBV DNA to accurately assess the dynamics of EBV infection. [165,166,167,168] Both host and EBV-derived miRNAs have been implicated in PTLD pathogenesis. [169,170,171,172,173] For EBV, the miRNAs of interest are derived from the BART and BHRF viral open reading frames, while the major host miRNAs of interest were miR-155, previously associated with B-cell lymphoma, and miR-194, a known regulator for IL-10. [165,169,170,171,172]

Levels of IL-10 in the serum have been shown to increase at the time of EBV+ PTLD diagnosis[174,175,176]. A correlation between IL-6 levels and PTLD development and progression has previously been described, though this result is not consistent across all studies. [174,175,176] Soluble CD30 (sCD30), a marker for B-cell activation, has previously been shown to be specifically elevated in transplant recipients who developed PTLD compared to healthy controls and transplant recipients who did not develop PTLD. [177] While the observed elevation of these cytokines and soluble molecules is interesting, none of the markers are particularly specific for PTLD development. Elevation of these markers has previously been described following a broad range of processes that could present as a potential confounder in organ transplant recipients, including viral infection, graft rejection, cancer, and autoimmunity. [178,179,180,181,182,183,184] As currently no biomarkers are actively used in the diagnosis or prognosis of PTLD, an acute need exists for an improved understanding of PTLD development in general and new methods of early detection of PTLD in particular. [165]

In comparison to PTLD following solid organ transplantation, PTLD in hematopoietic stem cell transplant (HSCT) recipients presents with both similarities and unique features. The similarities include a strong association with EBV and immunosuppressive therapy, while the unique features include the increased incidence of PTLD observed after T-cell depletion and use of a cord blood donor. In the event that HSCT was given as treatment for lymphoma, it can be difficult to distinguish between a relapse and PTLD. Thus, these cases are often excluded from consideration when evaluating the risk of PTLD after HSCT. Graft vs host disease (GVHD) is an additional complicating factor, as some studies have shown an increased risk of PTLD following GVHD, although it is difficult to assess whether this is the result of the GVHD itself or the immunosuppressive treatment used (anti-thymocyte globulin). [185,186,187,188] The relatively high mortality associated with GVHD following HSCT also complicates the assessment of the mortality associated with PTLD following HSCT. Altogether, it is clear that the risk of PTLD following both solid organ transplantation and HSCT is considerable.

1.6.4. Individuals suffering from chronic infections

One of the most important risk factors for lymphomagenesis is chronic inflammation. [201,202,203] Thus, most models for lymphomagenesis involve some form of antigenic or environmental trigger for inflammation, with the most common causal agents being the above discussed autoimmune reactions and chronic infections. [203] Here, some of the most well-characterized associations between chronic infection and lymphomagenesis will be further described. Several viral, bacterial and parasitic infections have been linked to lymphoma development. For viral infections, lymphomagenesis is usually mediated by one or more of the following mechanisms: chronic inflammation, suppression of the host immune system, introduction of mutations in the host genome during viral insertion and activation of viral oncogenes inducing host cell transformation. [204] The Epstein-Barr virus (EBV) was first discovered in 1964 in the endemic form of BL in sub-Saharan Africa. [37] The virus was shown to be capable of inducing oncogenic transformation of human leukocytes *in vitro* in 1968. [205] Nevertheless, EBV infection is mostly asymptomatic and EBV has been shown to be latently present in B-cells of most of the world's adult population. [206] This interesting contradiction shows that additional factors are required after EBV infection to induce malignant transformation of B-cells. In the following decades, three chromosomal translocations were discovered in BL between the *MYC* oncogene on chromosome 8 and one of the IGH, IGK or IGL gene loci on chromosome 14, 2 or 22 respectively. [207,208,209] These translocations effectively connect the *MYC* oncogene to the transcriptional regulators of an IG locus resulting in constitutive expression of Myc and proliferation of clonal B-cells. However, Myc overexpression also induces apoptosis, requiring a second independent event promoting B-cell survival before malignant transformation. [37,210,211,212] EBV infection provides one avenue towards this anti-apoptotic function through the expression of the viral protein EBNA1 (see below). [212] Superinfection with *Plasmodium falciparum* malaria can worsen this effect by inducing EBV-specific T-cell exhaustion, while simultaneously promoting B-cell activation and stimulating the EBV lytic cycle. [213,214,215] EBV has also been implicated in the pathogenesis of HL, PTLD, DLBCL, PCNSL and other

subtypes of lymphoma. [40,169,175,216,217,218,219]

To understand the ways that EBV might contribute to lymphomagenesis, mechanistic insight into the interactions between EBV and the host genome is essential. EBV-infected cells in latency III, the growth state, express the nuclear antigens EBNA 1, 2, 3A, 3B, 3C, and -LP, latent membrane proteins (LMPs 1, 2A, and 2B), viral miRNAs and the non-coding Epstein–Barr-encoded RNA (EBER), many of which are relevant to EBV-related lymphomagenesis. [37,220,221] In latency 0, memory B cells infected with EBV downregulate latent gene expression to avoid recognition by EBV-specific immune cells. [37] Upon division during normal memory B-cell homeostasis, the infected B-cells enter latency I by switching on EBNA1, as EBNA1 is required for the segregation of viral episomes to daughter cells. [222] The latency I state most closely resembles the state of EBV-positive BL. The latency II or default program of EBV results in expression of EBNA1, LMP1 and LMP2. [223] LMP1 is a functional homologue of CD40, driving NF-kB activation and downstream signaling pathways, while LMP2 mimics the presence of a functional B cell receptor. [224,225] Both LMP1 and LMP2 stimulate B-cell survival. EBNA1 is a viral protein enabling persistence of the EBV genome in the host nucleus through its carboxyterminal DNA-binding domain. [226] Recently, a particular EBNA1 binding site sequence in the human genome consisting of an 18-bp imperfect palindromic was identified on chromosome 11q23. [226] Repetitive sequences in the DNA have long been known to present challenges to genome stability, as replicative stress can lead to errors during DNA replication at these sites and result in the formation of aberrant structures before mitosis. Thus, particular repetitive stretches of DNA have been named “fragile sites” and their location correlates with recurrent breakpoints in cancer. [226] These breakpoints promote carcinogenesis through deletion of tumor suppressor genes, amplification of oncogenes or through the generation of fusion oncogenes through rearrangements initiated by breakage at the fragile site. Interestingly, the recently identified EBNA1 binding site is located relatively close to a well-known tumor suppressor gene, the *ATM* gene (6 Mb proximal) and a well-known proto-oncogene, the mixed lineage leukemia (*MLL)* gene (4 Mb distal). [226] Aberrations in *ATM* gene are associated with a variety of cancers, including lymphoma and leukemia. Alterations in the *MLL* gene are associated with 70 % of infant leukemias and 10 % of adult acute myeloid leukemias. EBNA1 binding was observed to induce breakage of chromosome 11, which could putatively result in the production of the variety of structural variants on chromosome 11 observed in EBV-associated cancers. [226]Table 4

Hepatitis C virus (HCV) is associated with B-NHL, especially MZL and DLBCL in addition to cirrhosis, hepatocellular carcinoma and liver failure. [77] In contrast to EBV, direct infection of B-cells by HCV has not been convincingly shown, though binding of HCV protein E2 to the CD81 receptor is capable of inducing SHM of the IG gene locus through AID activation. [228] Approximately half of individuals chronically infected with HCV have asymptomatic cryoglobulinemia, transforming to NHL in up to 5 % of patients, though progression rates vary significantly geographically. [253] In cryoglobulinemia, chronic HCV infection induces a benign monoclonal B-cell expansion producing an IgM antibody with RF activity. [77] Strikingly, HCV-associated nodal MZL utilizes IGHV1-69 combined with IGKV3-20 or IGKV3-15, reminiscent of the previously discussed RF stereotypy in pSS. [41,42,43,44,45,46,47] This similarity between a HCV-triggered aberrant B-cell proliferation and an autoimmune-based MALT lymphoma is fascinating and suggests that shared underlying mechanisms can be triggered by remarkably diverse processes.

Table 4
Chronic infections associated with NHL development.

Chronic infection	Associated NHL subtypes	Pathogenic mechanisms	Biomarkers for NHL development	References
Epstein-Barr Virus (EBV)	BL, PTLD, DLBCL, PCNSL, B-NHL n. sp.	Anti-apoptotic function through EBNA1, translocations involving *MYC,* super infection involving *Plasmodium Falciparum.* LMP1 is a functional homologue of CD40, while LMP2 mimics the presence of a functional B cell receptor, both stimulating B-cell survival. EBNA2 mimics the Notch1 pathway. Viral non-coding RNAs may also play a pathogenic role.	EBV and host miRNA’s, host protein markers	[37,205,211,214, 227]
Hepatitis C Virus (HCV)	MZL, DLBCL, B-NHL n. sp.	IG stereotypy, induction of SHM through AID through CD81.	Unknown	[41,43,44,228]
Human T cell lymphotropic virus type 1 (HTLV-1)	ATLL	Tax-1 activates the NF-κB signaling pathway, modulating DNA damage repair and stimulation of proliferation through cell cycle progression, immune surveillance suppression.	sCD30	[229,230,231,232, 233]
Human immunodeficiency virus (HIV)	BL, DLBCL, PCNSL, PEL	Co-infection with EBV, HHV-8, HCV. Expression of viral proteins influencing B-cell function and activation, e.g. aberrant expression of single-stranded DNA cytosine deaminase and *RAG1* through Tat. Suppression of T-cell functions impairs tumor surveillance and may promote expansion of (EBV- and/or HHV8-infected) B cells.	IL-10, IL-6, sCD27, sCD30, free light chain	[36,38,234,235, 236,237,238,239, 240,241]
Human Herpesvirus-8 (HHV-8)	BL, DLBCL	Co-infection with HIV. Gamma herpes virus with tropism for lymphocytes, endothelial cells, keratinocytes and marrow stromal cells. LNA1 inhibits *TP53* and *RB1*, impairing apoptosis of infected cells. v-Cyc is a viral homologue of cyclin D and binds to CDK6, resulting in resistance to CDK inhibitors, progression through the cell cycle, and uncontrolled cell division. vFLIP inhibits apoptosis by blocking Fas-mediated caspase activation and activating NF-κB.	Unknown	[235,242]
Helicobacter pylori	MALT lymphoma	Ectopic B-cell structures reminiscent of Peyer’s patches in the stomach lining, chronic inflammation through the CagA protein and the VacA toxin.	miR-155	[32,243,244,245, 246,247,248]
Borrelia burgdorferi	Primary cutaneous lymphoma	Unclear	Unknown	[249]
Chlamydophila psittaci	ocular adnexal MZL	Unclear	Unknown	[48,250]
Campylobacter jejuni	immunoproliferative small intestine lymphoma	Unclear	Unknown	[244,251]
Plasmodium Falciparum malaria	BL	Co-infection with EBV. Plasmodium infection may cause extended germinal center reactions, increasing the risk for B cell transformation in the germinal center.	Unknown	[213,252]

