## Phylogeny

Orthologues of IκB kinase β (IKKβ) are reported in Mus musculus (Ikbkb) and Xenopus laevis (xIKKβ), with strong conservation in the kinase domain (Xu et al., 2011). Together with its paralogue IKKα (≈50 % sequence identity; ≈70 % overall homology), IKKβ defines the catalytic branch of the IKK family (Unknown Authors, 2022). The wider IKK family (IKKα, IKKβ, IKKε, TBK1) forms a distinct serine/threonine kinase clade classified in the “OTHER” group of the human kinome (Hauenstein et al., 2014).

## Reaction Catalyzed

ATP + protein-L-serine ⇌ ADP + protein-O-phospho-L-serine (Hauenstein et al., 2014).

## Cofactor Requirements

Catalytic activity requires divalent Mg²⁺; in vitro assays employed 10 mM MgCl₂ (Xu et al., 2011).

## Substrate Specificity

• Canonical targets: IκBα Ser32/Ser36, IκBβ Ser19/Ser23, p105 Ser927/Ser932, RelA Ser536 (Hauenstein et al., 2014; Unknown Authors, 2022).  
• High-affinity docking is mediated by substrates carrying a linear YDDFXF/YDDΦxΦ motif (e.g., IκBα 303-314) that binds a basic pocket at the dimer interface (Unknown Authors, 2022; Li et al., 2024).  
• Additional validated substrates include p53 Ser362/Ser366, TSC1 Ser487/Ser511, AMPK, PFKFB3, FOXO3a, Bad, PUMA, and SNAP-23 Ser95/Ser120 (Antonia et al., 2021; Unknown Authors, 2012).  
• No universal phosphorylation consensus beyond an S/TP preference in activation-loop substrates has been defined (Xu et al., 2011).

## Structure

IKKβ is tri-modular: kinase domain (residues 16-307), ubiquitin-like domain (310-394), scaffold/dimerization domain (410-666) and a C-terminal NEMO-binding segment (Xu et al., 2011; Hauenstein et al., 2014). Crystal structures (PDB 4KIK, 3QA8/3QAD) reveal an SDD-mediated asymmetric dimer containing one phosphorylated (active) and one unphosphorylated (inactive) protomer, illustrating trans-activation (Liu et al., 2013). Phosphorylation of Ser177/Ser181 in the activation loop realigns the C-helix and completes the hydrophobic spine (Karin, 1999; Xu et al., 2011). A positively charged pocket formed by both SDDs binds the YDDFXF substrate motif (Unknown Authors, 2022).

## Regulation

• Activation-loop phosphorylation at Ser177/Ser181 by TAK1, MEKK3, IRAK1 or by dimer-driven trans-autophosphorylation is essential for activity (Hauenstein et al., 2014).  
• Autophosphorylation of distal C-terminal serines (e.g., Ser771) provides negative feedback and accelerates inactivation (Karin, 1999).  
• Dephosphorylation by PP2A and PP6 reverses activation (Hauenstein et al., 2014).  
• NEMO-dependent clustering and binding to Lys63-linked or unanchored polyubiquitin chains promote oligomerization and activation (Unknown Authors, 2012).  
• O-GlcNAcylation enhances kinase activity in p53-deficient cells (Unknown Authors, 2012).

## Function

IKKβ is the principal catalytic subunit of the canonical NF-κB pathway, activated by TNF-α, IL-1β, LPS, and genotoxic or metabolic stress (Antonia et al., 2021; Hauenstein et al., 2014). Phosphorylation-induced degradation of IκB proteins releases NF-κB dimers, promoting transcription of genes controlling inflammation, survival and metabolism (Karin, 1999).

NF-κB-independent functions include:  
– Phosphorylation of p53, FOXO3a and Bad to trigger β-TrCP-mediated degradation (Antonia et al., 2021).  
– Phosphorylation of TSC1 to activate mTOR signalling (Unknown Authors, 2012).  
– Phosphorylation of SNAP-23 to regulate mast-cell exocytosis (Unknown Authors, 2012).

Upstream activators comprise TAK1, MEKK3, IRAK1, PDK1 and ubiquitin-linked scaffolds (Hauenstein et al., 2014; Unknown Authors, 2012). Gene knockout causes embryonic lethality with massive liver apoptosis and immune defects (Adli et al., 2010; Salzmann et al., 2020). Tissue-specific ablation can improve skeletal-muscle regeneration and mitigate inflammatory skin disease (Salzmann et al., 2020).

## Inhibitors

ATP-competitive: PS-1145, AS602868, TPCA-1, SC-514 (Unknown Authors, 2012; Ivanenkov et al., 2011).  
Allosteric: BMS-345541 (Paul et al., 2018).  
Natural products: Honokiol, Wedelolactone, Apigenin, Curcumin, Resveratrol (Paul et al., 2018; Ivanenkov et al., 2011).  
Structural probe: Staurosporine analogue K252a (co-crystallised in PDB 4KIK) (Liu et al., 2013).

## Other Comments

Constitutive IKKβ activity contributes to oncogenesis by suppressing apoptosis and is implicated in Hodgkin’s lymphoma, solid tumours, rheumatoid arthritis, asthma, colitis, myocardial injury and metabolic disorders (Karin, 1999; Unknown Authors, 2012).

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