REVIEWS

MECHANISMS OF B-CELL LYMPHOMA PATHOGENESIS

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Abstract | Chromosomal translocations involving the immunoglobulin loci are a hallmark of many types of B-cell lymphoma. Other factors, however, also have important roles in the pathogenesis of B-cell malignancies. Most B-cell lymphomas depend on the expression of a B-cell receptor (BCR) for survival, and in several B-cell malignancies antigen activation of lymphoma cells through BCR signalling seems to be an important factor for lymphoma pathogenesis. Recent insights into the lymphomagenic role of factors supplied by the microenvironment also offer new therapeutic strategies.

CD79A AND CD79B
Components of the B-cell receptor that mediate signalling following crosslinking.

In the Western world, about 20 new cases of lymphoma are diagnosed per 100,000 people per year[1]. About 95% of the lymphomas are of B-cell origin, the rest are T-cell malignancies. This might be surprising at first glance, given the similar frequency of B and T cells in the human body, but is understandable considering the specific factors that influence the pathogenesis of B-cell lymphomas. About 15 types of B-cell lymphoma are distinguished in the current World Health Organization lymphoma classification[2] (TABLE 1). The distinction of these lymphomas is not only relevant in terms of lymphoma pathogenesis, but also regarding the consequences for treatment of the patients. This is because the various types of B-cell lymphoma can have very different clinical behaviours, and therefore require diverse treatment strategies.

Exciting progress has been made in the past 20 years to elucidate the cellular origin of human B-cell lymphomas and the identification of key transforming events, in particular the role of chromosomal translocations in lymphoma pathogenesis. However, it is becoming clear that B-cell tumours are not as autonomous as previously thought — key factors that are crucial for normal B-cell differentiation and survival are also required for the malignant growth of most B-cell lymphomas. What is the cellular origin of B-cell lymphomas and what are the main transforming events? How do antigen activation of the B-cell receptor (BCR) and the cellular microenvironment contribute to the pathogenesis of B-cell lymphomas?

Cellular origin of B-cell lymphomas

B-cell development takes place in distinct differentiation steps that are characterized by the specific structure of the BCR. The BCR is composed of two identical heavy-chain and two identical light-chain immunoglobulin (Ig) polypeptides that are covalently linked by disulphide bridges. Other components of the BCR are the CD79A AND CD79B molecules, which contain cytoplasmic immunoreceptor tyrosine-based activation motifs. These motifs transmit signals following BCR crosslinking. The intracellular signalling components activated by BCR crosslinking include several tyrosine kinases. Depending on the differentiation stage of the B cell that recognizes an antigen and on the activation of other B-cell surface receptors that modulate BCR signalling, the activated B cell might be induced to proliferate and/or undergo further differentiation steps[3].

Early B-cell development, which occurs in the bone marrow, concludes when a B-cell precursor successfully rearranges Ig heavy- and light-chain genes and is equipped with a functional surface antigen receptor (FIG. 1). Cells that express a functional (and non-autoreactive) BCR differentiate into mature naive B cells and leave the bone marrow, whereas B-cell precursors that fail to express a BCR undergo apoptosis[3]. Mature naive B cells can be activated by antigen binding to the BCR and participate in immune responses. In T-cell-dependent immune responses, antigen-activated B cells undergo clonal expansion in structures called 'germinal centres'

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Summary

• A hallmark of many types of B-cell lymphoma is reciprocal chromosomal translocations involving one of the immunoglobulin loci and a proto-oncogene. As a consequence of such translocations, the oncogene comes under the control of an active immunoglobulin locus, causing deregulated, constitutive expression of the translocated gene.

• Normal B cells depend on B-cell receptor (BCR) expression for survival. The selection for expression of a BCR also seems to operate in most malignant B cells.

• Although there is strong evidence that most B-cell lymphomas depend on BCR expression, there are a few exceptions — namely classical Hodgkin's lymphoma, primary mediastinal B-cell lymphoma, some post-transplant lymphomas, and the rare primary effusion lymphomas.

• In several lymphomas, there is a strong indication that the lymphoma cells recognize an antigen and that stimulation by antigen binding contributes to the survival and proliferation of lymphoma cells.

• In many lymphomas, such as follicular lymphoma, mucosa-associated lymphoid tissue lymphomas and classical Hodgkin's lymphoma, the tumour microenvironment seems to be important for the survival and/or proliferation of the lymphoma cells.

• The recognition that the survival and/or proliferation of many B-cell lymphomas depends on their interaction with other cells in the microenvironment, as well as on expression of the B-cell receptor and, sometimes, antigen activation, might lead to novel treatment options for B-cell lymphomas.

(GCs), where the the Ig genes are modified by somatic hypermutation and class-switch recombination (FIGS 1,2).

As distinct stages of B-cell development and differentiation are characterized by the particular structure of the BCR and expression patterns of differentiation markers, and as these processes often take place in specific histological structures, analysis of these features was used to determine the origin of the various human B-cell lymphomas[4,5] (TABLE 1). The rationale for such a classification of B-cell lymphomas is based on the observation that malignant B cells seem to be 'frozen' at a particular differentiation stage, which reflects their origin[4,6,7]. One of the main concepts emerging from these studies is that most types of B-cell lymphoma are derived from GC or post-GC B cells[4,5] (BOX 1).

The cellular origin of B-cell lymphomas was further clarified, and previously unrecognized distinct lymphoma subtypes were also identified, by gene-expression profiling of human B-cell lymphomas and normal B-cell subsets. Such studies identified, for example, a GC B-cell gene-expression signature that is associated with follicular lymphoma, Burkitt's lymphoma and a subset of diffuse large B-cell lymphomas[8]. These findings supported the GC B-cell origin of these tumours. Gene-expression profiling studies of other malignancies also revealed unexpected relationships, in terms of gene-expression patterns. For example, in addition to B-cell chronic lymphocytic leukaemia (B-CLL) cells with mutated Ig variable (V)-region genes, B-CLL cells with unmutated Ig V-region genes showed greatest similarity to memory B cells that had undergone somatic hypermutation, indicating that both subtypes of B-CLL are related to memory B cells[9]. Moreover, a subset of diffuse large B-cell lymphomas was identified that, among the various B-cell subsets included in the analysis, most closely resembled

in-vitro-activated B cells[8]. In these cancer cells, the transformation process might have been associated with an alteration of the gene-expression profile, masking the signature of the cell of origin, as seems to be the case in classical Hodgkin's lymphoma (see below). It is also possible that the normal B-cell counterpart of some cancer types might not have been identified yet. In the activated B-cell type of diffuse large B-cell lymphoma, the normal counterpart could be a poorly defined, small subset of GC B cells that is undergoing plasmacytoid differentiation, or a post-GC immunoblast population[7].