Abbreviations: DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; B-NHL n. sp., B-cell non-Hodgkin lymphoma subtype not specified; MZL, marginal zone lymphoma; PCNSL, primary central nervous system lymphoma; ATLL, adult T-cell leukemia/lymphoma; PEL, primary effusion lymphoma;

As the name indicates, human T cell lymphotropic virus type 1 (HTLV-1) predominantly infects T-cells and is endemic across parts of the Middle East, Asia, Africa, the Caribbean and Australia. [204] HTLV-1 transmission occurs through bodily fluids, primarily during breastfeeding and sexual contact. Of the estimated 10 million people infected with HTLV-1 across the world, most (>95 %) will remain asymptomatic, though the remainder (2-5 %) progress to an aggressive form of leukemia called adult T-cell leukemia/lymphoma (ATLL) after an extended latency period. [229] While HTLV-1 predominantly infects $CD4^+$ T-cells, other cell types including CD8+ T-cells, endothelial cells, B-lymphocytes, myeloid cells, and fibroblasts can be infected as well. [231,232] Several oncogenic mechanisms are at play during HTLV-1 infection. First, prolonged infection with HTLV-1 may induce chronic inflammation, production of reactive oxygen species and nitrogen radicals, damaging the cell membrane and DNA and inducing cellular stress. [254] Second, insertion of HTLV-1 oncogenes reduces tumor suppressor gene expression and induces mitosis. [255] Third, HTLV-1 infection promotes immune escape by inhibiting immune surveillance. [230,233,234,255,256]

Although many of the most severe symptoms of HIV infection can presently be managed through antiretroviral therapy (ART), HIV infection still carries an excess risk of lymphoma development. [234] HIV infection is particularly associated with BL, DLBCL, primary CNS lymphoma (PCNSL), HL, and primary effusion lymphoma (PEL). [38,59,257] Lymphoma in HIV-infected patients is often driven by co-infection with human-herpesvirus-8 (HHV-8) or EBV due to general loss of CD4 T-cells and/or the loss of EBV- or HHV-8 specific CD8 T-cells. [38,234,235] Coinfection with HBV or HCV virus also results in an increased risk of lymphoma. [36,236,237,238,239,240,241,258,259] HIV itself may directly contribute to lymphomagenesis as well, through expression of viral proteins (Tat, gp120, gp17 and CD40-L) influencing B-cell function and activation; Tat, for example, induces aberrant expression of single-stranded DNA cytosine deaminase and *RAG1*, resulting in DNA damage and translocation of the *MYC* gene to the IGH locus. [237,238,239] Biomarkers for lymphoma development in HIV patients include B-cell activation markers previously described in other lymphoma subtypes. HIV patients with elevated levels of free light chains (FLC) in the serum carry an eightfold increased risk of lymphoma. [240] IL-10 and IL-6 levels are also elevated prior to diagnosis of HIV-associated lymphoma. [241,258] In cohort studies, HIV viremia and depth of CD4 nadir increase lymphoma risk. [259] Even planned interruption of ART results in a 3.7-fold increased lymphoma risk. [259]

Alongside viral infections, several bacterial infections have also been shown to increase lymphoma risk, with *Helicobacter pylori (H. pylori)* being the best described. [243,244] *H. pylori* is specifically associated with the development of gastric MALT lymphoma, an indolent NHL subtype. [243] *H. pylori* has adapted for long term colonization of the human gastric mucosa. [243] The current model for lymphomagenesis is that *H. pylori* first attracts B- and T-lymphocytes to the stomach lining by inducing chronic inflammation. Next, the lymphocytes form an ectopic follicle and proliferate upon antigen stimulation. Finally, the activated B-cells progress to MALT lymphoma. [32,244,245,246,247,260] Eradication of *H. pylori* through antibiotics and proton-pump inhibitors results in long term remission of gastric MALT lymphoma in 60-90 % of patients. [248] Other bacteria associated with lymphoma risk include *Borrelia burgdorferi* with primary cutaneous lymphomas, *Chlamydophila psittaci* with ocular adnexal marginal zone lymphoma (OAMZL), and *Campylobacter jejuni* with immunoproliferative small intestine lymphoma. [249,250,251] Notably, the relationship between OAMZL and specific bacterial infections has only been shown in some geographical areas, primarily in Italy. Interestingly, 11 % of patients with OAMZL clones present with the same RF stereotypy previously observed in HCV-related lymphoma and in pSS-associated MALT lymphoma. [48] Additionally, BCR specificity for *Moraxella catarrhalis* and *Rothia mucilaginosa*-derived antigens has been shown for the nodular lymphocyte predominant form of Hodgkin lymphoma, suggesting an infectious driver of this type of lymphoma. [261,262]

In summary, a diverse set of pathogens have the capacity to influence lymphoma development, resulting in unique drivers for lymphomagenesis. Nonetheless, parallels in the form of chronic inflammation, targeted signaling pathways and antigenic stimulation can be observed across pathogens which are associated with lymphomagenesis. Interestingly, direct interaction between pathogens may further increase the risk of lymphomagenesis, as described for EBV and *Plasmodium falciparum* malaria and for HIV and gamma herpesviruses.

1.6.5. Interplay of exposome and aging with predisposing conditions

Environmental exposures have been epidemiologically and experimentally implicated in the risk of lymphoma development. [263] Notably, evidence supporting an association between different exposures and lymphoma is often difficult to establish, as the overall incidence of lymphoma is relatively low and the degree of exposure is difficult to quantify retrospectively. Nonetheless, several risk factors associated with lymphoma development have been reported. Studies by the International Agency for Research on Cancer (IARC) and International Lymphoma Epidemiology Consortium (InterLymph) have documented hundreds of exposures associated with lymphoma risk. [264,265] The influence of ionizing radiation on lymphoma risk in particular has been extensively investigated, although results remain inconclusive, with external comparisons typically showing lymphoma rates similar to the general population, while internal analyses (comparing rates for exposed workers *vs.* unexposed workers rather than *vs.* the general population) tend to suggest a dose-dependent excess lymphoma risk. [266] This discrepancy may be partially explained through the healthy worker effect, meaning the average worker tends to be healthier than the average member of the general population, resulting in an artificial underestimation of cancer risk when performing external comparisons. A higher incidence of CLL among those working or living on a farm has been consistently shown. [263,267,268] The increased incidence of CLL among farmers has been contributed to various potential causes, including exposure to pesticides and exposure to immunogenic particles or oncogenic viruses from livestock. [267,268] An epidemiological association between insecticides and lymphoma has been shown, but no direct toxicological evidence supporting this association exists. [268] An association between herbicides and lymphoma has not been consistently shown across studies, though some evidence exists supporting an increased relative risk of lymphoma for the highest exposure quartile among pesticide users exposed to glyphosate, one of the most heavily used herbicides worldwide. [34,269] Additionally, a recent meta-analysis showed a significantly increased relative risk of lymphoma after glyphosate exposure. [34] Other risk factors associated with lymphoma include smoking status, residential or occupational exposure to petroleum, exposure to benzene and occupational exposure to metals, occupational exposure to chlorinated solvents, and employment as hairdresser. [270,271,272,273,274,275] Smoking status was particularly associated with T-NHL subtypes and HL was associated with smoking status as well. An important mediator of the interaction between environmental exposures and lymphoma risk may be immune dysregulation. Specifically, exposure to pollutants, such as polychlorinated biphenyls (PCBs), may result in immunomodulation, thereby significantly altering outcomes following (viral) infection. As an example, expression levels of *miR-155*, a microRNA previously associated with B-cell lymphomas, were significantly increased *in vitro* in chicken embryo fibroblasts following exposure to PCBs and infection with the avian lymphoma-causing Gallid Herpes Virus 2, illustrating the potential for chemical induction of immunomodulation to affect the risk of lymphoma development. [276]

Factors protective for lymphoma risk have been reported as well, most notably a diagnosis with any atopic condition (including allergy, hay fever, asthma, or eczema) as well as recreational sun exposure. [263,277] The reduced lymphoma risk among those suffering from atopic conditions remains poorly understood, but may involve the extensive

modulation of immune function in these conditions. [263] Increased vitamin D production may explain the protective effect of recreational sun exposure, as vitamin D has been shown to have antiproliferative effects on lymphoma cell lines. [278] Previous studies into the relationship between vitamin D and lymphoma risk have however been inconclusive. [279,280]

The overall incidence of lymphoma is strongly increased among the elderly, resulting in a median age for non-Hodgkin lymphoma patients of 67 years. In many international prognostic scoring systems, age over 60 remains an adverse risk factor for overall survival and treatment response. [281] Interestingly, the dominance of particular lymphoma subtypes also changes between age groups, where children present with a dominance of Hodgkin and Burkitt lymphoma, adults over 40 present with predominantly DLBCL and follicular lymphoma. Aging has significant impact on a diverse set of molecular pathways, affecting many essential processes in the body. The hallmarks of aging include: loss of proteostasis, disabled macro-autophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, chronic inflammation, genomic instability, epigenetic reprogramming, altered intercellular communication, dysbiosis, telomere attrition and stem cell exhaustion. [282] Interestingly, several of these hallmarks overlap with the hallmarks of cancer, namely: genomic instability, epigenetic alterations, chronic inflammation, and dysbiosis. [283] Strikingly, chronic inflammation and genomic instability were common factors shared by many of the lymphoma predisposition syndromes previously discussed in this review, revealing putative mechanistic similarities mediating lymphoma risk between the natural aging process and lymphoma predisposition syndromes. When considering the modulating influence of exposure to foreign agents, an older individual will also have accumulated a significant exposure to various pollutants during their lifetime and slow acting agents will have had more time to have an impact, compared to a younger individual with a similar yearly exposure.

