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The noncanonical NFκB pathway: Regulatory mechanisms in health and disease

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Abstract

The noncanonical NFκB signaling pathway mediates the biological functions of diverse cell survival, growth, maturation, and differentiation factors that are important for the development and maintenance of hematopoietic cells and immune organs. Its dysregulation is associated with a number of immune pathologies and malignancies. Originally described as the signaling pathway that controls the NFκB family member RelB, we now know that noncanonical signaling also controls NFκB RelA and cRel. Here, we aim to clarify our understanding of the molecular network that mediates noncanonical NFκB signaling and review the human diseases that result from a deficient or hyper-active noncanonical NFκB pathway. It turns out that dysregulation of RelA and cRel, not RelB, is often implicated in mediating the resulting pathology.

This article is categorized under:

Immune System Diseases > Molecular and Cellular Physiology
Cancer > Molecular and Cellular Physiology
Immune System Diseases > Stem Cells and Development

KEYWORDS

immune disorders, inflammatory disease, lymphoid cancers, NFκB, RelB

Abbreviations: ARD, ankyrin repeat domain; BAFF, B-cell activating factor; CD40L, CD40 ligand; cIAP, cellular inhibitor of apoptosis; CID, combined Immunodeficiency; GM-CSF, granulocyte-macrophage colony stimulating factor; HL, Hodgkin's lymphoma; IKK, inhibitor of κB kinase; IκB, inhibitor of κB; mTECs, medullary thymic epithelial cells; NEMO, NFκB essential modulator; NFκB, nuclear factor kappa B; NIK, NFκB-inducing kinase; PCM, plasma cell myeloma; RANKL, receptor activator of NFκB ligand; RHD, rel-homology domain; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; TRAF, TNF receptor-associated factors.

Benancio N. Rodriguez and Helen Huang contributed equally to this work.

1 | INTRODUCTION

The nuclear factor kappa B (NFκB) transcription factor family is comprised of 15 possible dimers that derive from combinatorial interactions of three large subunits RelA, RelB, and cRel and two small dimerization partners p50 and p52 (Hayden & Ghosh, 2004; Hoffmann & Baltimore, 2006). Their activities are regulated by an NFκB signaling network that mediates two distinct signaling pathways (S. Mitchell et al., 2016): the canonical (also called classical) pathway that responds to inflammatory stimuli such as pathogen-associated molecular patterns or inflammatory cytokines, and the noncanonical (also called alternative) pathway that responds to cell differentiation, maturation or survival factors (Basak & Hoffmann, 2008; Pomerantz & Baltimore, 2002). Canonical NFκB signaling controls immune and inflammatory responses that are often rapid and transient. Noncanonical NFκB signaling is critical for diverse aspects of hematopoietic development, secondary immune organs, and immune homeostasis (Sun, 2017).

The defining hallmark distinguishing the noncanonical from the canonical NFκB pathway is the kinase complex that activates it. Canonical NFκB signaling involves the NEMO-containing inhibitor of κB kinase 1/2 (IKK1/2) complex, whereas noncanonical signaling involves a NEMO-independent IKK1 homodimer complex and NFκB-inducing kinase (NIK) (Basak et al., 2012; Basak & Hoffmann, 2008; Shih et al., 2011, 2012; Sun, 2012; Taniguchi & Karin, 2018) (Figure 1).

Noncanonical NFκB signaling is triggered by diverse stimuli that control cell survival, growth, maturation, and differentiation of myeloid and lymphoid cells (Table 1). These stimuli include tumor necrosis factor (TNF) super family members B-cell activating factor (BAFF) (Claudio et al., 2002), CD40 ligand (CD40L) (Coope et al., 2002), LTα1β2 heterotrimer (Dejardin et al., 2002), OX40 (Murray et al., 2011), and receptor activator of NFκB ligand (RANKL) (Novack et al., 2003), as well as granulocyte-macrophage colony stimulating factor (GM-CSF) and M-CSF (Jin et al., 2014) (Figure 1, top right).

The canonical and noncanonical pathways were originally described to activate distinct NFκB effectors, that is, RelA or cRel versus RelB, respectively (Brasier, 2006; Pomerantz & Baltimore, 2002; Sun, 2011) (Figure 1a). Subsequent studies revealed that both pathways control the activity of all three transcriptional effectors: the noncanonical pathway also controls the stimulus-induced disassembly of the IκBsome (also referred to as kappaBsome) and release of associated

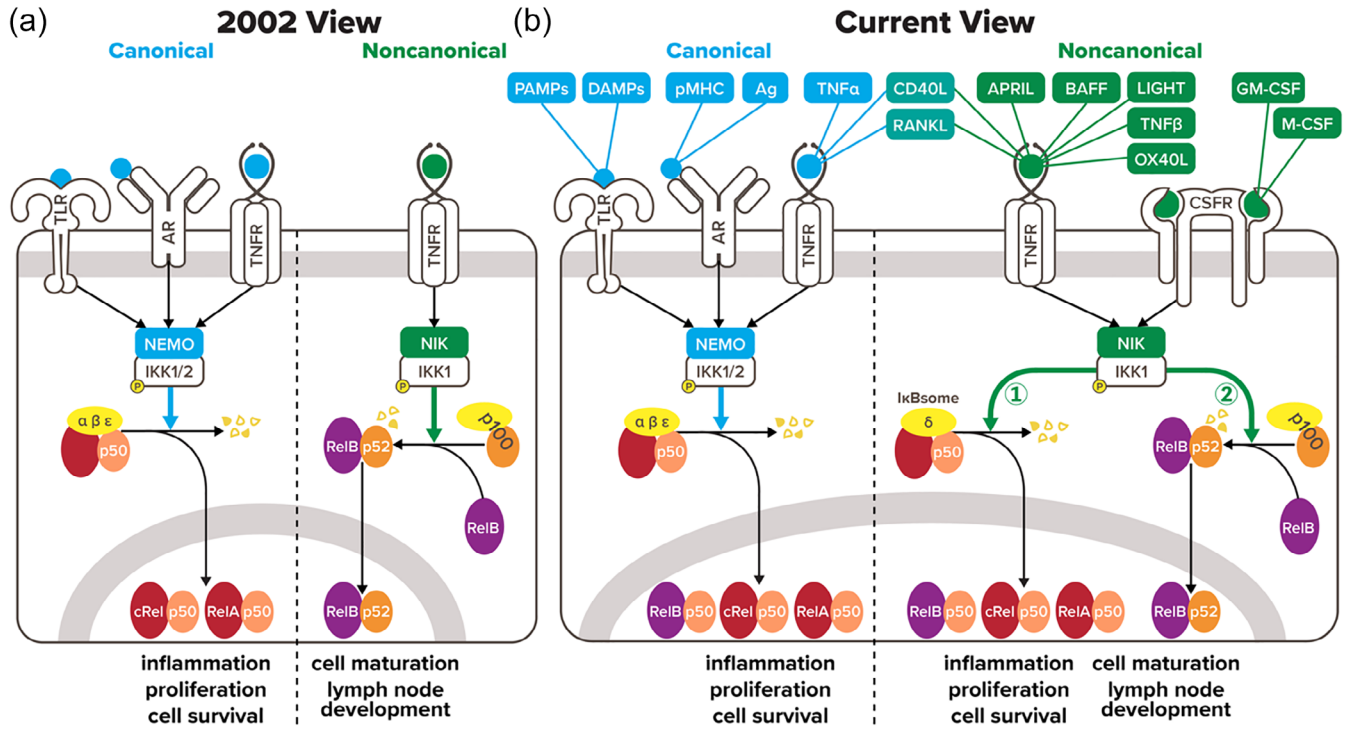

FIGURE 1 NFκB signaling via the canonical and noncanonical pathways—an evolving understanding. (a). The understanding of the molecular mechanisms based on studies published prior to 2002. Two distinct pathways that produce distinct dimers. (b). Our current understanding: Two interconnected pathways that produce activation of overlapping set of NFκB dimers. AR, antigen receptor; CSFR, colony stimulating factor; TLR, toll-like receptor; TNFRSF, TNF receptor superfamily.

