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Mechanisms of NF-κB deregulation in lymphoid malignancies

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Running Title: NF-κB in lymphoid malignancies

Abstract

Deregulations promoting constitutive activation of canonical and non-canonical NF-κB signaling are a common feature of many lymphoid malignancies. Due to their cellular origin and the pivotal role of NF-κB for the normal function of B lymphocytes, B-cell malignancies are particularly prone to genetic aberrations that affect the pathway. Key positive regulators of NF-κB signaling can act as oncogenes that are often prone to chromosomal translocation, amplifications or activating mutations. Negative regulators of NF-κB have tumor suppressor functions and are frequently inactivated either by genomic deletions or point mutations. Whereas some aberrations are found in a variety of different lymphoid malignancies, some oncogenic alterations are very restricted to distinct lymphoma subsets, reflecting the clonal and cellular origin of specific lymphoma entities. NF-κB activation in many lymphoma cells is also driven by the microenvironment or chronic signaling that does not rely on genetic alterations. A number of drugs that target the NF-κB pathway are in preclinical or clinical development, revealing that there will be new options for therapies in the future. Since each lymphoma entity utilizes distinct mechanisms to activate NF-κB, a major challenge is to elucidate the exact pathological processes in order to faithfully predict clinical responses to the different therapeutic approaches.

Keywords: Lymphoma / B-cell receptor / NF-κB

1. Overview on the NF-κB system

Nuclear factor kappaB (NF-κB) comprises a family of transcription factors that are ubiquitously expressed in mammalian cells, but whose activity is tightly controlled by inhibitory IκB proteins. With p65/RelA, c-Rel, RelB, p105/p50 (NF-κB1) and p100/p52 (NF-κB2) the NF-κB family consists of five family members that share a conserved N-terminal REL homology domain (RHD), which mediates dimerization, nuclear translocation and association to genomic κB consensus sequences to regulate transcription of NF-κB target genes (**Figure 1**). RelA, c-Rel and RelB contain C-terminal transactivation domains (TAD) that are important for transcriptional activation. p50 and p52 are generated after processing of the precursor p105 and p100, respectively. They lack TADs and can only activate transcription in heteromeric complexes. The RHD also mediates the interaction of NF-κB to IκB proteins that bind to NF-κB via the ankyrin repeat domain (ARD). IκB proteins function as NF-κB inhibitors like the small cytosolic IκBα, IκBβ, IκBε or the precursor proteins p105/NF-κB1 and p100/NF-κB2 that sequester NF-κB in the cytosol. Signal degradation motifs in the cytosolic IκBs contain two conserved serine residues that are phosphorylated by IκB kinases (IKK) upon cell stimulation, which leads to their ubiquitination and proteasomal degradation. Further, so called atypical IκB proteins like BCL3 and IκBζ are not prone to stimulus dependent degradation, but they act primarily in the nucleus where they can modulate NF-κB transcriptional activity by binding to p50/p50 or p52/p52 homodimers [1, 2].

NF-κB activation in response to extracellular stimulation is controlled by two major pathways: The canonical and non-canonical NF-κB signaling pathways (**Figure 2**). Canonical NF-κB signaling is induced upon stimulation by pro-inflammatory cytokines (e.g. TNF, IL1), pathogen-associated molecular patterns (PAMPs) from bacteria and viruses, B- or T-cell antigen receptor (BCR or TCR) agonists, chemicals or radiation. All upstream signaling pathways converge at the IκB kinase (IKK) complex that consists of

the regulatory subunit NEMO (NF-κB essential modulator; IKKγ) and the catalytic subunits IKKα (IKK1) and IKKβ (IKK2) [3, 4]. Upon stimulation, NEMO-dependent activation of IKKβ catalyzes the phosphorylation of small cytosolic and precursor IκB proteins, which are subsequently recognized by βTRCP-containing Cullin-RING E3 Ligase (CRL) complex and rapidly degraded by the ubiquitin proteasome system (UPS). Canonical signaling mainly releases NF-κB heterodimers consisting of p50/RelA and p50/c-Rel, but also p50/p50 homodimers, from IκB inhibition. NF-κB nuclear translocation induces a rapid transcriptional response and expression of target genes involved in inflammation, immune regulation, protection from apoptosis and cell proliferation. Under physiological conditions, canonical NF-κB signaling is transient and shut down by auto-regulatory feedback mechanisms that involve NF-κB triggered induction of negative regulators such as IκBα, IκBε and TNFAIP3/A20.

Whereas canonical signaling is activated in response to most inducers, activation of NF-κB by the non-canonical pathway is restricted to a subset of TNF family members such as lymphotoxin-β (LTβ), B-cell activating factor (BAFF) and CD40L (**Figure 2**) [5]. Non-canonical stimuli promote the destabilization of TRAF2/3-cIAP E3 ligase complexes that trigger degradation of the protein kinase NIK (NF-κB inducing kinase) in unstimulated cells. Stabilized NIK phosphorylates and activates IKKα, which in turn phosphorylates C-terminal serines of p100 to label the precursor for UPS-dependent processing to p52. Ultimately, non-canonical signaling promotes the accumulation, nuclear translocation and transcriptional activation of p52/RelB heterodimers. In contrast to the canonical response, non-canonical signaling is considerably delayed and more sustained and has been associated with developmental processes such as formation of secondary lymphoid organs.

Owing to the critical involvement of NF-κB proteins for B-cell development, maintenance and function of peripheral and mature B-cells [6], deregulation in

canonical and non-canonical NF-κB signaling pathways are a common feature in many B-cell malignancies. Mature B-cells activation and survival depends on signaling pathways emanating from the BCR, BAFF-R, CD40R or Toll-like receptor4 (TLR4) and oncogenic mutations, chromosomal translocations and copy number alterations are frequently found in key components that connect these receptors to NF-κB. Thus, the physiological role of NF-κB renders B-cells highly susceptible to aberrations that promote lymphomagenesis. Here, we will provide an overview describing key mechanisms and consequences that trigger pathological activation of canonical and non-canonical NF-κB in lymphoid malignancies. Other reviews within this issue will more specifically highlight the molecular aberrations within distinct malignancies.

2. NF-κB in lymphoid malignancies – a brief history

NF-κB was originally described as nuclear protein that binds to the κB light chain enhancer in the B-cell lymphoid lineage [7]. However, the first vertebrate REL proteins cloned were the avian retroviral protein v-Rel and its cellular homolog c-Rel [8, 9]. The discovery that retroviruses encoding v-Rel are highly oncogenic and transforming cells *in vitro* and *in vivo* gave a first hint that deregulated NF-κB can contribute to tumorigenesis [10]. First evidence for an involvement of mammalian NF-κB proteins in human lymphomas and leukemias came from the identification of chromosomal rearrangements involving NF-κB family members [10, 11]. NFKB2 translocation deleting the C-terminal ankyrin repeats and thus inhibitory function of p100 have been found in B-cell lymphomas [12, 13]. Further, REL gene amplifications were frequently found in human lymphomas [14] and the nuclear IκB protein BCL3 was originally identified from a chromosomal translocation t(14;19) placing it under control of the immunoglobulin heavy chain (IGH) locus in B-cell chronic lymphocytic leukemia (CLL) [15]. Even though the pathways regulating NF-κB were unclear at the time, these early

findings already suggested an important contribution of deregulated NF-κB activity in the development of lymphoid cancer.

