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Mini review

IκB kinase β (IKKβ/IKK2/IKBKB)—A key molecule in signaling to the transcription factor NF-κB

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Abstract

IKKβ/IKBKB (IκB kinase beta), also designated as IKK2, was named after its function of phosphorylating IκB molecules, the inhibitors of NF-κB transcription factors. The kinase activity of IKKβ targets two adjacent serine residues of IκB leading to ubiquitination and proteasomal degradation of the inhibitor, followed by release and activation of NF-κB. Many signaling pathways that activate NF-κB converge at the level of IKKβ. Examples of stimuli leading to IKKβ and subsequent NF-κB activation include inflammatory cytokines (IL-1, TNFα), endotoxins (lipopolysaccharide), viral infection and double strand RNA as well as physical signals such as UV-irradiation.

Transcription factors of the NF-κB protein family have a great variety of functions in regulating the immune system, cellular differentiation, survival and proliferation.

NF-κB is an essential factor in acute as well as chronic inflammation, a pathological state which is either cause or co-factor in a great variety of diseases. Moreover, recent data suggest that many variants of cancer are characterized by elevated constitutive activity of NF-κB, which can act as a survival factor for malignant cells by its predominantly anti-apoptotic function. Given the tight regulation of NF-κB by IκB molecules and the central role of IKKβ in phosphorylation and degradation of the inhibitor, IKKβ is a very promising target for pharmaceutical substances aiming at interfering with NF-κB activation.
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1. Introduction

The currently best-documented function of IKKβ is to activate members of the NF-κB transcription factor family via the so-called classical (or canonical) pathway by phosphorylation of IκB inhibitors [1–3]. NF-κB transcription factors play an important role in the balance between cell survival and apoptosis and are involved in the regulation of cell proliferation and development or differentiation of various cell types [4,5]. Changes in activity and/or regulation of IKKβ and NF-κB are found in many diseases associated with chronic or acute inflammation and more recently it became evident that NF-κB exhibits higher constitutive activity or aberrant regulation in various forms of cancer [4,6–12].

The functional entities of NF-κB transcription factors are homo- or heterodimers of members of this gene/protein family, consisting of the proteins NF-κB1 (p50 and the precursor p105), NF-κB2 (p52 and the precursor p100), RelA (p65), RelB and c-Rel. All these molecules contain a homologous DNA-binding domain (the Rel homology domain); however, just three of them (RelA/p65; RelB and c-Rel) contain a transactivation domain. Transcriptionally active NF-κB dimers contain one of these three factors. In non-activated cells NF-κB dimers are associated with molecules of

Abbreviations: IκB, inhibitor of NF-κB; IKKa, IκB kinase a; IKKβ, IκB kinase β; IL-1, interleukin-1; NEMO, NF-κB essential modulator; NF-κB, nuclear factor-kappa B; TCR, T cell receptor; TNFα, tumor necrosis factor alpha.

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the IκB protein family (mainly IκBα, IκBβ and IκBε), which inhibit NF-κB binding to DNA [13] and shift the steady state localization to the cytosol [4]. This model is supported by structural data of IκB/NF-κB complexes [14,15]. The precursor forms of p52 and p50 (p100 and p105, respectively) contain pro-domains, which are homologous to IκB molecules and fulfill the same inhibitory role. Both NF-κB and IκBα molecules shuttle between cytosol and nucleus [16–18], but in the presence of IκBα the predominant steady state localization of the complex is in the cytosol.

