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Review

Pathways towards indolent B-cell lymphoma — Etiology and therapeutic strategies

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ABSTRACT

Although patients with indolent B-cell lymphomas have a relatively good survival rate, conventional chemotherapy is not curative. Disease courses are typically characterized by multiple relapses and progressively shorter response duration with subsequent lines of therapy. There has been an explosion of innovative targeted agents in the past years. This review discusses current knowledge on the etiology of indolent B-cell lymphomas with respect to the role of micro-organisms, auto-immune diseases, and deregulated pathways caused by mutations. In particular, knowledge on the mutational landscape of indolent B-cell lymphomas has strongly increased in recent years and harbors great promise for more accurate decision making in the current wide range of therapeutic options. Despite this promise, only in chronic lymphocytic leukemia the detection of *TP53* mutations and/or del17p currently have a direct effect on treatment decisions. Nevertheless, it is expected that in the near future the role of genetic testing will increase for prediction of response to targeted treatment as well as for more accurate prediction of prognosis in indolent B-cell lymphomas.

1. Introduction

Indolent B-cell lymphomas represent approximately one third of all B-cell non-Hodgkin lymphomas. Although patients with these types of lymphoma have a relatively good survival rate, morbidity and mortality are significant, especially considering the fact the majority of these lymphomas is considered incurable. This review discusses recent developments in the etiology of indolent B-cell lymphomas which can provide a rationale for prioritizing and combining novel agents.

In form and function, cells of indolent B-cell lymphomas resemble their normal counterparts and act in close contact with and are dependent on their micro-environment. This dependence on the micro-environment is evidenced by the difficulty to culture indolent B-cell lymphoma cells which indicates that these cells cannot proliferate autonomously but require stimulatory signals. Examples of signals that can stimulate the development of B-cell lymphoma include long-standing inflammatory conditions in the context of infection or auto-immune disease. Another line of evidence for the role of antigenic stimulation of lymphomas comes from the fact that in multiple types of B-cell lymphoma, stereotyped B-cell receptors have been shown, indicating that specific antigens are implicated in lymphomagenesis. The first part of this review is concerned with these processes driving the development of B-cell lymphomas.

A second issue is: what makes neoplastic B-cells different from normal B-cells? Which genetic events are present? It is already known for a long time that the early genetic alterations like the t(14;18) in follicular lymphoma are actually a common occurrence in healthy individuals and thus not sufficient to make a lymphocyte malignant. The genetic revolution is rapidly changing our understanding of B-cell lymphomas and in the second part of this review, the pathways and mutations involved in B-cell lymphomagenesis and the drugs that target them are discussed.

2. Micro-organisms

Multiple different species of bacteria have been implicated in the development of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissues (EMZL) with *Helicobacter pylori* being the best studied and most convincing example (Table 1). H. pylori can be detected in up to 92% of EMZL of the stomach and eradication of the

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Table 1
Micro-organisms in indolent B-cell lymphomas.

Micro-organism	Related lymphoma	Summary of association
Helicobacter pylori	MALT lymphoma of the stomach	Strong evidence for association: • H. pylori present in up to 92% of MALT lymphomas. • Eradication results in long-term remission in three quarters of patients with early-stage disease. • Translocations in *BIRC3*, *MALT1* and/or *BCL10* predict resistance to eradication treatment.
Chlamydophila psittaci	Ocular adnexal MALT lymphoma	Some evidence for association • *C. psittaci* present in subset of OAMZL, varying between regions and with detection methods. • Response to antibiotic treatment in a subset of patients with *C. psittaci* positive lymphoma, but also in patients with *C. psittaci* negative lymphoma.
Borrelia burgdorferi	Cutaneous MALT lymphoma	Some evidence for association • *B. burgdorferi* DNA present in a subset of cutaneous MALT lymphoma. • Anecdotal reports of lymphoma response to antibiotic treatment.
Campylobacter jejuni	Immunoproliferative small intestinal disease (IPSID)	Anecdotal reports of association and lymphoma response to antibiotics.
Achromobacter xylosidans	Pulmonary MALT lymphoma	*A. xylosidans* DNA detected more frequently in pulmonary MALT lymphoma than control tissue in a single study.
Epstein Barr virus	No specific type	Only very rarely reported in low-grade B-cell lymphoma
Hepatitis C virus	MALT lymphoma (particularly non-gastric), SMZL, NMZL, LPL, FL	Strong evidence for association • Co-occurrence of HCV infection and lymphoma, with strong geographical variation. • Regression of lymphoma with antiviral therapy in 62–100% of patients.

bacterium by antibiotic treatment results in complete and long-lasting remission of lymphoma in three quarters of patients with early-stage disease [1–5]. In EMZL of the stomach but also of the ocular adnexa (discussed below), the micro-organisms involved do not stimulate the neoplastic B-cells directly, but rather cause an inflammatory milieu with induction of a Th1 immune response with influx of CD4 positive T-cells which stimulate B-cell proliferation through CD40-CD40L interaction. At the same time, the cytotoxic T-cell response is impaired [6]. These factors lead to the outgrowth of autoreactive B-cells which can progress to lymphoma after the acquisition of mutations. With respect to gastric EMZL, most regress after removing the inflammatory stimulus by eradication of H. pylori, but some gastric EMZLs have become H. pylori independent. Factors associated with the lack of a response to H. pylori eradication include a higher disease stage and the presence of specific translocations involving the *BIRC3*, *MALT1*, or *BCL10* gene [7–9]. In both instances, it is suspected that the lymphoma cells have already become independent of the antigenic stimulus. However, even in diffuse large B-cell lymphoma (DLBCL) of the stomach, H. pylori eradication has been reported to result in long-term remission in up to two-thirds of patients, indicating that high-grade lymphomas may also be antigen-dependent [10,11].