Transforming events

Reciprocal chromosomal translocations involving one of the Ig loci and a proto-oncogene are a hallmark of many types of B-cell lymphoma[10,11] (TABLE 2). As a consequence of such translocations, the oncogene comes under the control of the active Ig locus, causing a deregulated, constitutive expression of the oncogene. Three types of breakpoints can be distinguished in the Ig loci. Some translocations, such as the $BCL2$–IgH translocation associated with follicular lymphoma, have breakpoints that are directly adjacent to Ig heavy chain J-region (J_H) gene segments or that are adjacent to regions where the Ig heavy chain D-region (D_H) joins the J-region ($D_H J_H$) (FIG. 1). As the breakpoints also often show loss of nucleotides at the end of the J_H or D_H segments and the addition of non-germline-encoded nucleotides — typical features of V(D)J recombination — it is likely that these translocations happen as mistakes during V(D)J recombination in early B-cell development in the bone marrow[12–14]. In other translocations, the breakpoints are found within or adjacent to rearranged V(D)J genes, and these V-region genes are always somatically mutated. These and additional features indicate that such translocations occur as by-products of the somatic hypermutation process[10,15], which is associated with DNA strand breaks[15–17]. The third type of translocation is characterized by breakpoints in the IgH constant region switch regions, in which DNA breaks are introduced during class switching. This indicates that these events occur during class-switch recombination.

The causes for the generation of DNA strand breaks in the oncogenes involved in Ig-associated translocations are less clear[10]. Some of these genes, however, undergo aberrant somatic hypermutation, and therefore acquire DNA strand breaks in the same regions where the chromosomal breakpoints are located (see below)[18]. Regarding the $BCL2$–IgH translocations associated with follicular lymphoma, it was recently shown that the DNA in the major breakpoint region of the $BCL2$ gene often acquires an altered structure that is cut by the RAG nucleases, which mediate V(D)J recombination. This finding indicates that in these translocations, RAG-mediated DNA cleavage is responsible for the DNA breaks in both partners involved in the translocation[19]. RAG enzymes might also be involved in chromosomal translocations through another mechanism — RAGs have been shown to possess transposase activity, so some translocation events could be explained by double-ended transposition events[20,21].

Table 1 | **Human mature B-cell lymphomas**

Lymphoma	Features	Frequency among lymphomas (%)*	Proposed cellular origin
B-cell chronic lymphocytic leukaemia (B-CLL)	Leukaemia of small B cells that express the CD5 antigen, involving peripheral-blood and bone-marrow cells. Common in elderly patients. Called 'small lymphocytic lymphoma' when lymph-node cells are predominantly involved. Patients with leukaemia cells that lack variable (V)-region gene mutations have a worse prognosis than patients with mutations in V-region genes.	7	Memory B cell? Naive B cell? Marginal-zone B cell?
Mantle-cell lymphoma	Lymphoma arises from cells that populate the mantle zone of follicles, express CD5 and show aberration in cyclin-D1 expression. Nearly all cases are associated with *BCL1–IgH* translocation.	5	CD5+ mantle-zone B cell
B-cell prolymphocytic leukaemia	Chronic B-cell malignancy related to B-CLL. Over 50% of cancer cells represent prolymphocytes (large lymphocytes with clumped chromatin and prominent nucleolus).	<1	Memory B cell
Follicular lymphoma	A nodal lymphoma with a follicular growth pattern. Lymphoma cells morphologically and phenotypically resemble GC B cells. Most cases are associated with *BCL2–IgH* translocation.	20	GC B cell
Hairy-cell leukaemia	Chronic B-cell malignancy involving spleen and bone marrow. Very few circulating leukaemia cells. Tumour cells form 'hairy' projections.	<1	Memory B cell
MALT lymphoma	Extranodal marginal-zone B-cell lymphoma. Develops mostly in aquired lymphoid structures.	7	Marginal-zone B cell
Nodal marginal-zone lymphoma	Lymphoma with primary presentation in lymph nodes. Lymphoma cells resemble marginal-zone or monocytoid B cells, but often have heterogenous cytology, which ranges from small to large lymphocytes and includes plasma cells.	2	Marginal-zone B cell? Monocytoid B cell?
Splenic marginal-zone lymphoma	Micronodular lymphoid infiltration in the splenic white pulp. Mostly small IgD+ lymphoma cells that replace normal follicles and the marginal-zone region. Frequently involves infiltration into bone marrow and circulation.	1	Subset of naive B cells that have partially differentiated into marginal-zone B cells?
Burkitt's lymphoma	Fast growing. Mostly extranodal. Characterized by a *MYC–Ig* translocation. Patients with endemic form are EBV-positive in nearly all cases. Patients with sporadic form are EBV-positive in about 30% of cases.	2	GC B cell
Diffuse large B-cell lymphoma	Heterogenous group of lymphomas characterized by large B cells. Several subtypes are recognized. Morphological variants include centroblasts and immunoblasts.	30–40	GC or post-GC B cell
Primary mediastinal B-cell lymphoma	Subtype of diffuse large B-cell lymphoma located in the mediastinum. Tumour cells are large B cells but also show a number of similarities to Reed–Sternberg cells of classical Hodgkin's lymphoma. Most frequently occurs in young women.	2	Thymic B cell
Post-transplant lymphoma	Mostly of the diffuse large-cell lymphoma type. Lymphomas that arise in patients after organ transplantation. Immunosuppressive treatment confers risk of uncontrolled proliferation of EBV-infected B cells that can develop into lymphomas.	<1	GC B cell
Primary effusion lymphoma	Frequently occurs in patients with AIDS or patients who have received organ transplants. Lymphoma cells are found as effusions in serous cavities, such as pleura, pericardium or peritoneum.	<0.5	(Post) GC B cell
Lymphoplasmacytic lymphoma	Involves lymph nodes, bone marrow and spleen. The tumour-cell population is composed of small B cells, plasmacytoid lymphocytes and plasma cells. Most patients present with a serum monoclonal protein, usually of the IgM type.	1	(Post) GC B cell
Multiple myeloma	Neoplastic proliferation of plasma cells in the bone marrow.	10	Plasma cell
Classical Hodgkin's lymphoma	Characterized by bizarre, large tumour cells. Hodgkin and Reed–Sternberg cells account for less than 1% of cells in the tumour, and are admixed with various non-neoplastic cell types. Tumour cells show a phenotype not characteristic of any normal haematopoietic cell type.	10	Defective GC B cell
Lymphocyte-predominant Hodgkin's lymphoma	Rare indolent subtype of Hodgkin's lymphoma. Lymphoma cells show a B-cell phenotype, represent a small population in the tissue, and grow in association with follicular dendritic cells and T-helper cells. Good prognosis.	0.5	GC B cell

