## Phylogeny

STK16 is a member of the Numb-associated kinase (NAK) family—together with AAK1, BIKE/BMP2K and GAK—and is conserved in all examined eukaryotic lineages (Wang et al., 2019a; Wang et al., 2019b). In the priority kinome classification it is placed in the “Other” kinase group (Liu et al., 2017; Tanaka et al., 2022; Wang et al., 2019a), although other authors have assigned it to the CAMK or AGC groups (Tanaka et al., 2022; Johnson et al., 2023). STK16 shares ~25 % amino-acid identity with Aurora kinase A (Rangwala et al., 2022).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Al-Fahad et al., 2024; Wang et al., 2019a).  
The enzyme also autophosphorylates, including on Tyr198, and is therefore described as dual-specificity (Rangwala et al., 2022; Wang et al., 2019b).

## Cofactor Requirements

Mg²⁺ or Mn²⁺ ions are required for catalytic activity (Al-Fahad et al., 2024; Eswaran et al., 2008; Wang et al., 2019a; Tanaka et al., 2022).

## Substrate Specificity

Positional-scanning peptide library screens defined a preferred consensus motif  
X-X-P/V/I-Φ-H/Y-T*-N/G-X-X-X (Φ = aliphatic; T* = phospho-acceptor) (Eswaran et al., 2008; Wang et al., 2019a). STK16 primarily phosphorylates threonine but can also target serine, and its global specificity profile was confirmed by PSPA analysis (Johnson et al., 2023).

## Structure

The 305-residue protein contains an N-terminal region, the protein kinase catalytic domain and a short C-terminus (Wang et al., 2019a). The crystal structure (PDB 2BUJ) reveals an atypical activation segment with a β-sheet and a large α-helical insertion (activation-segment C-terminal helix, ASCH) that stabilises a constitutively active conformation without activation-loop phosphorylation (Eswaran et al., 2008; Wang et al., 2019a). Arg147 in the HRD motif helps anchor this arrangement (Wang et al., 2019a). A flexible loop (residues 98–106) is important for ligand binding (Al-Fahad et al., 2024). Some reports describe a canonical activation loop typical of protein kinases (Al-Fahad et al., 2024; Liu et al., 2017).

## Regulation

• N-terminal myristoylation at Gly2 is required for subsequent palmitoylation that anchors the kinase to Golgi membranes; reported palmitoyl-cysteines include Cys6/Cys8 or Cys13-15 (Eswaran et al., 2008; Wang et al., 2019a; Rangwala et al., 2022).  
• Autophosphorylation at Thr185, Ser197 and, critically, Tyr198 maintains constitutive activity and governs Golgi and plasma-membrane localisation as well as cell-cycle progression (Wang et al., 2019a; Wang et al., 2019b).  
• Protein abundance is controlled by KCTD17-mediated ubiquitin-proteasome degradation (Tanaka et al., 2022).

## Function

STK16 is ubiquitously expressed with highest levels in liver, kidney, testis, thymus, spleen and heart (Eswaran et al., 2008; Wang et al., 2019a; Guinea et al., 2006). It resides mainly at the Golgi apparatus but translocates to the nucleus when the Golgi is disrupted (Eswaran et al., 2008; Guinea et al., 2006). Reported interactors include DRG1, ENO1, MAL2, actin, GlcNAcK and WDR1 (Al-Fahad et al., 2024; Eswaran et al., 2008; Wang et al., 2019a). Verified substrates are DRG1 (Thr100) and 4EBP1 (Eswaran et al., 2008; Wang et al., 2019b). Functionally, STK16 contributes to TGF-β signalling, Golgi assembly, TGN secretion/sorting, regulation of actin dynamics and progression through G2/M, prometaphase and cytokinesis (Al-Fahad et al., 2024; Liu et al., 2017; Wang et al., 2019a). Direct binding to actin regulates polymerisation in a kinase-activity- and concentration-dependent manner (Liu et al., 2017).

## Inhibitors

• Neratinib: predicted binding free energy −36.6 kcal mol⁻¹ (Al-Fahad et al., 2024).  
• Natural products NPC132329 and NPC160898 show in-silico inhibitory potential (Al-Fahad et al., 2024).  
• STK16-IN-1 is an experimental, selective inhibitor that suppresses kinase activity and cancer-cell proliferation (Liu et al., 2017; Wang et al., 2019a; Wang et al., 2019b).

## Other Comments

Elevated STK16 activity has been linked to cancer progression, and its inhibition is proposed to enhance the effectiveness of anti-mitotic chemotherapies (Al-Fahad et al., 2024; Unknown authors, 2016; Wang et al., 2019a).

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