## Phylogeny

TAOK1 is an evolutionarily conserved kinase with orthologs in invertebrates, such as *Drosophila* (fly dTao) and *C. elegans* (kin-18), and vertebrates including fish, rodents, and humans (beeman2023neurodevelopmentaldisorder–associatedmutations pages 3-4, beeman2023neurodevelopmentaldisorder–associatedmutations pages 6-7, beeman2023neurodevelopmentaldisorder–associatedmutations pages 15-20). According to the kinome classification by Manning et al. (2002), TAOK1 is assigned to the STE kinase group and is a member of the STE20 family (beeman2023neurodevelopmentaldisorder–associatedmutations pages 1-3, beeman2023neurodevelopmentaldisorder–associatedmutations pages 20-25, chao2021identificationofa pages 1-3). The STE20 family comprises 30 serine-threonine kinases organized into 10 subfamilies (chao2021identificationofa pages 1-3). TAOK1 is further classified within the MAP4K subfamily (chao2021identificationofa pages 5-7).

## Reaction Catalyzed

The enzyme catalyzes the ATP-dependent phosphorylation of serine and threonine residues on target proteins (johnson2023anatlasof pages 12-18, beeman2023neurodevelopmentaldisorder–associatedmutations pages 1-3). The reaction is as follows: ATP + [a protein] -> ADP + [a phosphoprotein]

## Cofactor Requirements

The catalytic activity of TAOK1 is dependent on the cofactor Mg2+ (beeman2023neurodevelopmentaldisorder–associatedmutations pages 1-3, chao2021identificationofa pages 1-3).

## Substrate Specificity

Based on the atlas of substrate specificities for the human serine/threonine kinome, TAOK1 exhibits a preference for basophilic substrates, which is consistent with other STE20 kinases (johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 12-18). The consensus substrate motifs feature arginine residues near the phosphorylation site, with specific patterns resembling R-x-x-S/T or R-x-S/T (johnson2023anatlasof pages 12-18).

## Structure

TAOK1 is a 1001-amino acid protein composed of an N-terminal kinase domain (residues 1–320) and a C-terminal coiled-coil domain (residues 321–901) that folds into a triple helix bundle (beeman2023neurodevelopmentaldisorder–associatedmutations pages 3-4, beeman2023neurodevelopmentaldisorder–associatedmutations pages 20-25). The kinase domain features a canonical bilobal structure with a C-helix, a structurally intact hydrophobic spine, and an activation loop essential for catalytic activity (johnson2023anatlasof pages 4-5, chao2021identificationofa pages 1-3). Its ATP-binding pocket contains a highly conserved hinge region with key residues E79 and C81 (chao2021identificationofa pages 5-7). While no crystal structure is available, a homology model for the kinase domain was built using the TAOK2 structure (PDB ID: 2GCD) as a template, and the overall protein structure was predicted using AlphaFold 2.0 (chao2021identificationofa pages 4-5, beeman2023neurodevelopmentaldisorder–associatedmutations pages 11-12). The C-terminal triple helix is a unique lipid-binding module that directly binds plasma membrane phosphoinositides, such as PI(4,5)P2, via a positively charged convex surface (beeman2023neurodevelopmentaldisorder–associatedmutations pages 1-3, beeman2023neurodevelopmentaldisorder–associatedmutations pages 20-25, beeman2023neurodevelopmentaldisorder–associatedmutations pages 4-6).

## Regulation

TAOK1’s activity and subcellular localization are regulated by autophosphorylation (beeman2023neurodevelopmentaldisorder–associatedmutations pages 1-3). Autophosphorylation at Ser181 in the catalytic loop serves as a marker of its kinase activity (beeman2023neurodevelopmentaldisorder–associatedmutations pages 3-4, beeman2023neurodevelopmentaldisorder–associatedmutations pages 15-20). Additionally, autophosphorylation at threonine residues Thr440 and Thr443, located within the triple helix region, negatively regulates the protein’s association with the plasma membrane (beeman2023neurodevelopmentaldisorder–associatedmutations pages 1-3, beeman2023neurodevelopmentaldisorder–associatedmutations pages 25-26). This phosphorylation event functions as a switch that blocks membrane binding, promoting a cytosolic and active state of the kinase and establishing a cycle between an active, cytosolic form and an inactive, membrane-bound form (beeman2023neurodevelopmentaldisorder–associatedmutations pages 6-7, beeman2023neurodevelopmentaldisorder–associatedmutations pages 25-26).

## Function

TAOK1 is highly expressed in neurons within the neocortex, hippocampus, and cerebellum, where it localizes to the plasma membrane and dendritic spines (beeman2023neurodevelopmentaldisorder–associatedmutations pages 3-4, beeman2023neurodevelopmentaldisorder–associatedmutations pages 15-20). It functions as a plasma membrane remodeling kinase that induces membrane protrusions to regulate neuronal morphogenesis and dendritic arborization (beeman2023neurodevelopmentaldisorder–associatedmutations pages 1-3). Upstream, TAOK1 is phosphorylated by the Hippo pathway kinase MST3 (beeman2023neurodevelopmentaldisorder–associatedmutations pages 1-3). Downstream, TAOK1 activates the p38 MAPK cascade by phosphorylating MAP2K3 and MAP2K6 and also phosphorylates MARK2 to regulate cytoskeletal stability (chao2021identificationofa pages 1-3, chao2021identificationofa pages 5-7). The kinase is also involved in the G2/M DNA damage checkpoint, apoptosis, and negative regulation of IL-17-mediated signaling (chao2021identificationofa pages 1-3, chao2021identificationofa pages 11-12).

## Inhibitors

The kinase activity of TAOK1 can be inhibited by small molecules. Compound 43 is a pharmacological inhibitor that causes TAOK1 to localize to the plasma membrane, mimicking the phenotype of kinase-dead mutants (beeman2023neurodevelopmentaldisorder–associatedmutations pages 3-4). A separate structure-based virtual screen identified compounds 1, 2, and 3 as dual inhibitors of TAOK1 and MAP4K5 that competitively bind the ATP-binding pocket; compound 2 has an IC50 of approximately 1.83 µM for TAOK1 (chao2021identificationofa pages 4-5, chao2021identificationofa pages 5-7).

## Other Comments

The TAOK1 gene is highly intolerant to mutation (pLI score 0.998) (beeman2023neurodevelopmentaldisorder–associatedmutations pages 3-4). De novo variants that abrogate kinase activity are associated with neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD), intellectual disability, and developmental delay (beeman2023neurodevelopmentaldisorder–associatedmutations pages 1-3, chao2021identificationofa pages 11-12). NDD-associated missense mutations within the kinase domain (e.g., S111F, L167R, A219V, R269Q) yield a catalytically inactive protein that is constitutively trapped at the plasma membrane, causing aberrant membrane protrusions and defective dendritic development (beeman2023neurodevelopmentaldisorder–associatedmutations pages 3-4, beeman2023neurodevelopmentaldisorder–associatedmutations pages 25-26). TAOK1 dysregulation is also implicated in cancer malignancy and neurodegeneration through the modulation of tau phosphorylation (chao2021identificationofa pages 1-3, chao2021identificationofa pages 11-12).

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