TABLE 1 Noncanonical NFκB pathway stimuli and receptors.

Ligands	Receptors	Major receiving cell type	Major functions	References
BAFF (B-cell activating factor)	BAFFR	B and T cells	Peripheral and marginal zone B-cell development, T-cell co-stimulation, immunoglobulin (Ig) isotype switching.	(Schneider, 2005)
LTα1β2 and LIGHT	LTβR	Fibroblasts	Lymph node and Peyer patch formation disrupted; B cell germinal center and B cell—DC interactions disrupted.	(Dejardin et al., 2002)
APRIL (A proliferation-inducing ligand)	Proteoglycans	B and T cells	Plasma cell survival, isotype switching.	(Schneider, 2005)
CD154 (CD40L)	CD40	B cells	Promotes germinal center (GC) formation, immunoglobulin (Ig) isotype switching, somatic hypermutation (SHM) of the Ig to enhance affinity for antigen, and the formation of long-lived plasma cells and memory B cells. Promotes survival.	(Elgueta et al., 2009)
		Dendritic cells and macrophages	Promotes cytokine production, the induction of costimulatory molecules on their surface, and facilitates the cross-presentation of antigen. Promotes survival.	(Elgueta et al., 2009)
CD153 (CD30L)	CD30	Activated B and T cells	Immune surveillance and crosstalk between B and T cells. Promotes T cell proliferation and survival, inducing cytokine production, and regulating apoptosis.	(van der Weyden et al., 2017)
CD70 (CD27L)	CD27	Naive T, memory B and T cells and some NK cells	Formation of memory and plasma B cells, differentiation of γδ T cells. Contributes to cell proliferation, survival, differentiation, and effector function.	(Flieswasser et al., 2022)
CD252 (OX40L)	CD134 (OX40)	Activated T cells	Promote T-cell division and survival, augmenting the clonal expansion of effector and memory populations as they are being generated to antigen. suppresses the differentiation and activity of Treg.	(Croft et al., 2009)
4-1BBL	4-1BB (CD137)	Activated T and NK cells	Promote T-cell survival. Enhances NK cell proliferation, cytokine production, and antibody-dependent cell-mediated cytotoxicity (ADCC).	(Kim et al., 2022)
EDA-A2	XEDAR (EDAR2 or TNFRSF27)	Ectodermal cells, T cells, many cancer cells	Induce ectodermal differentiation, but largely unknown due to recent discovery.	(Sinha et al., 2002; Verhelst et al., 2015; Zhang et al., 2021)
GM-CSF	GMCSFR	Dendritic cells	Promote differentiation and survival of dendritic cells from monocyte/macrophages.	(Jin et al., 2014)
M-CSF	MCSFR	Macrophages, Osteoclasts	Promote differentiation and survival of macrophages from monocytes.	(Jin et al., 2014; Novack et al., 2003)
RANKL	RANK	Osteoclasts	Promote differentiation and survival of osteoclasts from monocytes/macrophages.	(Novack et al., 2003)
TWEAK	FN14	Fibroblasts	Promote tumor cell pathogenesis.	(Saitoh et al., 2003)

Note: (Croft et al., 2009; Elgueta et al., 2009; Flieswasser et al., 2022; Kim et al., 2022; Saitoh et al., 2003; Schneider, 2005; Sinha et al., 2002; van der Weyden et al., 2017; Verhelst et al., 2015; X. Zhang et al., 2021).

NFκB dimers (Basak et al 2009, Basak et al., 2012, S. Mitchell et al., 2016), while the canonical pathway can activate RelB by virtue of the IκBα-RelB:p50 complex (Figure 1b).

Despite these mechanistic insights of the past decade, the old paradigm of equating the two NFκB signaling pathways with distinct NFκB transcriptional factors remains prevalent in the literature of NFκB-mediated pathologies, potentially misleading diagnoses or drug target identification. Here, we will first summarize the genetic evidence that indicates the involvement of all NFκB family members in noncanonical NFκB signaling, present what is known about the molecular network that transduces it, and then discuss its role in a variety of hematologic diseases.

2 | MOUSE KNOCKOUTS CONNECT NFκB SUBUNITS TO BOTH CANONICAL AND NONCANONICAL SIGNALING

Genetic loss-of-function studies can define the biological functions of molecular regulators. The key signaling kinase of the noncanonical pathway is NIK (Basak & Hoffmann, 2008). Patients with mutated NIK experience deficiencies in lymph node development and B-cell lymphopenia (Luftig et al., 2001; J. P. Mitchell & Carmody, 2018). Similarly, gene-targeted NIK knockout mice and the $NIK^{aly/aly}$ loss-of-function mutant also exhibit a number of phenotypes associated with the ligands and receptors (e.g., LTβR which is required for lymph node development and BAFFR which promotes B-cell survival) that activate the noncanonical pathway (Thu & Richmond, 2010). Conversely, a stabilizing mutation in NIK which constitutively activates the noncanonical NFκB pathway was found to reduce the progression of acute myeloid leukemia in mice by enhancing the differentiation process of leukemic cells (Xiu et al., 2018). Thus, NIK mutant phenotypes are consistent with it being the key signaling node for the ligands and receptors that activate the noncanonical pathway.

However, mice and humans that harbor either homozygous loss of function mutations of *Nfkb2*, *Rela, Rel*, and *Relb* genes show diverse phenotypes that cannot be neatly categorized as being inflammatory versus developmental or indicate involvement in canonical versus noncanonical NFκB pathways.

Nfkb2 encodes p100, the substrate of NIK/IKK1 and the key signal transducer of the noncanonical pathway. While *nfkb2*-deficient mice are overtly healthy, they show complex dysregulation of inflammation rather than phenotypes that mimic those caused by NIK deficiency (Caamaño et al., 1998). This may be understood because p100 is the precursor for both p52 and the oligomeric IκBδ inhibitor within the IκBsome. Thus, on one hand, *nfkb2* deficiency results in an absence of the RelB:p52 dimer, which normally contributes to inflammatory responses in intestinal epithelial cells that protect mice from Citrobacter infection (Banoth et al., 2015) and may also exacerbate experimental colitis (Chawla et al., 2021). On the other hand *nfkb2* deficiency results in an absence of IκBδ which normally limits the proportion of RelA;P50 and cRel:p50 dimers being associated with canonical IκBs thereby finetuning the cell's responsiveness to inflammatory stimuli (Basak et al., 2007; Shih et al., 2009). Why *nfkb2* deficiency does not mimic NIK knockout defects in lymph node development remains unknown but could be due to compensation by other NFκB family members including the RelB:p50 dimer which becomes more prevalent in *nfkb2*-deficient cells. How *nfkb2* deficiency causes the complete lack of mature B-cells in mice and combined immunodeficiency (CID) in humans (K. Chen et al., 2013) remains unclear.