Additionally, aging is known to lead to clonal restriction of the hematopoietic stem cell population, resulting in an increased risk for the development of hematological malignancies. These clonal expansions are characterized as clonal hematopoiesis of indeterminate potential (CHIP), with an incidence of around 10 % among individuals aged 70 to 80. [284,285,286] CHIP is similar to monoclonal gammopathy of undetermined significance (MGUS) for multiple myeloma and monoclonal B-lymphocytosis (MBL) for CLL in the sense that these conditions themselves do not necessarily carry significant morbidity, but like CHIP are associated with a 1 %-2 % rate of transformation into malignancy. [287] Importantly, the putative driver mutations observed in most CHIP cases overlap primarily with those observed in myelodysplastic syndrome, myeloproliferative neoplasms and acute myeloid leukemia. A potential link between clonal restriction of the hematopoietic stem cell population and the development of lymphoid neoplasms is controversial and further study is required to clarify whether such a relationship exists at all.

Thus, lymphoma predisposition is not only the product of a genetic predisposition or dysregulation of the immune system, but should be studied in the context of the environment that the individual has been exposed to during their lifetime.

2. Conclusion

Lymphoma predisposition is a multifaceted phenomenon that can manifest in many different ways (Fig. 3). The increased risk of lymphoma development is the result of a series of changes to fundamental biological processes through an internal or external factor. The fact that particular predisposing conditions tend to result in particular NHL subtypes suggests an unexplored relationship between the specific biological defect and a key driver for that NHL subtype, suggesting the insights gained from lymphoma-predisposing conditions may yield crucial insights into lymphoma development in patients without an overt predisposition. Common features of conditions predisposing to lymphoma include: persistent inflammation, impaired tumor surveillance and viral clearance, recurrent DNA damage or malfunctioning

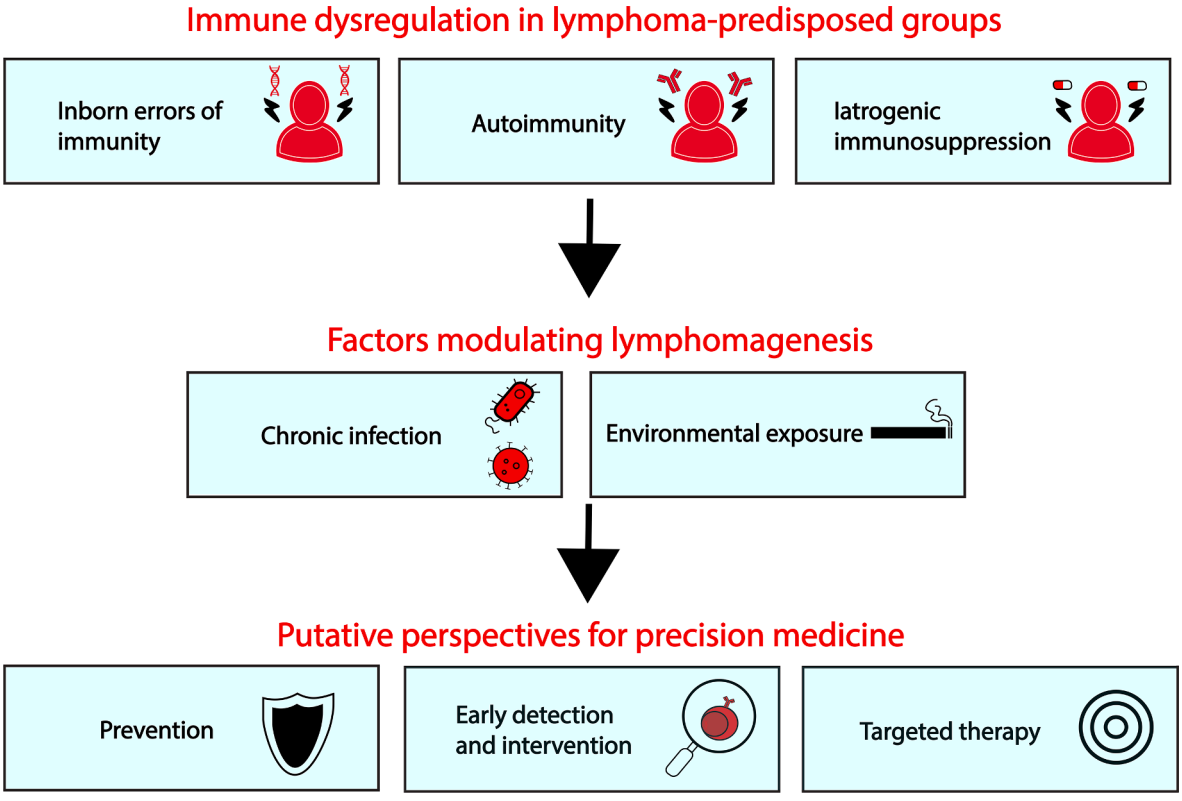

Fig. 3. Perspectives for precision medicine in lymphoma-predisposed groups.

DNA repair, and dysregulation of fundamental cellular processes such as activation, proliferation and apoptosis. Our understanding of lymphoma predisposition has evolved considerably over the last decades and has accelerated with the advent of novel technologies. It has become clear that there are many more forms of lymphoma predisposition than previously anticipated and undoubtedly others remain to be discovered. These novel insights clearly illustrate the potential for prevention of lymphoma development and early detection and intervention upon lymphoma development. Improved understanding of the underlying mechanisms for the earliest stages of lymphoma development will be essential to reduce the burden of lymphoma through the development of tailored treatment protocols.

Declaration of Competing Interest

None.

Acknowledgments

The authors gratefully acknowledge the members of the LOGIC consortium for fruitful discussion on the topic of immune dysregulation and lymphoma.

Funding disclosure statement

TRANSCAN / Dutch Cancer Society grant (179; NOVEL consortium).

