## Phylogeny

IKBKE (IKKε) is a non-canonical IκB kinase belonging to the IKK-related kinase family of serine/threonine protein kinases (hacker2006regulationandfunction pages 53-57, tu2013structureandubiquitinationdependent pages 1-2). Kinome classification places the IKK family, including IKBKE (also known as IKKi), in the “Other” group of atypical protein kinases (hacker2006regulationandfunction pages 53-57, hacker2006regulationandfunction pages 43-48, wang2005genomicstructureand pages 1-2). Some sources, however, place IKBKE within the CMGC (CDK, MAPK, GSK3, CLK) group (xu2011crystalstructureof pages 1-2, yin2020advancesinikbke pages 1-2, hacker2006regulationandfunction pages 48-53, xiao2022roleofikkε pages 1-2). It is phylogenetically distinct from the canonical IKKs (IKKα and IKKβ), sharing only 24-31% amino acid sequence identity with them (durand2018rolesforthe pages 1-3, yin2020advancesinikbke pages 1-2, hacker2006regulationandfunction pages 53-57). IKBKE is a close homolog of TANK-binding kinase 1 (TBK1), sharing approximately 64-67% sequence homology (hacker2006regulationandfunction pages 53-57, yin2020advancesinikbke pages 1-2, durand2018rolesforthe pages 1-3).

## Reaction Catalyzed

IKBKE catalyzes the ATP-dependent transfer of a γ-phosphate group to serine or threonine residues on target protein substrates (yin2020advancesinikbke pages 1-2, xiao2022roleofikkε pages 1-2). Reaction: ATP + [target protein]-L-serine/threonine = ADP + [target protein]-L-serine/threonine phosphate (bulek2011theinduciblekinase pages 8-9).

## Cofactor Requirements

The kinase activity of IKBKE requires ATP as the phosphate donor cofactor (bulek2011theinduciblekinase pages 8-9, yin2020advancesinikbke pages 1-2). Its catalytic function is also dependent on divalent cations such as Mg²⁺ or Mn²⁺ (johnson2023anatlasof pages 4-4, wang2005genomicstructureand pages 1-2).

## Substrate Specificity

Analysis of substrate specificity motifs classifies IKBKE within a cluster (cluster 13) that deviates from the major basophilic, proline-directed, and acidic kinase groups (johnson2023anatlasof pages 2-3). The consensus phosphorylation motif for kinases in this cluster is characterized by basic residues both N- and C-terminal to the phosphorylation site and a dominant selection for an aromatic residue (phenylalanine, tyrosine, or tryptophan) at the +3 position (johnson2023anatlasof pages 2-3). However, other analyses from the same study show IKBKE has preferences for basophilic motifs like R-x-x-S/T or acidic sequence environments (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 4-4).

## Structure

IKBKE is an ~80-84 kDa protein of 716 amino acids (full-length isoform v1) with a multi-domain architecture (yin2020advancesinikbke pages 1-2, hacker2006regulationandfunction pages 53-57, luo2025anexaminationof pages 8-10). Its key domains include an N-terminal Kinase Domain (KD, aa 9–300) responsible for ATP binding and phosphotransferase activity, with Lys38 being critical for function; a Ubiquitin-like Domain (ULD, aa 350–383) important for kinase activity and substrate interaction; a C-terminal Scaffold Dimerization Domain (SDD) that contains a Leucine Zipper (LZ, aa 500–527) and a Helix-Loop-Helix (HLH, aa 578–619) motif; and a domain interacting with DEAD-box protein 3 (DDX3, aa 383–647) that promotes autophosphorylation (xiao2022roleofikkε pages 1-2, xiao2022roleofikkε pages 2-3, durand2018rolesforthe pages 1-3, yin2020advancesinikbke pages 1-2). Unlike canonical IKKs, IKBKE lacks a NEMO-binding domain (NBD) (durand2018rolesforthe pages 1-3, yin2020advancesinikbke pages 1-2). Structural studies of related kinases IKKβ and TBK1 indicate that the inactive conformation features a displaced C-helix (αC helix) in an “out” position, which disrupts catalytically essential interactions (xu2011crystalstructureof pages 2-4, tu2013structureandubiquitinationdependent pages 2-4). While the hydrophobic spine is not explicitly detailed for IKBKE, these structural changes imply a disrupted spine characteristic of an inactive kinase state (xu2011crystalstructureof pages 2-4). Activation requires phosphorylation of Ser172 within the activation loop of the KD (xiao2022roleofikkε pages 1-2, durand2018rolesforthe pages 11-12).