A role for *Chlamydophila psittaci* has been suggested in the pathogenesis of ocular adnexal EMZL (OAMZL), following from the observation that it can be detected in up to 80% of OAMZL [12,13] and that antibiotic treatment results in remission in a subset of patients [13]. However, the presence of *C. psittaci* in OAMZL varies greatly between studies, which can at least partially be explained by geographical differences [12–22]. In addition, differences in detection protocols for *C. psittaci* could also be part of the explanation as studies from similar regions (e.g. Italy, the Netherlands, United States) have showed strong differences in *C. psittaci* incidence in OAMZL.

With respect to treatment, most studies showed partial or complete responses in approximately 45% of patients with OAMZL treated with doxycycline antibiotics [23]. However, only two of three studies showed improved response in *C. psittaci*-positive cases. In those two studies, the response rates were 66% vs. 50% and 64% vs. 38% for *C. psittaci* positive vs. negative patients [24,25]. These results suggest that although *C. psittaci* may have a role in the development of OAMZL and is amenable to antibiotic treatment, other (Doxycycline sensitive) bacteria or direct anti-tumor effects of the antibiotics used may also have a role in eradication of the lymphoma. Conversely, detection methods may be insufficient. In conclusion, the role of antibiotic treatment in OAMZL is speculative at best and requires additional study.

In the rare cutaneous EMZL, *Borrelia burgdorferi* has been suggested as a causative agent, with varying frequencies depending on the region where the studies were performed. In endemic areas, up to 40% of cutaneous EMZL showed evidence of Borrelia infection [26–28]. Anecdotal reports have shown tumor response to antibiotic therapy against Borrelia [23].

In immunoproliferative small intestinal disease (IPSID), *Campylobacter jejuni* has been reported as a possible causative micro-organism [29,30]. However, the evidence for this association is limited to anecdotal reports and no clinical studies have been performed. In pulmonary EMZL, *Achromobacter xylosidans* has been detected with increased frequency in lymphomas in comparison to controls, but these results are limited to a single study and have not been validated clinically [31]. Finally, regarding the role of bacteria in the pathogenesis of indolent lymphoma, epidemiological studies have shown an association between an increased risk of CLL and a history of pneumonia [32]. In primary intraocular B-cell lymphoma, the presence of *Toxoplasma gondii* has been reported [33].

Co-occurrence of Hepatitis C virus (HCV) infection and lymphoma has been reported in multiple types of non-Hodgkin lymphoma, including indolent B-cell lymphomas. Within the group of indolent B-cell lymphomas, lymphoplasmacytic lymphoma and marginal zone lymphoma (MZL, particularly splenic MZL and non-gastric MALT lymphoma) are most often associated with HCV infection. However, the association between B-cell lymphoma and HCV has varied significantly between studies, with stronger associations in those areas with a higher HCV prevalence. In systematic reviews, 13%–18% of B-cell lymphomas were HCV-associated [34–36]. In addition to epidemiological data, regression of lymphoma after eradication of HCV with antiviral therapy provides further evidence for a role of HCV in B-cell lymphoma development. Response of lymphoma to antiviral treatment has been recorded in extranodal, splenic, and nodal MZL and in smaller numbers of lymphoplasmacytic lymphoma (LPL) and follicular lymphoma (FL) [37–44]. The studies reported thus far with a total number of almost 200 patients, reported an overall response rate of 62–100% and complete response rate of 50–89% [45]. Accordingly, antiviral treatment

can be considered as first-line treatment in patients with indolent B-cell lymphoma in whom immediate antilymphoma therapy is not necessary due to limited stage of disease or low tumor burden. Novel agents against HCV (e.g. sofosbuvir, simeprevir) are also promising in the setting of lymphoma arising in patients with HCV. In two recent case reports, regression of SMZL was reported after interferon free HCV treatment [46,47], but formal studies have not been reported yet. The mechanisms by which HCV induces lymphoma are not well understood, but possibilities include chronic antigenic stimulation and/or a direct oncogenic effect of the virus [36].

3. Stereotyped B-cell receptors

Although micro-organisms have been implicated in the development of B-cell lymphoma, the neoplastic B-cells usually do not have BCRs that recognize antigens belonging to these micro-organisms. Therefore, infections appear to contribute mainly by forming a pro-inflammatory environment rather than directly stimulating the neoplastic cells. The question then arise to what extent antigen stimulation is necessary for B-cell lymphoma development and which antigens are involved. With respect to the first part of this question, several lines of evidence argue for a role of antigens in lymphomagenesis.

First, the BCR is retained in the majority of B-cell lymphomas and most lymphoma cells cannot survive autonomously ex vivo. This suggests a dependence on the micro-environment and on signaling through the BCR [48]. Second, studies into the structure of the B-cell receptor have revealed stereotyped B-cell receptors in different types of B-cell lymphoma.

