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REVIEW

Mechanisms and consequences of constitutive NF-κB activation in B-cell lymphoid malignancies

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The discovery of constitutive nuclear factor-κB (NF-κB) activation in Hodgkin's lymphoma tumor cells almost two decades ago was one of the first reports that directly connected deregulated NF-κB signaling to human cancer. Subsequent studies demonstrated that enhanced NF-κB signaling is a common hallmark of many lymphoid malignancies, including Hodgkin lymphoma, mucosa-associated lymphoid tissue lymphoma, diffuse large B-cell lymphoma and multiple myeloma. By inducing an anti-apoptotic and pro-proliferative gene program, NF-κB is involved in lymphoma survival and growth. Identification of somatic mutations that led to activation of oncogenes and inactivation of tumor suppressor genes in the pathway revealed that specific pathogenic mechanisms are responsible for constitutive NF-κB activation in different lymphoma entities. Thus, the identification of distinct oncogenic events is reflecting the diverse cellular origins of the different lymphomas. Further, elucidation of the mechanisms that drive NF-κB in lymphoma is of high clinical relevance as it will allow the design of target-directed precision therapy. Indeed, a number of drugs that impair constitutive NF-κB activation in lymphoid malignancies are currently in preclinical or clinical development.

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INTRODUCTION

The nuclear factor-κB (NF-κB) transcription factor family consists of five mammalian family members, namely p65 (RelA), c-Rel, RelB, p105/p50 (NF-κB1) and p100/p52 (NF-κB2). They share an N-terminal-conserved REL homology domain, which allows dimerization, nuclear translocation and recruitment to κB DNA binding sites in the vicinity of many target genes. p65, c-Rel and RelB also contain transactivation domains and by forming various homo- or heterodimeric complexes, NF-κB proteins have been shown to either induce (for example, p50/p65, p50/c-Rel, p52/RelB complexes) or repress (for example, p50/p50 complexes) transcription. p50 and p52 are generated by an internal processing event from the larger precursor molecules NF-κB1/p105 and NF-κB2/p100, respectively. Activation of NF-κB is tightly controlled primarily in the posttranslational level by the prototypical IκB (inhibitors of NF-κB) proteins IκBα, IκBβ and IκBε, as well as the precursors NF-κB1/p105 and NF-κB2/p100 that sequester NF-κB complexes on the cytoplasm. Cytosolic IκBs are degraded in response to external or internal stimulation leading to NF-κB release and nuclear uptake. The very large number of NF-κB-activating stimuli as well as NF-κB target genes underscores that the NF-κB system serves key functions in many biological processes including immune and stress responses, apoptosis, proliferation, differentiation and development.[1–4]

NF-κB activation in response to extracellular stimulation is mainly controlled by the canonical (classical) and noncanonical (alternative) signaling pathways. The IκB kinase (IKK) complex consisting of the two catalytic subunits IKKα (IKK1) and IKKβ (IKK2) and the regulatory component NEMO (NF-κB essential modulator; IKKγ) acts as the gatekeeper of the canonical pathway.[5] Inflammatory cytokines, bacterial or viral agents, antigenic peptides, chemicals or radiation trigger IKK activation, which subsequently catalyzes the phosphorylation of cytosolic IκBs. Phosphorylated IκBs are recognized and rapidly removed by the ubiquitin proteasome system to allow nuclear translocation of canonical NF-κB, mainly consisting of p50/p65 and p50/c-Rel complexes. Canonical NF-κB signaling is transient and transcriptional responses are limited by autoregulatory feedback mechanisms that involve the NF-κB-dependent induction of negative regulators like IκBα or the ubiquitin-editing enzyme A20 that counteracts IKK activation.[6] The noncanonical NF-κB pathway is strongly induced only by a subset of tumor necrosis factor receptor (TNFR) family member ligands, such as CD40 ligand, lymphotoxin β (Ltβ) and B-cell activating factor (BAFF). Noncanonical NF-κB signaling involves the NIK (NF-κB-inducing kinase)-dependent activation of IKKα, which in turn phosphorylates the NF-κB2/p100 precursor leading to its proteolytic processing by the proteasome and primarily nuclear accumulation of p52/RelB heterodimers. NIK itself is a highly unstable protein and degradation is mediated by an ubiquitin–ligase complex consisting of TRAF2 (TNF receptor activating factor2) and c-IAP1/2 (inhibitor of apoptosis 1/2). TRAF3 works as a bridging factor that couples the TRAF2 and c-IAP1/2 complex to NIK to enhance its degradation. Only upon recruitment of TRAF2/c-IAP1/2 to the CD40 or BAFF receptor, TRAF3 is polyubiquitinated and degraded, leading to the stabilization and activation of NIK, IKKα phosphorylation and noncanonical NF-κB activation.[7] In contrast to the canonical pathway, noncanonical signaling in general promotes a delayed and sustained response and often controls developmental processes, such as B-cell maturation.

In normal cells, NF-κB activation is tightly regulated to control its strong anti-apoptotic and pro-proliferative activity. Especially, B

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lymphocytes rely on NF-κB activation during different stages of their life cycle, such as development, maturation and activation. Thus, it is not surprising that deregulations in the NF-κB pathway are frequent in human lymphoid malignancies. In fact, the mechanisms of NF-κB deregulation often reflect the cellular origin of the aberrant lymphoma cells and a detailed understanding of pathogenic processes uncovers options for specific therapeutic interventions.

