## Phylogeny

TAOK2 is one of three vertebrate paralogs (TAOK1, TAOK2, TAOK3) within the evolutionarily conserved thousand-and-one amino acid kinase (TAOK) family; invertebrates possess a single ortholog (Byeon & Yadav, 2024; Fang et al., 2020). Kinome analyses place the family in the germinal-center kinase (GCK) subgroup of the Ste20-like protein kinases and designate TAOK2 as MAP3K17 (Byeon & Yadav, 2024; Fang et al., 2020). One study classifies TAOKs instead as MAP4Ks (Yoder et al., 2023). The N-terminal kinase domain shares high amino-acid identity with TAOK1 (~90 %) and TAOK3 (~83 %) (Fang et al., 2020).

## Reaction Catalyzed

ATP + protein → ADP + phosphoprotein (Byeon & Yadav, 2024; Fang et al., 2020).

## Cofactor Requirements

ATP and Mg²⁺ are required for catalytic activity (Byeon & Yadav, 2024; Yoder et al., 2023).

## Substrate Specificity

Kinome-wide positional scanning peptide arrays classified TAOK2 as a basophilic serine/threonine kinase (Cluster 1) that favors basic residues (Arg/Lys) N-terminal to the phospho-acceptor, consistent with R-x-x-S/T or R-x-S/T motifs (Johnson et al., 2023). Detailed PSSM data were reported but not reproduced here.

## Structure

TAOK2 contains an N-terminal catalytic domain (residues 1–320) with the conserved lysine and DFG motif, followed by a large C-terminal regulatory region harboring a serine-rich stretch, 2–3 coiled-coil segments and a leucine-rich repeat (Byeon & Yadav, 2024; Fang et al., 2020). Crystal structures of the kinase domain are available (rat: PDB 1U5Q, 1U5R; human: PDB 6BDN) (Fang et al., 2020). The TAOK2α isoform possesses a hydrophobic segment predicted to form six transmembrane helices plus an amphipathic helix that anchors the protein to the endoplasmic reticulum (Byeon & Yadav, 2024). AlphaFold2 models of full-length TAOK2α/β have been generated (Byeon & Yadav, 2024).

## Regulation

• Autophosphorylation initiates kinase activity (Byeon & Yadav, 2024).  
• MST3 phosphorylates Thr468, promoting dendritic spine and synapse formation (Byeon & Yadav, 2024).  
• Ser181 is phosphorylated during mitosis (Byeon & Yadav, 2024).  
• Activity is induced by osmotic stress (sorbitol, NaCl), taxol, and genotoxic radiation (Byeon & Yadav, 2024).  
• Catalytic activity reduces direct microtubule binding; TAOK2α is cleaved by caspases during apoptosis (Byeon & Yadav, 2024).  
• Regulation by dimerization has not been described (Byeon & Yadav, 2024).

## Function

Expression: Ubiquitous, enriched in brain and testis (Byeon & Yadav, 2024; Fang et al., 2020).

Signaling pathways & substrates  
• Functions as a MAP3K upstream of p38 (via MAP2K3/6) and JNK (via MEK4) (Byeon & Yadav, 2024; Fang et al., 2020).  
• Phosphorylates LATS1/2, thereby influencing Hippo signaling and YAP/TAZ activity (Byeon & Yadav, 2024).  
• Additional substrates: Septin7 Thr426, tau, and tubulin (Byeon & Yadav, 2024; Fang et al., 2020).

Interacting partners  
RhoA (TAOK2β), EB1, and myosin Va bind the kinase (Byeon & Yadav, 2024).

Physiological roles  
• Regulates cell proliferation, cytoskeletal dynamics, mitosis, apoptosis, and immune responses (Byeon & Yadav, 2024).  
• Critical in neurodevelopment: dendritic spine maturation, PSD95 stability, neuronal migration, and ER–microtubule tethering (Byeon & Yadav, 2024).  
• Binds viral dsRNA to limit replication of several viruses (Byeon & Yadav, 2024).

## Inhibitors

ATP-competitive inhibitors 43 and 63 inhibit TAOK1/2/3 with nanomolar IC₅₀ values; compound 43 lowers tau phosphorylation in neural models (Fang et al., 2020). NCGC00188382 shows cellular activity against TAOK3 (Fang et al., 2020). Broad-spectrum inhibitors staurosporine and MST1 inhibitor 9E1 also target TAOK kinases but lack specificity (Fang et al., 2020).

## Other Comments

The TAOK2 gene (16p11.2) is frequently altered in neurodevelopmental disorders, notably autism spectrum disorder and intellectual disability; an ASD-linked A135P kinase-dead variant fails to rescue dendritic arborization defects (Byeon & Yadav, 2024). TAOK2 phosphorylates tau (implicating it in Alzheimer’s disease) and participates in cascades downstream of the Parkinson-related kinase LRRK2 (Fang et al., 2020). Context-dependent tumor-suppressive or pro-resistance roles have been reported in cancer (Fang et al., 2020). Two main splice isoforms exist: TAOK2α (1235 aa; JNK-dependent apoptosis, ER-microtubule tethering) and TAOK2β (1049 aa; RhoA-mediated actin regulation) (Byeon & Yadav, 2024).

## References

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