*These numbers refer to the frequencies in Europe and North America. AIDS, acquired immune deficiency syndrome; EBV, Epstein–Barr virus; Ig, immunoglobulin; MALT, mucosa-associated lymphoid tissue; GC, germinal centre.
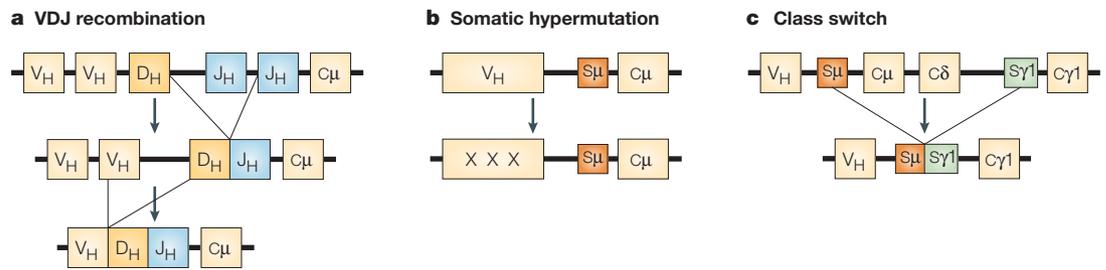
a VDJ recombination

b Somatic hypermutation

c Class switch

Figure 1 | **Molecular processes that remodel immunoglobulin genes.** Immunoglobulins (Igs) are expressed by B cells and consist of variable (V) regions, which interact with antigen, and constant (C) regions, which mediate the effector functions of Igs. To create a functional Ig, B cells must rearrange DNA segments that encode the heavy (H)- and light-chain (not shown) regions of the variable genes. **a** | First, through a process called 'V(D)J recombination', three gene segments, V_H, D_H and J_H, are joined to encode the H-chain variable region. The V regions of the κ- and λ-light chains, alternatively, are each encoded by two gene segments — the V_L and J_L genes (not shown). B-cell precursors first carry out D_H–J_H rearrangements in H-chain genes. These D_H–J_H rearrangements are followed by V_H–$D_H J_H$ rearrangements, resulting in the expression of a pre-B-cell receptor if the rearrangement is productive[3]. About 50 functional V_H gene segments, 27 D_H segments and 6 J_H segments are available in the germline, allowing the generation of a diverse repertoire of V_H gene rearrangements. The diversity is further increased by the addition or removal of nucleotides at the joining sites of the gene segments[3]. The cells then carry out rearrangements at their L-chain loci (not shown). The V-region of the Ig gene is ultimately connected to the C-region of the Ig gene (Cμ of IgM in diagram) **b** | The process of somatic hypermutation is activated when B cells reach the germinal centre (GC, shown in more details in FIG. 2). This process leads to the introduction of point mutations, deletions or duplications in the rearranged V-region of Ig genes (denoted by 'Xs' in the figure)[102]. These mutations occur in the V-region of Ig genes — not in the downstream Cμ region. **c** | Class switching results in the replacement of the originally expressed H-chain C-region gene with that of another Ig gene. In the diagram, the C-region for IgM (Cμ) and IgD (Cδ) are exchanged for the C-region of IgG (Cγ1) by recombination at the switch regions for these genes (Sμ and Sγ1, respectively). This results in an antibody with different effector functions but the same antigen-binding domain.

The process of somatic hypermutation contributes to lymphoma pathogenesis not only by causing chromosomal translocations, but probably also by targeting non-Ig genes. Two situations have to be distinguished. The genes encoding BCL6 and CD95 (also known as FAS) were found to contain mutations in a considerable fraction of normal GC and memory B cells, indicating that these genes are often targeted by the hypermutation machinery in normal B cells[22–24]. In rare instances, such mutations might promote the development of lymphomas. For example, inactivating mutations of *CD95* are found in about 20% of (post) GC B-cell lymphomas and could protect lymphoma cells from death induction by CD95-ligand-expressing cells[25]. In the case of the *BCL6* gene, the frequent occurrence of hypermutation might also cause translocations of this gene into Ig- as well as non-Ig-encoding loci. This possibility was indicated by the finding that the 5′ region of *BCL6*, which is the site of hypermutation, is also the region where chromosomal-translocation breakpoints are mostly found[18,23]. In diffuse large B-cell lymphomas, aberrant hypermutation of multiple oncogenes has been reported, which might also represent an important mechanism of pathogenesis[18].

Two of the molecular processes that could cause chromosome translocations or mutations in non-Ig genes occur exclusively (or at least mainly) in the GC — somatic hypermutation and class-switch recombination[26]. This could be one of the reasons that most B-cell lymphomas derive from GC B cells or their descendents. Class switching and somatic hypermutation do not occur in the DNA of T cells, which could also partly explain why B cells are more prone to undergo malignant transformation than T cells.

Whereas chromosome translocations involving Ig loci are clearly a hallmark of many types of B-cell lymphoma, many other transforming events have also been implicated in the pathogenesis of lymphomas, such as mutations in tumour-suppressor genes (such as *TP53* and the gene encoding IκBα), genomic amplifications (such as *REL*) and translocations not involving Ig loci (*API2–MALT1*) (TABLE 2).

Finally, viruses might also be involved in the transformation of B cells. The most well-known example is Epstein–Barr virus (EBV), which is found in nearly all endemic Burkitt's lymphomas, in many post-transplant and primary effusion lymphomas, and in about 40% of cases of classical Hodgkin's lymphoma (see REFS 27–30 for reviews) (TABLE 2). Another member of the herpes-virus family, human herpes virus 8, is implicated in the pathogenesis of primary effusion lymphomas[31]. The oncogenic features of herpes virus 8 are not well understood, but it was recently shown that the viral protein FLIP activates the transcription factor NF-κB, which is an important survival factor in primary effusion lymphoma cells[32].