CONTROL OF NF-κB BY CELL-INTRINSIC AND EXTRINSIC MECHANISMS IN CLASSICAL HODGKIN'S LYMPHOMA

With an annual incidence rate of almost 3 cases per 100 000 persons, Hodgkin's lymphoma is one of the most frequent types of lymphoma.[8] On the basis of histology and immunohistochemistry, two major subclasses can be discriminated, namely classical Hodgkin's lymphoma and nodular lymphocyte-predominant Hodgkin's lymphoma. Hodgkin's lymphoma is an unusual type of lymphoid malignancy because only very few cells—often <1%—represent the malignant tumor cells in the affected lymph nodes. In Hodgkin's lymphoma, these large mononucleated Hodgkin cells or multinucleated Hodgkin–Reed Sternberg (HRS) cells are surrounded by many inflammatory cells, such as activated B and T cells, macrophages and granulocytes. The identification of clonal rearrangements and somatic mutations in immunoglobulin (Ig) heavy- and light-chain genes clearly demonstrated the B-cell lineage derivation and clonal origin of HRS cells. Most likely, the tumor cells derive from germinal center (GC) B cells that acquired unfavorable Ig mutations or lost Ig transcription during the GC reaction.[9–11] Additional transforming events in the course of Hodgkin's lymphoma development are apparently preventing negative selection by impairing the induction of apoptosis in these aberrant GC B cells. In line with this model, Hodgkin's lymphoma-derived cell lines as well as primary HRS cells display high constitutive activity of IKK/NF-κB, which triggers cell survival and growth by inducing an anti-apoptotic and pro-proliferative gene program.[12–15]

The causes of constitutive NF-κB activity have not yet been completely resolved, but canonical and noncanonical NF-κB signaling is enhanced in HRS cells (Figure 1). Cell-extrinsic and cell-intrinsic mechanisms seem to contribute to NF-κB activation in the tumor cells. HRS cells express several TNFR family members on the surface, including RANK and CD30 that can stimulate the canonical signaling or in the case of CD40 the noncanonical NF-κB signaling pathways.[16] Further, HRS cells themselves as well as the surrounding inflammatory cells produce high amounts of the respective ligands that can lead to a situation of chronic stimulation in either an autocrine or a paracrine manner.[14,15] As NF-κB itself is controlling expression of many of these cytokines, constitutive NF-κB in Hodgkin's lymphoma may at least partially be explained by a vicious feed-forward cycle. However, high constitutive NF-κB activity in affected lymph nodes is largely confined to the malignant HRS cells and not seen in the surrounding inflammatory environment.[13,17] Thus, also cell-autonomous deregulations like the inactivation of negative feedback mechanisms that normally restrict cellular NF-κB activity must account for the constitutive NF-κB activation in Hodgkin's lymphoma tumor cells.

In North America and Europe, ~20–50% of classical Hodgkin's lymphoma are infected with Epstein–Barr virus (EBV) and infection is more often observed in older patients.[18] Several lines of evidence underscore that EBV is of pathogenic relevance through enhancing NF-κB activity. On the molecular level, the cytosolic domains of the EBV-encoded latent membrane protein 1 (LMP1) and LMP2A mimic a constitutively active CD40 receptor and BCR, respectively.[19,20] Indeed, LMP1 can induce canonical and noncanonical NF-κB signaling independent of ligand stimulation (Figure 1) and transgenic expression of LMP1 can promote B-cell

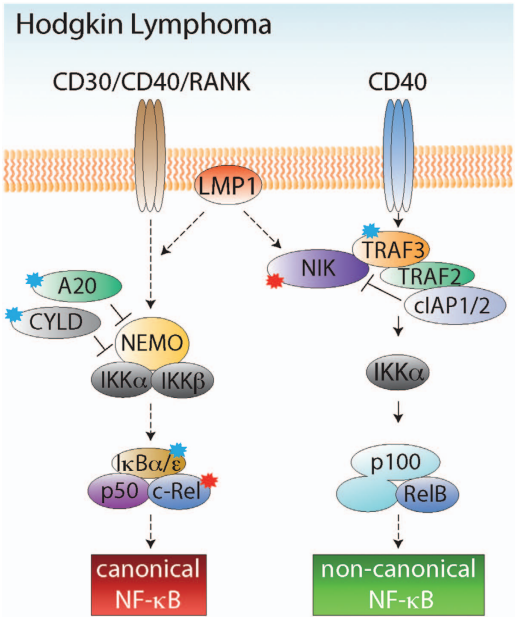

Figure 1. Constitutive canonical and noncanonical NF-κB activation in Hodgkin's lymphoma. Genetic lesions comprising loss-of-function mutations (blue stars) in *TNFAIP3* (A20), *CYLD* and *NFKBIA/E* or gain-of-function alterations (red stars) in *REL* are the major cause for the constitutive activity of the canonical NF-κB pathway. Activation of CD30/CD40 or RANK can contribute to canonical NF-κB activity in Hodgkin's lymphoma. The noncanonical pathway in HRS cells is primarily driven by activation of CD40 or via aberrations of *TRAF3* or *MAP3K14* (NIK) genes. Signaling via the EBV-encoded latent membrane protein 1 (LMP1) in EBV-positive cases of Hodgkin's lymphoma promotes both NF-κB pathways.

lymphomas in mice.[21–25] Even though LMP1 is expressed in Hodgkin's lymphoma patients, there is no clear correlation between expression and prognosis.[26] For LMP2A it was initially shown that its expression counteracts BCR signaling,[27] but transgenic LMP2A expression also promotes B-cell survival and proliferation.[28–30] However, the function of LMP2A in enhancing NF-κB signaling in Hodgkin's lymphoma is less clear, because HRS cells have largely lost their B-cell phenotype concomitant with the downregulation of many BCR signaling adaptors.[31–33] Nevertheless, LMP2A-triggered NF-κB activation may be involved in preventing apoptosis in the initial phase of Hodgkin's lymphoma pathogenesis.