In chronic lymphocytic leukemia (CLL), multiple subsets with specific stereotyped receptors have been recognized, with approximately one third of CLLs having a stereotypic BCR [49]. Part of these stereotypes are associated with a specific clinical presentation or prognosis. In splenic MZL, about one third of lymphomas express the same immunoglobulin heavy chain variable gene. The fact that the BCRs in different lymphomas show a similar IGH structure suggests selection of tumor cells by specific antigens or superantigens [50].

If B-cell lymphomas are dependent on antigens for their survival, then which antigens are responsible? In both SMZL and CLL, it has been shown that the BCRs of the neoplastic cells are often reactive to self-antigens, including antigens which are expressed during cell death [51–55]. In addition, reactivity to viral bacterial and fungal antigens has also been suggested, but the bacteria implicated are different from those previously discussed in the context of MALT lymphoma. In CLL, the neoplastic cells can express BCRs that react with epitopes on common bacteria [56]. Also in CLL, an association between usage of the immunoglobulin heavy chain variable 4-34 (IGH4-34) gene and activation of EBV and CMV, suggesting that viral antigens could facilitate clonal expansion and neoplastic transformation [57].

4. Auto-immune diseases

Auto-immune diseases are associated with an increased risk of lymphoma [58]. In particular Sjögren's syndrome and systemic lupus erythematosus were associated with an increased risk of lymphoma in a large pooled analysis [59]. With respect to indolent B-cell lymphomas in the context of auto-immune disease, development of MZL in Sjögren's syndrome is the most striking example. Patients with Sjögren's syndrome have a 7-fold increased risk of non-Hodgkin lymphoma and a 1000-fold increased risk of MZL of the parotid gland [59]. Clinical and laboratory feature that predict lymphoma development include permanent swelling of the salivary glands, oral and ocular symptoms, vasculitis, lymphadenopathy, purpura, cryoglobulinemia, lymphopenia, low C4, M-protein and germinal center-like structures in the salivary gland.

With respect to the pathophysiology of lymphoma development in Sjögren's syndrome, it has been suggested that the B-cell clone often has a B-cell receptor with rheumatoid factor (RF) activity, being directed against the Fc portion of IgG [60–63]. The hypothesis is then that polyclonal B-cells which are activated in the auto-immune inflammatory environment acquire additional mutations and eventually grow out to become a B-cell lymphoma [62].

5. Preneoplastic conditions

Much has been learned about the pathogenesis of indolent lymphomas from precursor lesions, which include precursors of FL and monoclonal B-cell lymphocytosis (MBL).

Deregulation of BCL2 by the t(14;18) translocation is the hallmark genetic lesion of FL. However, this translocation in itself is insufficient for neoplastic transformation. This is well illustrated by studies into FL and its precursors. With highly sensitive techniques, cells harboring the t(14;18) translocation can be detected in over half of the healthy adult population, of which only a very small minority will develop FL [64,65]. These cells carrying the t(14;18) are antigen experienced and it is hypothesized that multiple re-entries in the germinal center with aberrant somatic hypermutation induce mutations, thereby contributing to oncogenesis. In situ follicular neoplasia (ISFN, also termed follicular lymphoma in situ) is a coincidentally detected phenomenon in lymphoid tissue in which BCL2 and CD10 positive cells colonize germinal centers without architectural distortion. The cells in these follicles have a t(14;18) translocation, but also carry additional genomic alterations [66], suggesting that ISFN could represent a step in between the t(14;18) positive cells detected in healthy individuals and overt FL. Only approximately 5% of individuals with ISFN have developed FL in small studies [67].

MBL is the presence of a monoclonal or oligoclonal B-cell expansion with a B-cell count of $< 5 \times 10^9$ B-cells/L in the absence of symptoms of an overt lymphoproliferative disease. Most cases of MBL (approximately 75%) have an immunophenotype resembling CLL, but other phenotypes are also encountered. Blood samples collected before a diagnosis of CLL consistently show a monoclonal B-cell population, indicating that CLL is preceded by MBL [68]. However, the large majority of MBLs do not progress to CLL. MBL with a low number of clonal B-cells in the peripheral blood ($< 0.5 \times 10^9$/L), termed 'low count' MBL, virtually never progress to CLL whereas 'high count' MBL progresses to CLL at a rate of 1–2% per year and requires follow-up [69,70]. With respect to the immunogenetic profile, low-count MBL is different from CLL with more frequently mutated IGHV genes and a very low prevalence of BCR stereotypy in low-count MBL, whereas high-count MBL resembles CLL with respect to IGHV mutation status and BCR stereotypy [71]. On the contrary, cytogenetic aberrations found in CLL can also be found in low-count MBL, indicating that these lesions are not necessarily associated with progression [72]. High count MBL and low-stage CLL show similar mutational patterns, further indicating that these conditions are part of the same spectrum [73]. Low-count MBL appears to be a different entity which might be related to aging [71].

6. Deregulated pathways

Recent large sequencing efforts in indolent B-cell lymphomas have substantially increased our knowledge on the molecular pathways that are deregulated in these lymphomas. With the concurrent development of drugs that target these specific pathways, the role of targeted treatment for indolent B-cell lymphoma is likely to increase (Fig. 1). Although some indolent B-cell lymphomas are characterized by highly recurrent mutations, most lymphoma subtypes show a low number of genes with a moderate mutation frequency followed by a long tail of genes that are mutated in a low number of cases. The pathways that are most frequently affected are discussed below and summarized in Table 2.

