## Phylogeny

• Orthologs: Homo sapiens TAOK3, Mus musculus Taok3, Rattus norvegicus Taok3, Danio rerio taok3, Drosophila melanogaster Tao, Caenorhabditis elegans Kin-18 (yoder2023expressionanalysisof pages 10-12).  
• Kinome position: STE group → STE20 family → TAO subfamily (manning2002theproteinkinase pages 3-3).  
• Vertebrate paralogy: TAOK3 shares 82.7 – 88.6 % amino-terminal kinase-domain identity with TAOK1 and TAOK2 (fang2020thediverseroles pages 1-3).  
• Sequence similarity extends to Hippo-pathway MST1/2 catalytic cores (poirier2024theinductionof pages 1-5).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (fang2020thediverseroles pages 1-3).

## Cofactor Requirements

Catalytic phosphorylation requires Mg²⁺ as the divalent metal cofactor (yoder2023expressionanalysisof pages 6-7).

## Substrate Specificity

• Global phosphoproteomic profiling places TAOK3 in motif class 14 (“TAO family”) with a distinct Ser/Thr recognition pattern determined by positional amino-acid preferences (johnson2023anatlasof pages 12-18).  
• The same atlas confirms phosphorylation of both serine and threonine acceptors by TAOK3 (johnson2023anatlasof pages 18-20).

## Structure

• Domain architecture: N-terminal kinase domain (residues 1–319), central serine-rich segment (~350–380), two to three C-terminal coiled-coil regions; TAOK3 lacks the leucine-rich repeat present in TAOK2 (fang2020thediverseroles pages 1-3).  
• Crystal structure: PDB 6BDN shows the canonical bilobal fold with conserved VAIK, HRD and DFG catalytic motifs and an ordered activation loop; hydrophobic regulatory spine and αC-helix adopt active-like alignment (fang2020thediverseroles pages 13-15).  
• AlphaFold modelling indicates an additional PH-C1 tandem that mediates membrane association (poirier2024theinductionof pages 37-39).  
• A triple-helical C-terminal coiled-coil is conserved across TAOK kinases and may contribute to oligomerisation (byeon2024pleiotropicfunctionsof pages 3-4).

## Regulation

• Phosphorylation at Ser324 correlates with enzymatic activation (unknownauthors2021thousandandone pages 15-21).  
• ATM-dependent phosphorylation links DNA damage to p38 pathway activation (fang2020thediverseroles pages 3-5).  
• Autophosphorylation during mitosis supports spindle positioning and cell rounding (fang2020thediverseroles pages 17-19).  
• TAOK3 phosphorylates SHP-1 on Thr394, triggering SHP-1 ubiquitination and degradation to sustain T-cell-receptor signalling (poirier2024theinductionof pages 48-50).  
• Membrane binding via the PH-C1 module provides spatial control of kinase activity (poirier2024theinductionof pages 37-39).

## Function

• Expression: highest in peripheral blood leukocytes, spleen and thymus, with additional abundance in stomach, kidney and brain; within brain, enriched in oligodendrocyte precursor cells (fang2020thediverseroles pages 1-3, byeon2024pleiotropicfunctionsof pages 3-4).  
• DNA-damage checkpoint: ATM → TAOK3 → MAP2K3/6 → p38/MAPK14 governs G2/M arrest (fang2020thediverseroles pages 3-5).  
• JNK modulation: TAOK3 suppresses basal MAPK8/JNK activity and attenuates EGF-induced JNK signalling (fang2020thediverseroles pages 3-5).  
• Hippo signalling: phosphorylates MST1/2 and LATS1/2 downstream of GPCR inputs (poirier2024theinductionof pages 33-35).  
• Immune regulation: binds LCK and targets SHP-1 to maintain proximal T-cell-receptor signalling and IL-2 secretion (poirier2024theinductionof pages 1-5).  
• B-cell development: controls ADAM10 surface expression to direct marginal-zone B-cell fate (fang2020thediverseroles pages 5-8).  
• Mitosis: interacts with Rnd3 to coordinate cell rounding and spindle orientation (fang2020thediverseroles pages 17-19).  
• Invasion: regulates trafficking of TKS5α-positive endosomes, promoting invadopodia formation and tumour growth (iizuka2021serinethreoninekinasetao3mediated pages 6-8).

## Inhibitors

• Compound 43: ATP-competitive, selectively inhibits TAOK1-3 with biochemical IC₅₀ ≈ 15 nM for TAOK2 and low off-target activity (fang2020thediverseroles pages 13-15).  
• Compound 63: TAO-selective with IC₅₀ ≈ 19–39 nM against TAOK1/2; comparable potency reported for TAOK3 (fang2020thediverseroles pages 13-15).  
• SBI-581: oxindole inhibitor, IC₅₀ = 42 nM for TAO3, ~5-fold selectivity over MEKK3, orally bioavailable in mice (iizuka2021serinethreoninekinasetao3mediated pages 6-8).  
• NCGC00188382: cellular activity 25–300 nM in pancreatic cancer lines; inhibits TAOK3 along with Aurora-B and CDK7 (fang2020thediverseroles pages 13-15).  
• SW034538 and SW083688: inhibit TAOK2 with IC₅₀ = 300 nM and 1.3 µM respectively; show cross-reactivity to TAOK3 (fang2020thediverseroles pages 13-15).  
• Staurosporine: broad-spectrum kinase blocker with measurable TAOK3 activity (fang2020thediverseroles pages 13-15).

## Other Comments

• Cancer: TAOK3 enhances microtubule-drug resistance in breast cancer via NF-κB activation (fang2020thediverseroles pages 17-19); supports stemness in pancreatic cancer (fang2020thediverseroles pages 15-16); predicts recurrence in prostate cancer (fang2020thediverseroles pages 15-16); drives invadopodia-mediated invasion (iizuka2021serinethreoninekinasetao3mediated pages 6-8).  
• Neurodegeneration: phosphorylates tau and is a substrate of LRRK2 in Parkinson’s disease models, linking to tauopathies and axonal dysfunction (fang2020thediverseroles pages 11-13).  
• Immunopathology: required for house-dust-mite-induced asthma through TH2 and ILC2 responses (byeon2024pleiotropicfunctionsof pages 7-9).  
• Pain genetics: SNPs near TAOK3 correlate with postoperative morphine requirement and pain sensitivity (fang2020thediverseroles pages 11-13).  
• Neurodevelopment: de-novo missense variants p.T199A and p.R632W are associated with autism spectrum disorder and schizophrenia (hu2021clinicalandneurobiological pages 4-5).

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