The detection and the proof of a functional relevance of constitutive NF-κB activity in classical Hodgkin's lymphoma[13] encouraged the search for mutations in the pathway. Indeed, HRS cells carry several somatic alterations that lead to a gain- or loss-of-function of positive or negative NF-κB regulators, respectively (Table 1). As a result, both the canonical and noncanonical NF-κB pathways are constitutively turned on in the HRS cells (Figure 1). Copy number gains of the *REL* locus are found in >30% of classical Hodgkin's lymphoma and correlate with the presence of nuclear c-Rel staining in primary Hodgkin's lymphoma cells.[34–36] Also, elevated expression of the proto-oncogene BCL3 is a common feature of the HRS cells.[37] The atypical nuclear IκB protein BCL3 can enhance canonical NF-κB transcription and target gene expression by binding to p50 homodimers.[38] BCL3 copy number gains or juxtaposition of BCL3 to the IGH locus have been reported in HRS cells,[37,39] but it remains unclear whether IGH translocations actually contribute to BCL3 overexpression, as Ig transcription is usually silenced in the HRS cells.[10]

Table 1. Common NF-κB pathway mutations in B cell lymphoid malignancies

NF-κB pathway mutations	*Hodgkin's lymphoma*	*Activated B-cell-like diffuse large B-cell lymphoma*	*Primary mediastinal B-cell lymphoma*	*Mucosa-associated lymphoid tissue lymphoma*	*Multiple myeloma*	*Reference*
Gain-of-function						
CD79A		GM ITAM (2/68)				100
CD79B		GM ITAM (34/161)				100
CARD11		GM CC (7/73) GM (4/37)				107,118
MYD88		GM TIR (68/174) TIR-L265P (45/155)		GM TIR-L265P (5/56)		120
BCL10			CNG 1p22 (BCL10) (rare)	CHT (1;14)(p22;q32) BCL10-IGH (rare)		57,148
MALT1			CNG 18q21 (MALT1 & BCL2 loci) (9/37)	CHT (11;18)(q21;q21) cIAP2-MALT1 (67/417) CHT (14;18)(q32;q21) MALT1-IGH (12/66)		61,75,148
REL	CNG (11/31)		CNG (15/20)			34,94
MAP3K14/NIK	CNG (5/16)				CHT NIK-IGH/ IGL (rare)	50,127,128
BCL3	CHT (14;19)(q32;q13) IGH-BCL3 (1/20) CNG (3/20)					39
LTβR					CNG (MD 1/125)	128
Loss-of-function						
NFKBIA (IκBα)	GM (1/10)	GM (1/10)				17
NFKBIE (IκBε)	GM (1/6)					42,150
TNFAIP3 (A20)	GM (12/30) CNL 6q23-24 (9/21)	GM 6q23.3 (9/37) CNL (5/64)	GM (5/14) CNL 6q23-24 (frequent)	GM/CNL (3/23)		43,44,149
TRAF3	CNL (MD 3/20)				CNL (BD 6/158); (MD 19/158)	50,128
CYLD	CNL (BD 1/29); (MD 10/29)				CNL (BD 1/62); (MD 11/62)	46,128
TRAF2		GM (1/37)			CNL (BD 1/62); (MD 1/62)	118,128
cIAP1/2					CNL (BD 1/62); (MD 1/62)	128

Abbreviations: BD, biallelic deletion; CHT, chromosomal translocation; CNG/CNL, copy number gain/loss; GM, gene mutation; MD, monoallelic deletion; NF, nuclear factor. Only mutations found in primary patient samples are listed. In parenthesis the frequency of mutations is depicted as positive versus total cases analyzed (X/Y). In case no data on absolute number of patients were available, rare stands for $\leqslant$5% of mutations and frequent stands for $>$5% of mutations.

Besides these activating events, several negative regulators of canonical NF-κB are prone to frequent mutations in Hodgkin's lymphoma. In all, 10–20% of primary Hodgkin's lymphoma cells carry inactivating point mutations in *NFKBIA* and *NFKBIE* coding for the cytosolic NF-κB inhibitors IκBα and IκBε.[17,40–42] With ~40%, the *TNFAIP3/A20* gene is even more frequently mutated in classical Hodgkin's lymphoma.[43,44] *TNFAIP3* codes for the ubiquitin-editing enzyme A20, which terminates upstream IKK activation in response to various stimuli.[45] Reintroduction of A20 counteracts NF-κB activation and impairs survival of HRS cell lines underscoring its potential as a tumor suppressor in Hodgkin's lymphoma.[43,44] Interestingly, an HRS cell line (L428) that carries inactivating mutations in IκBα and IκBε is resistant to A20 overexpression, revealing that downstream mutations render the cells largely independent of NF-κB upstream signaling events.[44] Biallelic or monoallelic mutations of the *CYLD* gene were reported in primary HRS cells.[46] Just like A20, CYLD codes for a deubiquitinating enzyme that counteracts IKK/NF-κB signaling and can act as a tumor suppressor,[47] but the functional consequences of the mutations in Hodgkin's lymphoma have not been analyzed in detail. HRS cells are also characterized by high nuclear levels of p52 and RelB, indicative of aberrant noncanonical NF-κB signaling.[48,49] Recurrent copy number gains in the *MAP3K14* gene that codes for NIK and rare monoallelic deletions of TRAF3, two key regulators of noncanonical NF-κB signaling, have been found in classical Hodgkin's lymphoma.[50] NIK is stabilized in HRS cell lines and in primary Hodgkin's lymphoma cells, and its knockdown impairs viability of Hodgkin's lymphoma cell lines.[49] Further, just like for p65 or c-Rel, elimination of RelB expression is toxic to HRS cell lines, suggesting that parallel activation of canonical and noncanonical NF-κB is critical for survival of Hodgkin's lymphoma cells. Future results will need to resolve how these pathways may cooperate in pathogenesis of classical Hodgkin's lymphoma.

Hodgkin's lymphoma is a cancer with a favorable diagnosis, and current radiation therapy and chemotherapy achieve cure rates of $\geqslant$85% even in late-stage patients.[51] However, Hodgkin's lymphoma patients are often diagnosed at a relatively young age and precision therapies that target NF-κB pro-survival signaling could help to avoid or at least reduce chemotherapy and reduce long-term adverse effects.