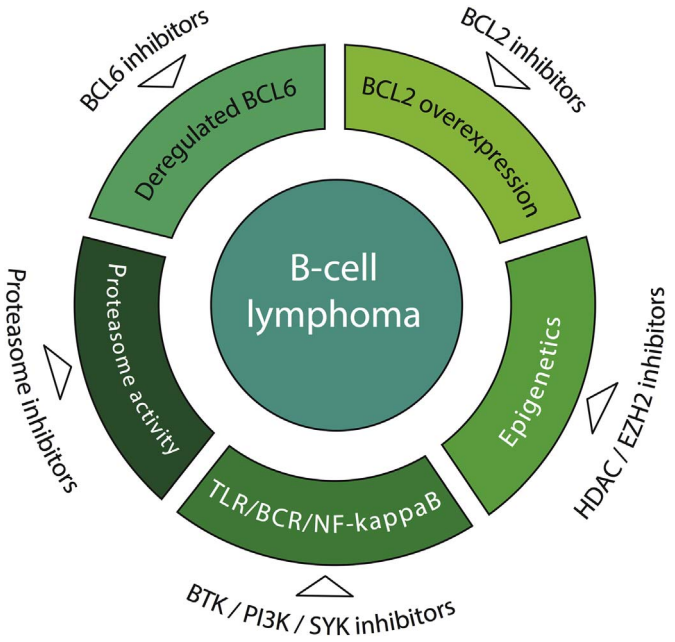

Fig. 1. Deregulated pathways in B-cell lymphoma with targeted treatments.

6.1. DNA damage response and apoptosis (TP53, BCL2, and ATM)

6.1.1. TP53

TP53 is one of the most extensively studied tumor suppressor genes and is well known for its association with a poor prognosis and refractoriness to conventional chemotherapy in CLL. In fact, TP53 mutations and del17p are the only mutations that currently have a direct impact on patient care, with a preferred treatment with novel inhibitors (ibrutinib as single agent or idelalisib combined with anti CD20 treatment) in patients with TP53 mutated CLL with a treatment indication [74,75]. The current standard method of TP53 mutation detection is Sanger sequencing and a for next-generation sequencing a cut-off of mutations present in > 10% allelic fraction is recommended by the European Research Initiative on CLL (www.ericll.org). However, small TP53 mutated subclones are also associated with a worse prognosis and become predominant under conventional treatment, ultimately causing treatment refractoriness [76]. Therefore, low frequency TP53 mutations in CLL, which can be detected by sensitive next generation sequencing techniques, may be of clinical relevance, and should be reported with caution until validation of their prognostic and predictive impact in a larger patient group. Whether treatment with for instance BTK inhibitors will provide similar benefit as it does in patients with > 10% allelic fraction remains to be elucidated. In addition to CLL, an association between TP53 mutations and a worse prognosis has also been shown for FL and MZL [77,78].

6.1.2. BCL2

BCL2 is an anti-apoptotic protein which was initially discovered as the deregulated gene involved in the t(14;18) translocation in FL [79]. In the physiological situation, it is part of the balance between pro-apoptotic and anti-apoptotic proteins in the intrinsic/mitochondrial apoptotic pathway. In the large majority of FLs, overexpression of BCL2 can be explained by the t(14;18) translocation which puts BCL2 under the control of the IGH enhancer. More rarely, translocations between BCL2 and the immunoglobulin light chain loci are encountered. However, many small B-cell lymphomas other than FL express BCL2 without evidence of a BCL2 rearrangement. This can be explained by other mechanisms of BCL2 expression, especially physiological expression, but also *BCL2* amplification, hypomethylation, or deletion of microRNAs that downregulate BCL2 [80–83].

BCL2 is a target for BCL2 inhibitors venetoclax and navitoclax which are currently under investigation for their effectiveness is multiple lymphoma subtypes. In Europe, the European Medicines Agency (EMA) has approved venetoclax for the treatment of CLL with 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor and also for the treatment of CLL in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor. In the United States, venetoclax has been approved by the Food and Drug Administration (FDA) for treatment of patients with CLL with a 17p deletion who have received at least one prior therapy.

Table 2
Mutated genes and their relevance in indolent B-cell lymphomas.