RelA deficiency results in a loss of inflammatory response gene expression (Cheng et al., 2017; Hoffmann et al., 2003). RelA's DNA binding function and transactivation domains are both required for its gene expression role (Ngo et al., 2020). In mice, *rela* deficiency results in E15 embryonic lethality (Beg et al., 1995) due to diminished expression of anti-apoptotic genes that protect fetal liver cells from tonic TNF that orchestrates the developing hematopoietic system (Beg & Baltimore, 1996). When the embryonic lethality is rescued by compound deficiency with TNF or TNFR1, the resulting mice are severely immunocompromised and show diminished lymph node development (Alcamo et al., 2001; Badran et al., 2017), a hallmark of knockouts of noncanonical pathway-inducing receptor LTβR. However, it is unclear whether the diminished expression of organogenic chemokine is directly due to an absence of RelA or indirectly due to an absence of RelA-dependent RelB expression.

cRel deficiency leaves mice overtly healthy but deficient in adaptive immune responses, which can be traced back to reductions in B-cell proliferation and survival during the germinal center reaction (Guldenpfennig et al., 2023) and reductions in cytokine secretion by T-cells (Hövelmeyer et al., 2022) and to some extent macrophages (Sanjabi et al., 2000). Patients with cRel-deficiency show reduced $CD19^{+}$ B-cell numbers and proliferative responses resulting in low or undetectable circulating IgG and IgA antibody levels (Beaussant-Cohen et al., 2019). Furthermore, they are more susceptible to infection by *Mycobacterium tuberculosis* among other pathogens, in part due to lack of T-cell proliferation

(Beaussant-Cohen et al., 2019). However, cRel is not only involved in the response to mitogenic stimulation—in mice, it also seems to mediate the effect of BAFF, a noncanonical stimulus, as evidenced by cell survival and transcriptomic profiling studies (Almaden et al., 2014).

RelB deficiency results in a loss of lymph nodes akin to LTβR signaling mutants (Weih et al., 1995), but also a prominent phenotype of multiorgan inflammation (Gasparini et al., 2014; Weih et al., 1995) that cannot be accounted for by abnormalities in immune developmental processes associated with the noncanonical pathway. Recent studies have found human patients with complete or partial RelB loss-of-function mutations show remarkably similar pathology in which unchecked inflammatory responses lead to CID (Merico et al., 2015; Sharfe et al., 2015, 2022). Instead, these abnormalities points to a role of RelB in inhibiting RelA-driven inflammation (Navarro et al., 2023), harkening back to its initial description as an inhibitor of NFκB-driven gene expression, called I-Rel (Ruben et al., 1992). Further, RelB-deficient patients have abnormally high levels of memory $CD4^+$ $CD45RO^+$ T-cells (Sharfe et al., 2015, 2022), in contrast to cRel-deficient patients where these cells are abnormally low (Beaussant-Cohen et al., 2019). Earlier work described RelB's role in mediating endotoxin tolerance via epigenetic mechanisms of histone modifications (X. Chen et al., 2009). Increased RelB:p50 levels in *nfkb2*-deficient intestinal epithelial cells may also be responsible for the observed reduction in inflammatory gene expression (Banoth et al., 2015; Chawla et al., 2021), though this possibility has yet to be addressed experimentally. In aggregate, these observations suggests that RelB's primary physiological role is as a brake on RelA or cRel mediated inflammatory and immune responses, and that its potential role as a transcriptional effector of noncanonical ligands to control cell survival, maturation, or differentiation remains uncertain.

Is there genetic evidence that indicates which NFκB dimers are the transcriptional effectors of the noncanonical pathway? In vitro osteoclast differentiation is dependent on the noncanonical stimulus RANKL and shows a requirement for both RelA and RelB, with the former preventing apoptosis and the latter driving differentiation (Vaira, Alhawagri, et al., 2008; Vaira, Johnson, et al., 2008). Similarly, the noncanonical NFκB-activating ligand BAFF prolongs the survival of B-cells in vitro in a RelB-dependent manner, through its role in potentiating B-cell activation during IgM stimulation depends on cRel (Almaden et al., 2014). However, whether T-cell responses to the noncanonical NFκB stimulus Ox40 are mediated by RelB or cRel remains unclear (Murray et al., 2011). Finally, GM-CSF stimulated dendritic cell development activates NFκB dimers involving RelA, cRel, and RelB, and knockout studies suggest a subtle, partially redundant role of RelB in their differentiation and activation (O'Keeffe et al., 2005; Shih et al., 2012). In sum, all three NFκB effectors — RelA, cRel, and RelB — appear to mediate the physiological functions of noncanonical stimuli.

3 | MOLECULAR MECHANISMS OF NONCANONICAL NFκB SIGNALING

To understand the molecular mechanisms of NFκB dimer activation via the noncanonical NFκB pathway, we must first consider the basal steady state. In the absence of stimulation, newly synthesized NIK is constantly proteosomally degraded (Varfolomeev et al., 2007) due to its rapid ubiquitination by TNF receptor-associated factor 3 (TRAF3) (Zarnegar et al., 2008), TRAF2 and their interaction partners, cellular inhibitor of apoptosis 1 and 2 (cIAP1/2) (Vallabhapurapu et al., 2008). The resultant low NIK levels allow for *Nfkb2*-encoded p100 to accumulate in the cytoplasm and oligomerize into high molecular weight complexes that may also contain the *nfkb1*-encoded p105. These complexes are termed IκBsomes. When a p100 ankyrin-repeat domain (ARD) is accessible to bind p50-containing NFκB dimers RelA:p50, cRel:p50, and RelB:p50 (Basak et al., 2007; Tao et al., 2014), it is referred to as IκBδ. (When the p105 ARD is accessible to bind NFκB dimers it is referred to as IκBγ.) Thereby, in the absence of noncanonical signaling, IκBδ sequesters latent NFκB dimers, similar to how IκBα-, -β, and -ε sequester latent NFκB dimers in the absence of canonical signaling. While IκBδ-bound NFκB dimers are released upon noncanonical signaling, IκBα-, -β or -ε-bound NFκB complexes are released upon canonical signaling.

Upon stimulation with their cognate ligands, the TNF receptor (TNFR) superfamily members trimerize and recruit TRAF2, TRAF3, cIAP1, and cIAP2 to the ligated receptor complex. Rather than ubiquitinating NIK, cIAP1/2 now ubiquitinate TRAF2/3 and themselves for degradation (Varfolomeev et al., 2007). This allows NIK to accumulate in the cytoplasm. NIK then autophosphorylates, recruits and phosphorylates IKK1 homodimers to p100 (Liu et al., 2012; Xiao et al., 2001) (Figure 2, top right), which then activates NFκB via two molecular mechanisms that are detailed below.