The augmented liver cell apoptosis and embryonic lethality of RelA deficient mice provided evidence that physiological NF-κB activation by cytokines and other stimuli counteracts apoptosis [16]. Further, NF-κB promotes cell cycle progression [17]. Thus, cell survival and proliferation - two hallmarks of cancer - are tightly controlled by NF-κB. In line, the observation of strong NF-κB activity in primary Hodgkin cells and Hodgkin-derived lymphoma cell lines was the first example of constitutive NF-κB activation in human cancer cells and suggested that cell-intrinsic mechanism can account for deregulated NF-κB activation in tumor cells [18, 19]. RelA activation also prevented cell death and augmented cell growth in the pathological setting of Hodgkin lymphoma (HL) [18]. Subsequent studies revealed that cell-intrinsic survival of many human cancers relies on constitutive NF-κB, including breast, lung, colon, pancreatic and prostate cancer, suggesting that targeting the NF-κB system is a promising approach for anti-cancer therapies [20]. However, the critical role of canonical IKKβ/NF-κB signaling in many physiological settings and especially the severe liver cell toxicity associated with genetic disruption or pharmacological inhibition of the pathway prevented the clinical development of IKKβ inhibitors for cancer therapy. Nevertheless, recent advances in understanding the specific lesions and deregulated pathways in distinct lymphoma entities paved the way for more selective therapeutic strategies and first drugs like Ibrutinib that targets the IKKβ upstream kinase BTK (Bruton's tyrosine kinase) have now successfully entered the clinic [21].

3. Aberrations in core canonical NF-κB signaling components

The importance of canonical NF-κB signaling in many lymphoid malignancies was strongly supported by the identification of gain- or loss-of-function mutations in core

components of the pathway in HL, diffuse large B-cell lymphoma (DLBCL), peripheral mediastinal B-cell lymphoma (PMBL) or CLL. As noted earlier, constitutive anti-apoptotic and pro-proliferative NF-κB activity was initially found as a common feature of HL cells [18]. In HL, malignant Hodgkin-Reed Sternberg (HRS) cells are surrounded by activated B- and T-cells, suggesting that the cellular milieu promotes NF-κB activation through cell-extrinsic mechanisms, e.g. through the interaction of CD40L on CD4 T-cells and CD40 on HRS cells [22]. Even though the inflammatory environment certainly contributes to NF-κB signaling in vivo, the robust and persistent NF-κB activation in cultured Hodgkin cell lines clearly indicated the existence of cell-autonomous events [23]. HRS cells have lost BCR specific signaling and gene expression [24] and constitutive NF-κB activity is often triggered by mutations in canonical NF-κB signaling components downstream of the IKK complex. Inactivating point mutations have been found in the IκB genes NFKBIA/IκBα (~10%) and NFKBIE/IκBε (~15%) [25-27]. Malignant HRS cells are rare and often less than 1% of the cell mass in an affected lymph node [24], hampering the identification of somatic mutations in HL and making it quite likely that not all lesions have been found or that the frequencies of IκB mutations are underestimated. In line with a tumor suppressor function, expression of degradation resistant IκBα superrepressor is toxic to cell lines derived from HL or activated B-cell type (ABC) DLBCL that are both dependent on constitutive NF-κB activation [18, 28]. NFKBIA/IκBα mutations were also reported in ABC DLBCL and NFKBIE/IκBε mutations have been identified in CLL, DLBCL, mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL) [29]. NFKBIE/IκBε aberrations in CLL patients (~7%) are associated with poor prognosis and inactivation of IκBε contributes to augmented NF-κB activation [29]. Thus, IκB proteins can act as tumor suppressors and contribute to sustained NF-κB survival signaling in lymphoid malignancies. At what stage of the diseases the IκB mutations become pathological significance is not clear, but it is worthwhile to speculate

that these downstream mutations and augmented NF-κB may facilitate an escape from negative selection of either B-cells that have lost BCR expression and signaling as in the case of HRS cells [24] or B-cells that carry autoreactive BCRs as in the case of CLL [30]. Of note, all Hodgkin-derived cell lines also display constitutive activation of the IKK complex [23], suggesting that additional yet undiscovered epistatic mechanisms independent of BCR signaling can promote upstream IKK/NF-κB activation in HL.

Further, cell-intrinsic enhancement of canonical NF-κB signaling is reflected by copy number gains in the REL locus (~30%) and elevated nuclear expression of c-Rel is a common feature in HL [31]. Despite lower frequencies, REL gene amplifications have been found in many other lymphomas, including DLBCL, PMBL and CLL [32]. In contrast to p50, p52, RelB, RelA or constitutively active IKKβ, c-Rel – just like v-Rel – is able to transform avian lymphoid cells [33]. The transforming potential of c-Rel relies on DNA binding and transactivation, but it is increased if one of the two C-terminal TADs is removed, indicating that oncogenicity requires the right balance of transcriptional activation [34]. Even though c-Rel does not transform mouse or human lymphoid cells, overexpression of a human REL mutant lacking the C-terminal TAD1 enhances oncogenic properties in a human B-cell lymphoma line and is sufficient to convert a germinal center B-cell type (GCB) DLBCL gene signature into an expression profile of aggressive ABC DLBCL [35]. Moreover, a truncated splice variant of c-Rel has been identified that is expressed in lymphoma cell lines and DLBCL patient samples, underscoring that alterations affecting the C-terminus of c-Rel are critical for inducing lymphomagenesis [36]. Thus, substantial evidence indicates that aberrant c-Rel expression contributes to lymphomagenesis, but still the pathological functions of c-Rel are largely unclear.

Not only the NF-κB family member c-Rel is prone to mutations, but chromosomal aberrations involving the nuclear IκB protein BCL3 that modulates NF-κB transcription

is frequent in lymphomas [37]. BCL3 copy number gains have been found in HL (~15%) [38]. In addition, the translocation t(14;19)(q32;q13) that juxtaposes BCL3 next to the IGH locus leading to enhanced BCL3 expression was found in many lymphoid malignancies including CLL, follicular lymphoma (FL), MZL and HL [38, 39]. The function of BCL3 in lymphomas is still not completely resolved, but binding of nuclear BCL3 to p50 homodimers augments canonical NF-κB activity [40]. Interestingly, BCL3 alterations are also found in anaplastic large cell lymphomas (ALCL) that resemble HL with respect to gene signatures and molecular aberrations [40]. In fact, ALCLs originate from cytotoxic T-cells, but have lost expression of T-cell specific genes which is reminiscent to HRS cells that are derived from germinal center (GC) B-cells, but have lost BCR specific signaling and gene expression [24, 41]. Thus, it seems that lesions in BCL3 are often found in lymphoma that have lost their lymphoid identity, but the reason for this is yet unknown.

Besides BCL3, also the atypical nuclear IκB protein IκBζ (also known as MAIL) is deregulated in lymphoma. Genomic amplifications of the NFKBIZ/IκBζ locus are frequent in ABC DLBCL that are addicted to constitutive IKK/NF-κB activity [42]. Independent of the genomic alterations, high expression of IκBζ is a common feature of ABC DLBCL tumors [43]. By binding to nuclear p50 and p52, IκBζ triggers expression of many NF-κB survival genes and acts as an essential modulator of NF-κB activity in ABC DLBCL [43] Conflicting data have been obtained regarding the expression level of IκBζ in other lymphoma and especially HL, but more recent data indicate that the pro-survival function of IκBζ is restricted to some NF-κB-driven lymphomas [43, 44]. Overall, nuclear modulators such as BCL3 and IκBζ strongly affect oncogenic NF-κB activity, but their direct contribution to the development and maintenance of lymphoid malignancies is still not clearly defined.

4. Mechanisms of aberrant non-canonical NF-κB signaling

Besides strong canonical NF-κB signaling, some lymphoid malignancies are characterized by high nuclear activity of the NF-κB family members p52 and RelB that are activated in response to the non-canonical signaling pathway [45-48]. In non-canonical NF-κB signaling, NIK phosphorylates and activates IKKα, which subsequently promotes the processing of the p100/NF-κB2 precursor to trigger activation of p52/RelB heterodimers. In resting cells, NIK is constantly degraded by an ubiquitin-ligase complex consisting of TRAF2/3 and the E3 ligases cIAP1/2 that mark NIK for rapid proteasomal degradation (**Figure 2**) [5]. TRAF2/3 serve as bridging factors that couple c-IAP1/2 complex to NIK to foster its degradation.