Lymphoma subtype	Mutated gene	Relevance of mutation present
Chronic lymphocytic leukemia/small lymphocytic lymphoma	*TP53*	Associated with worse prognosis. Treatment with novel inhibitors (ibrutinib, idelalisib)
	NOTCH1	Associated with worse prognosis and rituximab resistance
	BIRC3	Associated with worse prognosis
	SF3B1	Associated with worse prognosis
	ATM	Associated with worse prognosis
Follicular lymphoma	*BCL2*	Translocation specific for FL Mutations associated with disease progression
	MLL2, *EZH2*, *EP300*, *MEF2B*	Histone-modifying genes frequently affected in FL
	CARD11, *CD79A/B*, *PRKCB*	NF-kappaB activating mutations, present in one third of follicular lymphomas.
	TP53	Associated with worse prognosis
	TNFRSF14	Affected by loss of 1p36 or mutations
MALT lymphoma	*BIRC3*, *MALT1*, *BCL10*	Involved in translocations activating NF-kappaB and predicting resistance to H. pylori eradication in gastric MALT lymphoma
	TNFAIP3	Frequently mutated NF-kappaB inhibitor
Splenic marginal zone lymphoma	*NOTCH2*	Mutated in 10–25% of SMZLs, master regulator of marginal zone differentiation
	KLF2	Mutated in 20–40% of SMZLs, causing NF-kappaB activation. Associated with short time to first treatment.
	TNFAIP3, *MYD88*, *TRAF3*	NF-kappaB activating mutations
	CARD11	
	TP53	Associated with short overall survival
Lymphoplasmacytic lymphoma	*MYD88*	Mutated in > 90% of LPLs. In LPL (but not DLBCL) associated with response to ibrutinib
	CXCR4	Mutations in 30% of LPLs, associated with ibrutinib resistance
Nodal marginal zone lymphoma	Recurrent mutations reported in *MLL2*, *PTPRD*, *NOTCH2*, *KLF2*, *TNFAIP3* and *CD79B*	

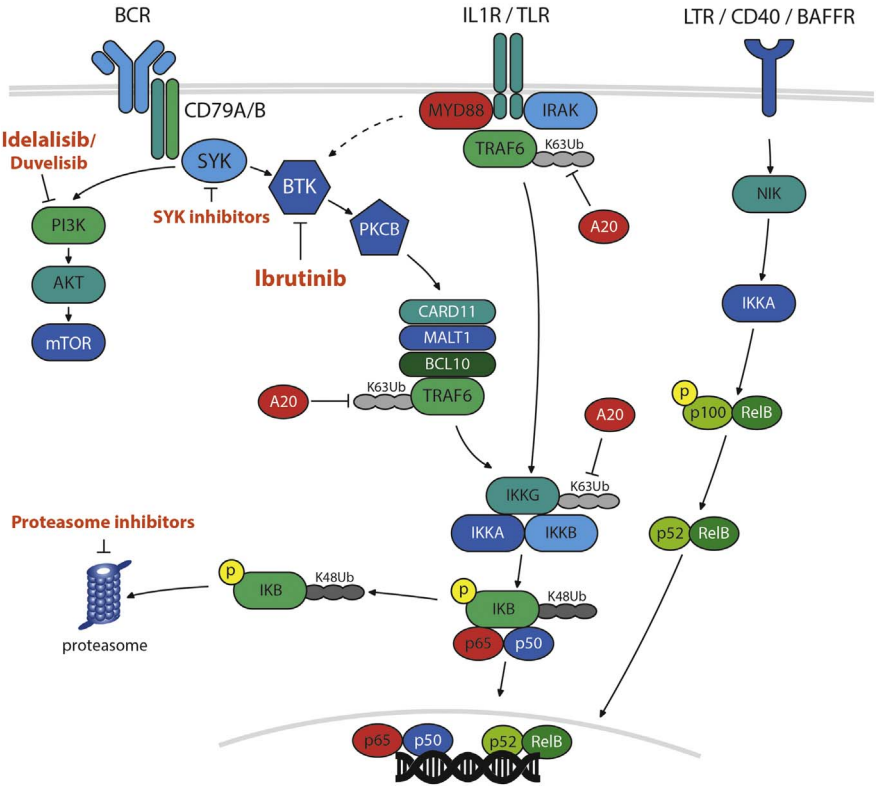

Fig. 2. Overview of BCR/TLR/NF-kappaB signaling with targeted treatments. Non-canonical signaling via LTR/CD40/BAFFR is indicated on the right. Canonical NF-kappaB signaling is indicated on the left. Activation of BCR signaling induces NF-kappaB activation via SYK, BTK, and PKCB. In addition, BCR signaling activates the PI3K pathway. IL1R and TLR signaling also induce NF-kappaB activation. In lymphoplasmacytic lymphoma, mutated MYD88 causes BTK activation. Ibrutinib, SYK inhibitors and idelalisib/duvelisib target different steps in these signaling cascades. Proteasome inhibitors decrease breakdown of inhibitors of NF-kappaB, causing decreased NF-kappaB signaling.

Abbreviations: BAFFR: B-cell activating factor receptor; BCR: B-cell receptor; IL1R: interleukin-1 receptor; LTR: lymphotoxin B receptor; NF-kappaB: nuclear factor kappa B; TLR: Toll-like receptor.

6.1.3. ATM

Inactivation of *ATM* (located at 11q22) by deletion and/or mutation is a frequent event in CLL with deletions of 11q22-23 in < 10% in newly diagnosed CLLs, rising to approximately 20% at the time of first treatment. Mutations in *ATM* are present in 10–15% of CLL at first diagnosis and approximately 15% at the time of first treatment [75]. Together, genetic lesions are present in *ATM* in CLL in approximately 20% at the time of diagnosis and approximately 35% at the time of first treatment [84]. The *ATM* gene encode for a serine/threonine kinase which prevents cell cycle progression and activated DNA repair mechanisms in the event of chromosomal double strand breaks.