References

[1] T. Boehm, J.B. Swann, Origin and evolution of adaptive immunity, Annu. Rev. Anim. Biosci. 2 (2014) 259–283.
[2] R. Alaggio, et al., The 5th edition of the World Health Organization classification of haematolymphoid tumors: lymphoid neoplasms, Leukemia 36 (2022) 1720–1748.
[3] S.H. Swerdlow, et al., The 2016 revision of the World Health Organization classification of lymphoid neoplasms, Blood 127 (2016) 2375–2390.
[4] E. Campo, et al., The international consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee, Blood 140 (2022) 1229–1253.
[5] K.R. Shankland, J.O. Armitage, B.W. Hancock, Non-hodgkin lymphoma, Lancet 380 (2012) 848–857.
[6] E.N. Mugnaini, N. Ghosh, Lymphoma, Prim. Care 43 (2016) 661–675.
[7] J. Ferlay, et al., Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018, Eur. J. Cancer 103 (2018) 356–387.
[8] B. Coiffier, et al., Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte, Blood 116 (2010) 2040–2045.
[9] C. Sarkozy, et al., Cause of death in follicular lymphoma in the first decade of the rituximab era: a pooled analysis of French and US cohorts, J. Clin. Oncol. 37 (2019) 144–152.
[10] S. Ma, et al., Efficacy of venetoclax plus rituximab for relapsed CLL: 5-year follow-up of continuous or limited- duration therapy, Blood 138 (2021) 836–846.
[11] J.P. Alderuccio, J.A. Florindez, I.M. Reis, W. Zhao, I.S. Lossos, Treatments and outcomes in Stage I extranodal marginal zone lymphoma in the United States, Cancers 13 (8) (2021) 1803.
[12] J.R. Cerhan, S.L. Slager, Familial predisposition and genetic risk factors for lymphoma, Blood 126 (2015) 2265–2273.
[13] L.R. Goldin, M. Bjorkholm, S.Y. Kristinsson, I. Turesson, O. Landgren, Elevated risk of chronic lymphocytic leukemia and other indolent non-Hodgkin's lymphomas among relatives of patients with chronic lymphocytic leukemia, Haematologica 94 (2009) 647–653.
[14] L.R. Goldin, M. Bjorkholm, S.Y. Kristinsson, I. Turesson, O. Landgren, Highly increased familial risks for specific lymphoma subtypes, Br. J. Haematol. 146 (2009) 91–94.
[15] L.R. Goldin, et al., Familial aggregation and heterogeneity of non-Hodgkin lymphoma in population-based samples, Cancer Epidemiol. Biomark. Prev. 14 (2005) 2402–2406.
[16] P.J. Hengeveld, M.D. Levin, P.M. Kolijn, A.W. Langerak, Reading the B-cell receptor immunome in chronic lymphocytic leukemia: revelations and applications, Exp. Hematol. 93 (2021) 14–24.
[17] D.B. Roth, N.L. Craig, VDJ recombination: a transposase goes to work, Cell 94 (1998) 411–414.
[18] K. Hiom, M. Melek, M. Gellert, DNA transposition by the RAG1 and RAG2 proteins: a possible source of oncogenic translocations, Cell 94 (1998) 463–470.
[19] D.F. Robbiani, M.C. Nussenzweig, Chromosome translocation, B cell lymphoma, and activation-induced cytidine deaminase, Annu. Rev. Pathol. 8 (2013) 79–103.
[20] R. Kuppers, Mechanisms of B-cell lymphoma pathogenesis, Nat. Rev. Cancer 5 (2005) 251–262.
[21] H. Ohno, Pathogenetic role of BCL6 translocation in B-cell non-Hodgkin's lymphoma, Histol. Histopathol. 19 (2004) 637–650.
[22] C.M. Rudin, C.B. Thompson, B-cell development and maturation, Semin. Oncol. 25 (1998) 435–446.
[23] J.M. Di Noia, M.S. Neuberger, Molecular mechanisms of antibody somatic hypermutation, Annu. Rev. Biochem. 76 (2007) 1–22.
[24] X. Chi, Y. Li, X. Qiu, V(D)J recombination, somatic hypermutation and class switch recombination of immunoglobulins: mechanism and regulation, Immunology 160 (2020) 233–247.
[25] S. Husby, K. Gronbaek, Mature lymphoid malignancies: origin, stem cells, and chronicity, Blood Adv. 1 (2017) 2444–2455.
[26] Y. Kikushige, T. Miyamoto, Hematopoietic stem cell aging and chronic lymphocytic leukemia pathogenesis, Int. J. Hematol. 100 (2014) 335–340.
[27] J.A. Martinez-Climent, L. Fontan, R.D. Gascoyne, R. Siebert, F Prosper, Lymphoma stem cells: enough evidence to support their existence? Haematologica 95 (2010) 293–302.
[28] C.F. Skibola, J.D. Curry, A. Nieters, Genetic susceptibility to lymphoma, Haematologica 92 (2007) 960–969.
[29] M. Similuk, V.K. Rao, J. Churpek, M. Lenardo, Predispositions to lymphoma: a practical review for genetic counselors, J. Genet. Couns. 25 (2016) 1157–1170.
[30] I. Chua, I. Quinti, B. Grimbacher, Lymphoma in common variable immunodeficiency: interplay between immune dysregulation, infection and genetics, Curr. Opin. Hematol. 15 (2008) 368–374.
[31] K. Ekstrom Smedby, et al., Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium, Blood 111 (2008) 4029–4038.
[32] E. Zucca, et al., Molecular analysis of the progression from Helicobacter pylori-associated chronic gastritis to mucosa-associated lymphoid-tissue lymphoma of the stomach, N. Engl. J. Med. 338 (1998) 804–810.
[33] E. Zintzaras, M. Voulgarelis, H.M. Moutsopoulos, The risk of lymphoma development in autoimmune diseases: a meta-analysis, Arch. Intern. Med. 165 (2005) 2337–2344.
[34] L. Zhang, I. Rana, R.M. Shaffer, E. Taioli, L. Sheppard, Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: a meta-analysis and supporting evidence, Mutat. Res. Rev. Mutat. 781 (2019) 186–206.
[35] S. Yadlapati, P. Efthimiou, Autoimmune/inflammatory arthritis associated lymphomas: who is at risk? Biomed. Res. Int. 2016 (2016), 8631061.
[36] Q. Wang, et al., Chronic Hepatitis B and C virus infection and risk for non-hodgkin lymphoma in HIV-infected patients: a cohort study, Ann. Intern. Med. 166 (2017) 9–17.
[37] M. Vockerodt, et al., The Epstein-Barr virus and the pathogenesis of lymphoma, J. Pathol. 235 (2015) 312–322.
[38] R. Vangipuram, S.K. Tyring, AIDS-associated malignancies, Cancer Treat. Res. 177 (2019) 1–21.
[39] A.K. Singavi, A.M. Harrington, T.S. Fenske, Post-transplant lymphoproliferative disorders, Cancer Treat. Res. 165 (2015) 305–327.
[40] C. Shannon-Lowe, A.B. Rickinson, A.I. Bell, Epstein-Barr virus-associated lymphomas, Philos. Trans. R. Soc. Lond. B Biol. Sci. (2017) 19;372(1732): 20160271.
[41] M. Carbonari, et al., Hepatitis C virus drives the unconstrained monoclonal expansion of VH1-69-expressing memory B cells in type II cryoglobulinemia: a model of infection-driven lymphomagenesis, J. Immunol. 174 (2005) 6532–6539.
[42] E.D. Charles, et al., Clonal expansion of immunoglobulin M+CD27+ B cells in HCV-associated mixed cryoglobulinemia, Blood 111 (2008) 1344–1356.
[43] R. Marasca, et al., Immunoglobulin gene mutations and frequent use of VH1-69 and VH4-34 segments in hepatitis C virus-positive and hepatitis C virus-negative nodal marginal zone B-cell lymphoma, Am. J. Pathol. 159 (2001) 253–261.
[44] V. De Re, et al., Pre-malignant and malignant lymphoproliferations in an HCV-infected type II mixed cryoglobulinemic patient are sequential phases of an antigen-driven pathological process, Int. J. Cancer 87 (2000) 211–216.
[45] R.J. Bende, et al., Among B cell non-Hodgkin's lymphomas, MALT lymphomas express a unique antibody repertoire with frequent rheumatoid factor reactivity, J. Exp. Med. 201 (2005) 1229–1241.
[46] R.J. Bende, et al., Salivary gland mucosa-associated lymphoid tissue-type lymphoma from Sjogren's syndrome patients in the majority express rheumatoid factors affinity-selected for IgG, Arthritis Rheumatol. 72 (2020) 1330–1340.
[47] A. Visser, et al., Repertoire analysis of B-cells located in striated ducts of salivary glands of patients with Sjogren's syndrome, Front. Immunol. 11 (2020) 1486.
[48] A. Dagklis, et al., Immunoglobulin gene repertoire in ocular adnexal lymphomas: hints on the nature of the antigenic stimulation, Leukemia 26 (2012) 814–821.
[49] S. Jaramillo, et al., Prognostic impact of prevalent chronic lymphocytic leukemia stereotyped subsets: analysis within prospective clinical trials of the German CLL Study Group (GCLLSG), Haematologica 105 (2020) 2598–2607.
[50] K. Gemenetzi, et al., Higher-order immunoglobulin repertoire restrictions in CLL: the illustrative case of stereotyped subsets 2 and 169, Blood 137 (2021) 1895–1904.
[51] A. Agathangelidis, F. Psomopoulos, K. Stamatopoulos, B Stereotyped, Cell receptor immunoglobulins in B cell lymphomas, Methods Mol. Biol. 1956 (2019) 139–155.
[52] A. Agathangelidis, et al., Higher-order connections between stereotyped subsets: implications for improved patient classification in CLL, Blood 137 (2021) 1365–1376.

