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Survey

Alternative pathways of NF-κB activation: A double-edged sword in health and disease

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Abstract

While the classical pathway of NF-κB activation plays critical roles in a wide range of biological processes, the more recently described ''non-canonical'' NF-κB pathway has important but more restricted roles in both normal and pathological processes. The non-canonical NF-κB pathway, based on processing of the *nf-κb2* gene product p100 to generate p52, appears to be involved in B-cell maturation and lymphoid development. Deregulated activation of this pathway has been observed in a variety of malignant and autoimmune diseases, thus inhibitors that specifically target p100 processing might be predicted to have potential roles as immunomodulators and in the therapy of malignant diseases. We review current understandings of NF-κB activation, particularly the mechanisms of p100 processing under both physiological and pathological conditions.

Keywords: NF-κB; Cancer; Autoimmune disease; Therapeutic target; Protein processing

Contents

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1. Two major pathways to NF-κB activation

Nuclear factor of κB (NF-κB) plays a central role in regulation of diverse biological processes, including immune response, development, cell growth and survival [1–4]. Deregulated function of NF-κB contributes to the development of a variety of human diseases, particularly immune-related diseases and cancers [5–7]. NF-κB is not a single protein but a collection of dimeric transcription factors composed of members of the Rel family with five closely related DNA binding proteins: RelA (p65), RelB, c-Rel, NF-κB1/p50 and NF-κB2/p52. All five NF-κB members share a highly conserved 300-amino-acid-long N-terminal Rel homology domain (RHD) responsible for DNA binding, dimerization and nuclear translocation (Fig. 1). In resting cells, NF-κB dimers are sequestered in the cytoplasm as latent complexes through binding to members of a family of ankyrin repeat domain (ARD)-containing inhibitors called IκB (inhibitor of κB) proteins, which interact with the RHD of NF-κB proteins [1–3]. Accordingly, the major pathway leading to NF-κB activation called canonical NF-κB pathway is based on inducible IκB degradation allowing NF-κB dimers (mainly p65/p50 dimers) to accumulate in the nucleus and activate transcription (Fig. 2).

Although they share structural similarities and bind to related DNA motifs termed κB sites, the five NF-κB proteins can be further classified into two groups based on the differences in their mode of synthesis and the structure and function of their C-terminal sequences (Fig. 1). One group consists of the RelA/p65, RelB and c-Rel proteins that contain transcription activation domains at their C-termini and are synthesized directly as mature forms. The other group includes NF-κB1/p50 and NF-κB2/p52, which are generated from large precursor proteins, p105 and p100, respectively. Interestingly, the C-terminal regions of p105 and p100 do not contain transactivation domain but instead consist of a series of ankyrin repeats, the characteristic domain of IκB [1,2]. Indeed, both p105 and p100 function as IκB-like inhibitors of NF-κB [13,14]. Therefore, the processing of p105 and p100, which selectively degrades their C-terminal portions, works as an alternative mechanism for NF-κB activation. Whereas the processing of p105 is constitutive, p100 processing is tightly controlled and highly inducible [15]. The NF-κB activation mediated by p100 processing, resulting in nuclear translocation of p52-containing dimers, thus is termed non-canonical NF-κB pathway (Fig. 2).

2. Canonical NF-κB pathway (degradation-based activation)

2.1. IKK—the key to NF-κB activation

The canonical pathway can be rapidly and transiently activated by a large variety of stimuli, such as mitogens, cytokines, microbial components and DNA damage [16]. Most, if not all, of these stimuli will lead to activation of a specific IκB kinase (IKK), a multiprotein complex with a high molecular weight of approximately 700–900 kDa as determined by gel filtration [17–19]. Once activated, IKK phosphorylates specific serines within the IκB proteins (Fig. 1), triggering their ubiquitination by a ubiquitin ligase complex containing the β-transducin repeat-containing protein (β-TrCP). The IκB is then degraded by the 26S proteasome, thus allowing the release, modification and translocation of NF-κB dimers into the nucleus to induce gene expression (Fig. 2). IKKα, one catalytic subunit of IKK, is also responsible for inducible phosphorylation of p100, a key step for p100 processing (see non-canonical pathway below for details). Thus, IKK is required for activation of both canonical and non-canonical NF-κB signaling pathways (Fig. 2).

2.2. Different function of IKK components and IKK activation

The IKK complex was originally found to contain three subunits: two highly homologous catalytic subunits, IKKα (IKK1) and IKKβ (IKK2), and an essential regulatory subunit, IKKγ (also known as NEMO, NF-κB Essential Modulator; IKKAP1, IKK Associated Protein 1; FIP-3, Type 2 Adenovirus E3-14.7-kD Interacting Protein 3) [2–4]. However, the size of the IKK complex (700–900 kDa) implies the presence of additional component(s). Indeed, recent studies suggest that CDC37, Hsp90 and ELKS may serve as additional components of the IKK complex [20,21]. While the functional role of CDC37 and Hsp90 in the IKK complex needs further investigation, it seems clear that ELKS functions as another essential regulatory subunit of the IKK complex [20–22]. So, the IKK complex consists of at least four functional subunits, two catalytic subunits (IKKα and IKKβ) and two regulatory subunits (IKKγ and ELKS). Although the subunits of IKK usually exist in the same complex, recent studies favor a model that they may also dynamically associate and dissociate with each other, and can also function in separate complexes [23–27].