6.2. B-cell receptor/toll-like receptor/NF-kappaB signaling

Signals from multiple receptors converge on the NF-kappaB pathway (Fig. 2). Canonical and non-canonical NF-kappaB signaling are distinguished. Canonical NF-kappaB signaling starts from the B-cell receptor, T-cell receptor, Toll-like receptors (TLR), interleukin-1 receptor (IL1R) or tumor necrosis factor receptor (TNFR). Through multiple steps which include the proteins CD79A/B, SYK, BTK, CARD11, BCL10, TRAF6 and MYD88, the inhibitor of kappa-B kinase (IKK) complex is activated. Activation of this complex results in the removal of inhibitory elements from NF-kappaB proteins, allowing these proteins to enter the nucleus to regulate transcription. NF-kappaB signaling is negatively regulated by deubiquitinases which include CYLD (cylindromatosis) and TNFAIP3 (also known as A20).

The non-canonical pathway is activated by signaling from the lymphotoxin B receptor, B-cell activating factor receptor (BAFFR), and CD40. This activates NF-kappaB inducible kinase (NIK, also known as MAP3K14) and CHUK, also eventually resulting in translocation of NF-kappaB proteins to the nucleus.

Deregulation of pathways that converge on NF-kappaB is frequently observed in lymphomas. In indolent B-cell lymphomas, extranodal marginal zone lymphoma is the most prominent example with frequent translocations involving *MALT1*, *BIRC3* (also known as *API2*), and *BCL10* [85–89]. In addition, extranodal MZLs harbor frequent mutations in genes involved in NF-kappaB signaling including *TNFAIP3* [90]. Also in SMZL and NMZL, mutations in genes involved in NF-kappaB signaling are frequent and most notably include *TNFAIP3*, *IKBKB*, *CARD11*, *BIRC3* and rarely *MYD88* [78,91–95]. *MYD88* mutations are present in the large majority of LPLs, which is very helpful for diagnosis [93,96–98]. Almost all mutations affect the TIR domain with NF-kappaB activation as a result. In a subset of CLL/SLL, mutations in *BIRC3* are detected with enrichment in fludarabine-refractory cases [99]. In patients with *TP53* mutated CLL, additional mutations in *BIRC3* are associated with an even worse prognosis. *MYD88* mutations have been found in a small subset of CLL/SLLs, mainly in cases with mutated IGHV [98].

In FL, mutations in genes involved in BCR/NF-kappaB signaling are relatively frequent with mutations in *CARD11*, *TNFAIP3*, *CD79A/B*, and/or *PRKCB* being present in a third of FLs [100]. Interestingly, mutations in NF-kappaB genes were gained at transformation [100]. Mutations in *TNFRSF14* are also frequently present in FL, being reported in approximately one third of cases [100–102]. TNFRSF14 is a putative tumor suppressor which can signal through the NF-kappaB pathway after binding of one of its ligands which include LIGHT, BTLA or CD160 [103]. However, as loss-of-function mutations in *TNFRSF14* are observed in FL, these mutations would cause a decrease rather than an increase of NF-kappaB activation. The tumor suppressor effect of TNFRSF14 can be explained by the fact that in the unmutated situation, triggering of TNFRSF14 by its ligand LIGHT increases the sensitivity to FAS-induced apoptosis. Disruption of TNFRSF14 would then make cells less sensitive to apoptosis, contributing to lymphomagenesis [104,105].

6.2.1. B-cell receptor signaling inhibitors

Multiple drugs have recently become available that targets signaling to NF-kappaB (Fig. 2). Ibrutinib blocks this signaling by binding covalently to BTK at cysteine 481, thereby preventing phosphorylation and blocking of downstream signaling [106,107]. Ibrutinib has been approved by the FDA for treatment of patients with CLL, recurrent MCL, Waldenström macroglobulinemia and recently also marginal zone lymphoma. In Europe, its use has been approved for patients with CLL,

recurrent MCL, and Waldenström macroglobulinemia. In addition, efficacy of ibrutinib has been shown in DLBCL, mainly in the activated B-cell-like (ABC) subtype [108,109]. However, not all patients show a response to ibrutinib and both primary and secondary mechanisms of resistance have been identified [108]. Primary resistance mechanisms have been mainly studied in MCL and DLBCL and include mutations that cause activation the non-canonical NF-kappaB pathway (e.g. *TRAF2* and *TRAF3*), mutations that activate the canonical NF-kappaB pathway independent of *BTK* (*MYD88* mutations) [109,110]. In lymphoplasmacytic lymphoma (LPL), *MYD88* mutations predict response rather than resistance to ibrutinib, which is in line with experiments showing BTK phosphorylation after mutant MYD88 overexpression in LPL [111]. MYD88 ^{L265P} mutations are present in the large majority (> 90%) of lymphoplasmacytic lymphomas [96,112,113], and patients with *MYD88* mutated LPL show a major response in 91% versus only 29% in patients with *MYD88* wildtype LPL [114]. Mutations in *CXCR4* are associated with a decreased response to ibrutinib in LPL with a major response rate of 91% vs. 62% for patients with LPL without and with *CXCR4* mutations. This might be caused by activation of AKT signaling by *CXCR4* mutations in which the mechanism might be similar to that in MCL as discussed above [115,116]. CXCR4 is a G-protein coupled chemokine receptor with a role in lymphocyte homing and migration. *CXCR4* mutations of WHIM-like type are present in 30% of LPLs. WHIM-like describes the presence of nonsense and frameshift mutations that are also present in the germline of patients with Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome.