Role of the BCR in B-cell lymphomas

Role of the BCR in the survival of normal B cells. Throughout their lives, B cells undergo stringent selection for expression of the appropriate BCR. Pre-B cells are selected for a pre-BCR (composed of Ig heavy chains and surrogate light chains), and immature B cells are selected for expression of a non-autoreactive, functional BCR. After these steps, GC B cells are only able to survive the GC reaction and differentiate into memory or plasma cells if somatic mutations in their V-region genes result in expression of a BCR with increased affinity for a

CD95
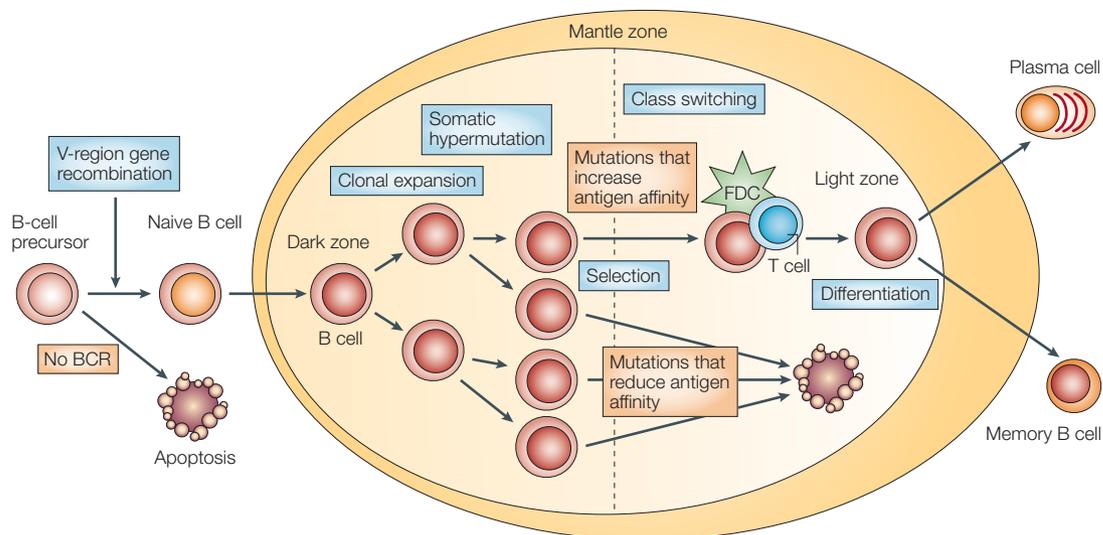Cell-surface receptor that
mediates apoptosis signalling.

Figure 2 | **B-cell differentiation in the germinal-centre reaction.** Mature (naive) antigen-activated B cells that receive signals known as 'T-cell help' are driven into primary B-cell follicles in secondary lymphoid organs such as lymph nodes, where they establish germinal centres (GCs; lightest yellow region) [103]. The naive IgM[+]IgD^{+} B cells that constitute the primary B-cell follicle are replaced by the proliferating GC B cells and displaced to the outside of the follicle, where they form a mantle zone around the GC. In the GC, a dark zone and a light zone can be distinguished (left and right sides, respectively). The dark zone mainly consists of proliferating GC B cells, whereas the GC B cells in the light zone are resting[103]. In proliferating GC B cells, the process of somatic hypermutation is activated, which leads to the introduction of mutations at a high rate into the rearranged Ig variable (V)-region genes of the B cells[102]. Most mutations are disadvantagous for the cells— such as those that lead to reduced affinity of the BCR for antigen and cause cells to undergo apoptosis. A few GC B cells will acquire mutations in the BCR that increase their affinity for antigen, and these cells will be positively selected. The selection process presumably takes mainly place in the light zone, where the GC B cells are in close contact with CD4^{+} T cells and follicular dendritic cells (FDCs). A fraction of these GC B cells undergo class-switch recombination[104]. Finally, GC B cells differentiate into memory B cells or plasma cells and leave the GC microenvironment.

cognate antigen[3]. Even mature resting B cells are constantly under selective pressure to express the BCR — ablation of BCR expression in mice leads to the apoptotic death of BCR-negative B cells[33,34]. So, it seems that this BCR dependency is a main determinant of B-cell survival. It is still debated whether the survival signal supplied by the BCR is an autonomous signal or is initiated by low-level BCR activation by antigen.

BCR dependency of B-cell lymphomas. The selection for expression of a BCR also seems to occur in malignant B cells. Indeed, most B-cell lymphomas still express a BCR, although sometimes at relatively low levels[35–37] (BOX 2). The proposal that there is a need for BCR-derived survival signals is indirectly supported by the observation that translocations into the Ig-loci are virtually always found on the non-productively rearranged Ig loci, with a few exceptions[38]. As the three Ig-gene-remodelling processes that are implicated in the generation of these translocations — V-region gene recombination, class switching and somatic hypermutation (FIG. 1) — principally occur in both Ig alleles, translocation events should happen at nearly equal frequency on the expressed Ig allele and the non-expressed allele. However, as the expressed Ig alleles are not found to be inactivated by translocation events, it seems that at least at the time that the translocations happened, the inability to form a BCR was incompatible with survival of the cells and development into a B-cell tumour.

Further evidence that the BCR supplies important survival signals to B-cell lymphoma cells is provided by the observation that treatment of patients who have follicular lymphoma with ANTI-IDIOTYPIC ANTIBODIES did not result in the emergence of BCR-negative lymphoma variants — either through downregulation of BCR expression or by selected outgrowth of clones with inactivating Ig V-region gene mutations[39,40]. Finally, several types of lymphoma show ongoing V-region gene mutation during tumour clone expansion[39,41–44]. As a considerable fraction of mutations would interfere with BCR expression or function, such as nonsense mutations or replacement mutations that prevent proper heavy- and light-chain pairing, it is notable that such lymphomas also retain BCR expression[35,37]. Indeed, it has been determined that two types of destructive somatic mutation — nonsense mutations and deletions or duplications causing reading-frame shifts — account for nearly 10% of mutation events, if mutations accumulate under non-selective conditions[15,45]. So, the rare occurence of BCR-loss variants of lymphomas with ongoing somatic hypermutation, such as follicular lymphoma, Burkitt's lymphoma, lymphocyte-predominant Hodgkin's lymphoma or mucosa-associated lymphoid tissue (MALT) lymphomas, is a strong indication that lymphoma cells undergo selection for BCR expression. Therefore, the survival signals supplied by BCR expression in normal B cells might also promote survival of B-cell lymphoma cells.

ANTI-IDIOTYPIC ANTIBODIES
Antibodies that bind to the unique determinants in the V-region of another antibody.

