Phylogeny  
• Orthologs identified in Homo sapiens, Mus musculus, Danio rerio, Drosophila melanogaster and Caenorhabditis elegans, demonstrating deep metazoan conservation of the IKK module (unknownauthors2002roleofi pages 35-40, karin1999thebeginningof pages 3-4).  
• Assigned to the CAMK-like group, IκB kinase (IKK) family in the human kinome according to Manning et al. (unknownauthors2002roleofi pages 35-40, unknownauthors2012ikkbiology pages 19-21).  
• Shares ~50 % sequence identity and an equivalent KD–ULD–SDD layout with IKKβ, reflecting divergence within the IKK sub-family (mulero2019nfκbiκband pages 224-227).  
• A basic surface at the kinase/ULD interface unique to IKKα underlies selective binding to NF-κB–inducing kinase (NIK) and p100 (polley2016structuralbasisfor pages 1-3).

Reaction Catalyzed  
ATP + protein-Ser/Thr → ADP + protein-Ser/Thr-P (unknownauthors2012ikkbiology pages 1-2, unknownauthors2002roleofi pages 35-40).

Cofactor Requirements  
Catalysis requires divalent cations, with Mg²⁺ preferred and Mn²⁺ tolerated (unknownauthors2002roleofi pages 35-40).

Substrate Specificity  
• Consensus motif: acidic residues at positions −2/−3 preceding a serine or threonine phospho-acceptor, typified by the IκBα sequence DSGLDS (unknownauthors2002roleofi pages 35-40).  
• Docking determinant: YDDFxF motif on substrates is recognised by IKKα and allows broad residue flexibility (unknownauthors2022characterizationofproteinprotein pages 214-220).  
• Validated phosphosites: IκBα Ser32/Ser36; NF-κB2/p100 Ser866/Ser870 plus auxiliary Ser99/Ser108/Ser115/Ser123 (unknownauthors2022characterizationofproteinprotein pages 86-91).

Structure  
• Modular organisation:  
– N-terminal kinase domain (KD) harbouring catalytic Lys44, Glu63, Asp166 and activation loop Ser176/Ser180 (unknownauthors2002roleofi pages 35-40).  
– Ubiquitin-like domain (ULD) packs against the KD and contributes to oligomerisation (mulero2019nfκbiκband pages 224-227).  
– Scaffold/dimerisation domain (SDD) containing leucine-zipper and helix-loop-helix elements that drive back-to-back dimer formation (mulero2019nfκbiκband pages 224-227).  
– C-terminal NEMO-binding segment required for holo-complex assembly (mulero2019nfκbiκband pages 224-227).  
• 3-D architecture: X-ray and cryo-EM structures (e.g., PDB 5TQW, 5EBZ) reveal a dimer that can hexamerise in crystallo; a positively charged KD/ULD face forms the NIK interface (polley2016structuralbasisfor pages 1-3).  
• Conserved kinase-fold elements include a hydrophobic spine and ordered C-helix in the active state (unknownauthors2002roleofi pages 35-40).  
• Asymmetric dimerisation principles resolved for IKKβ are structurally transferable to IKKα (liu2013crystalstructureof pages 1-2).

Regulation  
• Phosphorylation  
– Ser176/Ser180: activating sites targeted by NIK in the non-canonical pathway and by TAK1 in canonical signalling (unknownauthors2002roleofi pages 35-40, unknownauthors2012ikkbiology pages 19-21).  
– Tyr188 autophosphorylation or Src-mediated phosphorylation further enhances activity (unknownauthors2012ikkbiology pages 1-2).  
• Ubiquitination  
– Lys63-linked chains assembled by TRAF6 promote activation; CYLD removes these chains, leading to attenuation (unknownauthors2002roleofi pages 35-40, unknownauthors2012ikkbiology pages 19-21).  
• Dephosphorylation by PP2A reverses activation-loop phosphorylation (unknownauthors2002roleofi pages 35-40).  
• Higher-order oligomerisation facilitates trans-autophosphorylation; NEMO binding couples IKKα dimers to receptor-proximal ubiquitin scaffolds (mulero2019nfκbiκband pages 224-227).

Function  
• Expression: ubiquitous with pronounced levels in immune cells and epidermis (unknownauthors2002roleofi pages 35-40).  
• Upstream stimuli: TNFα, IL-1β, LPS (canonical); LTβR, CD40, BAFFR (non-canonical) converge via TAK1 or NIK to activate the kinase (unknownauthors2002roleofi pages 35-40).  
• Principal substrates and partners:  
– Cytoplasmic: IκBα and related inhibitors (canonical NF-κB); p100 in NF-κB2 processing (non-canonical) (unknownauthors2022characterizationofproteinprotein pages 86-91).  
– Nuclear: histone H3, SRC-3, IRF7, SMRT corepressor—linking IKKα to chromatin remodelling and interferon induction (unknownauthors2002roleofi pages 35-40, unknownauthors2022characterizationofproteinprotein pages 86-91).  
– Complex constituents: IKKβ and NEMO form the canonical heterotrimer; homodimeric IKKα predominates in the non-canonical pathway (unknownauthors2002roleofi pages 35-40).  
• Biological roles:  
– Drives canonical NF-κB activation by phosphorylating IκBs, enabling rapid RelA/p50 nuclear translocation (unknownauthors2012ikkbiology pages 1-2).  
– Essential for non-canonical signalling that generates RelB/p52 dimers critical for lymphoid organogenesis (unknownauthors2022characterizationofproteinprotein pages 86-91).  
– NF-κB-independent functions in cell-cycle control and epidermal differentiation through nuclear substrates (unknownauthors2012ikkbiology pages 7-8).

Inhibitors  
ATP-competitive inhibitors with reported potency against IKKα include BMS-345541, MLN120B, BAY 65-1942 and TPCA-1 (unknownauthors2002roleofi pages 35-40, unknownauthors2012ikkbiology pages 19-21).

Other Comments  
• Germline loss-of-function mutations in CHUK cause combined immunodeficiency with ectodermal dysplasia due to impaired non-canonical NF-κB activation (riller2024compoundheterozygousmutations pages 1-3, unknownauthors2002roleofi pages 35-40).  
• Somatic or regulatory mutations that elevate IKKα signalling have been documented in diverse cancers, underscoring its oncogenic potential (unknownauthors2002roleofi pages 35-40).

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