[53] A.S. Bansal, J. Bruce, P.G. Hogan, P. Prichard, E.E. Powell, Serum soluble CD23 but not IL8, IL10, GM-CSF, or IFN-gamma is elevated in patients with hepatitis C infection, Clin. Immunol. Immunopathol. 84 (1997) 139–144.
[54] G. Fattovich, et al., Serum levels of soluble CD30 in chronic hepatitis B virus infection, Clin. Exp. Immunol. 103 (1996) 105–110.
[55] M. al-Janadi, A. Wabel, S. Raziuddin, Soluble CD23 and interleukin-4 levels in autoimmune chronic active hepatitis and systemic lupus erythematosus, Clin. Immunol. Immunopathol. 71 (1994) 33–37.
[56] N. Lavoine, et al., Constitutional mismatch repair deficiency syndrome: clinical description in a French cohort, J. Med. Genet. 52 (2015) 770–778.
[57] B. Wolska-Kusnierz, et al., Nijmegen breakage syndrome: clinical and immunological features, long-term outcome and treatment options—a retrospective analysis, J. Clin. Immunol. 35 (2015) 538–549.
[58] A. Alunno, M.C. Leone, R. Giacomelli, R. Gerli, F. Carubbi, Lymphoma and lymphomagenesis in primary Sjogren's syndrome, Front. Med. 5 (2018) 102.
[59] A. Krishnan, J.A. Zaia, HIV-associated non-Hodgkin lymphoma: viral origins and therapeutic options, Hematol. Am. Soc. Hematol. Educ. Progr. 2014 (2014) 584–589.
[60] E. Baecklund, K.E. Smedby, L.A. Sutton, J. Askling, R Rosenquist, Lymphoma development in patients with autoimmune and inflammatory disorders—what are the driving forces? Semin. Cancer Biol. 24 (2014) 61–70.
[61] L. Deng, et al., Hepatitis B virus-associated diffuse large B-cell lymphoma: unique clinical features, poor outcome, and hepatitis B surface antigen-driven origin, Oncotarget 6 (2015) 25061–25073.
[62] K. Hemminki, X. Liu, J. Ji, A. Forsti, Origin of B-cell neoplasms in autoimmune disease, PLoS One 11 (2016), e0158360.
[63] D. Jagadeesh, B.A. Woda, J. Draper, A.M. Evens, Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations, Curr. Treat. Options Oncol. 13 (2012) 122–136.
[64] U. Kopylov, et al., Risk of lymphoma, colorectal and skin cancer in patients with IBD treated with immunomodulators and biologics: a Quebec claims database study, Inflamm. Bowel Dis. 21 (2015) 1847–1853.
[65] D.S. Kotlyar, et al., Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis, Clin. Gastroenterol. Hepatol. 13 (5) (2015) 847–858.
[66] X. Ye, et al., Genomic characterization of lymphomas in patients with inborn errors of immunity, Blood Adv. 6 (18) (2022) 5403–5414.
[67] L. Amaya-Uribe, M. Rojas, G. Azizi, J.M. Anaya, M.E. Gershwin, Primary immunodeficiency and autoimmunity: a comprehensive review, J. Autoimmun. 99 (2019) 52–72.
[68] H. Chapel, R. Geha, F. Rosen, Primary immunodeficiency diseases: an update, Clin. Exp. Immunol. 132 (2003) 9–15.
[69] B.M. Jonkman-Berk, et al., Primary immunodeficiencies in the Netherlands: national patient data demonstrate the increased risk of malignancy, Clin. Immunol. 156 (2015) 154–162.
[70] M.A. Martin-Mateos, M. Piquer Gibert, Primary immunodeficiencies and B-cell lymphomas, Bol. Med. Hosp. Infant. Mex. 73 (2016) 18–25.
[71] N. Romberg, et al., CVID-associated TACI mutations affect autoreactive B cell selection and activation, J. Clin. Investig. 123 (2013) 4283–4293.
[72] F. Suarez, et al., Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies, J. Clin. Oncol. 33 (2015) 202–208.
[73] N. Raje, et al., Utility of next generation sequencing in clinical primary immunodeficiencies, Curr. Allergy Asthma Rep. 14 (2014) 468.
[74] M. Piquer Gibert, et al., Non-Hodgkin lymphoma in pediatric patients with common variable immunodeficiency, Eur. J. Pediatr. 174 (2015) 1069–1076.
[75] A. Attarbaschi, et al., Non-Hodgkin lymphoma and pre-existing conditions: spectrum, clinical characteristics and outcome in 213 children and adolescents, Haematologica 101 (2016) 1581–1591.
[76] C.M. Vajdic, et al., Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency? Blood 116 (2010) 1228–1234.
[77] L. Couronne, et al., From hepatitis C virus infection to B-cell lymphoma, Ann. Oncol. 29 (2018) 92–100.
[78] M. Greaves, M. Muschen, Infection and the perils of B-cell activation, Cancer Discov. 5 (2015) 1244–1246.
[79] A.E. Seif, Pediatric leukemia predisposition syndromes: clues to understanding leukemogenesis, Cancer Genet. 204 (2011) 227–244.
[80] K. Wimmer, et al., Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD), J. Med. Genet. 51 (2014) 355–365.
[81] E. Kroeze, et al., High prevalence of constitutional mismatch repair deficiency in a pediatric T-cell lymphoblastic lymphoma cohort, Hemasphere 6 (2022) e668.
[82] C. Durno, et al., Survival benefit for individuals with constitutional mismatch repair deficiency undergoing surveillance, J. Clin. Oncol. 39 (2021) 2779. +.
[83] A. Reiman, et al., Lymphoid tumors and breast cancer in ataxia telangiectasia; substantial protective effect of residual ATM kinase activity against childhood tumors, Br. J. Cancer 105 (2011) 586–591.
[84] R. Micol, et al., Morbidity and mortality from ataxia-telangiectasia are associated with ATM genotype, J. Allergy Clin. Immunol. 128 (2011) 382–389, e381.
[85] B. Wolska-Kusnierz, et al., Hematopoietic stem cell transplantation positively affects the natural history of cancer in nijmegen breakage syndrome, Clin. Cancer Res. 27 (2021) 575–584.
[86] S.O. Sharapova, et al., Geographical distribution, incidence, malignancies, and outcome of 136 eastern Slavic patients with Nijmegen breakage syndrome and NBN founder variant c.657_661del5, Front. Immunol. 11 (2021), 602482.
[87] M. Digweed, K. Sperling, Nijmegen breakage syndrome: clinical manifestation of defective response to DNA double-strand breaks, DNA Repair 3 (2004) 1207–1217.
[88] B. Dembowska-Baginska, et al., Non-Hodgkin lymphoma (NHL) in children with Nijmegen Breakage syndrome (NBS), Pediatr. Blood Cancer 52 (2009) 186–190.
[89] K.H. Chrzanowska, H. Gregorek, B. Dembowska-Baginska, M.A. Kalina, M. Digweed, Nijmegen breakage syndrome (NBS), Orphanet J. Rare Dis. 7 (2012) 13.
[90] N. Rezaei, E. Mahmoudi, A. Aghamohammadi, R. Das, K.E. Nichols, X-linked lymphoproliferative syndrome: a genetic condition typified by the triad of infection, immunodeficiency and lymphoma, Br. J. Haematol. 152 (2011) 13–30.
[91] T.A. Seemayer, et al., X-linked lymphoproliferative disease: twenty-five years after the discovery, Pediatr. Res. 38 (1995) 471–478.
[92] F. Candotti, Clinical manifestations and pathophysiological mechanisms of the Wiskott–Aldrich syndrome, J. Clin. Immunol. 38 (2018) 13–27.
[93] A. Shcherbina, F. Candotti, F.S. Rosen, E Remold-O'Donnell, High incidence of lymphomas in a subgroup of Wiskott–Aldrich syndrome patients, Br. J. Haematol. 121 (2003) 529–530.
[94] R. Yazdani, et al., Common variable immunodeficiency: epidemiology, pathogenesis, clinical manifestations, diagnosis, classification, and management, J. Investig. Allergol. Clin. Immunol. 30 (2020) 14–34.
[95] B. Gathmann, et al., Clinical picture and treatment of 2212 patients with common variable immunodeficiency, J. Allergy Clin. Immunol. 134 (2014) 116–126.
[96] E.S. Resnick, E.L. Moshier, J.H. Godbold, C. Cunningham-Rundles, Morbidity and mortality in common variable immune deficiency over 4 decades, Blood 119 (2012) 1650–1657.
[97] S. Shah, E. Wu, V.K. Rao, T.K. Tarrant, Autoimmune lymphoproliferative syndrome: an update and review of the literature, Curr. Allergy Asthma Rep. 14 (2014) 462.
[98] D.R. Matson, D.T. Yang, Autoimmune lymphoproliferative syndrome: an overview, Arch. Pathol. Lab. Med. 144 (2020) 245–251.
[99] S.E. Straus, et al., The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis, Blood 98 (2001) 194–200.
[100] C. Cunniff, et al., Health supervision for people with bloom syndrome, Am. J. Med. Genet. A 176 (2018) 1872–1881.
[101] L.R. Goldin, O. Landgren, Autoimmunity and lymphomagenesis, Int. J. Cancer 124 (2009) 1497–1502.
[102] A. Hansen, P.E. Lipsky, T. Dorner, B-cell lymphoproliferation in chronic inflammatory rheumatic diseases, Nat. Clin. Pract. Rheumatol. 3 (2007) 561–569.
[103] A. Klein, A. Polliack, A. Gafter-Gvili, Systemic lupus erythematosus and lymphoma: incidence, pathogenesis and biology, Leuk. Res. 75 (2018) 45–49.
[104] K. Hellgren, et al., Rheumatoid arthritis and risk of malignant lymphoma: is the risk still increased? Arthritis Rheumatol. 69 (2017) 700–708.
[105] P. Youinou, et al., B lymphocytes on the front line of autoimmunity, Autoimmun. Rev. 5 (2006) 215–221.
[106] P.E. Lipsky, Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity, Nat. Immunol. 2 (2001) 764–766.
[107] T. Dorner, P.E. Lipsky, Abnormalities of B cell phenotype, immunoglobulin gene expression and the emergence of autoimmunity in Sjogren's syndrome, Arthritis Res. 4 (2002) 360–371.
[108] L.K. Mercer, et al., Spectrum of lymphomas across different drug treatment groups in rheumatoid arthritis: a European registries collaborative project, Ann. Rheum. Dis. 76 (2017) 2025–2030.
[109] B.T. Hennessy, E.O. Hanrahan, P.A. Daly, Non-Hodgkin lymphoma: an update, Lancet Oncol. 5 (2004) 341–353.
[110] P. Brito-Zeron, et al., Characterization and risk estimate of cancer in patients with primary Sjogren syndrome, J. Hematol. Oncol. 10 (2017) 90.
[111] E. Martin-Nares, G. Hernandez-Molina, Novel autoantibodies in Sjogren's syndrome: a comprehensive review, Autoimmun. Rev. 18 (2019) 192–198.
[112] M.G.A. Broeren, et al., Proteogenomic analysis of the autoreactive B cell repertoire in blood and tissues of patients with Sjogren's syndrome, Ann. Rheum. Dis. 81 (2022) 644–652.
[113] W.J.J. Falkenburg, H.J. von Richthofen, T. Rispens, On the origin of rheumatoid factors: insights from analyses of variable region sequences, Semin. Arthritis Rheum. 48 (2019) 603–610.
[114] M. Singh, et al., Lymphoma driver mutations in the pathogenic evolution of an iconic human autoantibody, Cell 180 (2020) 878–894, e819.
[115] S. Salomonsson, et al., Cellular basis of ectopic germinal center formation and autoantibody production in the target organ of patients with Sjogren's syndrome, Arthritis Rheum. 48 (2003) 3187–3201.
[116] E. Theander, et al., Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjogren's syndrome, Ann. Rheum. Dis. 70 (2011) 1363–1368.
[117] F. Wolfe, K. Michaud, Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients, Arthritis Rheum. 50 (2004) 1740–1751.
[118] E. Baecklund, et al., Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis, Arthritis Rheum. 54 (2006) 692–701.
[119] A. Ichikawa, et al., Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: histology, Epstein-Barr virus, and clonality are important predictors of disease progression and regression, Eur. J. Haematol. 91 (2013) 20–28.