Exceptional B-cell lymphomas that do not express the BCR. Although evidence is strong that most B-cell lymphomas depend on BCR expression, there are a few exceptions (BOX 2). In classical Hodgkin's lymphoma, inactivating Ig V-region gene mutations that render

originally functional V-region gene rearrangements non-functional were detected in 25% of cases[46,47]. As only a small fraction of inactivating mutations that occur in mutating GC B cells can easily be identified (for example, nonsense mutations and deletions), it is

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Box 1 | Cellular origin of human B-cell lymphomas

Human B-cell lymphomas are assigned to their proposed normal B-cell counterpart. Most lymphomas are derived from germinal-centre (GC) B cells or from B cells that have passed through the GC, indicating its role in the pathogenesis of B-cell lymphoma. As shown in the figure, the GC is surrounded by a mantle zone of naive B cells, most of which express the CD5 marker — these might comprise a distinct B-cell subset. The marginal zone is a B-cell-rich zone located between B-cell follicles and the T-cell area in the spleen (a similar region is present in Peyer's patches, but usually not in lymph nodes). The origin of marginal-zone B cells is debated, and probably includes post-GC memory B cells and naive B cells involved in T-cell-independent immune responses. Extranodal mucosa-associated lymphoid tissue (MALT) lymphomas and nodal marginal-zone B-cell lymphomas (not shown) are presumably derived from marginal-zone B cells. Splenic marginal-zone B-cell lymphomas comprise both follicular and marginal-zone B cells, and often carry unmutated variable (V)-region genes. These lymphomas might therefore be derived from naive B cells prone to undergo marginal-zone B-cell differentiation[105]. Whereas most mantle-cell lymphomas are believed to be derived from CD5+ (naive) B cells of the mantle zone, about 20–30% of cases carry mutated V-region genes, indicating that they have passed through the GC. The origin of B-cell chronic lymphocytic leukaemia (B-CLL) cells has been debated. About half of the cases of B-CLL carry mutations in V-region genes. Both subsets of B-CLL have been proposed to derive either from CD5+ B cells, memory B cells or marginal-zone B cells[106]. Post-transplant lymphomas, which often develop in patients after organ transplantation, are often derived from antigen-selected, BCR-expressing GC B cells, whereas others might be derived from pre-apoptotic GC B cells[55–57]. Gene-expression profiling identified two main subtypes of diffuse large B-cell lymphoma (DLBCL), one with a profile resembling GC B cells (GC-type), and the other resembling *in-vitro*-activated B cells (ABC-type)[8]. Primary mediastinal B-cell lymphomas are believed to be derived from post-GC B cells of the thymus.

Solid arrows denote B-cell differentiation steps and broken arrows assign the various lymphomas to their proposed normal counterpart.
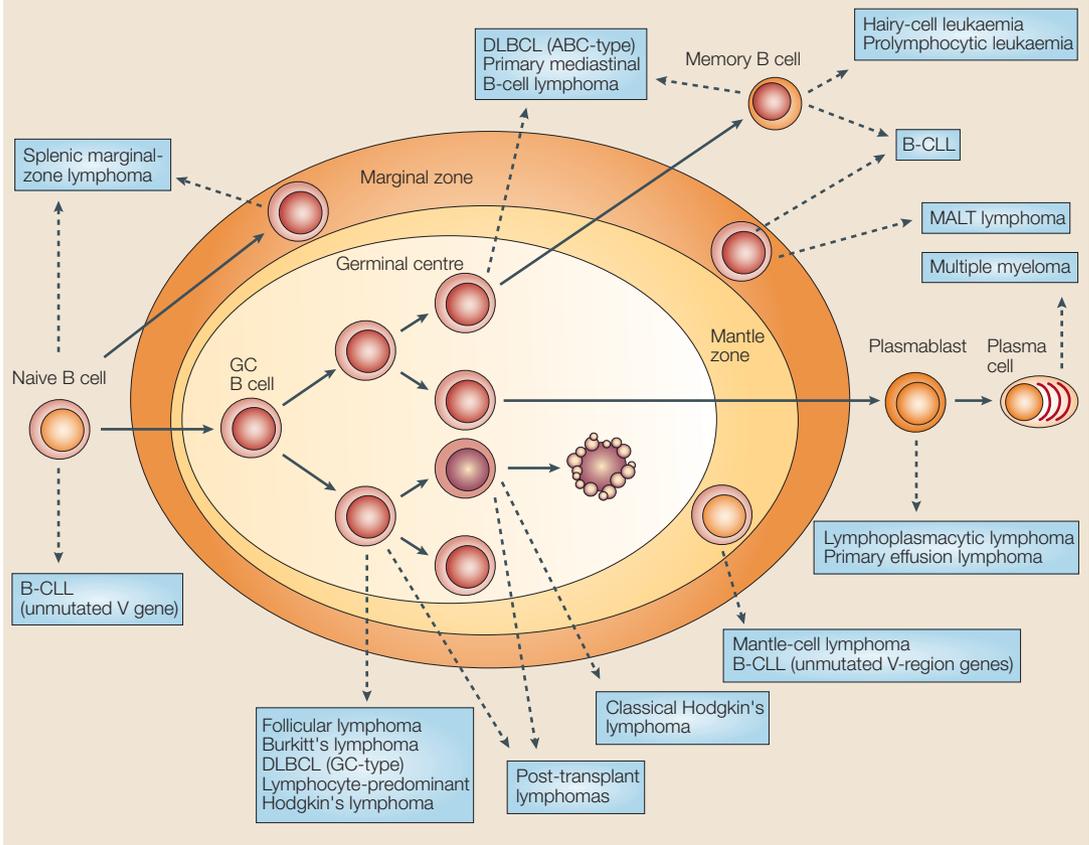
CD5
A cell-surface glycoprotein that is expressed by virtually all T cells and a subset of B cells.

possible that Hodgkin and Reed–Sternberg (HRS) cells — the tumour cells in patients with classical Hodgkin's lymphoma — in most if not all cases are derived from pre-apoptotic GC B cells that have lost the capacity to express high-affinity BCR. How can HRS cells escape selection to evade apoptosis? In about 40% of cases of classical Hodgkin's lymphoma, HRS cells are infected by EBV and express the EBV-encoded latent membrane protein 2A (LMP2A)[28]. LMP2A harbours an immunoreceptor tyrosine-based activation motif, which is also found in the CD79A and CD79B (also known as Igα and Igβ, respectively) molecules of the BCR and is required for BCR-mediated survival signalling[33]. Studies of transgenic mice that express LMP2A in B cells have shown that LMP2A expression can replace the BCR-mediated signals[48,49]. So, expression of LMP2A in an EBV-infected GC B cell that is undergoing hypermutation might rescue the cell from apoptosis following acquisition of unfavourable somatic V-region gene mutations. After acquisition of additional transforming events (other than EBV infection), that cell could, in rare instances, give rise to an HRS tumour clone[46]. The role of LMP2A in the established HRS cell clone, however, is less clear, because HRS cells have downregulated expression of central components of the BCR signalling cascade[50], including spleen tyrosine kinase (SYK) and SLP65, which seem to be essential for the function of LMP2A as a BCR surrogate[51,52].