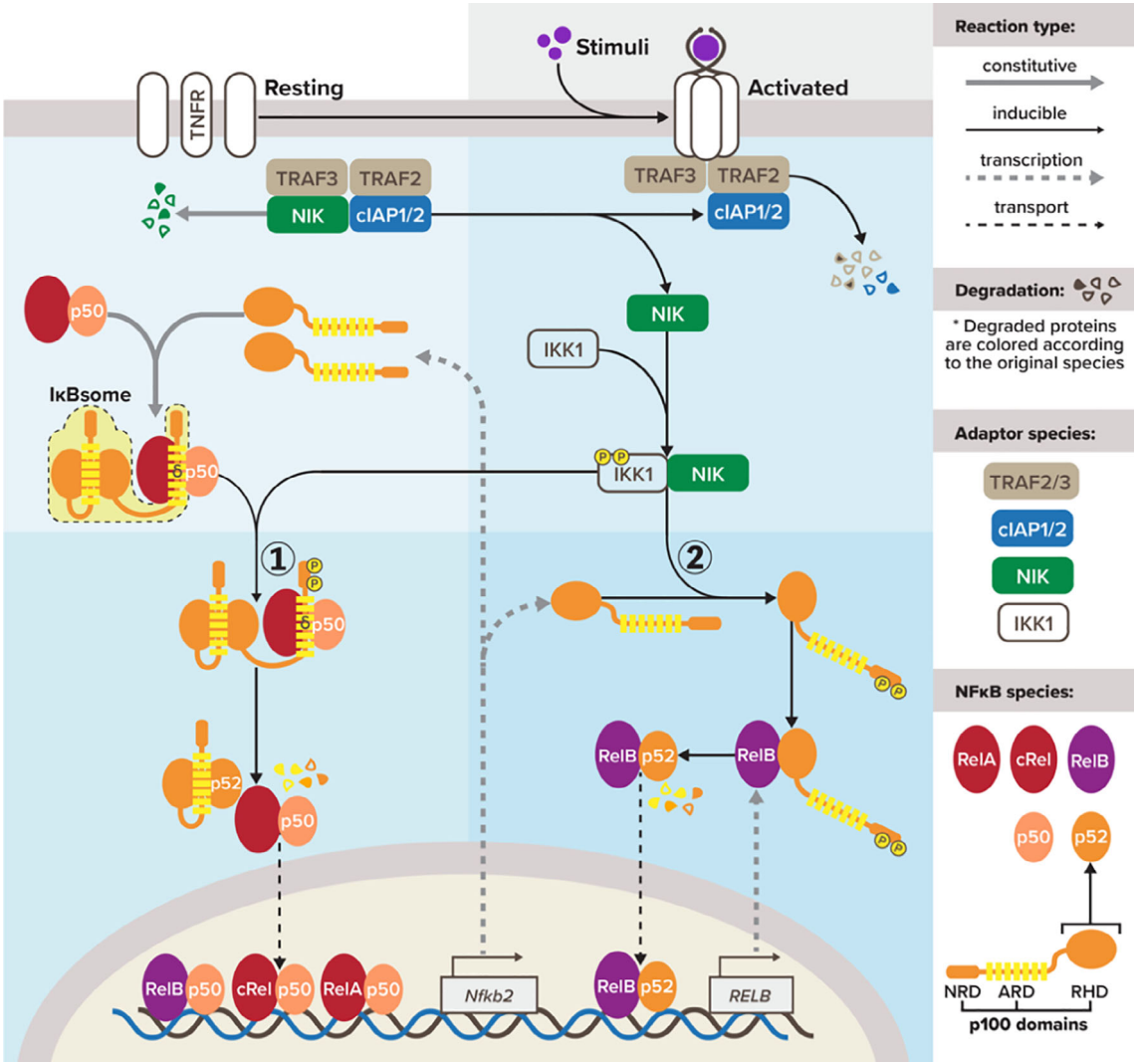

FIGURE 2 Activation and regulation of the noncanonical NFκB pathway. *Top left*: Constitutive degradation of NIK allows for IκBsome inhibition of latent NFκB dimers in resting cells. *Top right*: Ligand-induced recruitment of TRAF2-TRAF3-cIAP1/2 ubiquitin ligase complex to the receptor leads to NIK accumulation and IKK1 activation. *Bottom left*: noncanonical NFκB signaling via mechanism 1 triggers IκBsome degradation thereby releasing pre-existing RelA:p50, cRel:p50, and RelB:p50 into the nucleus. *Bottom right*: noncanonical NFκB signaling via mechanism 2 promotes the generation of de novo NFκB dimer RelB:p52 via p100 processing into p52. p100 is depicted with its three domains with distinct functions: Rel homology domain (RHD), ankyrin repeat domain (ARD), and NIK-responsive domain (NRD, also known as degradation domain). IκBsomes are portrayed as p100 dimers for simplicity, but they are oligomers, often tetramers of p100 and p105 (Savinova et al., 2009; Yılmaz et al., 2014).

3.1 | Mechanism 1: release of NFκB dimers from IκBδ

Active IKK1 phosphorylates p100, in its oligomerized IκBδ form, specifically on serines S866 and S870 (Liang et al., 2006). These two phosphorylated serines that are four residues apart recruit ubiquitin ligase βTrCP, which ubiquitinates K856. This triggers 26S proteasomal degradation of the C-terminal inhibitory ARD of p100 which mediates IκBδ function, leaving behind an autoinhibited, signal-unresponsive p100:p52 dimer (Basak & Hoffmann, 2008; Savinova et al., 2009). With the destruction of IκBδ, the sequestered NFκB dimers (e.g., RelA:p50, cRel:p50, and RelB:p50) are then released and enter the nucleus to activate target genes (Tao et al., 2014) (Figure 1b, bottom left). Because mechanism 1 releases pre-existing dimers (primarily containing p50), it is mechanistically analogous to canonical IκB signaling, and it responds faster and more transiently than mechanism 2 which depends on de novo synthesis of p100 and RelB proteins.

3.2 | Mechanism 2: processing of de novo P100

The constitutive transcription of the *Nfkb2* gene provides a continuous supply of de novo p100 in the cytoplasm. When IKK1 is activated it phosphorylates newly synthesized p100 monomer on serines S866 and S870 (Liang et al., 2006) leading to βTrCP recruitment, ubiquitination, and 26S proteasomal degradation of the ARD. When RelB is able to bind the de novo p100 by dimerizing with p100's rel homology domain (RHD), it is protected from degradation (Mordmüller et al., 2003). Additional IKK1-mediated phosphorylation of S99, S108, S115, and S123 on p100's RHD may also play a stabilizing role to ensure that p100 is processed to p52 rather than degraded (Christian et al., 2016). This signaling process must be dynamic: when a self-inhibited RelB:p100 dimer has formed, it is signal-unresponsive (Basak et al., 2007, 2008; Tao et al., 2014). The processed RelB:p52 dimer then translocates into the nucleus and binds DNA associated with target genes (Figure 1b, bottom right). Mechanism 2 responds more slowly, accumulating over time, and the resulting RelB:p52 activity is more persistent than the NFκB dimers released by mechanism 1.