Non-canonical NF-κB activation is a common feature of HL, multiple myeloma (MM) and t(11;18)-positive MALT lymphoma (see section 7) In line, copy number gains in MAP3K14/NIK gene (~30%) or copy number losses in TRAF3 gene (~15%) are recurrent in HRS cells and NIK is stabilized in Hodgkin cells [49], [50]. Also, mutations in non-canonical NF-κB component have been identified in ~17% of primary MM and the vast majority is affecting the non-canonical NF-κB signaling pathway. These include chromosomal translocation of MAP3K14/NIK as well as loss of function mutation in TRAF2, TRAF3, c-IAP1, c-IAP2 and NFKB2/p100 [45, 47, 51]. Of note, 50 % of the somatic mutations in MM lead to inactivation or deletion of TRAF3 resulting in high NIK protein levels [45, 47]. Elimination of NIK, RelB or p52 is highly toxic to HL and MM cells, underscoring the importance of non-canonical signaling for survival of the lymphomas [49, 52]. Recent comparative analyses revealed a substantial cross-talk of canonical and non-canonical NF-κB signaling in lymphoma. In fact, p50 and p52 are the predominant NF-κB subunits in Hodgkin cells and they significantly cross-contribute to canonical and non-canonical transcriptomes, respectively [53]. Moreover, depletion of NIK affected p100 and p105 precursor processing, indicating that the pathways are highly interconnected, which is in line with previous observations that NIK can also

trigger canonical NF-κB activation [54].

It is still not clear why especially MM and HL rely on enhanced non-canonical NF-κB signaling and in most cases the pathway is apparently driven in the absence of genetic alterations. In both lymphoma entities, signals from the tumor microenvironment and thus cell-extrinsic processes may at least partially contribute to strong non-canonical NF-κB activation. MM reside in the bone marrow and express high levels of the receptor TACI and BCMA. Their respective ligands BAFF and APRIL are present in the tumor microenvironment and have been shown to activate non-canonical NF-κB signaling [55]. Also, the inflammatory milieu of HL may provide ligands for activation, e.g. CD40L on CD4 T-cells may stimulate CD40 signaling to canonical and non-canonical NF-κB in HRS cells [22]. In addition, infection by Epstein-Barr virus (EBV) poses a potential risk for the development of HL and EBV-LMP1 acts as a constitutively active CD40 and induces both NF-κB pathways [56]. Thus, the tumor milieu may significantly contribute to NF-κB in these lymphoma entities.

More recent data also indicate a contribution of non-canonical NF-κB signaling in other lymphomas. A significant fraction of DLBCL biopsies also stained positive for nuclear p52 [46]. Deletions or mutations of TRAF3 were found in ~15% of DLBCL samples and in line with its role in regulating NIK degradation the genetic loss enhances canonical NF-κB [57, 58]. Ablation of TRAF3 and parallel overexpression of BCL6, a repressor of BLIMP1 and terminal B-cell differentiation, cooperate in inducing DLBCL in mice [58]. Further, transcriptome sequencing revealed that ibrutinib insensitive MCL carry recurrent mutations in TRAF2 and BIRC3/c-IAP2, leading to a stabilization of NIK, p100 processing and p52 activation [59]. Accordingly, these MCL cells are sensitive to NIK knock-down and inhibition. Taken together, these studies highlight a considerable and yet underappreciated cross-talk and interdependency of canonical and non-canonical NF-κB signaling in lymphoma. Further, analyses of oncogenic lesions and signaling

pathway activities may be used to stratify patients for specific therapies.

5. Chronic B-cell receptor triggers NF-κB activation

Given the necessity of a functional BCR at many stages of pre- to mature B-cell differentiation, it is not a surprise that deregulation in the signaling components connecting proximal BCR events to downstream signaling pathways and especially NF-κB contributes to the development of many lymphoid malignancies [6]. Preclinical and clinical data have demonstrated that pharmacological targeting of the protein kinase BTK by Ibrutinib represents a promising approach to treat a number of B-cell malignancies, such as MCL, CLL and DLBCL [60]. BTK is critical for activation of various signaling pathways downstream of the BCR including NF-κB. Thus, the success of Ibrutinib provided clinical proof that understanding of the BCR signaling pathways will promote novel therapeutic approaches and precision therapy in a number of lymphoid malignancies. However, the processes and functions of BCR triggered NF-κB activation in MCL and CLL are still poorly understood. CLL is characterized by an expansion of monoclonal, mature B-cells and strong evidence suggests that this is driven by antigen-dependent BCR ligation via auto-antigens or microbial antigens in the microenvironment or by autoreactive BCRs activation [61, 62]. The recent identification of inactivating mutations in NFKBIE/IκBε CLL underscores an involvement of canonical NF-κB (see section 3) [29]. However, somatic mutations in BCR signaling components are uncommon [63] and how BCR connects to NF-κB still needs to be analyzed.

The mechanisms and consequences of chronic BCR signaling have been intensively studied for DLBCL, which represents the largest group of non-Hodgkin lymphoma [64]. Gene expression profiling facilitated the classification of this heterogeneous lymphoma entity and revealed that survival of the ABC DLBCL subset strictly relies on constitutive IKK/NF-κB activity [65]. ABC DLBCL originate from an activated B-cell and key signaling components connecting the BCR signaling pathway to the IKK complex are critical for

NF-κB activation and ABC DLBCL survival. The essential signaling proteins encompasses BCR subunits (IgM, Igκ, CD79A and CD79B), protein kinases (SYK, BTK and PKCβ) as well as the CARD11/CARMA1-BCL10-MALT1 (CBM) signaling complex that bridges proximal BCR signaling to the canonical NF-κB pathway (**Figure 3**) [66, 67].

Chronic BCR signaling and CD79 mutations

Activation of chronic BCR signaling in ABC DLBCL is caused by various molecular aberrations that may or may not rely on oncogenic lesions. Activating mutations in the immunoreceptor tyrosine-based activation motif (ITAM) of either CD79B or CD79A have been identified in more than 20% of ABC DLBCL patients (**Figure 3**) [66]. The ITAMs are necessary for BCR activity and thus oncogenic mutations are unconventional, because they are not directly activating the BCR pathway. Instead, point mutations or deletions in the ITAMs of CD79A or B are impairing BCR internalization post-stimulation and thus preventing a negative feedback to shut down signaling. In line, survival of CD79 mutant ABC DLBCL is still relying on a functional BCR [66]. In agreement, self-antigens have been shown to function as BCR ligands on ABC DLBCL cells and auto-activation is responsible for maintaining survival of the cells [68]. Auto-reactivity of DLBCL cells may predict responsiveness to BCR pathway inhibitors and a first clinical study demonstrates that BTK inhibitor Ibrutinib is highly effective for the treatment of ABC DLBCL that rely on proximal BCR signaling [69]. How receptor internalization and BCR signaling is sustained in cells that do not carry CD79 mutations is still elusive, but further downstream mutation especially in the molecular scaffold CARD11 have been shown to render ABC DLBCL completely resistant to these upstream signaling events and the patients resistant to Ibrutinib [69].

