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REVIEW

NF-κB signaling pathway and its potential as a target for therapy in lymphoid neoplasms

Li Yu [a,b,1], Ling Li [c,1], L. Jeffrey Medeiros [a], Ken H. Young [a,d,*]

[a] Department of Hematopathology, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA
[b] Department of Hematology, The Second Affiliated Hospital of Nanchang University, Nanchang, China
[c] Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[d] The University of Texas Graduate School of Biomedical Science, Houston, TX, USA

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ABSTRACT

The NF-κB pathway, a critical regulator of apoptosis, plays a key role in many normal cellular functions. Genetic alterations and other mechanisms leading to constitutive activation of the NF-κB pathway contribute to cancer development, progression and therapy resistance by activation of downstream anti-apoptotic pathways, unfavorable microenvironment interactions, and gene dysregulation. Not surprisingly, given its importance to normal and cancer cell function, the NF-κB pathway has emerged as a target for therapy. In the review, we present the physiologic role of the NF-κB pathway and recent advances in better understanding of the pathologic roles of the NF-κB pathway in major types of lymphoid neoplasms. We also provide an update of clinical trials that use NF-κB pathway inhibitors. These trials are exploring the clinical efficiency of combining NF-κB pathway inhibitors with various agents that target diverse mechanisms of action with the goal being to optimize novel therapeutic opportunities for targeting oncogenic pathways to eradicate cancer cells.

1. Introduction

B-cell lymphomas are a heterogeneous group of neoplasms that originate from B cells that normally reside in lymphoid structures and extra-nodal tissues. Molecular analysis of lymphomas has shown that lymphoma cells co-opt normal cellular pathways to support their own growth and dissemination. In addition, the tumor microenvironment is important to the survival of lymphoma cells via tumor cell–microenviroment cellular interactions [1–3]. One of the most important normal cellular pathways is the nuclear factor-kappaB (NF-κB) pathway. NF-κB transcription factor family members are involved in many physiologic cellular functions including inflammation, apoptosis, cell survival, proliferation, angiogenesis, and innate and acquired immunity.

Constitutive activation of the NF-κB pathway is a feature of most types of B-cell lymphoma. NF-κB can be activated by acquired genetic lesions of different NF-κB members or key signaling molecules including cancer-related chromosomal translocations, deletion or mutations. These signaling molecules include mucosa-associated lymphoid tissue 1 (MALT1), BCL-10, caspase recruitment domain-containing protein 11 (CARD11), tumor necrosis factor receptor-associated factors 3 (TNFAIP3, A20), NF-κB2, and infection by viruses that produce oncoproteins [4–9]. Constitutive activation of the NF-κB pathway inhibits cell differentiation and apoptosis, promotes cell proliferation, and increases angiogenesis, cancer-related inflammation and metastatic potential [3,10]. Consequently, activated NF-κB is one of the prime therapeutic targets in lymphoma cells.

In this review, we summarize the essential functions of the NF-κB pathway and its signaling components in normal and lymphoma cells with a particular focus on novel molecular, clinical and preclinical studies. NF-κB functions as a crucial modulator of the extrinsic B-cell tissue microenvironment (TME) and intrinsic survival signaling pathways. Recent advances have greatly enhanced our understanding of NF-κB expression and have led to new insights into mechanisms involved in dysregulated gene expression in various subtypes of lymphoma. The new knowledge has yielded cellular targets of mechanism-mediated drug resistance and pointed to new therapeutic approaches for the treatment of patients with lymphoma.

2. Two NF-κB pathways

The NF-κB transcription factor family is composed of five subunits: RelA or p65, RelB, c-Rel or Rel, and p50 and p52 (with their precursors p105 and p100, respectively and known as NF-κB1 and NF-κB2). The Rel homology region, a ~300 residue long homologous element shared

* Corresponding author at: The University of Texas MD Anderson Cancer Center, Department of Hematopathology, 1515 Holcombe Boulevard, Houston, TX 77230-1439, USA.
E-mail address: khyoung@mdanderson.org (K.H. Young).
[1] These authors made equal contribution.

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by all subunits, is responsible for dimerization, inhibitor binding, nuclear localization, and DNA binding. Homodimeric and heterodimeric combinations formed by NF-κB proteins allow for functional NF-κB activation, with the exception of RelB that does not form a stable, detectable homodimer, but forms heterodimers selectively with p50 and p52 [11]. In quiescent cells, NF-κB transcription factors are located in the cytoplasm, whereas IκBα releases NF-κB factors allowing their translocation into the nucleus as stimulated by intracellular cues through a variety of surface receptors [12].

NF-κB signaling is categorized into canonical and non-canonical pathways that represent two independent, yet interlinked, pathways. The canonical pathway preferentially involves certain receptors, such as the B cell receptor (BCR), Toll-like receptors (TLRs), nucleotide oligomerization domain-like receptors, and TNF family receptors. Engagement of these receptors by ligands gives rise to activation of the heterotrimeric IκB kinase (IKK) complex, which consists of a, b, and c (NEMO) subunits [13]. Activated IKK directly phosphorylates IκBa, and, in its active form, starts the recognition and polyubiquitination by the bTrCP ubiquitin ligase, followed by proteasome degradation and release NF-κB to the nucleus [14] (Fig. 1).

Unlike the canonical pathway, the non-canonical NF-κB pathway depends on activation of the RelB subunit associated with p50 or p52. This pathway is activated preferentially by stimulation receptors, including the B-cell activating factor belonging to the TNF family receptors and CD40. These receptors activate NF-κB-inducing kinase, causing phosphorylation of a distinct inhibitor of the IKK complex that is composed of two IKKα subunits. This form of IKK phosphorylates p100, leading to its proteolytic processing into the NF-κB subunit p52, followed by the heterodimer, p52 and RelB, and translocation to the nucleus [13, 15] (Fig. 1).