4 | CROSS-REGULATION BETWEEN CANONICAL AND NONCANONICAL NFκB PATHWAYS

There are two ways in which NFκB and IκB proteins interface that results in cross-regulation between canonical and noncanonical pathways (Figure 3). First, canonical pathway activity is required for and may amplify noncanonical NFκB signaling by controlling the de novo synthesis of RelB and p100 that is required for "mechanism 2"—the stimulus-induced generation of RelB:p52. Specifically, the transcriptional synthesis of both RelB and p100 mRNAs are responsive to RelA activity and therefore a function of contemporaneous activity (Basak et al., 2008). (S. Mitchell et al., 2016; S. Mitchell & Hoffmann, 2019). Second, canonical pathway activity that preceded the presence of a noncanonical stimulus leads to an accumulation of unprocessed p100 which results in more IκBδ activity within the IκBsome to sequester higher amounts of NFκB dimers. This means that "mechanism 1"—the stimulus-induced release of pre-existing NFκB dimers (e.g., RelA:p50, RelB:p50, and cRel:p50) from IκBδ—is strengthened, increasing the responsiveness of the noncanonical signaling pathway (Basak et al., 2007), as well as diminishing the responsiveness of the canonical pathway to subsequent stimulation (Shih et al., 2009). In addition, it is important to point out that cross-regulation has been reported upstream of the IκB-NFκB network at the level of receptor proximal signaling complexes: it was shown that NIK can also augment signal-induced canonical NEMO activity (Thu & Richmond, 2010; Zarnegar et al., 2008), while TNF stimulation may transiently diminish LTβR-stimulated NIK activity (Mukherjee et al., 2017).

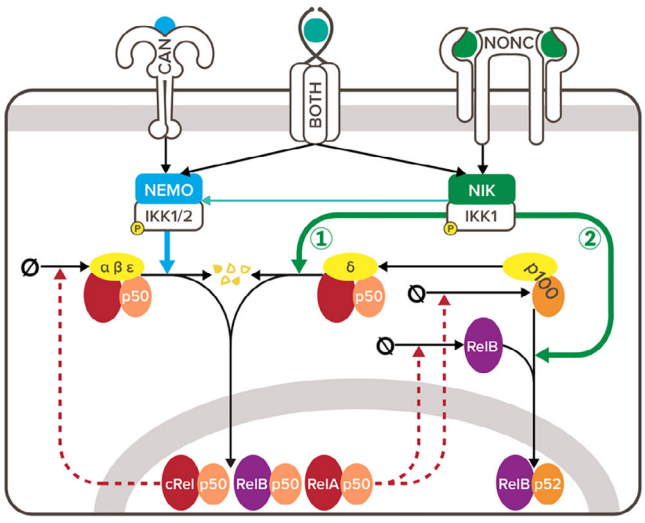

FIGURE 3 Crosstalk between canonical and noncanonical NFκB pathways. A canonical pathway stimulus may amplify noncanonical pathway-induced NFκB activity by increasing the availability of latent dimers and, to a lesser extent, inducing the synthesis of RelB (red dotted arrow) and the precursor of p52, p100. Receptors are labeled as canonical (CAN), noncanonical (NONC), or both (i.e., CD40 receptor).

These quantitative relationships are best dissected with the help of a mathematical model of the molecular network that controls NFκB dimer formation and activation. Such studies have revealed that due to cross-regulation from the canonical pathway, the noncanonical pathway activates mechanism 1 versus 2 in different proportions in different biological settings, depending on the cell type, ligand type, and cell state (S. Mitchell et al., 2023). This can result in nuclear NFκB activity biased toward RelA, cRel, or RelB, each of which have the potential to be the main noncanonical effector. For example, as NFκB subunits are expressed cell type-specifically the same stimulus may have different outcomes in different cells. While T-cells primarily rely on RelA as their main NFκB effector, B-cells mainly use cRel and RelB, and dendritic cells show even more RelB in their response (S. Mitchell et al., 2023). In another example, stimulation of B-cells with BAFF (a noncanonical stimulus) activates primarily RelA:p52 in naïve cells, but when they are responding to anti-IgM (a canonical stimulus), noncanonical signaling primarily potentiates cRel and RelA activity, by effectively removing the IκBδ brake on those dimers (Almaden et al., 2014; Mitchell et al., 2016). These mechanisms provide an explanation for why ligands that activate both the canonical and noncanonical pathways (e.g., CD40L) can produce strong multi-dimeric NFκB responses (Figure 3).

5 | DYSREGULATION OF NONCANONICAL NFκB SIGNALING IN DISEASE

Dysregulation of the noncanonical NFκB pathway has been implicated in a variety of human lymphoid diseases such as hematolymphoid neoplasms, autoimmune disorders, and immunodeficiency states (Gasparini et al., 2014). A list of these lymphoid diseases and their corresponding mechanisms of dysregulation are summarized in Tables 2 and 3. Here, we elaborate on the molecular mechanisms for two of those diseases, illustrating how noncanonical signaling may affect all three NFκB effector proteins, RelA, cRel, and RelB.

5.1 | Plasma cell myeloma

A clinically and genetically heterogeneous disease, plasma cell myeloma (PCM) often involves mutations in signaling mediators of the noncanonical pathway that lead to constitutive NFκB activity. These mutations are present in at least 17% of primary PCM tumors and 42% of PCM cell lines, as secondary drivers of the malignancy (Annunziata et al., 2007). Many of these mutations involve upregulation of NIK activity, downregulation of genes responsible for NIK degradation, including TRAF2/3 and BIRC2/3 (encodes cIAP1/2), or misregulation of downstream mediator of the noncanonical pathway, including IKK1 and NFkB2/p100 (Keats et al., 2007). Demchenko and colleagues showed elevated RelB and p52 expression and binding activity in all PCM cell lines tested (Demchenko et al., 2010), consistent with NIK-induced upregulation of RelB:p100 processing (mechanism 2). In addition, they identified elevated RelA and p50 binding activity in a subset of the cell lines evaluated. While the authors classified RelA:p50 activity as canonical and RelB:p52 as noncanonical, it is also possible that the elevated RelA:p50 observed is a result of increased NIK-induced IκBδ degradation, mediated by the noncanonical (NEMO-independent) pathway (mechanism 1) rather than the canonical pathway.

Not only does increased p100 processing elevate nuclear RelB level in PCM cells, p100-deficiency (due *to nfkb2* mutation) also upregulates nuclear RelB:p50 level due to the absence of inhibitory IκBδs (Roy et al., 2017). Given RelB's ability to autoinduce itself in a more prolonged fashion than RelA-mediated RelB transcription, it was shown to increase the resilience of TNF-primed p100-deficient PCM cells (KMS28PE cell line) to subsequent death ligand treatment. RelA and p52, on the other hand, were shown to be dispensable for the survival of these cells under the same treatment condition. Therefore, p100 depletion reinforces pro-survival response in PCM by prolonging NFκB activity via the autoregulatory RelB pathway, demonstrating a biased usage of *mechanism* 2 over *mechanism* 1. This presents RelB as the major noncanonical effector in a cell type-, ligand type-specific manner.

5.2 | T-cell dependent multi-organ autoimmunity

Regulatory medullary thymic epithelial cells (mTECs) mediate immune self-tolerance by presenting self-antigens to T-cell precursors and eliminating those with autoreactive T-cell receptors (Benlaribi et al., 2022). Interestingly, mutations in the p100 degron render p100 unresponsive to noncanonical signaling, resulting in an exaggerated IκBδ function

TABLE 2 Neoplasms driven by dysregulated noncanonical NFκB pathway activity.