[120] Y. Hoshida, et al., Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication, J. Rheumatol. 34 (2007) 322–331.
[121] X. Mariette, et al., Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France, Blood 99 (2002) 3909–3915.
[122] M.A. Lopez-Olivo, et al., Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis, JAMA 308 (2012) 898–908.
[123] Y. Chen, J. Sun, Y. Yang, Y. Huang, G. Liu, Malignancy risk of anti-tumor necrosis factor alpha blockers: an overview of systematic reviews and meta-analyses, Clin. Rheumatol. 35 (2016) 1–18.
[124] B. Lofstrom, C. Backlin, T. Pettersson, I.E. Lundberg, E. Baecklund, Expression of APRIL in diffuse large B cell lymphomas from patients with systemic lupus erythematosus and rheumatoid arthritis, J. Rheumatol. 38 (2011) 1891–1897.
[125] S. Bernatsky, et al., Cancer risk in systemic lupus: an updated international multi-centre cohort study, J. Autoimmun. 42 (2013) 130–135.
[126] J. Groom, et al., Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjogren's syndrome, J. Clin. Investig. 109 (2002) 59–68.
[127] S.S. Kassan, et al., Increased risk of lymphoma in sicca syndrome, Ann. Intern. Med. 89 (1978) 888–892.
[128] M. Kauppi, E. Pukkala, H. Isomaki, Elevated incidence of hematologic malignancies in patients with Sjogren's syndrome compared with patients with rheumatoid arthritis (Finland), Cancer Causes Control 8 (1997) 201–204.
[129] B.K. Davidson, C.A. Kelly, I.D. Griffiths, Primary Sjogren's syndrome in the North East of England: a long-term follow-up study, Rheumatology 38 (1999) 245–253.
[130] G. Valesini, et al., Differential risk of non-Hodgkin's lymphoma in Italian patients with primary Sjogren's syndrome, J. Rheumatol. 24 (1997) 2376–2380.
[131] M. Pertovaara, E. Pukkala, P. Laippala, A. Miettinen, A. Pasternack, A longitudinal cohort study of Finnish patients with primary Sjogren's syndrome: clinical, immunological, and epidemiological aspects, Ann. Rheum. Dis. 60 (2001) 467–472.
[132] Y. Liang, Z. Yang, B. Qin, R. Zhong, Primary Sjogren's syndrome and malignancy risk: a systematic review and meta-analysis, Ann. Rheum. Dis. 73 (2014) 1151–1156.
[133] E. Zucca, et al., Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, Blood 101 (2003) 2489–2495.
[134] B. Royer, et al., Lymphomas in patients with Sjogren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses, Blood 90 (1997) 766–775.
[135] A.E. Clarke, et al., Risk of malignancy in patients with systemic lupus erythematosus: systematic review and meta-analysis, Semin. Arthritis Rheum. 51 (2021) 1230–1241.
[136] S. Azrielant, et al., Correlation between systemic lupus erythematosus and malignancies: a cross-sectional population-based study, Immunol. Res. 65 (2017) 464–469.
[137] L. Mellemkjaer, et al., Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus, Arthritis Rheum. 40 (1997) 761–768.
[138] K.R. Tallbacka, T. Pettersson, E. Pukkala, Increased incidence of cancer in systemic lupus erythematosus: a Finnish cohort study with more than 25 years of follow-up, Scand. J. Rheumatol. 47 (2018) 461–464.
[139] M. Fallah, et al., Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study, Ann. Oncol. 25 (2014) 2025–2030.
[140] K.H. Yu, C.F. Kuo, L.H. Huang, W.K. Huang, L.C. See, Cancer risk in patients with inflammatory systemic autoimmune rheumatic diseases: a nationwide population-based dynamic cohort study in Taiwan, Medicine 95 (2016) e3540.
[141] T. Tarr, et al., Occurrence of malignancies in Hungarian patients with systemic lupus erythematosus: results from a single center, Ann. N. Y. Acad. Sci. 1108 (2007) 76–82.
[142] S.H. Chang, et al., Comparison of cancer incidence among patients with rheumatic disease: a retrospective cohort study, Arthritis Res. Ther. 16 (4) (2014) 428.
[143] K.Y. Kang, et al., Incidence of cancer among female patients with systemic lupus erythematosus in Korea, Clin. Rheumatol. 29 (2010) 381–388.
[144] F. Rees, et al., Burden of comorbidity in systemic lupus erythematosus in the UK, 1999-2012, Arthritis Care Res. 68 (2016) 819–827.
[145] A. Parikh-Patel, R.H. White, M. Allen, R. Cress, Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California, Cancer Causes Control 19 (2008) 887–894.
[146] A. Klein, A. Polliack, A. Gafter-Gvili, Rheumatoid arthritis and lymphoma: incidence, pathogenesis, biology, and outcome, Hematol. Oncol. 36 (2018) 733–739.
[147] G. Gridley, et al., Incidence of cancer among patients with rheumatoid-arthritis, JNCI J. Natl. Cancer Inst. 85 (1993) 307–311.
[148] P. Prior, Cancer and rheumatoid arthritis: epidemiologic considerations, Am. J. Med. 78 (1985) 15–21.
[149] Y.J. Chen, Y.T. Chang, C.B. Wang, C.Y. Wu, The risk of cancer in patients with rheumatoid arthritis: a nationwide cohort study in Taiwan, Arthritis Rheum. 63 (2011) 352–358.
[150] T. Yamada, et al., Incidence of malignancy in Japanese patients with rheumatoid arthritis, Rheumatol. Int. 31 (2011) 1487–1492.
[151] L.K. Mercer, et al., Risk of lymphoma in patients exposed to antitumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis, Ann. Rheum. Dis. 76 (2017) 497–503.
[152] L.K. Mercer, et al., Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population, Rheumatology 52 (2013) 91–98.
[153] E. Baecklund, et al., Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of diffuse large B cell lymphoma, Arthritis Rheum. 48 (2003) 1543–1550.
[154] K. Hellgren, K.E. Smedby, N. Feltelius, E. Baecklund, J. Askling, Do rheumatoid arthritis and lymphoma share risk factors? A comparison of lymphoma and cancer risks before and after diagnosis of rheumatoid arthritis, Arthritis Rheum. 62 (2010) 1252–1258.
[155] S. Romero, et al., Post-transplant lymphoproliferative disorders after solid organ and hematopoietic stem cell transplantation, Leuk. Lymphoma 60 (2019) 142–150.
[156] T. Schober, et al., Characteristics of early and late PTLD development in pediatric solid organ transplant recipients, Transplantation 95 (2013) 240–246.
[157] Z. Al-Mansour, B.P. Nelson, A.M. Evens, Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies, Curr. Hematol. Malig. Rep. 8 (2013) 173–183.
[158] R. Trappe, et al., Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial, Lancet Oncol. 13 (2012) 196–206.
[159] R. Asleh, H. Alnsasra, T.M. Habermann, A. Briasoulis, S.S. Kushwaha, Post-transplant lymphoproliferative disorder following cardiac transplantation, Front. Cardiovasc. Med. 9 (2022), 787975.
[160] A.L. Taylor, R. Marcus, J.A. Bradley, Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation, Crit. Rev. Oncol. Hematol. 56 (2005) 155–167.
[161] M.L. Nijland, M.J. Kersten, S.T. Pals, F.J. Bemelman, I.J. Ten Berge, Epstein-Barr virus-positive posttransplant lymphoproliferative disease after solid organ transplantation: pathogenesis, clinical manifestations, diagnosis, and management, Transplant. Direct 2 (2016) e48.
[162] A.M. Evens, et al., Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era, J. Clin. Oncol. 28 (2010) 1038–1046.
[163] B.P. Nelson, et al., Epstein-Barr virus-negative post-transplant lymphoproliferative disorders: a distinct entity? Am. J. Surg. Pathol. 24 (2000) 375–385.
[164] R. Reshef, et al., Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder, Am. J. Transplant. 11 (2011) 336–347.
[165] O.M. Martinez, Biomarkers for PTLD diagnosis and therapies, Pediatr. Nephrol. 35 (2020) 1173–1181.
[166] M. De Paschale, P. Clerici, Serological diagnosis of Epstein-Barr virus infection: problems and solutions, World J. Virol. 1 (2012) 31–43.
[167] D.E. Tsai, et al., EBV PCR in the diagnosis and monitoring of posttransplant lymphoproliferative disorder: results of a two-arm prospective trial, Am. J. Transplant. 8 (2008) 1016–1024.
[168] S. Ruf, et al., Comparison of six different specimen types for Epstein-Barr viral load quantification in peripheral blood of pediatric patients after heart transplantation or after allogeneic hematopoietic stem cell transplantation, J. Clin. Virol. 53 (2012) 186–194.
[169] A. Harris-Arnold, et al., Epstein-Barr virus modulates host cell MicroRNA-194 to promote IL-10 production and B lymphoma cell survival, Am. J. Transplant. 15 (2015) 2814–2824.
[170] K. Musilova, M. Mraz, MicroRNAs in B-cell lymphomas: how a complex biology gets more complex, Leukemia 29 (2015) 1004–1017.
[171] J. Hassan, et al., Plasma EBV microRNAs in paediatric renal transplant recipients, J. Nephrol. 31 (2018) 445–451.
[172] S.E.K. Fink, et al., A comprehensive analysis of the cellular and EBV-specific MicroRNAome in primary CNS PTLD identifies different patterns among EBV-associated tumors, Am. J. Transplant. 14 (2014) 2577–2587.
[173] M. Navari, et al., Molecular signature of Epstein Barr virus-positive Burkitt lymphoma and post-transplant lymphoproliferative disorder suggest different roles for Epstein Barr virus, Front. Microbiol. 5 (2014) 728.
[174] C. Hinrichs, et al., IL-6 and IL-10 in post-transplant lymphoproliferative disorders development and maintenance: a longitudinal study of cytokine plasma levels and T-cell subsets in 38 patients undergoing treatment, Transpl. Int. 24 (2011) 892–903.
[175] O.C. Baiocchi, et al., Epstein-Barr viral load, interleukin-6 and interleukin-10 levels in post-transplant lymphoproliferative disease: a nested case-control study in a renal transplant cohort, Leuk. Lymphoma 46 (2005) 533–539.
[176] M. Barton, et al., Exploring beyond viral load testing for EBV lymphoproliferation: role of serum IL-6 and IgE assays as adjunctive tests, Pediatr. Transplant. 14 (2010) 852–858.
[177] T. Haque, et al., Soluble CD30: a serum marker for Epstein-Barr virus-associated lymphoproliferative diseases, J. Med. Virol. 83 (2011) 311–316.
[178] M. Fernandez-Ruiz, et al., Serum sCD30: a promising biomarker for predicting the risk of bacterial infection after kidney transplantation, Transpl. Infect. Dis. 19 (2017).
[179] J.J. Kovarik, et al., Identification of immune activation markers in the early onset of COVID-19 infection, Front. Cell. Infect. Microbiol. 11 (2021), 651484.
[180] P. Biswas, et al., Significant link between sCD30 changes and HIV Viremia in patients treated with HAART, J. Med. Virol. 78 (2006) 1513–1519.
[181] A. Nikaein, et al., Pre-transplant level of soluble CD30 is associated with infection after heart transplantation, Clin. Transplant. 21 (2007) 744–747.