Indeed, HRS cells have lost expression of nearly all B-cell-typical genes[50,53,54]. Whether this 'lost B-cell phenotype' is directly related to pathogenesis and/or the presumed derivation from crippled GC B cells is unclear. Perhaps, for a GC B cell, which because of disadvantageous somatic mutations does not receive appropriate survival signals and would therefore normally undergo apoptosis, it is advantageous to lose its B-cell identity as a means of becoming independent from the stringent selection for expression of a (high-affinity) BCR. Such a phenotypic change might be promoted by, or depend on, transforming events involved in HRS-cell generation. Alternatively, the loss

Table 2 | **Mechanisms of B-cell lymphoma pathogenesis**

Lymphoma	Chromosomal translocations	Tumour-suppressor gene mutations	Viruses	Other alterations
Mantle-cell lymphoma	CCND1–IgH (95)[107]	ATM (40)[108,109]		Deletion on 13q14 (50–70)[110]*
B-cell chronic lymphocytic leukaemia	–	ATM (30)[111,112], TP53 (15)[113]	–	Deletion on 13q14 (60)[114]*
Follicular lymphoma	BCL2–IgH (90)[12–14]	–	–	–
Diffuse large B-cell lymphoma	BCL6–various (35)[115,116], BCL2–IgH (15-30)[117], MYC–IgH or MYC–IgL (15)[118]	CD95 (10–20)[25], ATM (15)[119], TP53 (25)[120,121]	–	Aberrant hypermutation of multiple proto-oncogenes (50)[18]
Primary mediastinal B-cell lymphoma	–	SOCS1 (40)[122]	–	Aberrant hypermutation of multiple proto-oncogenes (70)[123]
Burkitt's lymphoma	MYC–IgH or MYC–IgL (100)[124,125]	TP53 (40)[113], RB2 (20–80)[126]	EBV (endemic, 95; sporadic, 30)[28]	–
Post-transplant lymphomas	–	–	EBV (90)[28]	–
Classical Hodgkin's lymphoma	–	IKBA (10-20)[127–129], IKBE (10)[130], CD95 (<10)[131]	EBV (40)[28]	REL amplifications (50)[132]
Lymphocyte-predominant Hodgkin's lymphoma	BCL6–various (48)[133]	–	–	–
Splenic marginal-zone lymphoma	–	–	–	Deletion on 7q22-36 (40)[134]*
MALT lymphoma	API2–MALT1 (30)[135], BCL10–IgH (5)[136,137], MALT1–IgH (15-20)[138], FOXP1–IgH (10)[139]	CD95 (5-80)[25,140,141]‡	Indirect role of Helicobacter pylori in gastric MALT lymphomas[85]	–
Lymphoplasmacytoid lymphoma	PAX5–IgH (50)[142]	–	–	–
Primary effusion lymphoma	–	–	HHV8 (95)[143], EBV (70)[28]	–
Multiple myeloma	CCND1–IgH (15-20)[144], FGFR3–IgH (10)[145], MAF–IgH (5-10)[146]	CD95 (10)[147]	–	Various MYC alterations (40)[148], RAS mutations (40)[149], deletion on 13q14 (50)[150]*

Numbers in brackets indicate the percentage of cases known to carry mutations in this gene. Lymphomas for which no specific transforming events have been identified are not listed. Also not listed are transforming events that occur in less than 5% of cases of a lymphoma type. *The genes relevant for lymphoma pathogenesis affected by these deletions have not yet been identified. ‡Different frequencies reported for different subtypes of MALT lymphoma. API2, apoptosis inhibitor 2; ATM, ataxia telangiectasia mutated; B-CLL, B-cell chronic lymphocytic leukaemia, CCND1, cyclin D1; EBV, Epstein–Barr virus; FGFR3, fibroblast growth factor receptor 3; FOXP1, forkhead box P1; HHV8, human herpes virus 8; IKBA, inhibitor of nuclear factor-κBα; IKBE, inhibitor of nuclear factor-κBε; MALT, mucosa-associated lymphoid tissue; MALT1, mucosa associated lymphoid tissue lymphoma translocation gene 1; PAX5, paired box gene 5; RB2, retinoblastoma-related gene 2; SOCS1, suppressor of cytokine signalling 1.

Box 2 | **The B-cell-receptor dependency of human B-cell lymphomas**

Different types of B-cell lymphoma express different levels of B-cell receptor (BCR), or BCRs with different specificities or levels or activity. Listed below are the details of BCR function in these various cancer types.

Lymphomas that express BCR
- Mantle-cell lymphoma.
- Diffuse large B-cell lymphoma.
- Splenic marginal-zone lymphoma.
- Lymphocyte-predominant Hodgkin's lymphoma.
- Hairy-cell leukaemia.
- Prolymphocytic leukaemia.
- Burkitt's lymphoma.
- Lymphoplasmacytic lymphoma.

Lymphomas associated with BCR expression and indication for antigen activation
- Follicular lymphomas arise and grow in the germinal centre and in some patient samples the BCR is autoreactive. The BCR variable domain contains mutations that promote carbohydrate modification.
- Gastric mucosa-associated lymphoid tissue lymphomas are in many cases associated with autoreactive BCR, particularly with rheumatoid factors.
- B-cell chronic lymphocytic leukaemia has a restricted variable (V)-region gene repertoire and the BCR is often autoreactive. A BCR specific to human T-cell lymphotropic virus 1 has been identified in patients who are infected with this virus.
- In hepatitis C virus (HCV)-associated lymphomas, HCV-specificity of BCR has been reported in some cases. Disease regression occurs after antiviral therapy.
- In primary central nervous system lymphomas, about half the cases express the same heavy-chain (V_H) gene segment (VH4-34), whereas other genes of the BCR are diverse, indicating tumour-cell stimulation by superantigen binding to the BCR.

Lymphomas that do not express BCR
- Classical Hodgkin's lymphomas are associated with inactivating immunoglobulin (Ig) V-region gene mutations in at least 25% of cases. Transcription factors that promote BCR expression are downregulated. A transcriptionally inactive chromatin structure is seen in these lymphomas.
- In post-transplant lymphomas, inactivating V-region gene mutations are observed in at least 10–20% of cases.
- Primary effusion lymphomas are not associated with inactivating Ig V-region gene mutations. However, downregulation of transcription factors that promote BCR expression is seen.
- Primary mediastinal B-cell lymphomas are not associated with inactivating Ig V-region gene mutations. Expression of transcription factors that regulate BCR expression is seen, but internal Ig enhancer activity is downregulated.