Disease	How is noncanonical signaling dysregulated?	Which NFκB?	References
Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL)	1. BAFF ligands are overexpressed in CLL patients and promotes the survival and activation of malignant B cells. 2. *BIRC3* (cIAP2), *TRAF3*, and *NFKB2* are recurrently mutated in CLL patients, among which *BIRC3* and *NFKB2* mutations are prognostic drivers. 3. Upregulation of RelB:p52 dimers promotes EZH2 expression, which allows cancer cells to bypass p53-induced senescence.	RelB	(1) (Haiat et al., 2006), (2) (Puente et al., 2015), (3) (Iannetti et al., 2014; Mulligan et al., 2023)
Mantle cell lymphoma (MCL)	Recurrent genetic aberrations in the negative regulators of noncanonical NFκB, *TRAF2*, and *BIRC3* (cIAP2), were identified in 15% of patients.	Unclear	(Rahal et al., 2014)
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissues (MALT lymphoma)	In 24% of stomach and 38% of lung MALT lymphoma, a chromosome translocation causes fusion of *MALT1* and *BIRC3* (cIAP2) gene, allowing BCR activation (where MALT1 acts as an adaptor in the CBM complex) to robustly activate noncanonical NFκB pathway (where cIAP2 cleaves NIK at arginine 325, generating a NIK fragment that retains kinase activity but resists to TRAF3-dependent proteasomal degradation) in addition to canonical NFκB.	Unclear	(Du, 2016; Raderer et al., 2023; Rosebeck et al., 2011)
Diffuse large B-cell lymphoma (DLBCL)	Deletions or mutations that inactivate negative regulator TRAF3 and mutations that activate positive regulators TRAF2/5 and RANK cause constitutive activation of noncanonical NFκB pathway.	Unclear	(Compagno et al., 2009; B. Zhang et al., 2015)
Primary effusion lymphoma (PEL)	Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded FLICE-inhibitory protein (vFLIP) activates p100 processing in the noncanonical NFκB pathway, independent of NIK or TRAFs.	Unclear	(Ballon et al., 2011; Cozzi et al., 2022; Matta & Chaudhary, 2004)
Classic Hodgkin Lymphoma (CHL)	1. Mutation of TRAF3 & copy number gains of the gene encoding NIK causes constitutive activation of noncanonical NFκB pathway. 2. In Epstein–Barr virus-positive cases of HL, the virus-encoded latent membrane protein 1 (LMP1) causes NFκB activation by mimicking an active CD40 receptor.	RelB	(Weniger & Küppers, 2016)
Plasma cell myeloma/ multiple myeloma	1. Deletions or mutations of TRAF2/3 and cIAP1/2. 2. Overexpression of CD40 and LTβR 3. Deletion of sequences in the ankyrin repeats (IκB-domain) of p100 makes it constitutively active and not inhibitory. 4. Upregulation of NIK in patient samples and cell lines, by translocation or amplification of NIK locus, or by NIK-EFTUD2 fusion causing its degradation resistance	RelA, RelB	(Morgan et al., 2020), (1, 2) (Keats et al., 2007), (3) (Demchenko et al., 2010), (4) (Annunziata et al., 2007)
Adult T-cell leukemia/ lymphoma (ATLL)	1. Human T-cell leukemia virus type 1 (HTLV-1)-encoded Tax protein constitutively activate the noncanonical NFκB pathway by directly interacting with p100, independent of TNF receptors. 2. Somatic mutations in negative regulators TRAF3 and A20 removes negative feedback. 3. Epigenetic downregulation of the microRNA miR-31 results in NIK overexpression and noncanonical NFκB activation. 4. Rearranged *NFKB2* gene encodes for truncated protein p58 lacking the entire inhibitory domain, causing constitutive activity.	p52	(1) (Harhaj & Giam, 2018), (2) (Kataoka et al., 2015), (3) (Yamagishi et al., 2012), (4) (Isogawa et al., 2008)
Cutaneous T-cell lymphoma (CTCL)	12.5% of CTCL patients have truncation of the autoinhibitory C terminus of *Nfkb2* gene, and 57.5% have heterozygous deletion of *NFKB2*. In HuT 78 cell line, rearranged *NFKB2* gene encodes for truncated proteins p84/p85 lacking transcriptional repressor activities.	Unclear	(Choi et al., 2015; J. Zhang et al., 1994)
ALK-negative anaplastic large cell lymphoma (ALK–ALCL)	Endogenous expression of CD30 induces constitutive noncanonical NFκB activation through binding and degrading of TRAF3.	Unclear	(Wang et al., 2021)

(Continues)

TABLE 2 (Continued)

Disease	How is noncanonical signaling dysregulated?	Which NFκB?	References
Ovarian carcinoma	In various ovarian cancer cell lines, RelB:p52-induced nucleic acid editing enzymes (APOBECs) cause hypermutations at cytosine residues, driving tumorigenesis.	RelB, p52	(Leonard et al., 2015; Uno et al., 2014)
Breast carcinoma	Elevated RelB expression supports self-renewal and mutagenesis of breast cancer cells: 1. In ER-negative breast cancer cell lines, RelB:p52-induced EZH2 can colocalize with RelA to the RelB promoter and support hyper-transcription of RelB in breast cancer cells. 2. In various breast cancer cell lines, RelB:p52-induced nucleic acid editing enzymes (APOBECs) cause hypermutations at cytosine residues, driving tumorigenesis.	RelB, p52	(Rojo et al., 2016), (1) (Lee et al., 2011), (2) (Leonard et al., 2015)
Prostate carcinoma	In 3 prostate cancer cell lines, p52 activity is elevated in a NIK-independent way, and supports androgen-dependent prostate cancer cell growth.	p52	(Nadiminty et al., 2010)
Pancreatic ductal adenocarcinoma (PDAC)	In 69% patient samples and most PDAC cell lines, constitutive degradation of TRAF2 and subsequent over-stabilization of NIK in pancreatic cancer cells contributes to their proliferation.	Unclear	(Döppler et al., 2013; Wharry et al., 2009)
Melanoma	Overexpression of TWEAK and LTβR constitutively activate noncanonical pathway and upregulate of RelB:p52 dimers, promoting EZH2 expression, which allows cancer cells to bypass p53-induced senescence.	RelB, p52	(De Donatis et al., 2016; Tegowski & Baldwin, 2018)
Non-small Cell Lung carcinoma (NSCLC)?	USP17 is highly expressed in 43% of NSCLC patients. In H1299 and D121 cell lines, elevated deubiquitinating enzyme USP17 expression increased NIK stability by destabilizing TRAF2 and TRAF3.	Unclear	(Lu et al., 2018; McFarlane et al., 2013)
Glioblastoma	One of the two mutations in TERT promoter that occur in 51% of glioblastoma, C250T allows p52 to transactivate TERT, which maintains the protective telomeres at the ends of chromosomes, allowing for indefinite proliferative potential in cancer cells.	p52	(Li et al., 2015; Olympios et al., 2021)

Note: (Ballon et al., 2011; Choi et al., 2015; Compagno et al., 2009; Cozzi et al., 2022; Demchenko et al., 2010; Döppler et al., 2013; Du, 2016; Haiat et al., 2006; Harhaj & Giam, 2018; Iannetti et al., 2014; Kataoka et al., 2015; Lee et al., 2011; Leonard et al., 2015; Li et al., 2015; Lu et al., 2018; Matta & Chaudhary, 2004; McFarlane et al., 2013; Mulligan et al., 2023; Nadiminty et al., 2010; Olympios et al., 2021; Puente et al., 2015; Raderer et al., 2023; Rahal et al., 2014; Rojo et al., 2016; Rosebeck et al., 2011; Tegowski & Baldwin, 2018; Uno et al., 2014; Wang et al., 2021; Weniger & Küppers, 2016; Wharry et al., 2009; Yamagishi et al., 2012; B. Zhang et al., 2015).