TRANSLOCATION OF BCR SIGNALING MEDIATORS IN MALT LYMPHOMA

Mucosa-associated lymphoid tissue (MALT) lymphoma, a variant of marginal zone B-cell lymphoma, is the most common extranodal lymphoma and accounts for up to 8% of Non-Hodgkin's lymphoma.[52] Commonly, it occurs in the stomach but can also develop in other mucosal surfaces, for example, the lung and the liver.[53] The development of gastric MALT lymphoma initially emerges from a persistent infection with *Helicobacter pylori*. In these early stages of gastric MALT lymphoma, proliferation of the neoplastic-B cells depends on an inflammatory environment that is likely driven by antigen-stimulated T cells.[54] MALT lymphomas are often characterized by a strong NF-κB activation that is driven by three independent chromosomal translocations involving the *BCL10* (B-cell lymphoma/leukemia), *MALT1* and *c-IAP2/API2* (inhibitor of apoptosis2) genes (Table 1).[53,55]

The translocation t(1;14)(p22;q32), which brings the *BCL10* gene under the control of the IGH enhancer, is a rare genetic aberration of MALT lymphomas. It promotes an overexpression and a nuclear localization of the BCL10 protein.[56,57] BCL10 is part of the CARMA1/CARD11-BCL10-MALT1 (CBM) complex that mediates IKK–NF-κB activation upon antigen receptor ligation in B and T cells.[58] Interestingly, transgenic mice expressing BCL10 in B cells display enhanced activity of canonical and noncanonical NF-κB signaling and develop splenic marginal zone hyperplasia,[59] suggesting that the translocation and overexpression can facilitate lymphomagenesis. However, the nuclear function of BCL10, its role in constitutive NF-κB activity and MALT lymphomagenesis is unclear.[60]

The second chromosomal translocation t(14;18)(q32;q21) is a more frequent aberration in MALT lymphoma (up to 18%), but it is not found in gastric MALT1 lymphoma.[61] It juxtaposes the *MALT1* gene next to the Ig heavy chain enhancer (*IGH-MALT1)* leading to overexpression of MALT1.[62] Within the CBM complex, MALT1 controls antigen-dependent lymphocyte activation downstream of BCL10 and it therefore acts as a key regulator of adaptive immunity.[58] It serves a dual role by functioning as a NF-κB signaling adapter within the CBM signaling complex and as a protease, supporting lymphocyte activation by cleaving a set of negative regulators.[63–66] Owing to its structural similarity to caspases, MALT1 has also been termed paracaspase.[67] Both scaffolding and enzymatic function of MALT1 are critical for the adaptive immune response but also for survival and proliferation of different B-cell malignancies.[68–70] As a consequence of MALT1 overexpression canonical NF-κB signaling in t(14;18) MALT lymphoma is increased.[71] However, the exact molecular mechanism of how the overexpression of MALT1 enhances NF-κB and promotes lymphomagenesis has not been resolved. Interestingly, a human-like MALT lymphoma can be induced in mice by overexpression of MALT1 in hematopoietic stem/progenitor cells, demonstrating the oncogenic potential of MALT1.[72] Further deletion of p53 accelerated tumor development and induced a transformation from MALT to a diffuse large B-cell lymphoma (DLBCL)-type tumor, providing a molecular link between these two lymphoma entities.

The common translocation t(11;18)(q21;q21) in MALT lymphoma localizes the *c-IAP2/API2* gene in proximity to the *MALT1* gene resulting in an oncogenic fusion protein that links the N-terminus of c-IAP2/API2 to the MALT1 C-terminus, including the intact paracaspase domain.[73,74] t(11;18)(q21;q21) is present in ~16% of all MALT lymphomas, but with a frequency between 23–48% it is enriched in gastric MALT lymphomas.[75,76] Transgenic expression of the API2–MALT1 fusion protein alone can induce expansion of marginal zone B cells, but it is not sufficient to induce development of B-cell lymphomas.[77] Interestingly, owing to the deletion of the RING finger, the c-IAP2 ligase activity is lost in the API2–MALT1 fusion protein and the expression of ligase-defective c-IAP2 alone is inducing abnormalities reminiscent to MALT lymphoma.[78] Thus, loss of tumor-suppressing c-IAP2 ligase activity may contribute to the oncogenic effect of API2–MALT1 *in vivo*. It will be interesting to see whether the stabilization of typical c-IAP2 substrates in t(11;18)-positive MALT lymphoma contributes to tumorigenicity.

Mechanistically, API2–MALT1 oligomerizes to activate both canonical and noncanonical NF-κB signaling autonomously from upstream signals.[78,79] The oligomerization of the fusion protein may provide a platform for the recruitment of downstream signaling factors. Whereas the baculovirus IAP repeat (BIR) domains of API2 associated with RIP1 (receptor interacting protein 1) and the E3 ubiquitin ligase TRAF2, the E3 ubiquitin ligase TRAF6 is recruited to the MALT1 moiety of the fusion (Figure 2). Deletion of the corresponding interaction sites within API2–MALT1 disrupts NF-κB activity, proving an involvement of these regulators for API2–MALT1-mediated canonical NF-κB signaling.[79–82] Recent data suggest that canonical NF-κB signaling involves TRAF2-dependent RIP1 ubiquitination to recruit NEMO to API2–MALT1 as well as TRAF6 catalyzed ubiquitination of NEMO to activate the IKK complex.[82] As API2–MALT1 contains the catalytically active paracaspase, it is able to cleave and inactivate the NF-κB-negative regulator A20, thereby further enhancing canonical NF-κB activation.[64] Just like in many other lymphoma entities, *TNFAIP3/A20* itself is prone to inactivating mutation in MALT lymphoma.[43]

Paracaspase activity of API2–MALT1 is also critical for the engagement of the noncanonical NF-κB pathway. In normal B cells, NIK is continuously degraded by TRAF3 to prevent NIK from IKKα phosphorylation and subsequent processing of NF-κB2/p100 precursor to activate p52/RelB heterodimers. The API2–MALT1 fusion protein bypasses BAFF- or CD40-triggered NIK stabilization by cleaving the N-terminal inhibitory TRAF3 binding

