## Phylogeny

Orthologous choline/ethanolamine kinases are present in Saccharomyces cerevisiae (Cki1p), Caenorhabditis elegans (CKA-2), Arabidopsis thaliana (CEK1), Mus musculus (Chka), and Rattus norvegicus (Chka), all conserving the Brenner HXDG phosphotransferase motif and overall dimeric architecture (janardhan2006cholinekinasean pages 8-9, malito2006elucidationofhuman pages 1-2).  
Phylogenetic analyses place CHKA, CHKB and CHKC in a discrete “ChoK” clade that belongs to the “other protein-kinase-like/atypical kinase” group of the human kinome, separate from classical ePK Ser/Thr and Tyr families (lacal2021cholinekinasean pages 24-26, chang2016phosphorylationofhuman pages 20-21).

## Reaction Catalyzed

ATP + choline ⇌ ADP + phosphocholine (preferred reaction)  
ATP + ethanolamine ⇌ ADP + phosphoethanolamine (lower catalytic efficiency) (malito2006elucidationofhuman pages 4-5, ramirez2011chka(cholinekinase pages 2-3).

## Cofactor Requirements

Catalysis requires two Mg²⁺ ions that bridge the β- and γ-phosphates of ATP and coordinate catalytic residues Ser121, Asp306, Asn311 and Asp330 (malito2006elucidationofhuman pages 5-7, ramirez2011chka(cholinekinase pages 1-2).

## Substrate Specificity

A definitive peptide consensus motif has not been established; no high-throughput kinase-substrate profiling data are available for CHKA, and intrinsic sequence preference remains undetermined (chang2016phosphorylationofhuman pages 22-23, gallegoortega2011involvementofhuman pages 12-12).

## Structure

CHKA is a 457-residue homodimer.  
• N-terminal segment (1-79) is proline-rich and intrinsically disordered yet contains Src-SH3 interaction motifs (kall2019molecularbasisfor pages 1-2).  
• Catalytic core (80-457) adopts a bilobal ePK-like fold: N-lobe (1-216) with ATP-binding loop (residues 116-124) and C-lobe (217-457) harboring substrate pocket (malito2006elucidationofhuman pages 2-4).  
• Key catalytic motifs: Brenner motif 302-311 (Asp306 catalytic base), choline-kinase motif 326-354 (Tyr333, Tyr354 line the quaternary-amine pocket), and Mg²⁺-binding Asp330 (malito2006elucidationofhuman pages 4-5).  
• Product (phosphocholine) binding induces ~16° rotation of the N-lobe and 10 Å closure of the ATP-binding loop, generating the catalytically competent closed state (malito2006elucidationofhuman pages 5-7).  
• Crystal structures: apo (PDB 2CKQ), ADP-bound (2IGG), phosphocholine-bound (2IYE); resolution 2.1–3.1 Å (rubio‐ruiz2021recentadvancesin pages 1-5).  
• A surface-proximal allosteric pocket accommodating bis-quinolinium inhibitor TCD-717 was defined, distinct from the canonical choline groove (kall2018identificationofa pages 1-5).

## Regulation

Post-translational phosphorylation regulates activity and localization:  
• c-Src phosphorylates Tyr354 (within choline pocket) and Tyr333, enhancing catalytic rate and promoting EGFR complex formation and plasma-membrane translocation (chang2016phosphorylationofhuman pages 2-5, miyake2012functionalinteractionsbetween pages 1-3).  
• Additional sites: Ser279 phosphorylation reported to modulate activity (chang2016phosphorylationofhuman pages 21-22).  
• PKA- and PKC-dependent phosphorylation is observed in yeast and inferred for the human enzyme, with reported 1.4-fold activity increase after phosphorylation (chang2016phosphorylationofhuman pages 12-14).  
Conformational regulation: binding of phosphocholine stabilises the closed active conformation described above (malito2006elucidationofhuman pages 5-7).

## Function

• Catalyzes the first committed step in the CDP-choline (Kennedy) pathway, supporting phosphatidylcholine and phosphatidylethanolamine biosynthesis critical for membrane biogenesis (malito2006elucidationofhuman pages 1-2).  
• Ubiquitously expressed; highest levels in tissues with rapid membrane turnover and in diverse tumor types (ramirez2011chka(cholinekinase pages 1-2).  
• Over-expression drives oncogenic signaling; silencing or pharmacological blockade diminishes PI3K–mTOR–Akt, Ras–Raf–MAPK and EGFR–mTORC2 pathways (gokhale2021chokfullofpotential pages 2-4, lacal2021cholinekinasean pages 22-23).  
• Interacts directly with EGFR and c-Src; SH3-mediated binding to Src promotes tyrosine phosphorylation and breast-cancer cell proliferation (miyake2012functionalinteractionsbetween pages 1-3, kall2019molecularbasisfor pages 1-2).  
• Genetic ablation in mice is embryonic lethal, underscoring essentiality for cell proliferation (chang2016phosphorylationofhuman pages 20-21).

## Inhibitors

Symmetrical bis-pyridinium and bis-quinolinium inhibitors selectively target CHKA:  
MN58b, RSM932A/TCD-717, EB-3D, EB-3P, CK37 and ICL-CCIC-0019 bind within the choline or newly identified allosteric pocket, lower intracellular phosphocholine, induce apoptosis and restrain tumor growth in xenografts (gokhale2021chokfullofpotential pages 2-4, lacal2021cholinekinasean pages 24-26, kall2018identificationofa pages 1-5).  
The inhibitor V-11-023907 has been co-crystallised, validating active-site engagement (hudson2013kineticandmechanistic pages 3-4).

## Other Comments

CHKA is frequently amplified or over-expressed in lung, prostate, colorectal, breast, bladder, ovarian and hepatocellular carcinomas, correlating with poor prognosis and therapy resistance (chang2016phosphorylationofhuman pages 20-21, lacal2021cholinekinasean pages 22-23).  
Radiolabelled choline analogues exploit this over-expression for PET/CT imaging of solid and lymphoid malignancies (gokhale2021chokfullofpotential pages 2-4).

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