Phylogeny  
TAOK1 is a member of the STE20 protein-kinase subfamily. Orthologues are present from invertebrates (Caenorhabditis elegans, Drosophila melanogaster) to vertebrates (fish, rodents, humans), indicating deep evolutionary conservation (Beeman et al., 2023; Nourbakhsh, 2021). Within the human kinome it is paralogous to TAOK2 and TAOK3; the three enzymes share a highly conserved N-terminal kinase domain but differ in C-terminal regulatory regions that confer distinct cellular roles (Beeman et al., 2023; Byeon & Yadav, 2024; Hu et al., 2021).

Reaction Catalyzed  
ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Beeman et al., 2023).

Cofactor Requirements  
Mg²⁺ is required for catalysis (Beeman et al., 2023).

Substrate Specificity  
TAOK1 activates the p38/MAPK stress pathway by phosphorylating MAP2K3 and MAP2K6 and controls cytoskeletal dynamics by phosphorylating MARK2 at Thr208, which in turn regulates tau–microtubule interactions (Beeman et al., 2023; Ning et al., 2025). A strict consensus sequence has not been defined, but targets align with the kinase’s roles in stress signalling and cytoskeletal regulation (Byeon & Yadav, 2024).

Structure  
The 1001-residue protein contains an N-terminal catalytic domain followed by extended coiled-coil segments. Structural models predict a triple-helical bundle within the coiled-coil region reminiscent of BAR-domain proteins, supporting membrane association (Beeman et al., 2023; Byeon & Yadav, 2024). Key regulatory phosphosites lie in the activation loop (Ser181) and distal C-terminal region (Thr440, Thr443) (Beeman et al., 2023).

Regulation  
• Autophosphorylation at Thr440/Thr443 blocks plasma-membrane binding, providing negative autoregulation.  
• Ser181 phosphorylation within the catalytic loop is required for full activity (Beeman et al., 2023).  
• TAOK1 acts downstream of GPCR signals that trigger the p38/MAPK cascade during DNA-damage responses and the G2/M checkpoint (Beeman et al., 2023; Hu et al., 2021).  
• MST3 and other upstream kinases modulate TAOK1 activity in neuronal development (Byeon & Yadav, 2024).

Function  
Highly expressed in the neocortex, hippocampus and cerebellum, TAOK1:  
• Activates MAP2K3/6-p38/MAPK14 signalling for DNA-damage-induced cell-cycle arrest (Beeman et al., 2023; Hu et al., 2021).  
• Phosphorylates MARK2, leading to tau release from microtubules and regulation of neurite outgrowth and dendritic arborisation (Beeman et al., 2023; Ning et al., 2025).  
• Stimulates the MAPK8/JNK pathway to promote apoptotic morphology (Beeman et al., 2023).  
These activities integrate stress responses, cytoskeletal remodelling and neuronal development (Byeon & Yadav, 2024).

Inhibitors  
Experimental small-molecule modulators have been described; for example, “Compound 43” alters TAOK1 activity in biochemical assays (Beeman et al., 2023; Byeon & Yadav, 2024).

Other Comments  
Loss-of-function or membrane-trapped TAOK1 variants cause neurodevelopmental disorders characterised by developmental delay, intellectual disability and autism spectrum phenotypes (Dulovic-Mahlow et al., 2019; Hunter et al., 2022; Beeman et al., 2023). Over-expression correlates with poor prognosis in several cancers, notably cervical carcinoma, positioning TAOK1 as a potential prognostic marker and therapeutic target (Ning et al., 2025).

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