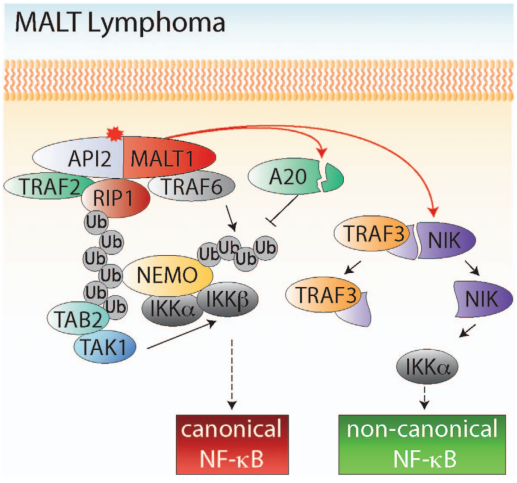

Figure 2. The API2–MALT1 fusion protein drives canonical and noncanonical NF-κB activity in late stage MALT lymphoma. The oncogenic translocation (red star) t(11;18)(q21;q21) involving *MALT1* and *c-IAP2/API2* in MALT lymphoma results in the production of the chimeric fusion protein API2–MALT1. The fusion protein promotes canonical NF-κB activity via oligomerization mediated recruitment of RIP1 and TRAF2 to the c-IAP2 part of the fusion protein. TRAF2-dependent ubiquitination of RIP1 recruits the IKK complex. TRAF6 is recruited to the MALT1 moiety to ubiquitinate NEMO. MALT1-dependent cleavage of the negative regulator A20 further enhances the canonical NF-κB activity. Additionally, cleavage of NIK by the MALT1 paracaspase results in the constitutive activation of NF-κB via the noncanonical pathway. The C-terminal part of NIK that emerges from the cleavage reaction is constitutively active and phosphorylates IKKα to induce NF-κB2/p100 processing.

domain on NIK generating a stable truncated NIK fragment that acts as a potent oncoprotein through uncontrolled activation of noncanonical NF-κB (Figure 2).[83] NIK is not a physiological substrate of MALT1 and only the binding to the API2 part of the fusion protein localizes NIK in close proximity to the paracaspase domain.[83] Thus, API2–MALT1 serves as an example for how an oncogenic fusion not only increases the enzyme activity, but also alters the substrate specificity. Of note, API2–MALT1 can also catalyze the cleavage of CYLD, another negative regulatory DUB in the NF-κB signaling pathway.[47] However, MALT1-dependent cleavage of CYLD is apparently primarily affecting JNK activation and a functional relevance for pathogenesis of MALT lymphoma is currently unclear.[84] Future analysis will need to resolve whether other potentially selective API2–MALT1 cleavage substrates exist that contribute to lymphomagenesis.

Therapeutically, MALT lymphomas are often treated by *H. pylori* eradication and a mild chemotherapy can be added in case of more advanced stages.[68] However, late-stage antibiotic-resistant cases that acquired chromosomal alterations may benefit from treatment with MALT1-inhibitory compounds that have been identified and shown to be active on MALT1-dependent DLBCL tumors.[85,86] In addition, NIK may represent a promising candidate for a target-directed therapy of MALT lymphoma characterized by the API2–MALT1 fusion.

CHRONIC BCR SIGNALING NUCLEATES NF-κB IN AN AGGRESSIVE SUBSET OF DIFFUSE LARGE B CELL LYMPHOMA

With an incidence rate of >7 patients per 100 000 persons, DLBCL is the most prevalent lymphoid neoplasm in adults.[8] Gene expression profiling of patient-derived tumor cells revealed a high grade of heterogeneity within this lymphoma entity.[87] Gene cluster analysis led to the identification of three subclasses of DLBCL, namely the GC B-cell-like (GCB) DLBCL, the activated B-cell-like (ABC) DLBCL and the primary mediastinal B-cell lymphoma (PMBL). ABC DLBCL and PBML exhibit high expression of an NF-κB target gene signature. More importantly, the molecular classification is also linked to significantly different clinical responses to current therapy and ABC DLBCL patients have a clearly inferior prognosis when compared with GCB DLBCL and PMBL subtypes.[88–90]

PMBL represents the smallest class of DLBCL that most likely arises from a rare B-cell population within the thymus.[91,92] Interestingly, the NF-κB gene signature of PMBL highly resembles the signature of the HRS cells derived from Hodgkin's lymphoma.[89,93] The molecular similarities between PMBL and Hodgkin's lymphoma further extend to common genetic alterations that drive constitutive NF-κB activity such as nuclear accumulation of c-Rel protein as a result of *REL* amplification that is found in 75% of PMBL cases (Table 1).[94] However, the functional consequences of c-Rel overexpression are not fully understood because *REL* gains have also been found in NF-κB-independent GCB DLBCL.[95] IKKβ inhibitors are toxic to PMBL cells revealing that the tumor cells rely on activation of upstream signaling pathways.[96] The exact mechanisms of IKK activation still need to be elucidated, but similar to many other NF-κB-driven lymphomas, PBML patients often harbor inactivating mutations and deletions in *TNFAIP3* coding for the IKK inhibitor A20.[44]

Consistent with the high gene signature similarities to an antigen-activated B cell, ABC DLBCL tumor cells depend on constitutive activation of canonical NF-κB.[97] The critical role of the canonical IKK/NF-κB pathway in ABC DLBCL is supported by the fact that specific small molecule IKKβ inhibitors are toxic for ABC DLBCL, but not the GCB DLBCL cells.[96] Further, B-cell-specific expression of constitutively active IKKβ in conjunction with inactivation of the tumor suppressor BLIMP1, a regulator of plasma cell differentiation, induces the development of ABC DLBCL-like tumors in mice.[98,99] Constitutive IKK activation in ABC