Oncogenic CARD11 mutations

In activated lymphocytes CARD11, BCL10 and MALT1 assemble a high molecular weight

signaling platform called CBM complex that bridges proximal BCR and TCR signaling events to canonical IKK/NF-κB [70]. CARD11, BCL10 and MALT1 are critical for NF-κB activation and survival of ABC DLBCL and the CBM complex is persistently assembled in all ABC DLBCL cells [67, 71]. Somatic gain-of-function mutations in CARD11 are frequently found in ABC DLBCL (~10%) (**Figure 3**) [57, 72]. Despite some preference for the ABC DLBCL subtype, a considerable number of GCB DLBCL also carry CARD11 activating mutations and these lymphoma cells are characterized by parallel induction of NF-κB target genes on top of a GCB gene signature [72, 73]. CARD11 and CD79B mutations have been also found in FL that acquired an ABC DLBCL-like feature, coinciding with a transformation from an indolent to a more aggressive pathology [74]. However, CARD11 is also mutated in a considerable fraction of indolent FL and it will be interesting to see if this mutation represents an early event in the course of DLBCL transformation or if oncogenic CARD11 may serve other functions in this lymphoma entity [75].

Activating mutations are mostly confined to the coiled-coil domain of CARD11 and are thought to induce an open conformation that allows the recruitment of BCL10-MALT1 independent of any upstream signaling events [72]. Indeed, oncogenic CARD11 provokes the formation of large BCL10 filamentous aggregates in ABC DLBCL cells [76] and these mutations render ABC DLBCL cells insensitive to BCR pathway inhibition like the BTK inhibitor Ibrutinib or the PKC inhibitor Sotrastaurin [77, 78]. Thus, quite in contrast to CD79 ITAM mutants, growth of CARD11 mutated ABC DLBCL is independent of a functional BCR [66]. The potency of oncogenic CARD11 is also revealed in studies analyzing mutations in murine and human B-cells. The expression of CARD11 mutants in activated B-cells is abolishing self-antigen induced cell death [79]. Further, human germline mutations in the CARD11 coiled-coil trigger B-cell expansion [80]. Expression of oncogenic CARD11 in murine B-cells induces aggressive lymphocyte proliferation and postnatal death of the mice [81]. In fact, in murine B-cells the effects of oncogenic

CARD11 are much more severe compared to the activation of NF-κB by expression of constitutively active IKKβ, suggesting that CARD11 may channel to other pathways besides NF-κB [79, 82]. Accordingly, oncogenic CARD11 is also activating the JNK signaling, which is necessary for cell proliferation and survival [81]. Moreover, CK1α associates with CARD11 in ABC DLBCL and it was suggested to promote and terminate CBM signaling [83]. Recently, CK1α was also shown to recruit the β-Catenin destruction complex to active CARD11, leading to a stabilization of β-Catenin, which in turn cooperates with NF-κB in the induction of distinct target genes in DLBCL cells [84]. Even though it is not yet clear in how far these different processes contribute to the potency of CARD11 mutations, the data indicate that CARD11 can connect to several oncogenic signaling networks to promote massive proliferation and survival in normal B-cells and B-cell lymphomas.

CBM and IKK complexes connect via cIAP and LUBAC E3 ligases

Upon T-cell receptor (TCR) engagement BCL10 and MALT1 are poly-ubiquitinated and thereby recruit the IKK regulatory subunit NEMO to the CBM complex leading to IKK activation [85, 86]. Similar, ubiquitination of MALT1 was shown in ABC DLBCL cells [83]. The identification that chronic BCR signaling in ABC DLBCL triggers recruitment of the linear ubiquitin chain assembly complex (LUBAC) to the CBM complex cells shed light on how IKK kinase activity is activated at the CBM [87, 88]. The LUBAC contains the E3 ubiquitin ligase HOIP (also known as RNF31), HOIL1 and SHARPIN and catalyzes the generation of linear Met1-linked ubiquitin chains that are promoting IKK/NF-κB activation in response to pro-inflammatory TNFα and IL-1β signaling [89]. Recent data unraveled that E3 ligase activities of the LUBAC and cIAP1/2 are cooperating in bridging the CBM complex to IKK activation in ABC DLBCL [90]. cIAP1/2 are binding to the CBM complex and catalyze the attachment of Lys63-linked ubiquitin chains on BCL10, which is necessary for recruitment of the LUBAC and the concomitant assembly of Met1-linked

chains on BCL10 and NEMO [90]. Genetic evidence for an involvement of LUBAC comes from two rare human germline polymorphisms in HOIP that are significantly enriched in ABC DLBCL patients compared to healthy individuals [88]. These data highlight that the identification and functional characterization of rare germline polymorphisms may unravel genetic risk factors for lymphomagenesis. The therapeutic relevance of these findings is supported by showing that peptide-based inhibition of HOIP as well as SMAC mimetics that degrade cIAP1/2 block growth of BCR-dependent ABC DLBCL [88, 90]. Just like for BTK and PKCβ inhibition, downstream CARD11 mutations render ABC cells resistant to HOIP and cIAP inhibitor treatment. Of note, the enzymatic function of HOIP seems to be more restricted to chronic BCR signaling in lymphoma cells, because B-cell specific inactivation of LUBAC by deletion of the catalytic RING domain of HOIP did not impair BCR-triggered IKK/NF-κB signaling in murine splenic B-cells [91].

MALT1 paracaspase activity

Besides its scaffolding function within the CBM complex, MALT1 contains a paracaspase domain and its proteolytic activity is induced upon antigen receptor binding in T- and B-cells [92]. In ABC DLBCL cells, MALT1 protease activity is constitutively enhanced and pharmacological inhibition proved that MALT1 cleavage activity is required for ABC DLBCL survival [71, 93-95]. Whereas poly-ubiquitination of MALT1 is required for scaffolding and recruitment of IKKs to the CBM [85], mono-ubiquitination drives MALT1 protease activity in T-cells and ABC DLBCL cells [96]. Structural data highlighted that MALT1 activation involves complex conformational rearrangements of MALT1 paracaspase and adjacent Ig3 domains [97]. Mepazine and Thioridazine were identified as allosteric inhibitors that abolish this activation step and keep MALT1 in an inactive conformation [95, 98]. Combinatorial treatment of MALT1 inhibitor Mepazine and BTK inhibitor Ibrutinib enhanced killing of CD79 mutant ABC DLBCL, but whereas oncogenic CARD11 expression induced resistance to Ibrutinib, these cells were still sensitive to

Mepazine [99]. Thus, MALT1 inhibitors may be clinically relevant for treating ABC DLBCL patients that either do not respond or develop resistance towards BTK or other BCR pathway inhibitors. Even though so far no BCR pathway mutations in MCL have been reported, a subgroup of MCL that is sensitive to BTK and PKC inhibitors exhibit chronic BCR signaling and NF-κB and MALT1 activation, suggesting that therapeutic use of MALT1 inhibitors may not be restricted to ABC DLBCL [59].

The pathological consequences of MALT1 protease activity and the relevant MALT1 substrates are still largely enigmatic. The NF-κB negative regulator A20 is cleaved and inactivated by MALT1 (**Figure 3**) [71]. The ubiquitin editing enzyme A20 is a potent negative regulator of IKK/NF-κB activation and deletions or mutations of the TNFIAP3/A20 gene are common in many lymphomas from various origins [46, 100, 101]. So, MALT1 cleavage represents an alternative mechanism to inactivate the A20 tumor suppressor specifically in ABC DLBCL. RelB is a substrate of MALT1 in ABC DLBCL and RelB overexpression impairs survival of ABC DLBCL suggesting that non-canonical counteracts canonical NF-κB signaling and survival of ABC DLBCL [102]. However, non-canonical NF-κB was suggested to act oncogenic in HL, MM and DLBCL (see section 4) and thus the reason for the tumor suppressing function of RelB in ABC DLBCL awaits further analyses [49, 52]. New data indicate that the MALT1 protease may also regulate the LUBAC that was shown to control CBM mediated IKK activation in DLBCL [88]. MALT1 cleaves CYLD in ABC DLBCL [93] and CYLD was shown to negatively regulate LUBAC and NF-κB activity after TNFα stimulation [103]. However, CYLD effects on LUBAC in ABC DLBCL have not been investigated. Further, the LUBAC subunit HOIL1 is a substrate of MALT1 in lymphocytes and lymphoma cells, but it is currently unclear whether this cleavage would impose a negative or positive effect on downstream signaling [104-106]. Taken together, the mechanistic influence of MALT1 protease activity in ABC DLBCL is still largely unresolved. NF-κB signaling in mice expressing catalytically inactive MALT1 is largely normal [107, 108], suggesting the existence of

MALT1 substrates that are not directly affecting NF-κB signaling. Interestingly, MALT1 cleavage of post-transcriptional regulators like Roquin and Regnase-1 is important for T-cell activation [109, 110], but it still needs to be shown whether Roquin and Regnase-1 are MALT1 targets in lymphoma cells.