These two NF-κB pathways regulate several different functions dependent on the cell type and stimulus applied [16,17]. The canonical pathway promotes inflammation, cell proliferation, and cell survival through the production of several inhibitors of apoptotic signaling, and also contributes to angiogenesis, tumor promotion and metastasis. The non-canonical pathway, instead, has anti-inflammatory activity and regulates lymphoid development and organization. In normal cells, regulation of NF-κB signaling is homeostatic and activation of these pathways is transient and stimulus dependent; various negative regulators modulate feedback mechanisms to terminate NF-κB signaling, such as re-accumulation of IκBα and induction of A20, an ubiquitin-editing enzyme. Interruption of homeostatic regulation of NF-κB signaling by a host of genetic aberrations in B cells plays an important role in the pathogenesis of lymphoid malignancies.

3. NF-κB function and pathway development in normal lymphoid tissues

Both canonical and non-canonical NF-κB pathways are essential for B-cell maturation at different differentiation stages. Compared with pro-B cells, pre-B cells have a more active canonical NF-κB pathway that promotes their transition from large to small pre-B cells [18]. The canonical and non-canonical NF-κB pathways control the production of λ-chain B-cells [19]. Those immature B-cells become transitional B cells through T1 and T2 stages, and develop into either mature follicular B cells or non-circulating marginal zone B-cells. At this stage, BCR cross-linking induces the activation of NF-κB and c-Rel to produce anti-apoptotic protein [20], induces the survival signaling mediated by BAFF, and increases the expression of *Nfκb2*. These events lead to generation of p100 protein [21], which, in turn, mediates the activation of the non-canonical NF-κB pathway. Notably, during B-cell generation and maintenance, NF-κB subunits have many physiological functions and play unique roles in the development and function of mature B lymphocytes (Table 1).

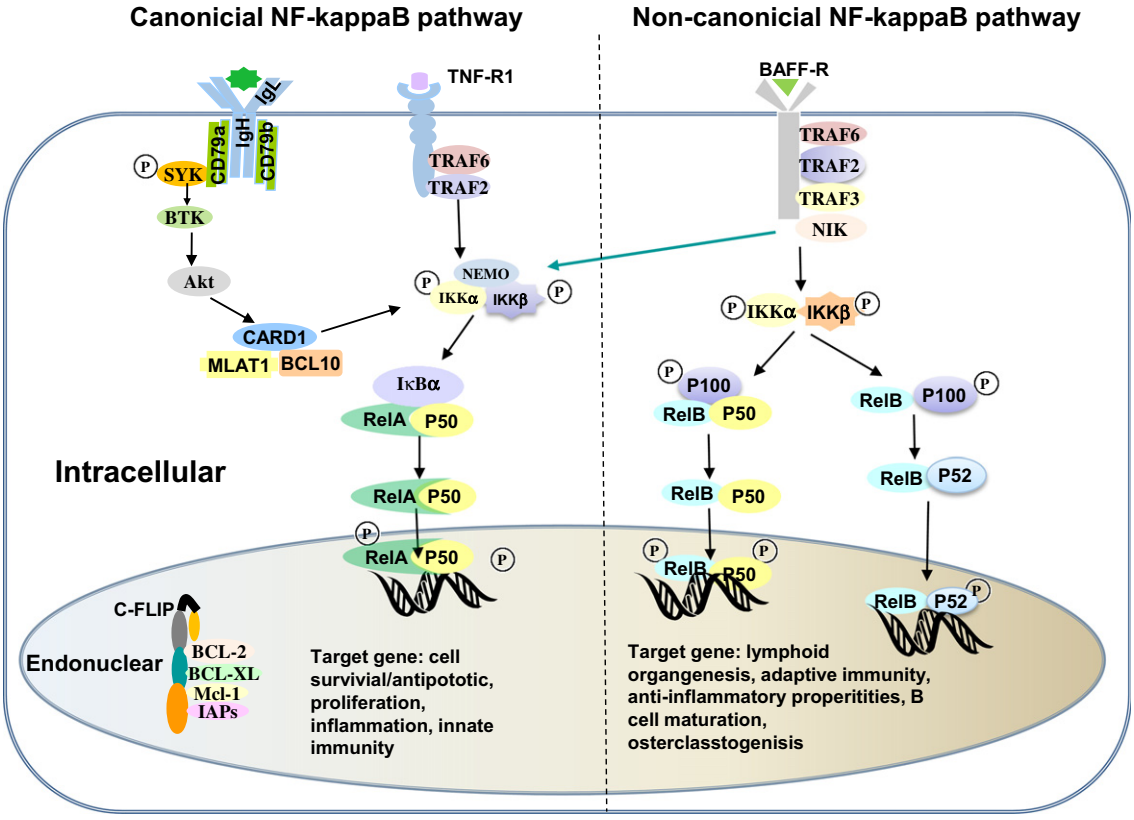

Fig. 1. The canonical and non-canonical NF-κB pathways. The canonical and non-canonical NF-κB signaling pathways are shown in the left and right of the figure. The canonical pathway is activated by the C-like receptors 4, TNF receptors' family, and the antigen receptors BCR and TCR, while the non-canonical pathway is activated by other receptors, such as BAFF-R, CD40, RANK, CD30, and LTβ-R. Arrows indicate activating steps.