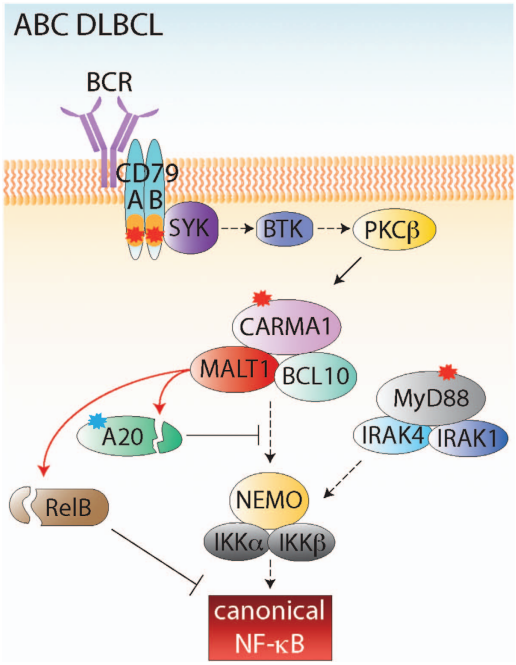

Figure 3. Chronic BCR signaling and MYD88 mutations promote canonical NF-κB in ABC DLBCL. Several genetic lesions drive canonical NF-κB activity in ABC DLBCL via chronic BCR signaling involving several critical signaling mediators, for example, SYK, BTK, PKCβ and the CBM complex. Many ABC DLBCL cases harbor somatic gain-of-function (red stars) mutations in *CD79A/B* or *CARD11* (*CARMA1*) genes, which promote high NF-κB activity. Further oncogenic mechanisms that contribute to canonical NF-κB result from mutations of *MYD88* and inactivation (blue stars) of *TNFAIP3/A20*. In addition, constitutive MALT1-dependent cleavage of A20 or RelB inhibits these proteins from interfering with canonical NF-κB signaling.

DLBCL cells is driven by chronic BCR signaling (Figure 3).[100] Accordingly, essential mediators of BCR signaling, like the adaptor CD79A/B, the tyrosine kinases SYK (spleen tyrosine kinase) and BTK (Bruton's tyrosine kinase), protein kinaseβ (PKCβ) and the components of the CBM signaling complex are indispensable for survival of ABC DLBCL cells.[100–102]

The key role of chronic BCR signaling for ABC DLBCL survival is supported by recurrent somatic mutations in downstream mediators that drive oncogenic activation of canonical NF-κB (Table 1). Approximately 20% of all ABC DLBCL patients harbor activating mutations in the ITAM (immune tyrosine activating motif) of either CD79B or, less common, CD79A.[100,103] Upon antigen binding, the Src kinase LYN phosphorylates the ITAM of CD79, a membrane-anchored adaptor that recruits SYK to the Ig chains.[104] However, LYN is also involved in shutting off BCR signaling and BCR internalization. ITAM mutations in CD79A and CD79B seem to render the ABC DLBCL cells more resistant towards this negative feedback.[100,105,106] In line with this, Ig downregulation is toxic to ABC DLBCL cells carrying CD79B mutations, revealing that survival still relies on a functional BCR.[100] Whether BCR ligation is still required is not yet resolved, but it is conceivable that ABC DLBCL derive from autoreactive B cells that are protected from anergy through chronic BCR signaling and subsequently acquire further downstream mutations. Of note, activating *CD79B* mutations have also been identified in GCB DLBCL patients (~3%) indicating that oncogenic BCR signaling may not be entirely restricted to the ABC subtype.[100]

About 10% of ABC DLBCL patients carry gain-of-function mutations within the coiled-coil domain of the *CARD11/CARMA1* gene.[107,108] Expression of CARMA1 coiled-coil mutants in GCB

DLBCL cells is able to induce canonical NF-κB signaling and an ABC-like gene signature underscoring the oncogenic potency of the mutations. Again, *CARD11* mutations have been identified in some GCB DLBCL patients (~4%) and these tumor cells retain the GCB-type gene signature, but in addition exhibit high expression of NF-κB target genes.[107] Mechanistically, coiled-coil mutations exert an activating effect, presumably by changing the conformation of the CARMA1 scaffold. In resting lymphocytes, CARMA1 adopts an autoinhibited conformation that is restrictive to the interaction of downstream signaling factors, like BCL10 and MALT1.[109] ABC DLBCL-derived coiled-coil mutations render the CARMA1 scaffold constitutively active independent of upstream signaling, and NF-κB activation in CARMA1-mutant cells is completely resistant to downregulation or inhibition of upstream kinases SYK, BTK or PKCβ.[100,110–112] Thus, quite in contrast to the oncogenic CD79B mutants, growth of CARMA1-mutated ABC DLBCL cells is not dependent on a functional BCR.[100] Indeed, introduction of oncogenic CARMA1-mutant alleles into antigen-activated B cells is sufficient to block self-antigen-induced cell death and promote B-cell proliferation *in vivo*.[113] Moreover, like the somatic mutations in DLBCL, human germline mutations in the CARMA1 coiled-coil domain selectively induce B-cell expansion.[114] These results suggest that autoreactive antigen receptors arising from hypermutations in activated B cells may cooperate with oncogenic CARMA1 missense mutations in the onset of ABC DLBCL development.

As a consequence of chronic BCR signaling and/or oncogenic driver mutations, the CBM complex is persistently assembled in all ABC DLBCL tumor cells.[70] Apart from its scaffolding function within the CBM complex, MALT1-proteolytic activity is strongly enhanced and essential for growth and survival of ABC DLBCL cells.[70,115,116] A constitutive monoubiquitination drives MALT1 activity in ABC DLBCL cells.[116] Further, PI3K–PDK1 signaling has been shown as a critical link in CD79B-mutated ABC DLBCL cells.[117] Functionally, inhibition of MALT1 activity causes accumulation of the IKK-negative regulator A20 and the nuclear NF-κB subunit RelB, which are both cleaved by MALT1 (Figure 3).[65,70,115] Like in most other NF-κB-driven lymphomas, the *TNFAIP3/A20* gene is often inactivated by point mutations, deletions or epigenetic silencing in ABC DLBCL.[43,118] Thus, MALT1-dependent cleavage may be an alternative mechanism to release the cells from the negative impact of A20. More unexpectedly, cleavage of the noncanonical RelB subunit enhances activation of canonical NF-κB target genes, suggesting that in contrast to all other lymphoma entities, activation of noncanonical NF-κB may counteract lymphomagenesis.[65] Clearly, the nuclear events that contribute to the oncogenic potential of NF-κB not only in ABC DLBCL but also in other lymphomas are not understood in detail. Recently, the atypical nuclear IκBζ was shown to be highly expressed in ABC DLBCL, but not in Hodgkin's lymphoma or multiple myeloma.[119] IκBζ is critical for ABC DLBCL survival and induces target gene expression selectively by associating with p50 or p52 homodimers. Future studies will need to address the complexity of nuclear pathogenic NF-κB regulation and whether IκBζ expression is linked to the opposing functions of RelB in different lymphoma entities.