6. NF-κB activation in response to MYD88 dependent innate immune signaling

Besides adaptive immune signaling, innate immune signaling by TLRs such as TLR4 that recognize lipopolysaccharides (LPS) is shaping the development and function of mature B-cells [111]. TLRs activate canonical NF-κB by associating with the adaptor MYD88, which in turn recruits and activates the protein kinases IRAK4 and IRAK1 to induce IKK activation by a TRAF6 and TAK1 dependent process [112]. The significance of this innate immune pathway is underscored by recurrent gain-of-function mutations in MYD88 that are found in almost 40% of ABC DLBCL, more than 90% of Waldenström's macroglobulinemia and less frequent in GCB DLBCL, MALT lymphoma, CLL and FL [63, 74, 113, 114]. The most prevalent MYD88 lesion is the missense mutation L265P in the Toll-interleukin receptor (TIR) domain, which is present in almost 30% of ABC DLBCL biopsies and induces NF-κB by accelerating binding and activation of IRAK4 (**Figure 3**) [113]. Importantly, B-cell specific mutation of endogenous murine MYD88 at L252P (equivalent to human L265P) is sufficient to induce lymphoproliferation and clonal lymphomas with morphological and immunophenotypical characteristics of ABC DLBCL [115]. Whereas in a previous mouse model expression of constitutively active IKKβ and simultaneous disruption of BLIMP1 was required for ABC DLBCL like development [82], in this case a single MYD88 mutation was sufficient to trigger lymphomagenesis. This may be explained by the ability of MYD88 to induce other pathways besides NF-κB such as IRF3 and IRF4 responses [112]. The therapeutic relevance of the MYD88-IRAK4 pathway is highlighted by the recent identification of highly selective IRAK4 inhibitors ND-2158 and ND-2110 [116]. IRAK4 inhibition impaired NF-κB and potently killed

MYD88 mutant ABC DLBCL cells in vitro and in vivo as a single agent or in combination with the BTK inhibitor ibrutinib or the Bcl-2 inhibitor ABT-199.

Mechanistically, MYD88 L265P mutation induced B-cell division when introduced into antigen-activated primary B-cells, but this effect requires continuous TLR9 signaling [117]. In line, oncogenic MYD88 relies on TLR7 and TLR9 signals in ABC DLBCL [118]. TLR7 and TLR9 are expressed on endosomes and recognize single-stranded RNA or CpG sequences, respectively. Thus, highly reminiscent to the situation of oncogenic CD79B mutant cells that depend on a chronic BCR activation by self-antigens [68], continuous TLR7/9 activation is driving NF-κB and survival of ABC DLBCL, providing a rationale for the use of inhibitors that target these innate receptors for ABC DLBCL therapy. It will be highly interesting to see whether other lymphomas that carry MYD88 mutations also rely on the activation of specific TLRs.

7. API2-MALT1 fusion protein activates canonical and non-canonical NF-κB

The chromosomal translocation t(11;18)(q21;p21) creating the oncogenic fusion protein API2-MALT1 is specific for mucosa-associated lymphoid tissue (MALT) lymphoma. MALT lymphoma is a common extranodal lymphoma that is initiated and in early stages requires Helicobacter pylori infection. The translocation t(11;18)(q21;q21) is characteristic for a subset of MALT1 lymphoma that arise independent of chronic infection [119]. It generates the fusion protein API2-MALT1, in which the N-terminus of c-IAP2/API2 (apoptosis inhibitor 2) is linked to the MALT1 C-terminus. API2-MALT1 is a potent oncogenic driver, which is reflected by the fact that t(11;18) positive lymphoma grow independent of infection and are associated with treatment resistance [120].

It is thought that the chimeric API2-MALT1 protein acts as a potent oncogene, because it combines the unique properties of API2 and MALT1 to induce a robust activation of canonical and non-canonical NF-κB signaling by multiple mechanisms (**Figure 4**). Three distinct mechanisms have been suggested to confer the unique oncogenic properties to

API2-MALT1. First, API2-MALT1 auto-oligomerizes via interaction of three baculovirus IAP repeats (BIR) in the API2 moiety and C-terminal MALT1 paracaspase domain, promoting strong activation of NF-κB signaling independent of upstream signals [121, 122]. Second, the fusion of API2 and MALT1 links two interactions surfaces that recruit multiple NF-κB mediators. Whereas TRAF2 and RIP1 bind to API2, TRAF6 associates with binding sites C-terminal to the MALT1 paracaspase domain and both mechanisms are required for maximal activation of canonical IKK/NF-κB [121, 123, 124]. Further, API2-MALT1 lacks the BCL10 binding region on MALT1, but association of BCL10 to the BIR of the API2 part was suggested to protect BCL10 from c-IAP2 catalyzed degradation [125]. However, the contributions of BCL10 to API2-MALT1 to NF-κB signaling and oncogenicity need to be resolved. Moreover, the API2 moiety was shown to recruit and potentially sequester pro-apoptotic SMAC/DIABLO, which may suppress apoptosis, but again the functional relevance has to be determined [126]. Third, the API2-MALT1 fusion generates a constitutively active MALT1 protease with a unique pattern of substrate cleavage. The protein kinase NIK is cleaved only by API2-MALT1 and not by MALT1, because the API2 moiety provides substrate recognition to bring NIK into proximity of the MALT1 paracaspase domain for cleavage [127]. In resting cells NIK is constantly degraded due to the N-terminal interaction with the TRAF2/3-c-IAP1/2 E3 ligase complexes (see section 1) [5]. Cleavage of NIK releases and stabilizes the C-terminal catalytic domain of NIK, which induces non-canonical NF-κB by phosphorylating IKKα to mediate p100/NF-κB2 processing and p52/RelB translocation (**Figure 4**) [127]. Similar, the tumor suppressor LIMA1 was identified as a specific substrate of API2-MALT1, but its inactivation by cleavage seems to affect API2-MALT1 oncogenicity independent of NF-κB [128]. Taken together, oncogenic potency of API2-MALT1 is explained by its ability to combine different features that strongly promote canonical and non-canonical NF-κB signaling via different routes. Further, API2-MALT1 represents an intriguing example how an oncogenic aberration is inducing enzyme

activity and at the same time changing substrate specificity.

