## Phylogeny

Orthologous proteins are found in Homo sapiens (TAOK3), Mus musculus (Taok3), Rattus norvegicus (Taok3), Danio rerio (taok3), Drosophila melanogaster (Tao) and Caenorhabditis elegans (Kin-18) (Yoder et al., 2023). Within the human kinome, TAOK3 is placed in the STE group → STE20 family → TAO subfamily (Manning et al., 2002). The amino-terminal kinase domain shares 82.7–88.6 % identity with the paralogues TAOK1 and TAOK2 (Fang et al., 2020). Sequence similarity also extends to the catalytic cores of Hippo-pathway MST1/2 kinases (Poirier et al., 2024).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (Fang et al., 2020)

## Cofactor Requirements

Catalytic activity requires Mg²⁺ as the divalent metal cofactor (Yoder et al., 2023).

## Substrate Specificity

Global phosphoproteomic profiling assigns TAOK3 to motif class 14 (“TAO family”), revealing a distinct Ser/Thr recognition pattern determined by positional amino-acid preferences; both serine- and threonine-containing sites are phosphorylated (Johnson et al., 2023).

## Structure

The protein contains an N-terminal kinase domain (residues 1–319), a serine-rich segment (~350–380) and two to three C-terminal coiled-coil regions; unlike TAOK2, it lacks a leucine-rich repeat (Fang et al., 2020).  
• Crystal structure PDB 6BDN shows the canonical bilobal fold with conserved VAIK, HRD and DFG motifs, an ordered activation loop, and correctly aligned hydrophobic spine and αC-helix (Fang et al., 2020).  
• AlphaFold modelling predicts an additional PH-C1 tandem that mediates membrane association (Poirier et al., 2024).  
• A conserved triple-helical C-terminal coiled-coil may promote oligomerisation (Byeon & Yadav, 2024).

## Regulation

• Phosphorylation of Ser324 correlates with activation (Unknown authors, 2021).  
• ATM-dependent phosphorylation links DNA-damage sensing to downstream p38 activation (Fang et al., 2020).  
• Autophosphorylation during mitosis supports spindle positioning and cell rounding (Fang et al., 2020).  
• TAOK3 phosphorylates SHP-1 on Thr394, promoting its ubiquitination and degradation to sustain T-cell-receptor signalling (Poirier et al., 2024).  
• Membrane localisation via the PH-C1 module provides spatial control of kinase activity (Poirier et al., 2024).

## Function

Expression is highest in peripheral blood leukocytes, spleen and thymus, with additional abundance in stomach, kidney and brain; within brain, the kinase is enriched in oligodendrocyte precursor cells (Fang et al., 2020; Byeon & Yadav, 2024).  
Key signalling roles include:  
• DNA-damage checkpoint: ATM → TAOK3 → MAP2K3/6 → p38 governs G2/M arrest (Fang et al., 2020).  
• JNK modulation: suppresses basal MAPK8/JNK activity and dampens EGF-induced JNK signalling (Fang et al., 2020).  
• Hippo pathway: phosphorylates MST1/2 and LATS1/2 downstream of GPCR inputs (Poirier et al., 2024).  
• Immune regulation: binds LCK and targets SHP-1 to maintain proximal TCR signalling and IL-2 secretion (Poirier et al., 2024).  
• B-cell development: controls ADAM10 surface expression to direct marginal-zone B-cell fate (Fang et al., 2020).  
• Mitosis: interacts with Rnd3 to coordinate cell rounding and spindle orientation (Fang et al., 2020).  
• Cancer invasion: regulates trafficking of TKS5α-positive endosomes, promoting invadopodia formation and tumour growth (Iizuka et al., 2021).

## Inhibitors

• Compound 43: ATP-competitive, IC₅₀ ≈ 15 nM against TAOK2 with low off-target activity; also inhibits TAOK3 (Fang et al., 2020).  
• Compound 63: TAO-selective, IC₅₀ ≈ 19–39 nM for TAOK1/2; comparable potency for TAOK3 (Fang et al., 2020).  
• SBI-581: oxindole inhibitor, IC₅₀ = 42 nM for TAOK3, ~5-fold selectivity over MEKK3, orally bioavailable in mice (Iizuka et al., 2021).  
• NCGC00188382: cellular activity 25–300 nM in pancreatic cancer lines; inhibits TAOK3 along with Aurora-B and CDK7 (Fang et al., 2020).  
• SW034538 and SW083688: inhibit TAOK2 (IC₅₀ = 300 nM and 1.3 µM) with cross-reactivity to TAOK3 (Fang et al., 2020).  
• Staurosporine: broad-spectrum kinase inhibitor with measurable TAOK3 activity (Fang et al., 2020).

## Other Comments

TAOK3 activity contributes to microtubule-drug resistance in breast cancer via NF-κB (Fang et al., 2020), supports stemness in pancreatic cancer, predicts recurrence in prostate cancer, and drives invadopodia-mediated invasion (Iizuka et al., 2021).  
Neurologically, TAOK3 phosphorylates tau and is a substrate of LRRK2 in Parkinson’s disease models (Fang et al., 2020), is required for TH2/ILC2-driven asthma (Byeon & Yadav, 2024), correlates with pain-sensitivity SNPs (Fang et al., 2020), and harbours de-novo variants (p.T199A, p.R632W) linked to autism spectrum disorder and schizophrenia (Hu et al., 2021).

## 9. References

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