Not only BCR signaling mediators are prone to frequent aberrations, but also the innate immune receptor adaptor MYD88 is somatically mutated in almost 40% of ABC DLBCL patients.[120] Interestingly, ~30% of the ABC DLBCL cases carry a *MYD88* gain-of-function mutation that leads to the amino-acid substitution L265P within the Toll–interleukin receptor (TIR) domain and thereby accelerates binding and activation of the downstream kinases IRAK4 (interleukin-1 receptor-associated kinase 4) and IRAK1. Similar to coiled-coil mutations in CARMA1, the TIR mutation presumably alters MYD88 conformation to promote IRAK4/1–IKK–NF-κB signaling.[103,120–122] Notably, 65% of the patients with *MYD88* mutations also harbor either *CD79* or *CARD11* mutations, revealing an extensive overlap between the two signaling pathways and suggesting a cooperation in driving survival of the tumors.[120] However, chronic BCR signaling may exert a dominant effect over MYD88 signaling, as CARMA1 depletion was shown to be toxic to exclusively MYD88-mutated cells. Nevertheless, a parallel knockdown of CD79A and MYD88 further decreased the viability of ABC DLBCL cells, suggesting that combinatorial treatment protocols with compounds that target both the pathways may be beneficial over a single-agent therapy.[120] Interestingly, the MYD88 L265P mutation is not restricted to ABC DLBCL, but is also a recurrent oncogenic aberration in other lymphoid malignancies, for example, Waldenstrom macroglobulinemia (90%), a rare lymphoid malignancy that is also driven by constitutive NF-κB activity, MALT lymphoma (~9%) and GCB DLBCL (~10%).[120,123,124]

Given the key survival function of chronic BCR signaling in ABC DLBCL, a number of selective inhibitors that target the pathway are currently evaluated in preclinical studies and clinical trials. Especially, the kinases SYK, BTK and PKCβ that link the BCR to the CBM–IKK–NF-κB signaling axis are attractive candidates.[103,111,125] For instance, the irreversible BTK inhibitor ibrutinib shows first promising effects in a phase II clinical trial on refractory/relapsed ABC DLBCL patients.[126] Small molecule inhibitors of MALT1 paracaspase have been shown to partially block NF-κB target gene expression and thereby selectively kill MALT1-dependent ABC DLBCL tumor cells in preclinical models.[85,86] As oncogenic MYD88 mutations are present in almost one-third of ABC DLBCL patients, the MYD88 pathway and especially the protein kinase IRAK4 is an attractive target.

ENHANCED CANONICAL AND NONCANONICAL NF-κB PATHWAYS IN MULTIPLE MYELOMA

With an incidence rate of >5 patients per 100 000 persons multiple myeloma constitutes by far the most frequent form of plasma cell neoplasms.[8] The heterogeneous tumor entity is characterized by long-lived plasmacytic B cells in the bone marrow. Multiple myeloma is a nearly incurable disease, and constitutive NF-κB activity is thought to critically contribute to the survival and proliferation as well as therapy resistance of the tumor cells. High amounts of the canonical NF-κB p65 subunit are present in almost 80% of multiple myeloma biopsies and these correlate with enhanced expression of anti-apoptotic NF-κB target genes.[127,128] In addition, strong nuclear accumulation of NF-κB p52 and RelB points to a key role of the noncanonical pathway as well. Constitutive RelB DNA binding is found in many primary multiple myeloma samples (~40%) and it also confers a clear pro-survival activity to multiple myeloma cells.[129] Cell-intrinsic and extrinsic processes seem to add to the sustained NF-κB activation in multiple myeloma. In fact, multiple myeloma survival seems to heavily rely on tumor microenvironment and signals from the stroma are essential especially during the onset of the disease. The TNF family ligands BAFF and APRIL (a proliferation-inducing ligand) activate the NF-κB pathway by binding to their highly abundant cognate BAFFR and TACI/BCMA receptors, respectively (Figure 4). These cell-extrinsic factors are not only required to maintain the survival of normal plasma cells, but also of the pre-malignant cells found in a condition called monoclonal gammopathy of undetermined significance that often precedes multiple myeloma.[130–132]

Besides the contribution of these extracellular factors, multiple myeloma tumor cells acquire several NF-κB pathway mutations that apparently render the cells more independent of ligand-mediated NF-κB signaling.[133] Mutations in positive and negative NF-κB regulators have been identified in ~9–17% of primary multiple myeloma tumors (Table 1). Interestingly, only a small subset of these lesions leading to activation of *TACI* or inactivation of *CYLD* and *NFKB1* are directly affecting canonical NF-κB.

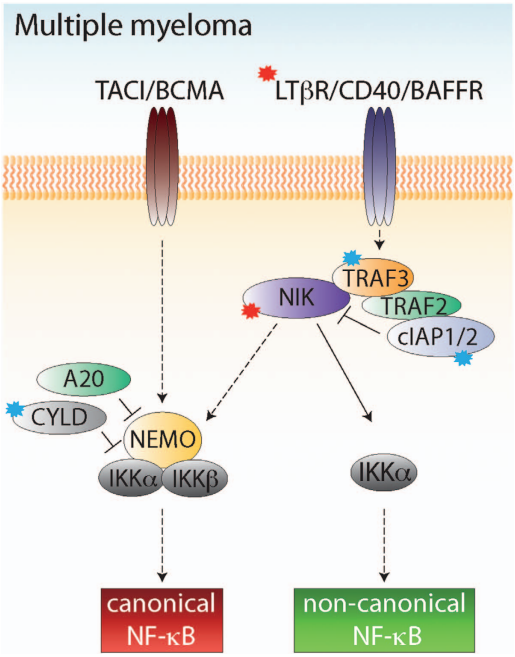

Figure 4. Stabilization of the NIK protein directs constitutive NF-κB activation in multiple myeloma. In early multiple myeloma the noncanonical NF-κB activity is activated through induction of BAFF receptor. TACI/BCMA receptor promotes canonical NF-κB pathway. Most genetic lesions identified in multiple myeloma patient biopsies contribute to the noncanonical NF-κB activation. The main mechanism involves the stabilization of NIK that activates IKKα and the subsequent processing of p100. NIK stabilization in multiple myeloma is achieved via several mechanisms: loss-of-function mutation (blue stars) in *TRAF3* or *cIAP1/2* by deletion/inactivation or gain-of-function (red stars) by amplification/overexpression of *MAP3K14/NIK*, *CD40* or *LTβR*. In addition, high levels of NIK can also trigger canonical IKK/NF-κB activation.