8. Conclusions and therapeutic implications

Studies within the last three decades revealed that chromosomal aberrations and deregulations leading to constitutive activation of NF-κB signaling are promoting the initiation and maintenance of B-cell malignancies. Tremendous progress has been made in understanding the pathological processes as well as consequences of deregulated NF-κB. Whereas some aberrations like the inactivation of the tumor suppressor TNFAIP3/A20 are common to many lymphomas, other oncogenic events like the chromosomal translocation t(11;18) creating API2-MALT1 fusion protein are limited to certain lymphoma sub-entities. Since many lymphoid malignancies are addicted to NF-κB, the pathway has been recognized as an 'Achilles Heel' for lymphoma survival and thus therapeutic intervention. However, ample evidence suggests that NF-κB is not only controlling immune activation but also immune homeostasis to prevent inflammatory diseases, suggesting that complete inhibition of canonical NF-κB causes systemic toxicity [129, 130]. Therefore, much work has focused on the specific upstream mechanisms governing IKK/NF-κB activation in lymphomas. The clinical success of the BTK inhibitor Ibrutinib for treating CLL, MCL and ABC DLBCL provided compelling proof that a detailed understanding of molecular deregulations driving chronic BCR signaling upstream of IKKs can lead to target-based therapies. However, many patients show primary or secondary resistances to Ibrutinib underscoring the necessity for alternative therapeutic approaches [131]. Recent preclinical data demonstrated promising therapeutic effects using pharmacological inhibitors against other key players triggering adaptive or innate immune signaling to NF-κB, e.g. PKCβ, cIAPs, MALT1 or IRAK4 [77, 90, 93, 95, 116]. Thus, new drugs and therapeutic options to target crucial signaling nodes will be available in the near future. Nevertheless, the hunt for new regulatory mechanisms and targets is still ongoing. Indeed, the potential of targeting non-canonical

NF-κB signaling has not been rigorously tested, even though the gate keeper kinase NIK is required for survival MM and other lymphomas [132]. In fact, cIAP inhibitors were shown to initially induce NIK expression in ABC DLBCL cells and congruently combinatorial inhibition of NIK and cIAPs was more efficient in killing the tumor cells [90]. Moreover, rather than inhibiting NF-κB upstream signaling, selective targeting of NF-κB downstream effects may be another attractive strategy to counteract lymphoma cell survival. For instance, a novel GADD45β/MKK7 protein-protein interaction inhibitor promotes death of MM cells by preventing NF-κB-dependent inhibition of pro-apoptotic MKK7/JNK signaling [133]. However, whereas JNK signaling was suggested to induce cell death in MM, JNK inhibitors exerted an anti-apoptotic role in ABC DLBCL [81]. Thus, inhibition of JNK may have beneficial or even adverse effects depending on the cellular origin, reflecting that intensive research is required to better predict patient responses to new precision therapies that are designed for treating subsets of patients. Finally, the 'Holy Grail' for therapy is combinatorial treatment using selective drugs that either block one pathway at different steps and/or simultaneously block multiple pathways. Given the numerous options, one important future challenge will be to rationally predict the most promising drug combination for further clinical development.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Figure Legends

Figure 1: Members of the NF-κB and IκB protein families. The Rel homology domain (RHD) responsible for dimerization, DNA binding and IκB inhibition is the common characteristic for NF-κB proteins. The RHD contains a nuclear localization sequence (NLS). Transcription activation domains are found in the C-terminus of RelA, c-Rel and RelB. p50 and p52 are generated upon cleavage of the precursor proteins p105 and p100, respectively. NF-κB1/p105 and NF-κB2/p100 belong to the IκB protein family, which share the ankyrin repeat domain (ARD) consisting of 5-7 ankyrin repeats. The ARD mediates interaction to the RHD of NF-κB. All predominantly cytosolic IκBs (p105, p100, IκBα, IκBβ, IκBε) contain a serine motif (SS), which is phosphorylated by IκB kinases to trigger their proteasomal degradation. A V-terminal death domain is found in p105 and p100). The atypical IκB protein IκBζ and BCL3 do not contain SS motifs and predominately localized in the nucleus to enhance transcription of p50 and p52 homodimers.

Figure 2: Canonical and non-canonical NF-κB signaling pathways. Canonical NF-κB signaling is induced upon activation of cytokine receptors (e.g. TNFR, IL-1R), pattern recognition receptors (TLR) or antigen receptors (BCR or TCR) and uses a variety of different adaptors to engage the IKK complex consisting of the regulatory subunit NEMO and the catalytic subunits IKKα and IKKβ. IKK phosphorylation of serine residues in cytosolic IκBs (IκBα, IκBβ and IκBε) and precursors (p105 and p100) triggers IκB ubiquitination and proteasomal degradation. Classical NF-κB dimers like p50/RelA and p50/c-Rel are released and enter the nucleus to induce transcription of target genes. Under physiological conditions the canonical NF-κB pathway induces a rapid but transient transcriptional response. Non-canonical NF-κB signaling is regulated by NIK, which is constantly degraded in resting cells by an E3 ligase complex consisting of

TRAF3/TRAF2 adaptors and the E3 ligases c-IAP1/2. Activation of a subset of TNFR family members like LTβR, CD40 and BAFFR leads NIK stabilization via inactivation of the TRAF/c-IAP complex. Augmented NIK levels catalyze phosphorylation of IKKα, which in turn phosphorylates NF-κB2/p100 to mark it for proteasomal processing and release of p52/RelB dimers that translocate to the nucleus. Non-canonical NF-κB signaling is delayed and induces a sustained transcriptional response.

Figure 3: Chronic active BCR and MYD88 signaling promotes canonical NF-κB in ABC DLBCL. NF-κB survival pathway is induced by recurrent oncogenic mutations (red stars) in critical components of BCR and TLR signaling pathway. Somatic gain-of-function mutation in the BCR adaptor CD79A and CD79B sustain BCR and SYK dependent signaling and enhance BTK and PKCβ triggered activation of the CARD11-BCL10-MALT1 (CBM) signaling complex. However, CD79 mutants still rely on a functional BCR. In contrast, oncogenic CARD11 mutations are disconnecting CARD11 from upstream signaling events and thus resistant to BCR signaling inhibitors. Upon CBM complex assembly, canonical IKK/NF-κB is activated. Also, proteolytic activity of MALT1 paracaspase is induced leading to cleavage of substrates like the tumor suppressor A20 and RelB, which have been associated with inhibition of NF-κB dependent survival signaling. Somatic gain-of function mutation are frequent in MYD88, leading to constitutive recruitment and activation of the IRAK4/IRAK1 protein kinases and activation of canonical NF-κB. Similar to CD79 mutations, MYD88 mutants are still relying on continuous signaling via endosomal TLR7 and TLR9. CARD: Caspase recruitment domain, CC: Coiled-coil domain, DD: Death domain, ITAM: Immunoreceptor tyrosine-based activation motif, Ig: Immunoglobulin domain, MAGUK: Membrane associated guanylte kinase domain, Paracas: Paracaspase domain, TIR: Toll-interleukin receptor domain.

Figure 4: Canonical and non-canonical NF-κB activation by API2-MALT1 in MALT lymphoma. The chimeric fusion protein API2-MALT1 is created by the chromosomal translocation t(11;18)(q21;q21) in MALT lymphoma. The oncogenic potential of API2-MALT1 relies on its ability to activate both NF-κB pathways by multiple mechanisms. API2-MALT1 auto-oligomerize leading to activation. The API2 moiety couples to TRAF2 and RIP1, which triggers RIP1 ubiquitination by an unknown E3 ligase to activate canonical IKK/NF-κB signaling. In parallel, recruitment of TRAF6 to the C-terminal MALT1 moiety induces API2-MALT1 and NEMO ubiquitination and thus canonical NF-κB activation. At the same time, the API2-MALT1 fusion constitutively activates the MALT1 paracaspase, which cleaves NIK in the N-terminus, deleting the TRAF3 interaction surface. Truncated NIK is constitutively active and phosphorylates IKKα to enhance non-canonical NF-κB signaling. BIR: Baculovirus IAP repeats, UBA: Ubiquitin association domain.

