CHAPTER 2

NF-κB Signal Transduction by IKK Complexes

Zhi-Wei Li* and Michael Karin

Abstract

Transcription factor NF-κB plays a major role in many physiological and pathological processes while its regulation is best understood in inflammatory and immune system.

The central event in NF-κB signaling pathway is the activation of IKK complex, the convergent point of diverse NF-κB activation signaling. This review addresses the cell signaling of IKK and NF-κB activation in response to various immune and inflammatory stimuli as revealed by the analysis of mice and cells lacking specific signaling transducers.

NF-κB, IκB, IKK and the Canonical Pathway for NF-κB Activation

NF-κB is a master transcription factor that plays a major role in inflammatory and immune response. It was originally found in nuclei of B cells and named for its ability binding the κ-chain enhancer of immunoglobulin in B cells. NF-κB was later found in the cytoplasm of all cell types, where it enters the nucleus upon stimulation. NF-κB transcription factors are evolutionarily conserved from insects to mammals. In mammals, the NF-κB family consists of five members (p65/RelA, RelB, c-Rel, p50/NF-κB1 and p52/NF-κB2). These proteins share an N-terminal domain of about 300 amino acids, which bears homology to the product of the v-rel oncogene, the Rel homology domain (RHD), and includes regions for DNA binding, dimerization and nuclear translocation (Fig. 1). DNA binding by NF-κB requires dimerization and most members of this family form both homo- and heterodimers except for RelB, which forms only heterodimers with p50 or p52. Mammalian NF-κB proteins can be classified into two groups; the first group, consisting of p65 (RelA), RelB and c-Rel, are expressed as mature proteins and possess a transcriptional activation domain at their C-termini. NF-κB dimers containing any one of these subunits can activate target gene transcription upon induction by certain stimuli. The second group consists of p50 (NF-κB1) and p52 (NF-κB2), which are first expressed as large precursors p105 and p100, respectively. NF-κB1 precursor p105 is constitutively processed to produce p50, whereas p52 is proteolytically released from p100 only upon stimulation. Both p50 and p52 lack a potent transcriptional activation domain and therefore cannot activate transcription as homodimers, or as p50/p52 heterodimers. In fact, p50/p52 dimers may suppress expression of NF-κB target genes.

The C-termini of p105 and p100 contain multiple ankyrin repeats, which are required for association with NF-κB and are the distinguishing structural feature of the IκBs, the specific inhibitors of NF-κB (Fig. 1). Therefore, p105 and p100 can serve an IκB-like function by
retaining RelA, RelB or c-Rel in the cytoplasm. Three major mammalian IκB proteins, IκBα, IκBβ and IκBε, have been identified.¹ These IκBs have overlapping yet distinct inhibitory specificity and thus can differentially inhibit NF-κB dimers. In addition, the C-terminal portion of p105 can be expressed as an independent transcript that encodes IκBγ, which is expressed only in the lymphoid cells. Another mammalian IκB family member is the nuclear protein Bcl-3.¹ Although it contains ankyrin repeats, Bcl-3 functions as a transcriptional activator with p50 or p52 homodimers, rather than an inhibitor of NF-κB. This activity may be caused by Bcl-3-mediated displacement of p50 or p52 homodimers from NF-κB binding site to allow binding of NF-κB molecules with transactivation domains, such as p65, c-Rel and RelB. Alternatively, Bcl-3 may also activate gene transcription by its own transactivation domain.² Bcl-3 production is inducible and is required for humoral immune response. Other two inducible IκB family members are IκBζ (also called MAIL or INAP) and IκBNS.³ ⁶ IκBζ is required for Toll-like receptor (TLR) and interleukin 1 (IL-1) receptor (IL-1R) activation induced production of IL-6,⁷ and IκBNS is induced by TCR (T cell receptor) activation,⁶ suggesting that other inducible IκBs may exist and respond to diverse stimulation. However, how these inducible IκB function has yet to be determined.

In addition to the ankyrin repeats, the C-terminal acidic region of IκBζ is necessary for their inhibitory activity. The PEST motif in the C-terminal acidic region of IκBζ is the target site of IκB phosphorylation that is responsible for the basal turnover of these proteins and their induced degradation in response to UV irradiation.⁸ The IκBs inhibit NF-κB activity by masking the nuclear localization signal (NLS) of NF-κB, thereby retaining NF-κB in the cytoplasm.