The majority of mutations are primarily associated with non-canonical NF-κB signaling, for example, gain-of-function mutations in *MAP3K14/NIK*, *CD40* and *LTβR* and loss-of-function mutations in *TRAF2/3*, *cIAP1/2* and *NFKB2*.[127,128,134] Even though the abundance of mutations would argue for a prominent role of noncanonical NF-κB signaling in the pathogenesis of multiple myeloma, selective IKKβ inhibition is highly toxic for multiple myeloma cells demonstrating that also canonical NF-κB activation is crucial for cancer cell survival.[127,135,136]

The protein kinase NIK serves a key role as most genetic aberrations in multiple myeloma affect NIK activity (Figure 4). To prevent constitutive NF-κB activation, NIK is inherently instable and degraded by the TRAF2/c-IAP1/2 E3 ligase complex in unstimulated cells. TRAF3 serves as a bridging factor to recruit TRAF2/c-IAP1/2 to NIK.[7] Although NIK overexpression can be directly achieved by amplifications or translocations of the NIK locus, NIK amounts are also often increased indirectly by inactivation of the negative regulator *TRAF3* and *c-IAP1/2* or in rare cases by activating mutations in *LTβR* (Table 1).[127,128] About 50% of all mutations in multiple myeloma involve the inactivation or deletion of the *TRAF3* gene. In most of these cases the NIK binding region on TRAF3 is deleted, resulting in a failure to recruit the TRAF2/c-IAP1/2 E3 ligase complex. In addition, biallelic deletions affecting *TRAF2* or *c-IAP1/2* genes have been identified in rare cases of multiple myeloma. Multiple myeloma cells with c-IAP1/2 losses express high TRAF3 and NIK amounts and congruently strong NF-κB activation is caused by destruction of the degradation machinery.[127,128] Also, a chromosomal translocation has been identified in a multiple myeloma cell line that fuses elongation factor EFTUD2 to NIK. As the EFTUD2-NIK fusion protein lacks the TRAF3 binding domain on NIK, stabilization of NIK is thought to be the primary cause for its oncogenic potential.[127] Interestingly, even though NIK is not directly involved in the canonical NF-κB pathway, its overexpression can directly promote IKKβ activation and thus induction of canonical NF-κB signaling, which may explain the enhancement of both the pathways.[137] Acting downstream of NIK, a C-terminal truncation product of NF-κB2/p100 has been detected in rare cases of multiple myeloma cells. Loss of the inhibitory ankyrin repeats of p100 promotes the generation of a constitutively nuclear p52 that can activate noncanonical NF-κB target gene expression.[134] Similar to NIK overexpression, loss of the inhibitory p100 C-terminus can also enhance nuclear p65 accumulation, revealing that mutations in the noncanonical pathway may well affect canonical NF-κB signaling.[138–140]

Given the key role of constitutive NF-κB activation for multiple myeloma survival, pharmaceutical interference represents a promising therapeutic approach. The introduction of proteasome inhibitors like bortezomib has delivered some improvements for multiple myeloma therapy and the blockage of NF-κB activation is thought to make a substantial contribution to the positive effects of proteasomal inhibitors.[141,142] However, several reports suggest that the primary effects of bortezomib are caused by unfolded protein response, endoplasmic reticulum stress and accumulation of aberrant antibodies, reflecting that this therapeutic approach does certainly not represent a highly selective strategy to interfere with NF-κB.[143,144] More specific approaches are being currently developed. Given the central role of TRAF3 and NIK for the activation of both, the canonical and noncanonical NF-κB pathway, pharmacological inactivation of NIK is certainly an interesting therapeutic option. Currently, there are several efforts made to generate potent NIK inhibitors,[145,146] but it may also be feasible to reduce NIK amounts. Moreover, recent results indicate that dual inhibition of the canonical and noncanonical NF-κB pathways may accelerate antitumor activity and overcome the proliferative and anti-apoptotic effects of the tumor microenvironment.[147]

CONCLUSIONS AND PERSPECTIVES

Since the initial discoveries of constitutive NF-κB activation in different lymphomas, tremendous progress has been made in our understanding of the genetic and molecular mechanisms as well as functional consequences of deregulated NF-κB signaling in lymphoid malignancies. Even though canonical IKK/NF-κB signaling is essential for survival of these lymphomas, severe adverse effects by the usage of IKKβ inhibitors seem to prevent targeting of the core pathway for cancer therapy. The hunt for genetic alterations and the molecular characterization of NF-κB signaling in lymphoma cells revealed the existence of some common aberrations, like the inactivation of the NF-κB negative regulator A20 in many different lymphomas. More importantly, other oncogenic events are more restricted to specific lymphoma entities, for example, the API2–MALT1 fusion in gastric MALT lymphoma, CD79B or CARMA1 mutations in ABC DLBCL, or NIK stabilization in multiple myeloma. Certainly, additional genetic lesions will be identified, but future analysis will also need to focus on the molecular mechanisms of how these aberrations are promoting NF-κB and lymphoma survival. On the basis of these results, it will be possible to design target-directed treatment approaches that more specifically interfere with deregulated NF-κB pathways in the tumor cells. First promising preclinical results have been obtained using BTK, PKCβ or MALT1 inhibitors to treat ABC DLBCL. Combinatorial treatment protocols that hit essential oncogenic processes in parallel may be envisioned to increase efficacy and to reduce the risk of drug resistance in highly malignant lymphomas.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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