In CLL, an unmutated BCR appears to be related to a better response to ibrutinib, which could be due to a larger dependence on BCR signaling in BCR unmutated CLL [108,117]. Secondary resistance to ibrutinib occurs as well. In both CLL and MCL, C481S mutations in *BTK* have been detected after ibrutinib therapy which were not present before therapy [118,119]. This mutation is located at the active site of BTK and causes a strong decrease in the affinity for ibrutinib for BTK. In addition, mutations in *PLCG2* have been detected after treatment with ibrutinib [119]. These are gain-of-function mutations which activate BCR signaling downstream of BTK [120].

Other novel drugs in targeting B-cell receptor signaling are directed against PI3K or SYK. Idelalisib and duvelisib are inhibitors of PI3K that target specific isoforms of the p110 subunit of PI3K. Idelalisib targets the delta isoform and duvelisib targets both the delta and gamma isoform. Idelalisib has been shown to be effective in patients with relapsed CLL [121] and indolent non-Hodgkin lymphoma (NHL), including FL, MZL, and LPL [122,123]. In MCL, idelalisib was also effective but the majority of patients showed only a short response duration [124]. Resistance mechanisms for idelalisib have not been studied as well as for ibrutinib, but higher expression of other PI3K isoforms has been suggested as a mechanism from in vitro studies [125]. In addition, activation of other oncogenic pathways such as MYC has been hypothesized as a mechanism for idelalisib resistance [126]. Idelalisib has been approved by the FDA for treatment of patients with relapsed CLL in combination with rituximab and for patients with relapsed FL and SLL. In Europe, idelalisib is authorized in combination with rituximab for use in patients with refractory FL and patients with refractory CLL or CLL with 17p deletion and/or *TP53* mutation in patients who are too frail for standard chemotherapy.

6.2.2. Proteasome inhibitors

Inhibition of the proteasome in hematological as well as solid tumors induces a wide range of effects including anti-proliferative and pro-apoptotic effects in vitro [127]. Although the ubiquitin-proteasome system also has key functions in normal cells, proteasome activity has been shown to be higher in hematological malignancies, forming a basis for in vivo use of proteasome inhibitors in these tumors [128,129]. In addition to NF-kappaB pathway inhibition, proteasome inhibitors cause inhibition of ERK signaling, upregulation of pro-apoptotic proteins, downregulation of anti-apoptotic proteins, anti-angiogenic effects, inhibition of DNA repair, disruption of tumor-microenvironment interactions, and stabilization of p21, p27, and p53 [130]. Proteasome inhibitors are currently registered for multiple myeloma (bortezomib, carfilzomib) and MCL (bortezomib). In addition, inhibitors of the immunoproteasome are under development. Immunoproteasomes are predominantly present in hematopoietic cells and immunoproteasome inhibition is therefore a potentially more targeted method of proteasome inhibition [127]. Furthermore, compounds that inhibit components of the ubiquitin-proteasome system other than the proteasome are being developed [127].

6.3. BCL6

The BCL6 gene located on chromosome 3q27 encodes a sequence specific repressor of transcription that serves as a master regulator of the germinal center phenotype. It is essential for formation of germinal centers, and mice lacking BCL6 are unable to form germinal centers [131]. In the normal germinal center, high proliferation occurs together with genomic instability due to somatic hypermutation. In this context, BCL6 functions as a repressor of normal control mechanisms of the cell cycle, DNA damage response, and cell death. Although this action is necessary to generate B-cells with high-affinity antibodies, it is also dangerous because it may lead to deregulated growth and therefore BCL6 expression is tightly regulated in the normal situation. However, deregulated BCL6 expression is a common event in B-cell lymphomas and multiple mechanisms can cause this. Translocations which put *BCL6* under the control of a strong promoter such as IGH are a frequent event in DLBCL and are also present in a subset of FLs [132–134]. Alternative mechanisms include mutations in binding sites for repressive transcription factors [135], mutations in *MEF2B* which is a transcriptional activator of *BCL6* [136], hypermethylation of intron 1 preventing silencing by CTCF [137], and posttranscriptional regulation [131].

6.3.1. BCL6 inhibitors

Studies into BCL6 inhibitors are currently limited to in vitro and mice studies. These studies show a strong response of tumors to BCL6 inhibition in vitro and in vivo, but oncogene addiction to BCL2 was observed in response to BCL6 inhibition, indicating that BCL6 inhibitors could be particularly useful in combination with BCL2 inhibitors [138–140]. In addition to drugs specifically targeting BCL6, histone deacetylase (HDAC) inhibitors also counteract the effects of BCL6 [141].

6.4. NOTCH signaling

Mammals possess 4 different NOTCH genes that encode for receptors involved in self-renewal and differentiation [142]. Upon binding of their ligands, a cleavage step causes release of the intracellular part of NOTCH which then translocates to the nucleus where it forms a protein complex with other proteins including MAML and histone acetyltransferases (e.g. EP300) [143]. This complex then stimulates transcription of a number of genes, resulting in increased expression of MYC and activation of the PI3K/AKT, mTOR, and NF-kappaB pathway [142–144]. NOTCH1 is essential for normal T-cell development, but is also frequently mutated in T-cell acute lymphoblastic leukemia [145]. These mutations occur in the heterodimerization and/or PEST domain. The PEST domain is the target for the FBXW7 ubiquitin protein ligase which targets NOTCH1 for the proteasome. Mutations in the PEST domain prevent ubiquitination and downregulation of NOTCH. Mutations in the heterodimerization domain cause enhanced cleavage of membranous NOTCH [145]. In indolent B-cell lymphomas, NOTCH1 mutations have been reported in a subset of CLL, SMZL, and FL [93,98,146–148]. In CLL, NOTCH1 mutations are detected in approximately 15% with a higher frequency in CLL with unmutated IGHV and/or trisomy 12 [75]. NOTCH1 mutations in CLL

are associated with a worse prognosis and a lack of response to rituximab treatment [149]. NOTCH2 is the master regulator of marginal zone differentiation and *NOTCH2* mutations are detected in up to one quarter of SMZLs with an association with short time to first treatment [78,93,95,147].