TABLE 3 Immune disorders driven by dysregulated noncanonical NFκB pathway activity.

Disease	How is noncanonical signaling dysregulated?	Dysregulation in which cell type?	Which NFκB?	References
T-cell dependent multi-organ autoimmunity	p100 degradation resistance (caused by mutations of p100 degron) causes an exaggerated IκB function of the mutated p100 proteins, reducing the viability of mTEC and T-reg cell population, leading to survival for autoreactive T-cells.	Medullary thymic epithelial cells (mTEC) and T-regulatory (T-reg) cells	RelA, cRel, and maybe RelB	(Wirasinha et al., 2020)
Inflammatory bowel disease (IBD)	1. Noncanonical NFκB ligands LT, CD40L, RANKL, BAFF, and EDA are all shown to be upregulated in the gastrointestinal mucosa of IBD patients, leading to increased inflammation in the gut. 2. Elevated processing of p100 exacerbates RelA activity in murine and human IBD.	Intestinal epithelial cells (IEC), immune cells	RelA	(1. McDaniel et al., 2016, 2. Chawla et al., 2021)
Celiac disease	Patient with monoallelic mutations in TRAF3 have reduced TRAF3 expression, driving increased noncanonical NFκB activation, pr. omoting production of autoantibodies.	B-cells	Unclear	(Rae et al., 2022)
Systemic lupus erythematosus (SLE)	1. BAFF is overexpressed in SLE patients and promotes the survival and activation of autoreactive B cells. 2. Exaggerated OX40 signal from myeloid APCs promotes the differentiation of Th cells toward the Tfh lineage, increasing T-cell helps for B-cells. 3. Patient with monoallelic mutations in TRAF3 have reduced TRAF3 expression, driving increased noncanonical NFκB activation, promoting production of autoantibodies.	B-cells and T-cells	Unclear	(1) (Davidson, 2012) (2) (Jacquemin et al., 2015), (3) (Rae et al., 2022)
Rheumatoid arthritis (RA)	Noncanonical NFκB ligands LIGHT, CD40L, RANKL and BAFF are all overexpressed in the RA synovial tissue as well as serum and peripheral blood of RA patients, promoting the survival and activation of autoreactive B and plasma cells. The elevated NIK level also leads to inflammation-induced osteoclastogenesis.	B-cells, T-cells, plasma cells, osteoclasts, macrophages, dendritic cells, synovial fibroblasts, and endothelial cells	Unclear	(Noort et al., 2015)
Common variable immunodeficiency (CVID)	1. Deficiency of BAFFR contributes to the impaired isotype switching and antibody production. 2. Deficiency of NIK-regulated B-cell expression of ICOSL diminish the ICOS signal required for Tfh cell generation.	B-cells and T-follicular helper (Tfh) cells	Unclear	(1. Salzer et al., 2012; Warnatz et al., 2009) (2. Hu et al., 2011; Roussel & Vinh, 2021)
HHV8-associated multicentric castleman disease (HHV8-associated MCD)	Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded FLICE-inhibitory protein (vFLIP) activates p100 processing in the noncanonical NF-κB pathway independent of NIK or TRAFs.	B-cells	Unclear	(Ballon et al., 2011; Kaplan, 2013; Matta & Chaudhary, 2004)

Note: (Davidson, 2012; Hu et al., 2011; Kaplan, 2013; Roussel & Vinh, 2021).