[182] V. Navikas, et al., Soluble CD30 levels in plasma and cerebrospinal fluid in multiple sclerosis, HIV infection and other nervous system diseases, Acta Neurol. Scand. 95 (1997) 99–102.
[183] T.T. Tsai, et al., An emerging role for the anti-inflammatory cytokine interleukin-10 in dengue virus infection, J. Biomed. Sci. 20 (2013) 40.
[184] H.F. Penaloza, et al., Opposing roles of IL-10 in acute bacterial infection, Cytokine Growth Factor Rev. 32 (2016) 17–30.
[185] P.R. Enok Bonong, et al., Factors associated with post-transplant active Epstein-Barr virus infection and lymphoproliferative disease in hematopoietic stem cell transplant recipients: a systematic review and meta-analysis, Vaccines 9 (3) (2021), 288.
[186] A.H. Blaes, et al., Monitoring and preemptive rituximab therapy for Epstein-Barr virus reactivation after antithymocyte globulin containing nonmyeloablative conditioning for umbilical cord blood transplantation, Biol. Blood Marrow Transplant. 16 (2010) 287–291.
[187] R. Al Hamed, A.H. Bazarbachi, M Mohty, Epstein-Barr virus-related post-transplant lymphoproliferative disease (EBV-PTLD) in the setting of allogeneic stem cell transplantation: a comprehensive review from pathogenesis to forthcoming treatment modalities, Bone Marrow Transplant. 55 (2020) 25–39.
[188] M. Kinzel, et al., Risk factors for the incidence of and the mortality due to post-transplant lymphoproliferative disorder after hematopoietic cell transplantation, Transpl. Cell. Ther. (2022);28(1): 53.e1 -53.e10..
[189] V. Leblond, et al., Lymphoproliferative disorders after organ-transplantation - a report of 24 cases observed in a single-center, J. Clin. Oncol. 13 (1995) 961–968.
[190] V.R. Dharnidharka, P.L. Ho, D.M. Stablein, W.E. Harmon, A.H. Mycophenolate Tejani, tacrolimus and post-transplant lymphoproliferative disorder: a report of the North American pediatric renal transplant cooperative study, Pediatr. Transplant. 6 (2002) 396–399.
[191] M.A. Govantes, et al., Incidence of post-transplantation lymphoproliferative disease in Andalusia (1990-2009), Transplant. Proc. 45 (2013) 3592–3594.
[192] G.J. Boyle, et al., Posttransplantation lymphoproliferative disorders in pediatric thoracic organ recipients, J. Pediatr. 131 (1997) 309–313.
[193] E.M. Sokal, et al., Early signs and risk factors for the increased incidence of Epstein-Barr virus-related posttransplant lymphoproliferative diseases in pediatric liver transplant recipients treated with tacrolimus, Transplantation 64 (1997) 1438–1442.
[194] D. Grant, et al., 2003 report of the intestine transplant registry—a new era has downed, Ann. Surg. 241 (2005) 607–613.
[195] L.J. Wozniak, et al., Clinical characteristics and outcomes of PTLD following intestinal transplantation, Clin. Transplant. 32 (2018) e13313.
[196] L. Finn, J. Reyes, J. Bueno, E. Yunis, Epstein-Barr virus infections in children after transplantation of the small intestine, Am. J. Surg. Pathol. 22 (1998) 299–309.
[197] J.E. Johansson, et al., Allogeneic haematopoietic stem-cell transplantation with reduced intensity conditioning for advanced stage Hodgkin's lymphoma in Sweden: high incidence of post transplant lymphoproliferative disorder, Bone Marrow Transplant. 46 (2011) 870–875.
[198] H.A. Hou, et al., Poor outcome in post transplant lymphoproliferative disorder with pulmonary involvement after allogeneic hematopoietic SCT: 13 years' experience in a single institute, Bone Marrow Transplant. 43 (2009) 315–321.
[199] H.C.E. Buyck, S. Ball, P. Junagade, J. Marsh, S. Chakrabarti, Prior immunosuppressive therapy with antithymocyte globulin increases the risk of EBV-related lymphoproliferative disorder following allo-SCT for acquired aplastic anaemia, Bone Marrow Transpl. 43 (2009) 813–816.
[200] S. Ocheni, et al., EBV reactivation and post transplant lymphoproliferative disorders following allogeneic SCT, Bone Marrow Transplant. 42 (2008) 181–186.
[201] B. Meresse, J. Ripoche, M. Heyman, N. Cerf-Bensussan, Celiac disease: from oral tolerance to intestinal inflammation, autoimmunity and lymphomagenesis, Mucosal Immunol. 2 (2009) 8–23.
[202] M. Bombardieri, C. Pitzalis, Ectopic lymphoid neogenesis and lymphoid chemokines in Sjogren's syndrome: at the interplay between chronic inflammation, autoimmunity and lymphomagenesis, Curr. Pharm. Biotechnol. 13 (2012) 1989–1996.
[203] C. Thieblemont, F. Bertoni, C. Copie-Bergman, A.J. Ferreri, M Ponzoni, Chronic inflammation and extra-nodal marginal-zone lymphomas of MALT-type, Semin. Cancer Biol. 24 (2014) 33–42.
[204] L.L. Zhang, J.Y. Wei, L. Wang, S.L. Huang, J.L. Chen, Human T-cell lymphotropic virus type 1 and its oncogenesis, Acta Pharmacol. Sin. 38 (2017) 1093–1103.
[205] J.H. Pope, M.K. Horne, W. Scott, Transformation of foetal human keukocytes in vitro by filtrates of a human leukaemic cell line containing herpes-like virus, Int. J. Cancer 3 (1968) 857–866.
[206] W. Henle, K. Hummeler, G. Henle, Antibody coating and agglutination of virus particles separated from the EB3 line of Burkitt lymphoma cells, J. Bacteriol. 92 (1966) 269–271.
[207] G. Manolov, Y. Manolova, Marker band in one chromosome 14 from Burkitt lymphomas, Nature 237 (1972) 33–34.
[208] L. Zech, U. Haglund, K. Nilsson, G. Klein, Characteristic chromosomal abnormalities in biopsies and lymphoid-cell lines from patients with Burkitt and non-Burkitt lymphomas, Int. J. Cancer 17 (1976) 47–56.
[209] M. Dean, R.B. Kent, G.E. Sonenshein, Transcriptional activation of immunoglobulin alpha heavy-chain genes by translocation of the c-myc oncogene, Nature 305 (1983) 443–446.
[210] G.L. Kelly, A.E. Milner, G.S. Baldwin, A.I. Bell, A.B. Rickinson, Three restricted forms of Epstein-Barr virus latency counteracting apoptosis in c-myc-expressing Burkitt lymphoma cells, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 14935–14940.
[211] M. Rowe, G.L. Kelly, A.I. Bell, A.B. Rickinson, Burkitt's lymphoma: the Rosetta Stone deciphering Epstein-Barr virus biology, Semin. Cancer Biol. 19 (2009) 377–388.
[212] M.J. Allday, How does Epstein-Barr virus (EBV) complement the activation of Myc in the pathogenesis of Burkitt's lymphoma? Semin. Cancer Biol. 19 (2009) 366–376.
[213] P.O. Sumba, et al., Microgeographic variations in Burkitt's lymphoma incidence correlate with differences in malnutrition, malaria and Epstein-Barr virus, Br. J. Cancer 103 (2010) 1736–1741.
[214] J.J. Rainey, et al., Spatial clustering of endemic Burkitt's lymphoma in high-risk regions of Kenya, Int. J. Cancer 120 (2007) 121–127.
[215] J.J. Rainey, et al., Spatial distribution of Burkitt's lymphoma in Kenya and association with malaria risk, Trop. Med. Int. Health 12 (2007) 936–943.
[216] P.G. Murray, L.S. Young, An etiological role for the Epstein-Barr virus in the pathogenesis of classical Hodgkin lymphoma, Blood 134 (2019) 591–596.
[217] Y. Pei, A.E. Lewis, E.S. Robertson, Current progress in EBV-associated B-cell lymphomas, Adv. Exp. Med. Biol. 1018 (2017) 57–74.
[218] K. Fish, R. Longnecker, EBV germinates lymphoma from the germinal center in a battle with T and NK cells, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 4571–4573.
[219] J.J. Castillo, et al., EBV-positive diffuse large B-cell lymphoma of the elderly: 2016 update on diagnosis, risk-stratification, and management, Am. J. Hematol. 91 (2016) 529–537.
[220] R. Amoroso, et al., Quantitative studies of Epstein-Barr virus-encoded MicroRNAs provide novel insights into their regulation, J. Virol. 85 (2011) 996–1010.
[221] T.C. Wu, et al., Detection of EBV gene expression in Reed-Sternberg cells of Hodgkin's disease, Int. J. Cancer 46 (1990) 801–804.
[222] D. Hochberg, et al., Demonstration of the Burkitt's lymphoma Epstein-Barr virus phenotype in dividing latently infected memory cells in vivo, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 239–244.
[223] D.A. Thorley-Lawson, A. Gross, Persistence of the Epstein-Barr virus and the origins of associated lymphomas, N. Engl. J. Med. 350 (2004) 1328–1337.
[224] R.G. Caldwell, J.B. Wilson, S.J. Anderson, R. Longnecker, Epstein-Barr virus LMP2A drives B cell development and survival in the absence of normal B cell receptor signals, Immunity 9 (1998) 405–411.
[225] D. Panagopoulos, P. Victoratos, M. Alexiou, G. Kollias, G. Mosialos, Comparative analysis of signal transduction by CD40 and the Epstein-Barr virus oncoprotein LMP1 in vivo, J. Virol. 78 (2004) 13253–13261.
[226] J.S.Z. Li, et al., Chromosomal fragile site breakage by EBV-encoded EBNA1 at clustered repeats, Nature 616 (2023) 504–509.
[227] P.J. Farrell, I. Cludts, A. Stuhler, Epstein-Barr virus genes and cancer cells, Biomed. Pharmacother. 51 (1997) 258–267.
[228] K. Machida, K.T. Cheng, N. Pavio, V.M. Sung, M.M. Lai, Hepatitis C virus E2-CD81 interaction induces hypermutation of the immunoglobulin gene in B cells, J. Virol. 79 (2005) 8079–8089.
[229] A. Trevino, et al., Prevalence of HTLV-1/2 infections in Spain: a cross-sectional hospital-based survey, AIDS Res. Hum. Retroviruses 26 (2010) 861–864.
[230] S. Takemoto, M. Iwanaga, Y. Sagara, T. Watanabe, Plasma soluble CD30 as a possible marker of adult T-cell leukemia in HTLV-1 carriers: a nested case-control study, Asian Pac. J. Cancer Prev. 16 (2015) 8253–8258.
[231] D.L. Longo, et al., Isolation of HTLV-transformed B-lymphocyte clone from a patient with HTLV-associated adult T-cell leukaemia, Nature 310 (1984) 505–506.
[232] Y. Koyanagi, et al., In vivo infection of human T-cell leukemia virus type I in non-T cells, Virology 196 (1993) 25–33.
[233] L. Chen, D. Liu, Y. Zhang, H. Zhang, H. Cheng, The autophagy molecule Beclin 1 maintains persistent activity of NF-kappa B and Stat3 in HTLV-1-transformed T lymphocytes, Biochem. Biophys. Res. Commun. 465 (2015) 739–745.
[234] A. Noy, Optimizing treatment of HIV-associated lymphoma, Blood 134 (2019) 1385–1394.
[235] A. Carbone, E. Cesarman, M. Spina, A. Gloghini, T.F. Schulz, HIV-associated lymphomas and gamma-herpesviruses, Blood 113 (2009) 1213–1224.
[236] H. Meijide, et al., Increased incidence of cancer observed in HIV/hepatitis C virus-coinfected patients versus HIV-monoinfected, AIDS 31 (2017) 1099–1107.
[237] S.A. Atallah-Yunes, D.J. Murphy, A. Noy, HIV-associated Burkitt lymphoma, Lancet Haematol. 7 (2020) e594–e600.
[238] F.B. Sall, et al., HIV-1 Tat protein induces aberrant activation of AICDA in human B-lymphocytes from peripheral blood, J. Cell. Physiol. 234 (9) (2019) 15678–15685.
[239] D. Germini, et al., HIV Tat induces a prolonged MYC relocalization next to IGH in circulating B-cells, Leukemia 31 (2017) 2515–2522.
[240] O. Landgren, et al., Circulating serum free light chains as predictive markers of AIDS-related lymphoma, J. Clin. Oncol. 28 (2010) 773–779.
[241] E.C. Breen, et al., B-cell stimulatory cytokines and markers of immune activation are elevated several years prior to the diagnosis of systemic AIDS-associated non-Hodgkin B-cell lymphoma, Cancer Epidemiol. Biomark. Prev. 20 (2011) 1303–1314.
[242] A. Carbone, A. Gloghini, KSHV/HHV8-associated lymphomas, Br. J. Haematol. 140 (2008) 13–24.
[243] M. Denic, E. Touati, H. De Reuse, Review: pathogenesis of helicobacter pylori infection, Helicobacter 25 Suppl 1 (2020) e12736.
[244] C. Melenotte, et al., Bacterial infection and non-Hodgkin's lymphoma, Crit. Rev. Microbiol. 46 (2020) 270–287.
[245] F.H. Yang, et al., NF-kappa B/miR-223-3p/ARID1A axis is involved in Helicobacter pylori CagA-induced gastric carcinogenesis and progression, Cell Death Dis. 9 (1) (2018) 12.