## Regulation

The catalytic activity of IKBKE is regulated by multiple post-translational modifications (PTMs) and protein-protein interactions. - **Phosphorylation:** Activation depends on trans-autophosphorylation at Ser172 in the activation loop, a process facilitated by interaction with DDX3 (durand2018rolesforthe pages 11-12, xiao2022roleofikkε pages 1-2, xiao2022roleofikkε pages 2-3). Phosphorylation at Thr501 regulates IKBKE-mediated STAT1 phosphorylation (xiao2022roleofikkε pages 1-2). - **Ubiquitination:** K63-linked polyubiquitination, mediated by a cIAP1/cIAP2/TRAF2 E3 ligase complex, is essential for kinase activity (durand2018rolesforthe pages 11-12, durand2018rolesforthe pages 3-5). Ubiquitination at Lys30, Lys401, and Met416 facilitates downstream NF-κB signaling (xiao2022roleofikkε pages 1-2). K48-linked polyubiquitination by TRIM6 also activates IKBKE during interferon stimulation (zhang2016rolesofiκb pages 1-2). - **SUMOylation:** SUMOylation at Lys231 affects nuclear localization and promotes NF-κB activation following DNA damage (xiao2022roleofikkε pages 1-2, xiao2022roleofikkε pages 2-3). - **Interacting Partners:** Adaptor proteins TANK, Sintbad, and NAP1 localize IKBKE to facilitate substrate specificity and activation (durand2018rolesforthe pages 3-5, yin2020advancesinikbke pages 1-2).

## Function

IKBKE is an inducible kinase primarily expressed in immune tissues like the spleen, thymus, and peripheral blood lymphocytes, with expression induced by stimuli such as LPS, TNF-α, and IL-1β (hacker2006regulationandfunction pages 53-57). - **Upstream Activators:** It is activated downstream of pattern recognition receptors such as TLRs and RIG-I-like receptors (yin2020advancesinikbke pages 9-10, yin2020advancesinikbke pages 1-2). - **Interacting Partners:** It forms complexes with TANK, TRAF2, Sintbad, NAP1, and DDX3 (durand2018rolesforthe pages 3-5, hacker2006regulationandfunction pages 53-57, xiao2022roleofikkε pages 1-2). - **Downstream Substrates and Signaling Pathways:** - **Innate Immunity:** IKBKE phosphorylates transcription factors IRF3 and IRF7, promoting their dimerization and nuclear translocation to induce type I interferon transcription (durand2018rolesforthe pages 1-3, yin2020advancesinikbke pages 1-2). It also phosphorylates STAT1 at Ser708 to drive expression of interferon-responsive genes (durand2018rolesforthe pages 1-3). - **NF-κB Pathway:** It enhances NF-κB activity by phosphorylating RelA/p65 (at Ser536 and Ser468), IκBα (at Ser36), and CYLD (at Ser418) (durand2018rolesforthe pages 3-5, hacker2006regulationandfunction pages 53-57, durand2018rolesforthe pages 11-12). - **Immune Regulation:** It suppresses T cell activation by phosphorylating NFATc1 (durand2018rolesforthe pages 1-3). - **Autophagy:** It phosphorylates p62/SQSTM1 at Ser403 to regulate autophagy (durand2018rolesforthe pages 1-3). - **Oncogenesis:** It activates oncogenic pathways involving Akt and the nuclear translocation of GLI1 and C/EBPβ (durand2018rolesforthe pages 3-5).

## Inhibitors

Several small-molecule inhibitors target the kinase activity of IKBKE, many of which are dual TBK1/IKBKE inhibitors (durand2018rolesforthe pages 3-5). Known inhibitors include BX795, amlexanox, CYT387, MRT67307, WO2009032861, SAR, and Domainex compounds (durand2018rolesforthe pages 11-12, yin2020advancesinikbke pages 9-10, xiao2022roleofikkε pages 1-2, zhang2016rolesofiκb pages 5-7). BX795 functions by blocking autophosphorylation at Ser172 (xiao2022roleofikkε pages 2-3).

## Other Comments

The human *IKBKE* gene is located on chromosome 1q32.1 and contains 22 exons, producing at least three isoforms via alternative splicing (xiao2022roleofikkε pages 1-2, yin2020advancesinikbke pages 1-2). A K38A mutation in the kinase domain abolishes its kinase activity (xiao2022roleofikkε pages 1-2). IKBKE is considered an oncogene, as its overexpression promotes tumor growth, invasion, and drug resistance, and its expression correlates with poor prognosis in various cancers including breast, glioma, pancreatic, ovarian, and non-small cell lung cancer (durand2018rolesforthe pages 1-3, durand2018rolesforthe pages 11-12, yin2020advancesinikbke pages 9-10). It is also implicated in metabolic diseases, as its expression is induced by high-fat diets and contributes to obesity, insulin resistance, and nonalcoholic fatty liver disease (NAFLD) (xiao2022roleofikkε pages 1-2).

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