The requirement for BCR expression is unclear in primary mediastinal B-cell lymphomas. These lymphomas lack detectable BCR expression and have downregulated expression of components of the BCR signalling cascade and activity of the internal IgH enhancer, but no samples with inactivating V-region gene mutations have been described[58–60]. Recent gene-expression studies revealed, surprisingly, that primary mediastinal B-cell lymphomas are in many aspects closely related to HRS cells of classical Hodgkin's lymphoma, and are more similar to this lymphoma than to other diffuse large B-cell lymphomas. But unlike Hodgkin's lymphoma, mediastinal lymphomas have largely retained a B-cell gene-expression pattern and are not associated with EBV infection[61,62].

In the rare primary effusion lymphomas, BCR expression is usually very low or undetectable, but no cases with inactivating mutations have been reported[63–65]. Notably, these lymphomas also lack expression of the transcription factors PU.1, OCT2 and BOB1, which are important regulators of Ig transcription[66]. The loss of these transcription factors could explain the downregulation of Ig expression in primary effusion lymphoma cells. These lymphomas also usually lack detectable expression of other B-cell markers, such as CD19 and CD20, indicating a loss of the B-cell phenotype in the effusion lymphomas that is similar to that of classical Hodgkin's lymphomas, although several aspects of their phenotype are also compatible with a plasmablastic differentiation[67].

Antigen activation of B-cell lymphomas
Is the ability of the BCR to transmit survival signals, or its ability to interact with antigen to activate lymphocyte proliferation, required for lymphomagenesis? Studies in several different lymphoma types have indicated that lymphoma cells recognize antigen, and that stimulation by antigen binding contributes to survival and proliferation of lymphoma cells (BOX 2). This concept was first proposed more than 40 years ago[68].

In B-CLL cells, the BCR has been frequently shown to bind AUTOANTIGENS[69,70]. In some cases, however, B-CLL cells show specificity for foreign antigens, such as viral proteins — this is the case in B-CLL that is positive for human T-lymphotropic virus type I (REF. 71). Moreover, seven subgroups of B-CLL have recently been identified that show strikingly similiar V_H and V_L gene-rearrangement sequences among members of a group[72–75]. Although it is possible that this finding is due to derivation of the lymphoma cells from a so-far-unrecognized B-cell subset with a highly restricted V-region gene repertoire, it is more likely that this reflects selection and activation of these cases by a restricted set of ANTIGENIC EPITOPES. In line with this view, five of the seven groups identified belong to the subclass of unmutated B-CLL, which has a phenotype reminiscent of antigen-activated B cells[76].

Restricted V-region gene usage is also a hallmark of primary central nervous system lymphoma. However, unlike the situation with B-CLL, this restriction only holds true for the expressed V_H gene segment, which is the same in about half of the cases[44,77]. This indicates

CD19
B-cell-specific surface molecule expressed from the earliest B-cell precursor stages up to the plasmablast stage. Regulates the responsiveness of B cells following B-cell-receptor crosslinking.

CD20
B-cell-specific surface marker expressed by pre-B and all mature B cells. Downregulated on plasma cells.

of the B-cell phenotype might be largely unrelated to derivation from crippled GC B cells, and might instead reflect transforming events in HRS-cell pathogenesis that render the cells independent from expression of a BCR. As a consequence, the HRS cells would no longer be under selective pressure to maintain their B-cell-specific expression programme and could adopt another phenotype.

Lymphoma clones with inactivating V-region gene mutations have also been observed in a fraction of cases of post-transplant lymphomas[55–57]. These are usually EBV positive and express all latent EBV genes, so it is possible that LMP2A promotes the survival of these crippled lymphoma cells.

binding of an antigen exclusively to the V_H gene segment, and that antigen might therefore be a SUPER-ANTIGEN. So, stimulation of B cells by a superantigen might be involved in the pathogenesis of primary central nervous system lymphomas.

Studies also indicate a role for antigen activation in the pathogenesis of follicular lymphoma. First, lymphoma cells from several patient samples were found to express BCR with autoreactivity[78]. Second, follicular lymphoma cells show ongoing somatic hypermutation during tumour-clone expansion, and the pattern of these mutations is indicative of their selection by antigen[79]. Third, about 80% of follicular lymphomas carry somatic V-region gene mutations that result in the generation of carbohydrate-linking motifs[80]. Such mutations were also found at a similar frequency in endemic Burkitt's lymphoma, but are present in less than 10% of cases of multiple myeloma, MALT lymphoma or normal B cells[80,81]. The strong selection for the acquisition of carbohydrate modifications to the BCR V region of follicular and endemic Burkitt's lymphoma cells indicates that these moieties are important for lymphoma formation. It is unclear whether the carbohydrates are involved in the recognition of antigens or in the interaction of the lymphoma cells with stromal elements.

Hepatitis C virus (HCV)-associated B-cell lymphomagenesis has been associated with viral antigens. One study demonstrated the direct binding specificity of the BCR for a viral-envelope protein[82]. Importantly, treatment of several patients with HCV-associated splenic B-cell lymphomas with anti-viral interferon therapy not only eliminated the virus, but also caused regression of the lymphoma[83]. The fact that several HCV-unrelated splenic B-cell lymphomas did not respond to interferon therapy supports the idea that the regression of the lymphoma is indeed caused by the elimination of the stimulating antigen, rather than sensitivity of the lymphoma cells themselves to interferon[83].

Foreign antigen seems to have an indirect role in activating B-cell-lymphoma clones in gastric MALT lymphomas. Here, nearly all cases are associated with chronic infection of the gastric mucosa by the bacterium *Helicobacter pylori*[84]. However, it is not the lymphoma cells that recognize the bacterium, but T-helper cells, which stimulate the proliferation of the lymphoma cells[85]. Notably, some studies have indicated that the lymphoma B cells recognize autoantigen(s)[86,87], and a recent analysis showed that a considerable fraction of gastric and salivary-gland MALT lymphomas (20–40% of cases) express autoantibodies with specificity for IgG (that is, rheumatoid factors)[88]. Foreign and autoantigens therefore seem to synergize in the pathogenesis of gastric MALT lymphomas.

Role of the lymphoma microenvironment

In many lymphomas, the tumour microenvironment is likely to be important for the survival and/or proliferation of the tumour cells. In follicular lymphoma, the tumour cells reside and proliferate in follicular structures in close association with T-helper cells and follicular dendritic cells, as is typical for normal GC B cells. Some

B cells belonging to the lymphoma clone can also be found in the interfollicular areas, but these cells show little proliferative activity[89]. So, the lymphoma cells seem to require the cellular interactions in the GC-like environment for their proliferation. This is supported by studies that showed that follicular lymphoma cells can proliferate *in vitro* only if they are cultured together with CD4+ T cells, or with stromal cells and an antibody against the CD40 receptor[90,91]. CD40 is expressed by follicular-lymphoma cells, and its activation is a main survival signal for normal GC B cells. Notably, it was recently shown that the survival of patients with follicular lymphoma is correlated with characteristic features of non-tumour cells in the lymphoma tissue[92]. So, it seems that follicular lymphoma cells retain key features of normal GC B cells, including the dependency on BCR expression and activation, as well as the interaction with T cells and follicular dendritic cells in the follicular microenvironment.