[246] R. Wada, et al., Structure of lamina propria lymphoid follicles and associated epithelium in the gastric mucosa during Helicobacter pylori infection in ulcer-bearing Mongolian gerbils, J. Submicrosc. Cytol. Pathol. 32 (2000) 159–167.
[247] A. Blosse, et al., Deregulation of miRNA in helicobacter pylori-induced gastric MALT lymphoma: from mice to human, J. Clin. Med. 8 (6) (2019), 845.
[248] W. Fischbach, M.E. Goebeler-Kolve, B. Dragosics, A. Greiner, M. Stolte, Long term outcome of patients with gastric marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT) following exclusive Helicobacter pylori eradication therapy: experience from a large prospective series, Gut 53 (2004) 34–37.
[249] C. Colli, et al., Borrelia burgdorferi-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases, J. Cutan. Pathol. 31 (2004) 232–240.
[250] A.J.M. Ferreri, et al., Chlamydophila psittaci is viable and infectious in the conjunctiva and peripheral blood of patients with ocular adnexal lymphoma: results of a single-center prospective case-control study, Int. J. Cancer 123 (2008) 1089–1093.
[251] M. Lecuit, et al., Immunoproliferative small intestinal disease associated with Campylobacter jejuni, N. Engl. J. Med. 350 (2004) 239–248.
[252] D.F. Robbiani, et al., Plasmodium infection promotes genomic instability and AID-dependent B cell lymphoma, Cell 162 (2015) 727–737.
[253] F. Dammacco, et al., Clinical practice: hepatitis C virus infection, cryoglobulinemia and cryoglobulinemic vasculitis, Clin. Exp. Med. 19 (2019) 1–21.
[254] H. Ohshima, H. Bartsch, Chronic infections and inflammatory processes as cancer risk-factors - possible role of nitric-oxide in carcinogenesis, Mutat. Res. 305 (1994) 253–264.
[255] R.J. Huebner, Todaro GJ,Oncogenes of RNA tumor-viruses as determinants of cancer, Proc. Natl. Acad. Sci. USA 64 (3) (1969) 1087–1094.
[256] C. Nishioka, et al., Serum level of soluble CD30 correlates with the aggressiveness of adult T-cell leukemia/lymphoma, Cancer Sci. 96 (2005) 810–815.
[257] T.M. Gibson, L.M. Morton, M.S. Shiels, C.A. Clarke, E.A. Engels, Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study, AIDS 28 (2014) 2313–2318.
[258] J.M. Pluda, et al., Parameters affecting the development of non-Hodgkin's lymphoma in patients with severe human immunodeficiency virus infection receiving antiretroviral therapy, J. Clin. Oncol. 11 (1993) 1099–1107.
[259] R.U. Hernandez-Ramirez, et al., Association of immunosuppression and HIV viraemia with non-Hodgkin lymphoma risk overall and by subtype in people living with HIV in Canada and the USA: a multicentre cohort study, Lancet HIV 6 (2019) E240–E249.
[260] O. Sokolova, M. Naumann, NF-kappaB signaling in gastric cancer, Toxins 9 (4) (2017), 119.
[261] L. Thurner, et al., B-cell receptor reactivity against Rothia mucilaginosa in nodular lymphocyte-predominant Hodgkin lymphoma, Haematologica (2023), https://doi.org/10.3324/haematol.2023.282698.
[262] L. Thurner, et al., Lymphocyte predominant cells detect Moraxella catarrhalis-derived antigens in nodular lymphocyte-predominant Hodgkin lymphoma, Nat. Commun. 11 (2020) 2465.
[263] S.L. Slager, et al., Medical history, lifestyle, family history, and occupational risk factors for chronic lymphocytic leukemia/small lymphocytic lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project, J. Natl. Cancer Inst. Monogr. 2014 (2014) 41–51.
[264] V.J. Cogliano, et al., Preventable exposures associated with human cancers, J. Natl. Cancer Inst. 103 (2011) 1827–1839.
[265] L.M. Morton, et al., Etiologic heterogeneity among non-Hodgkin lymphoma subtypes, Blood 112 (2008) 5150–5160.
[266] R.W. Harbron, E. Pasqual, Ionising radiation as a risk factor for lymphoma: a review, J. Radiol. Prot. 40 (2020) R151–R185.
[267] N. Pearce, D. McLean, Agricultural exposures and non-Hodgkin's lymphoma, Scand. J. Work Environ. Health 31 (2005) 18–25. Suppl 1discussion 15-17.
[268] A.J. De Roos, et al., Occupational insecticide exposure and risk of non-Hodgkin lymphoma: a pooled case-control study from the InterLymph Consortium, Int. J. Cancer 149 (2021) 1768–1786.
[269] G. Andreotti, et al., Glyphosate use and cancer incidence in the agricultural health study, JNCI J. Natl. Cancer Inst. 110 (2018) 509–516.
[270] M. Karakosta, E.M. Delicha, G. Kouraklis, K.N. Manola, Association of various risk factors with chronic lymphocytic leukemia and its cytogenetic characteristics, Arch. Environ. Occup. Health 71 (2016) 317–329.
[271] A. Seidler, et al., Solvent exposure and malignant lymphoma: a population-based case-control study in Germany, J. Occup. Med. Toxicol. 2 (2007) 2.
[272] S.R. O'Connor, P.B. Farmer, I. Lauder, Benzene and non-Hodgkin's lymphoma, J. Pathol. 189 (1999) 448–453.
[273] C.L. Callahan, et al., Case-control investigation of occupational exposure to chlorinated solvents and non-Hodgkin's lymphoma, Occup. Environ. Med. 75 (2018) 415–420.
[274] T.N. Sergentanis, P. Kanavidis, T. Michelakos, E.T. Petridou, Cigarette smoking and risk of lymphoma in adults: a comprehensive meta-analysis on Hodgkin and non-Hodgkin disease, Eur. J. Cancer Prev. 22 (2013) 131–150.
[275] A. Nieters, et al., Smoking and lymphoma risk in the european prospective investigation into cancer and nutrition, Am. J. Epidemiol. 167 (2008) 1081–1089.
[276] A. Badry, V.L.B. Jaspers, C.A. Waugh, Environmental pollutants modulate RNA and DNA virus-activated miRNA-155 expression and innate immune system responses: insights into new immunomodulative mechanisms, J. Immunotoxicol. 17 (2020) 86–93.
[277] A. Kricker, et al., Personal sun exposure and risk of non Hodgkin lymphoma: a pooled analysis from the Interlymph Consortium, Int. J. Cancer 122 (2008) 144–154.
[278] T. Hickish, et al., The effect of 1,25-dihydroxyvitamin D3 on lymphoma cell lines and expression of vitamin D receptor in lymphoma, Br. J. Cancer 68 (1993) 668–672.
[279] J. Polesel, et al., Linoleic acid, vitamin D and other nutrient intakes in the risk of non-Hodgkin lymphoma: an Italian case-control study, Ann. Oncol. 17 (2006) 713–718.
[280] P. Hartge, et al., Ultraviolet radiation, dietary vitamin D, and risk of non-Hodgkin lymphoma (United States), Cancer Causes Control 17 (2006) 1045–1052.
[281] D. Bron, et al., Unmet needs in the scientific approach to older patients with lymphoma, Haematologica 102 (2017) 972–975.
[282] C. Lopez-Otin, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, Hallmarks of aging: an expanding universe, Cell 186 (2023) 243–278.
[283] C. Lopez-Otin, F. Pietrocola, D. Roiz-Valle, L. Galluzzi, G. Kroemer, Meta-hallmarks of aging and cancer, Cell Metab. 35 (2023) 12–35.
[284] S. Jaiswal, et al., Age-related clonal hematopoiesis associated with adverse outcomes, N. Engl. J. Med. 371 (2014) 2488–2498.
[285] G. Genovese, et al., Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence, N. Engl. J. Med. 371 (2014) 2477–2487.
[286] M. Xie, et al., Age-related mutations associated with clonal hematopoietic expansion and malignancies, Nat. Med. 20 (2014) 1472–1478.
[287] M. Heuser, F. Thol, A. Ganser, Clonal hematopoiesis of indeterminate potential, Dtsch. Arztebl. Int. 113 (2016) 317–322.