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Figure1

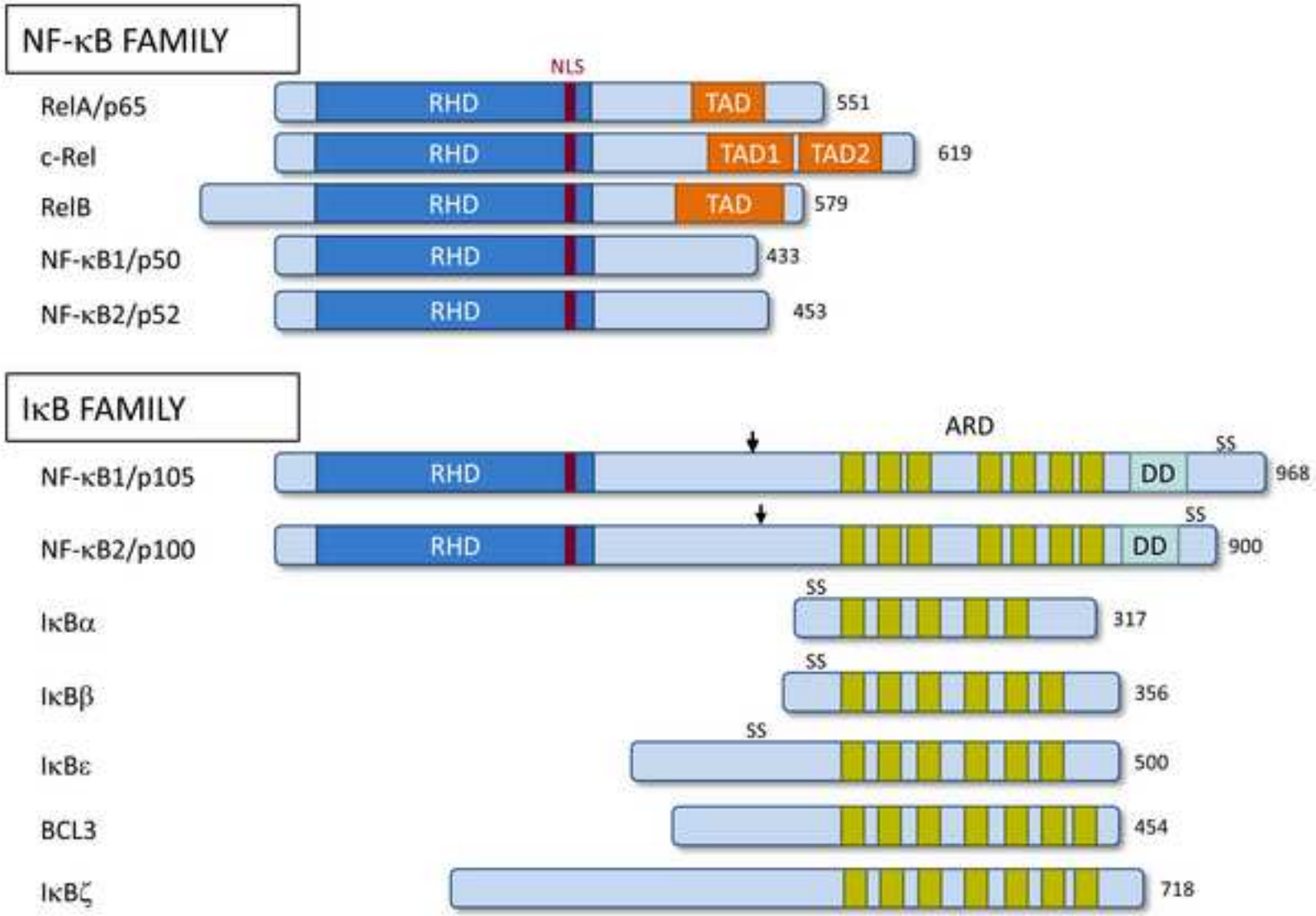

Figure 1

Figure2

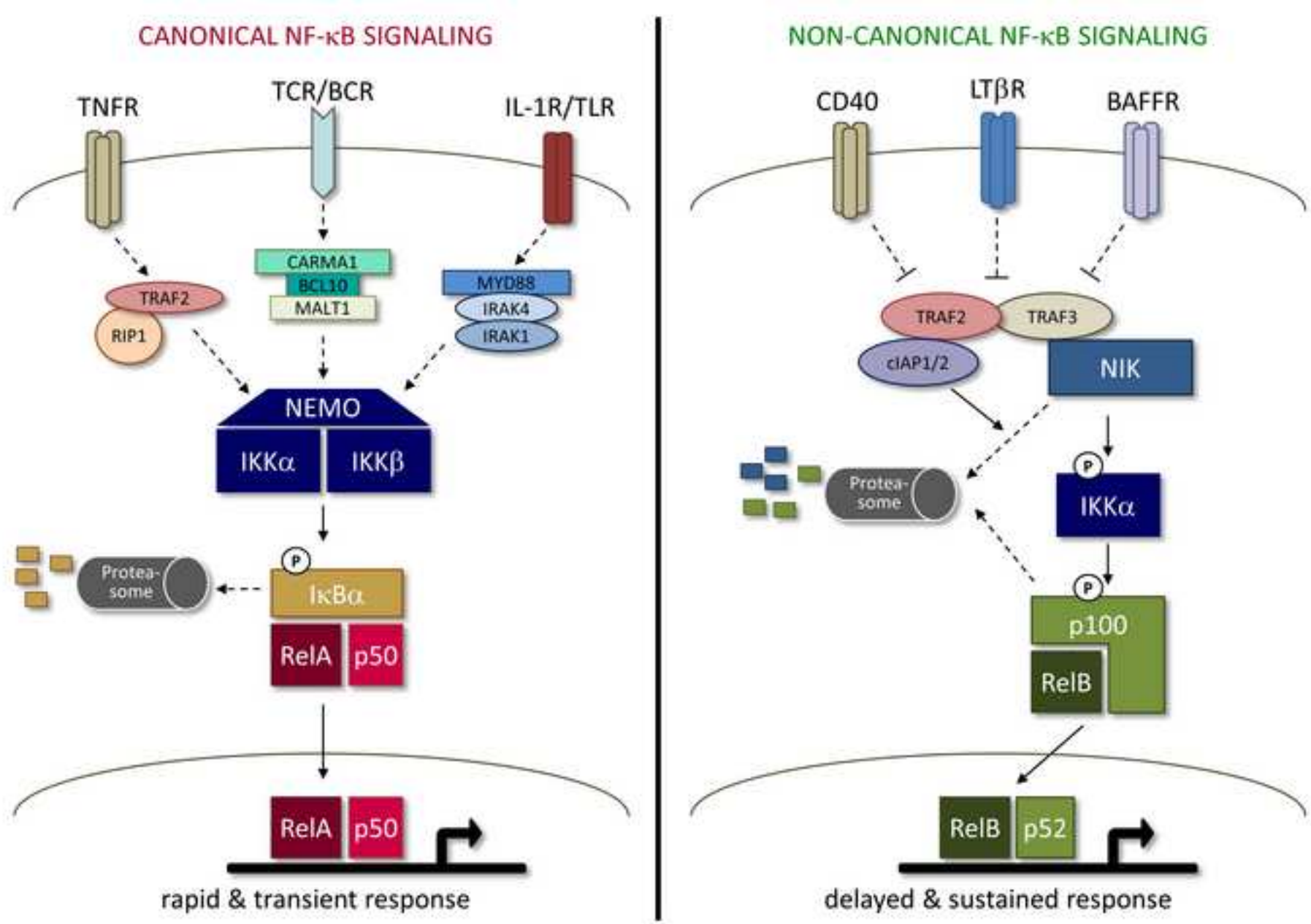