Low-grade gastric MALT lymphomas also depend on the interaction with tumour-infiltrating T cells. These lymphomas are closely associated with *H. pylori* infection. *In vitro*, *H. pylori* stimulates the proliferation of tumour-infiltrating T cells, but not of the lymphoma B cells directly[86,87]. These T cells then provide contact-dependent help to promote the survival and proliferation of the lymphoma cells[85]. The fact that elimination of *H. pylori* by antibiotic treatment often leads to regression of the lymphoma highlights the importance of this interaction in lymphoma progression[84].

In B-CLL, the leukaemic cells in the peripheral blood show very little proliferative activity, indicating that the expansion of the tumour clone might take place in other tissues affected by the lymphoma. Indeed, proliferation of B-CLL cells is largely restricted to proliferation centres in lymph nodes and bone marrow, where the cells are in intimate contact with CD4+ T cells and dendritic cells[93]. The *in vitro* survival of B-CLL cells can be significantly extended by culturing the leukaemic cells with stromal cells, and B-CLL cell proliferation can be induced by triggering the CD40 receptor[94,95]. As CD40L is expressed by a fraction of T cells in the proliferation centres[96], it is intriguing to speculate that the T cell–B-CLL interaction in that particular microenvironment provides important survival and proliferation signals for the malignant clone.

Histological analyses of classical Hodgkin's lymphoma cells have also indicated an important role of the cellular microenvironment in the pathogenesis of this B-cell malignancy. The HRS cells usually account for less than 1% of cells in the tumour tissue, and most of the cellular infiltrate is composed of T cells, eosinophils, macrophages, B cells, plasma cells and other cells. Although this cellular infiltrate could partly represent an (unsuccessful) inflammatory response against the HRS cells, there is evidence that at least a large fraction of the non-tumour cells is actively attracted by the HRS cells. For example, HRS cells attract CD4+ T cells by the secretion of large amounts of the cytokine TARC (thymus and activation-regulated chemokine), which is normally only expressed by dendritic cells[97]. Indeed, HRS cells

are usually in direct contact with T-helper cells. Importantly, although HRS cells have lost expression of most B-cell-specific genes, molecules important for interaction with T-helper cells (major histocompatibility complex class II, CD40, CD80 and CD86) are still expressed[47], indicating that this interaction with CD4+ T cells is important for the survival of the HRS cells. The dependency of HRS cells on their typical microenvironment is further supported by the difficulty of maintaining these cells in culture, by the inability of primary HRS cells to survive in immunodeficient mice, and by the observation that HRS cells only rarely disseminate to the peripheral blood[47].

Implications and future directions

In an emerging picture of B-cell malignancy, tumour progression not only depends on transforming events, such as chromosomal translocations, but also on survival signals mediated by the expression of a functional BCR and cellular interactions in the lymphoma microenvironment. In many lymphomas, BCR binding of foreign or autoantigens to stimulate proliferation might also be involved. Other than pathogen-derived antigens that cause chronic infections, certain autoantigens can also stimulate reactive B cells. This concept is also supported by the observation that several autoimmune diseases, such as Sjogren's syndrome, rheumatoid arthritis and autoimmune lymphoproliferative syndrome are commonly associated with an increased risk of lymphoma[98,99]. Moreover, autoantigen specificity for the BCR expressed by the lymphoma has been reported for some patients with autoimmune disease who developed lymphoma[100]. However, it could be that in some cases, antigen activation provides a chronic proliferative stimulus to B cells that only increases their risk of malignant transformation, and that antigen activation does not have an important role in progression of established lymphomas.

The finding that many lymphomas seem to arise from B-cell precursors that were 'frozen' at a particular stage of differentiation could reflect key features of lymphoma pathogenesis. For example, lymphoma-associated

translocations that disrupt the *BCL6* gene result in constitutive expression of this transcription factor, keeping the cells in a proliferative, GC B-cell-like stage, and prevents their differentiation into a resting post-GC B-cell stage. The dependency of lymphomas on BCR expression, antigen triggering and microenvironmental survival signals might contribute to the relatively close similarity between many B-cell lymphomas and their normal B-cell counterparts in terms of phenotype and gene-expression pattern. The dependency on such factors would select for a tumour phenotype that still resembles normal B cells in many aspects. In other instances, if the transforming events release the cells from such a dependency, the lymphoma cells would be free to acquire a markedly different phenotype. This might be best exemplified in classical Hodgkin's lymphoma, where the BCR-deficient HRS cells have lost most features of normal B cells.

Can new treatment options for B-cell lymphomas be developed from our current understanding of the role of the microenvironment in lymphoma progression and of antigen as the driving force for proliferation of lymphoma cells? Lymphomas might be treated by unconventional approaches, such as by interfering with survival or proliferation signals from other cells in the lymphoma microenvironment, by eliminating antigens that promote expansion of tumour cells, or by interfering with the BCR signalling pathway. The success in treating patients with *H. pylori*-associated gastric MALT lymphomas, or patients with HCV-associated B-cell lymphomas, by eliminating the infectious agents are the first promising examples of this approach. Finally, the gene-expression profiling studies of lymphomas might reveal previously unrecognized mechanisms of pathogenesis in B-cell lymphomas that could lead to novel therapeutic strategies. For example, the recognition that a subtype of diffuse large B-cell lymphoma expresses an active NF-κB signature led to the identification of a dependency of these lymphomas on constitutive NF-κB activity — making this transcription factor an attractive target for therapy[101].

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National Cancer Institute: http://cancer. gov/
Hodgkin's lymphoma | multiple myeloma
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Biography

Ralf Küppers studied biology and did his Ph.D. studies at the University of Cologne with Klaus Rajewsky. After finishing his Ph.D. in 1995, he remained in Cologne, setting up his own research group there. In 2000, he did a 6-month sabbatical at Columbia University with Riccardo Dalla-Favera, and in 2001 returned to Germany. Since 2004 he has been a professor of molecular genetics at the Institute for Cell Biology (Tumor Research), University of Duisburg-Essen, Essen, Germany. The main interests of his group are the pathogenesis of human B-cell lymphomas, in particular Hodgkin's lymphoma, and the study of normal B-cell development in humans. These two areas have been complemented by a third topic in recent years — the biology of Epstein–Barr virus infection and its role in lymphomagenesis.

LINKS

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IgH
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=3492

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OCT2
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