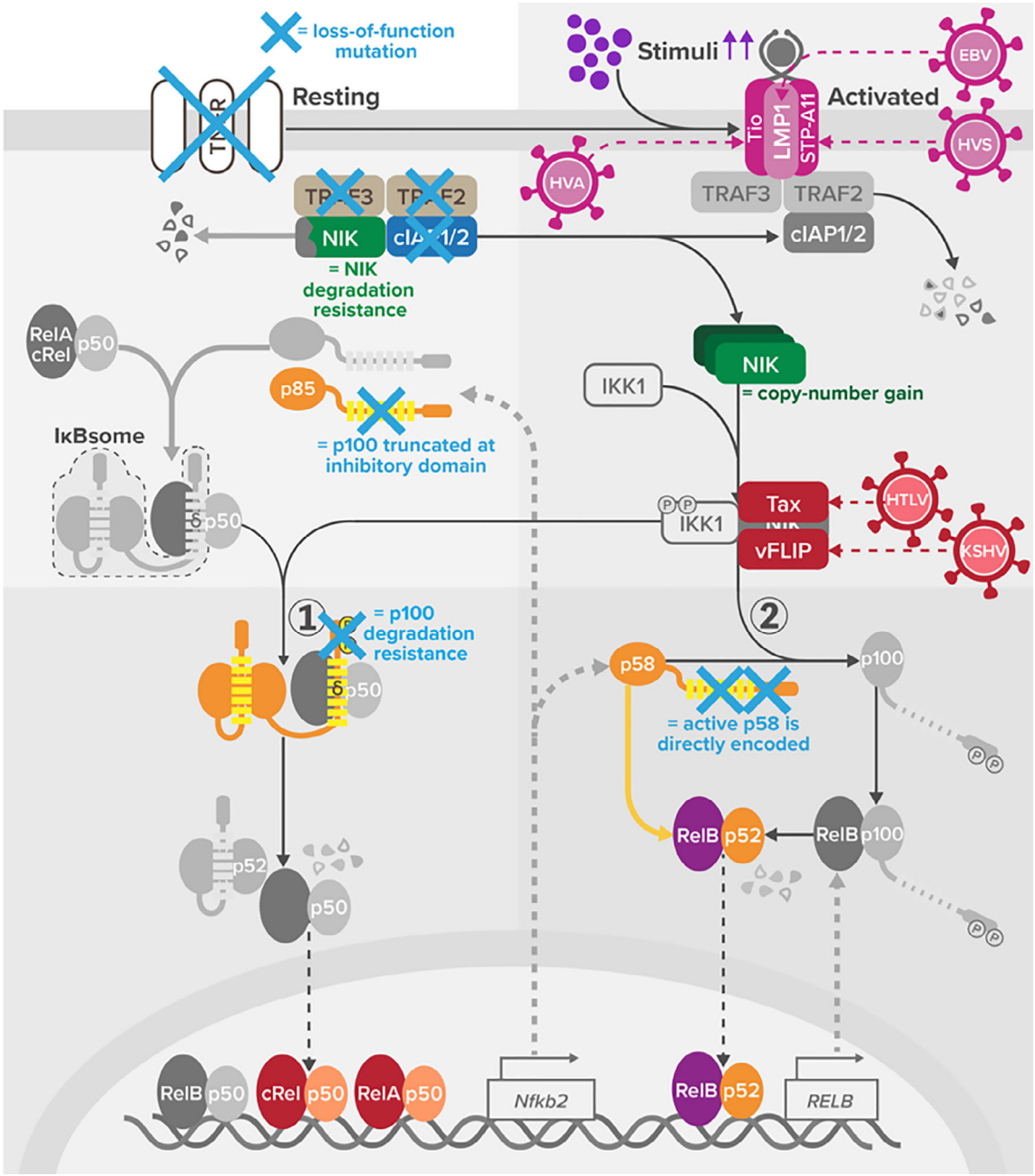

FIGURE 4 Pathologic dysregulation of the noncanonical NFκB pathway and effects. *Upregulation of noncanonical NFκB*: increased stimuli due to inflammation (purple), loss-of-function mutations in TRAF2/3 and cIAP1/2 or the inhibitory domain of NFkB2 (blue crosses), copy-number-gain of NIK (dark green), MALT-cIAP2-translocation-mediated or NIK-EFTUD2-translocation-mediated NIK degradation resistance (light green), and viral proteins (LMP1, Tio, STP-A11, Tax, and vFLIP) mimicking the function of activated TNFR (pink) or NIK (red). *Downregulation of noncanonical NFκB*: reduced TNF-family receptors (big blue cross) and p100 degradation resistance due to loss-of-function on its degron (orange). EBV, Epstein–Barr virus; HTLV, human T-cell leukemia virus; HVA, Herpesvirus Ateles; HVS, Herpesvirus saimiri; KSHV, Kaposi's sarcoma-associated herpesvirus.

that sequesters more RelA and cRel in the cytoplasm, thereby reducing mTEC viability (Riemann et al., 2017; Wirasinha et al., 2020). The lack of mTECs thus reduces negative selection of T-cells in the thymus, leading to autoimmunity. In addition, p100 degron mutations in T-regulatory cells may also reduce their viability (Klemann et al., 2019), causing a phenotype (Wirasinha et al., 2020) consistent with T-cell-specific RelA or cRel knockouts (Oh et al., 2017). These studies suggest that deficiency in *mechanism* 1 is at the root of the phenotype, either directly via reduced RelA-target gene expression or indirectly via reduced RelA-dependent RelB expression.

5.3 | Other human pathologies of the noncanonical pathway

Many components of the noncanonical NFκB pathway have been implicated in pathogenic misregulation in lymphoid cells, resulting in diverse human pathologies. Figure 4 complements Tables 2 and 3 by highlighting the mechanisms by which the noncanonical pathway is misregulated in these pathologies. In patients with systemic lupus erythematosus, inflammatory bowel disease, or rheumatoid arthritis, there is increased noncanonical NFκB ligand due to the inflammatory microenvironment (Jacquemin et al., 2015; McDaniel et al., 2016; Noort et al., 2015). Additionally, some viruses produce proteins that mimic ligated TNF-family receptors to constitutively activate the noncanonical pathway. For example, Epstein–Barr virus encodes latent membrane protein (LMP) that resembles the active CD40 receptor in Hodgkin's lymphoma (HL) (Kilger et al., 1998). On the flipside, functional reduction of TNF-family receptors, such as BAFFR, downregulates the noncanonical NFκB pathway and causes common variable immunodeficiency (Salzer et al., 2012; Warnatz et al., 2009). NIK is also frequently genetically upregulated in lymphoid neoplasms. Many neoplastic cells (e.g., diffuse large B cell lymphoma, mantle cell lymphoma, marginal zone lymphoma, PCM, and HL) carry loss-of-function mutations in negative regulators of NIK, including TRAF2/3 and cIAP1/2 (Gilmore, 2007; Keats et al., 2007). Gain-of-function mutations in *map3k14*, the NIK-encoding gene, such as copy-number-gain (17q21.31) and degradation resistance (by losing its TRAF3 binding domain), have also been observed in PCM and HL patients (Gilmore, 2007; Keats et al., 2007). In addition to genetic mutations, viral proteins (Herpesvirus-derived vFLIP and T-cell leukemia virus-derived Tax) also upregulate NIK's function by mimicking activated NIK (Morgan et al., 2020). Further downstream, numerous mutations on *the nfkb2* gene are pathological. *Nfkb2* mutants can upregulate the noncanonical pathway by producing the truncated p85, a p100-like protein that abrogates its transcriptional repressor domain, or the even more truncated p58, a p52-like molecule that not only lacks inhibitory function but is constitutively active (Isogawa et al., 2008; J. Zhang et al., 1994). Conversely, mutations of the *nfkb2* degron can downregulate noncanonical NFκB activity by resisting stimulus-induced degradation and maintaining its inhibition on NFκB effectors (Wirasinha et al., 2020).

It is worth noting that different types of diseases sometimes manifest in the same patient due to the diverse effects of noncanonical NFκB misregulation. For example, patients with germline TRAF3 mutations that reduce its expression, hence increasing NIK level, often exhibit autoimmune disorders (e.g., Sjögren's syndrome, celiac disease, and vasculitis), increased risk of B-cell malignancies (e.g., myeloma and diffuse large B cell lymphoma), and even recurrent bacterial infections, a sign of immunodeficiency (Rae et al., 2022). Based on the above discussion, we note that different NFκB dimers may be responsible for different pathologies mediated by different cell types in the same patient.

Generally, hyper-activation of the noncanonical pathway results in cancer and autoimmunity, due to upregulation of genes responsible for cell survival and proliferation, mutagenesis, and inflammation. On the other hand, hypo-activation typically results in immunodeficiency due to diminished cell survival, decreased isotype switching, and less T-cell/B-cell interaction, but can also trigger autoimmunity due to reduced survival of regulatory cells. While misregulation of the noncanonical pathway is implicated in numerous human pathologies, which of the NFκB effectors (RelA, cRel, or RelB) are responsible is rarely settled. Further experimentation coupled to mathematical network modeling is needed to gain more clarity on the molecular mechanisms underlying disease phenotypes.

6 | CONCLUSION

In this review, we have described our current understanding that the noncanonical NFκB pathway regulates RelA, cRel, and RelB, contrary to the original paradigm that categorizes RelA and cRel as canonical effectors and RelB as noncanonical effector. The noncanonical NFκB pathway controls RelA and cRel dimers by releasing the dimers from IκBδs, while it controls most RelB dimers by processing RelB:p100 into RelB:p52. Dysregulated noncanonical pathway activity has been associated with many diseases, including those highlighted in this review, and all NFκB dimers are potentially affected. To better characterize the molecular mechanisms underlying NFκB-mediated pathologies need to be addressed with careful experimentation and mathematical modeling to determine which NFκB dimers are dysregulated and what the promising drug targets are.

AUTHOR CONTRIBUTIONS

Benancio N. Rodriguez: Data curation (equal); writing – original draft (equal); writing – review and editing (supporting). **Helen Huang:** Data curation (equal); writing – original draft (equal); writing – review and

editing (supporting). **Jennifer J. Chia:** Data curation (supporting); writing – review and editing (supporting). **Alexander Hoffmann:** Conceptualization (lead); supervision (lead); writing – review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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