6.5. Epigenetic deregulation

Recent large-scale sequencing efforts have identified frequent mutations in genes involved in chromatin modulation in B-cell lymphomas [100,150–152]. These have been most extensively studied in DLBCL and FL in which mutations in *MLL2* (*KMT2D*), *CREBBP*, *EP300*, and *EZH2* were most frequently observed. Most of these mutations are loss-of-function mutations, except for mutations in *EZH2* which are gain-of-function. These mutations result in epigenetic silencing of specific genetic loci involved in cell cycle progression and regulation of the germinal center reaction, contributing to lymphomagenesis [153].

6.5.1. Epigenetic therapy

In hemato-oncology, HDAC inhibitors are mainly used for the treatment of patients with T-cell lymphoma, but limited studies have also been performed in B-cell lymphomas with variable results [154,155]. In addition to HDAC inhibitors, EZH2 inhibitors are under investigation for treatment of non-Hodgkin lymphomas [156].

6.6. Mitogen activated protein kinase (MAPK) signaling

In hairy cell leukemia, the BRAF V600E mutation has been identified by next-generation sequencing as a disease-defining genetic event [157]. BRAF is downstream from KRAS and upstream from MEK and ERK in the MAPK pathway. The BRAF V600E mutation causes constitutive activation of BRAF, resulting in cell survival [143]. For patients with relapsed or refractor hairy cell leukemia, the oral BRAF inhibitor vemurafenib is an effective treatment option [158–160].

7. Prediction of effective targeted treatment

With the increase of novel targeted treatments, the pressing question is which patient should receive which treatment. To select patients for treatment, the diagnosis still forms a starting point to select patients, but refinements are already being added. It is expected that the use of molecular diagnostics for treatment prediction will increase significantly as more and more mechanisms for resistance and sensitivity become known. It can also be expected that complexity will increase as more molecular events relevant for prediction of therapy response will be detected and more drugs developed. This also means that large clinical trials will become more difficult as each patient will have a different lymphoma with a different genetic background and novel approaches to clinical studies should be introduced.

With respect to mutation detection, many laboratories are now setting up panels for next-generation sequencing in lymphomas. Recently, the European Expert Group on NGS-based Diagnostics in Lymphomas (EGNL) summarized the current state-of-the-art in NGS for lymphomas and is now performing validation of a panel of 30 recurrently mutated genes [74].

Another question that needs to be answered in the near future is what diagnostic modalities will be required for therapy prediction. Immunohistochemistry and NGS are important techniques in this respect, but a mutation or changed protein expression is no guarantee for a therapy response. Mutations in non-coding regions, epigenetic alterations, and the micro-environment could all have an impact on the response to a particular treatment. In line with this, it will be necessary in the future to integrate the features of a lymphoma and the environment on different levels (i.e. genome, epigenome, proteome, micro-environment) to provide the most accurate prediction of therapy response.

8. Conclusion

Developments are following each other rapidly in the area of targeted treatment of indolent lymphoma and the (*epi*)genetic lesions involved. The challenge will be to determine which patient will benefit most from a given treatment at different time points of disease. It is expected that extensive genetic testing for prediction of treatment response at diagnosis, during follow-up and at relapse will be adopted in clinical practice soon, but for now only *TP53* mutations and del17p in CLL have a direct effect on treatment decisions. The long tail of different mutations in many types of lymphoma and the increasing number of drugs will require large studies to assess the impact of these mutations on prognosis and treatment response. This challenge is becoming even greater with the ever increasing knowledge from multiple sources (i.e. genome/epigenome, proteome, tumor micro-environment, clinical features). Tumor heterogeneity and natural and chemotherapy induced clonal evolution further increase complexity and will require sequential analyses to optimize and adapt therapy. Particularly in indolent B-cell lymphomas which are for the largest part incurable, decision making based on (*epi*)genetic profiling will be important.

Practice points

- Specific bacterial infections predispose to extranodal marginal zone lymphoma and are amenable to antibiotic treatment. However, the evidence is only conclusive for treatment of *Helicobacter pylori* in marginal zone lymphoma of the stomach.
- The mutational landscape of indolent B-cell lymphomas is rapidly being elucidated and it is expected that mutation detection will influence treatment decisions regarding targeted therapy.
- For now however, only demonstration of *TP53* mutations and/or del 17p in CLL/SLL have a direct impact on therapy.

Research agenda

- Correlation of mutational status with response to targeted treatment
- Development of functional assays to predict treatment responses more accurately.
- Refinement of diagnostic criteria based on subgroups that arise from large-scale sequencing efforts.

Conflict of interest

The authors declare no potential conflicts of interest.

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