Figure 2

Figure3

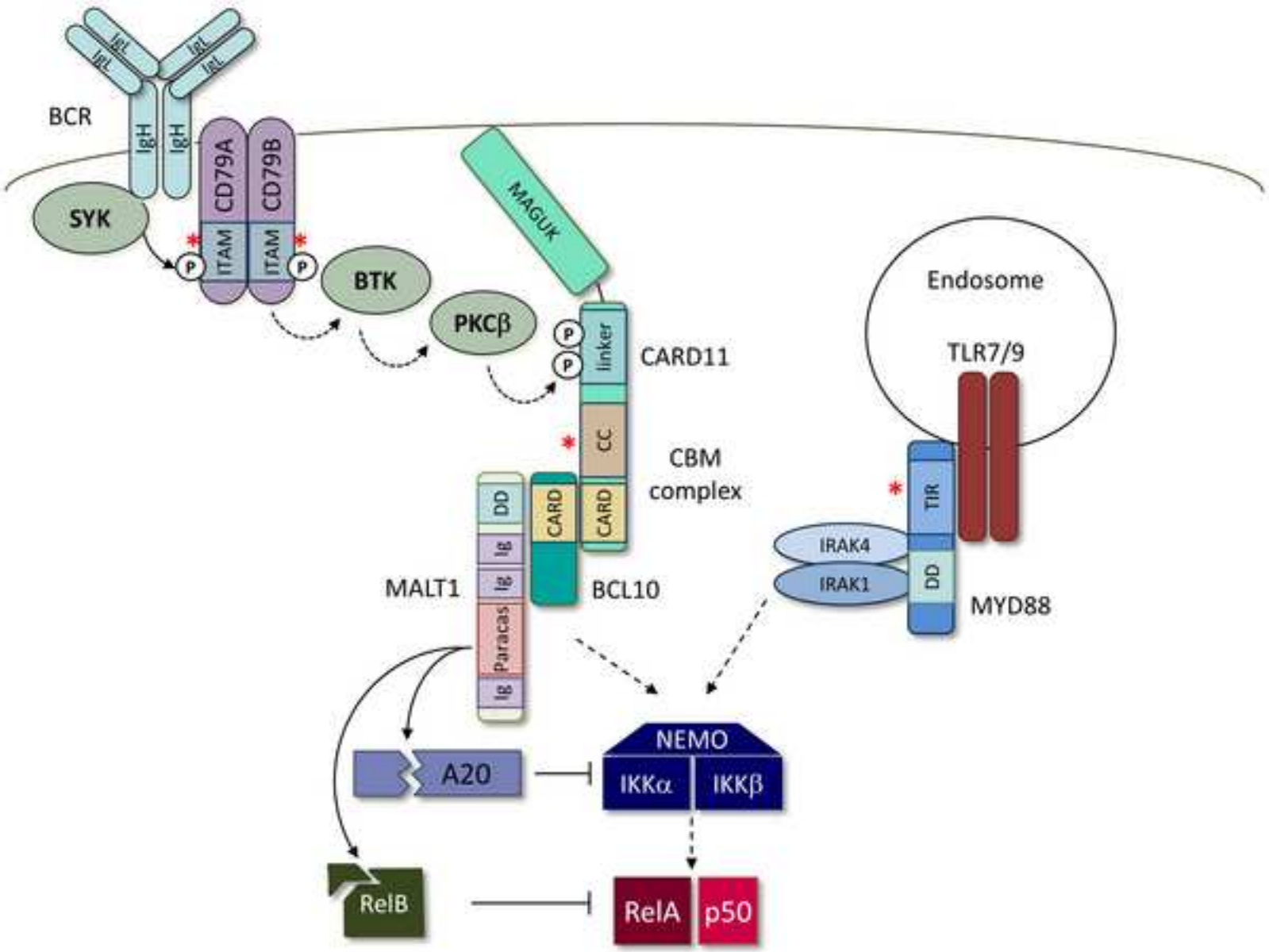

Figure 3

Figure4

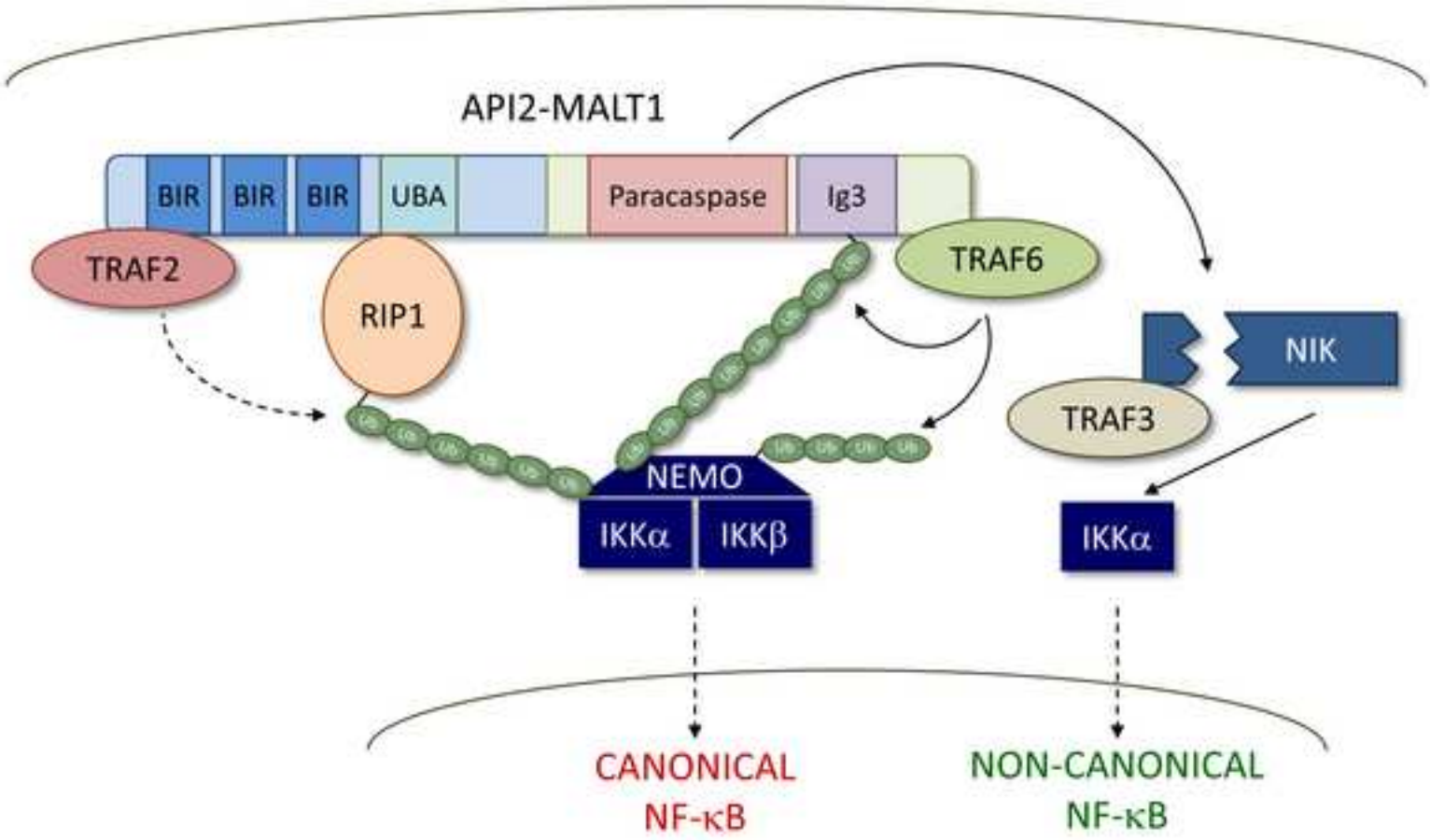

Figure 4