## Phylogeny

IKBKE (IKKε/IKKi) is a non-canonical IκB kinase in the IKK-related family of serine/threonine protein kinases. Kinome analyses generally classify the IKKs in the atypical “Other” kinase group, although several sources place IKBKE in the CMGC family. It shares only 24 – 31 % sequence identity with canonical IKKα/β, yet is closely related to TBK1 with ~64 – 67 % homology (Häcker & Karin, 2006; Durand et al., 2018; Yin et al., 2020).

## Reaction Catalyzed

ATP + [target protein]-L-Ser/Thr ⇌ ADP + [target protein]-L-Ser/Thr-phosphate (Bulek et al., 2011).

## Cofactor Requirements

ATP and divalent cations Mg²⁺ or Mn²⁺ are required for catalytic activity (Johnson et al., 2023; Wang et al., 2005).

## Substrate Specificity

Peptide-array profiling groups IKBKE in a minor specificity cluster characterised by basic residues flanking the phospho-site and a marked preference for an aromatic residue at +3. Additional data show activity towards basophilic motifs (R-x-x-S/T) and acidic sequence contexts (Johnson et al., 2023).

## Structure

Human IKBKE is a 716-residue (~80–84 kDa) kinase comprising:  
• N-terminal kinase domain (aa 9–300; catalytic Lys38; activation-loop Ser172)  
• Ubiquitin-like domain (aa 350–383)  
• C-terminal scaffold/dimerisation domain with leucine-zipper (aa 500–527) and helix-loop-helix (aa 578–619) motifs  
• DDX3-binding region (aa 383–647)

It lacks the NEMO-binding domain present in canonical IKKs. Structural comparisons with IKKβ/TBK1 show an inactive “αC-out” conformation; activation requires Ser172 phosphorylation (Xu et al., 2011; Tu et al., 2013; Xiao et al., 2022; Yin et al., 2020).

## Regulation

• Phosphorylation: trans-autophosphorylation on Ser172 (DDX3-facilitated) and Thr501 (STAT1 regulation)  
• Ubiquitination: K63-linked chains at Lys30, Lys401, Met416 via cIAP1/2-TRAF2; K48-linked chains by TRIM6 during IFN signalling  
• SUMOylation: Lys231 promotes nuclear localisation and NF-κB activation after DNA damage  
• Adaptor proteins: TANK, Sintbad and NAP1 localise/activate the kinase (Durand et al., 2018; Xiao et al., 2022; Zhang et al., 2016)

## Function

Inducible kinase highly expressed in spleen, thymus and peripheral blood lymphocytes; up-regulated by LPS, TNF-α and IL-1β (Häcker & Karin, 2006).  
Upstream signals: TLR and RIG-I-like receptor pathways.  
Interacting partners: TANK, TRAF2, Sintbad, NAP1, DDX3.  
Principal substrates / pathways:  
• IRF3/7 and STAT1 (Ser708) → type I IFN production  
• RelA/p65, IκBα, CYLD → NF-κB activation  
• NFATc1 → T-cell suppression  
• p62/SQSTM1 → autophagy  
• Akt, GLI1, C/EBPβ → oncogenic signalling (Durand et al., 2018; Yin et al., 2020)

## Inhibitors

Dual TBK1/IKBKE ATP-competitive inhibitors include BX795, amlexanox, CYT387, MRT67307, WO2009032861 compounds, SAR and Domainex series; BX795 blocks Ser172 autophosphorylation (Durand et al., 2018; Yin et al., 2020; Xiao et al., 2022; Zhang et al., 2016).

## Other Comments

The human IKBKE gene (chromosome 1q32.1, 22 exons) yields at least three splice variants. Catalytic residue mutation K38A abolishes activity. Over-expression is oncogenic (breast, glioma, pancreatic, ovarian, NSCLC) and contributes to obesity, insulin resistance and NAFLD (Durand et al., 2018; Yin et al., 2020; Xiao et al., 2022).

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