For full activation NF-κB has to be released from IκB, which is achieved by degradation of the inhibitor (or the inhibitory pro-domains of p100 and p105) by 26S proteasomes. Signal-induced proteasomal degradation of IκB or inhibitory pro-domains requires prior polyubiquitination, which is carried out by $SCF^{\beta TrCP}$-type E3 ligases [19–21]. This in turn is triggered by phosphorylation of IκB on two adjacent serine residues (Ser32/Ser36 in IκBα) in the N-terminal signal-response domain. Two kinases were reported to be capable of phosphorylating these residues: IKKα (IκB kinase α, IKBKA, IKK1) and IKKβ (IKBKB, IKK2, Fig. 1) [22–25]. IKKα and IKKβ form heterodimers and are found in a 700–900 kDa complex with a non-enzymatic accessory molecule named IKKγ [26] or NEMO (NF-κB essential modulator [27]). This complex, also known as IKK-signalosome, was postulated to contain two IKK-dimers and most likely a tetramer of IKKγ/NEMO [1]. IKKβ turned out to be the crucial kinase of the IKK-signalosome for activation of NF-κB by most inflammatory stimuli, which is considered the classical or canonical pathway of NF-κB activation. Signals activating this pathway comprise the inflammatory cytokines TNFα and IL-1, bacterial components like lipopolysaccharide (LPS) which activate Toll-like receptors (TLR) and signals that activate T-cell receptors (TCR) [2,4,5]. Interestingly, recent data indicate that IKKβ is dispensable for some pathways of canonical NF-κB activation, as it was observed that IKKα can activate NF-κB in response to IL-1, but not TNFα by forming functional IKK-complexes with NEMO even in the absence of IKKβ [28].

Despite tedious studies, the exact molecular mechanisms leading from the different stimuli to activation of the IKK-complex are not clear and there are most probably different modes of activating IKKβ. It was shown that various kinases (such as MEKK1, MEKK3, TAK1, NIK, NAK or PKC-theta, as reviewed in [4]) can activate IKKβ by phosphorylating serine residues within its activation loop (Ser177 and Ser181). Gene deletion experiments verified the importance of MEKK3 (mitogen-activated protein kinase/ERK kinase kinase-3) and TAK1 (TGFβ-activated kinase 1) in the canonical NF-κB activation pathway [29,30]. Besides activation by upstream kinases there is evidence that IKK molecules can also activate themselves by a transphosphorylation mechanism of homo- or heterodimers in a proximity-induced self-activation process [31,32]. While all these studies led to the identification of a variety of possible upstream signaling pathways, the mechanistic details of these signaling events are still not fully understood. In the last few years, it became increasingly clear that ubiquitination cascades upstream of IKK signalosomes play a pivotal role in signaling to effector molecules.

In this article, we want to highlight recent insights in the activation of IKKβ and NF-κB including specific ubiquitination events. We describe recently identified substrates of IKKβ which extend the role of IKKβ beyond the NF-κB signaling pathway. Furthermore, we report on pharmaceutical efforts to develop inhibitors or modulators of IKKβ, as these substances have an enormous potential of application in a great variety of diseases.

2. Signaling and function of IKKβ

2.1. Ubiquitination processes modulate signaling pathways converging on IKKβ

The current view of the canonical pathway of NF-κB activation is that specific and distinct ubiquitination processes are involved in the activation of the IKK-complex (Fig. 2) [3,33]. In fact, it was shown that the IκB kinase activity requires non-degradative ubiquitination even before the molecular identification of IKKs [34]. In general, binding of ligands such as IL-1 or TNFα to respective receptors induces association of adaptor molecules with cytosolic receptor domains. These adaptor molecules include RING finger-proteins of the TRAF family (TNF-receptor associated factors), with TRAF6 being essential for IL-1-mediated IKK activation and TRAF2 or TRAF5 as crucial factors in TNFα-induced signaling. Biochemical analysis of factors linking TRAF6 to IKK activation led to the identification of Ubc13/Uev1A as a dimeric E2 ubiquitin-conjugating enzyme complex and demonstrated that the RING domain of TRAF6 acts as E3 ligase catalyzing the formation of lysine-63-linked polyubiquitin chains [35]. In contrast to lysine-48-linked polyubiquitin chains, which

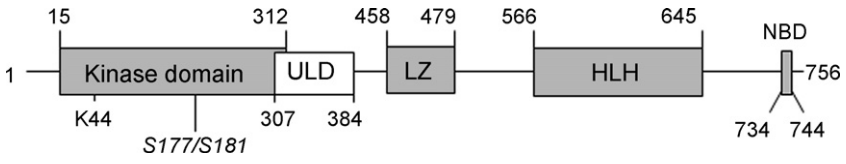

Fig. 1. Scheme of the IKKβ domain structure. ULD, ubiquitin-like domain; LZ, leucine zipper; HLH, helix–loop–helix domain; NBD, NEMO-binding domain. Numbering of domain borders differ slightly between different references. The catalytic active site lysine residue (K44) is indicated and the two serine-residues (S177/S181) of the activation loop, which are phosphorylated upon activation, are shown in *italics*.

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