## Phylogeny

SCYL2 belongs to the evolutionarily conserved SCY1-like (SCYL) protein family, which in mammals comprises SCYL1, SCYL2 and SCYL3. Phylogenetic analysis of the human kinome places SCYL2 in the “Other” kinase group and classifies it as a pseudokinase (Manning et al., 2002; Boudeau et al., 2006; Jacobsen & Murphy, 2017).

## Reaction Catalyzed

No experimentally verified ATP-dependent phosphoryl-transfer reaction has been demonstrated for SCYL2, and most reports therefore regard it as catalytically inactive. A single study described poly-L-lysine–stimulated autophosphorylation and in vitro phosphorylation of the β2-adaptin subunit of AP2 (Conner & Schmid, 2005), but this activity has not been independently confirmed.

## Cofactor Requirements

No cofactor requirements have been identified.

## Substrate Specificity

A consensus phosphorylation motif has not been defined. Comprehensive kinase-substrate profiling failed to detect substrate preferences (Johnson et al., 2023). Re-examination of several candidate proteins (auxilin, histone H1, MBP, clathrin, AP1/2 subunits) found no phosphorylation, although β2-adaptin was reported as a potential target in one study (Conner & Schmid, 2005).

## Structure

SCYL2 is a multidomain protein comprising:  
• N-terminal pseudokinase domain (residues 32–327) that retains ATP-binding capacity but carries inactivating substitutions in the VAIK, HRD and DFG motifs (e.g., D135→N) (Boudeau et al., 2006).  
• Central coiled-coil region.  
• C-terminal HEAT-repeat array followed by a poorly structured tail (Unknown authors, 2006).  
An AlphaFold structural model is available (UniProt Q6P3W7).

## Regulation

Specific post-translational modifications have not been mapped. The only reported stimulus is poly-L-lysine, which enhanced the weak in vitro kinase activity described for CVAK104/SCYL2 (Conner & Schmid, 2005).

## Function

SCYL2 is ubiquitously expressed and acts as a scaffold/regulator in clathrin-mediated endocytosis and vesicular trafficking. It localises to the Golgi, trans-Golgi network and endosomes, where it binds clathrin heavy chain and AP1/AP2 adaptor complexes (Boudeau et al., 2006; Gingras et al., 2015). In the nervous system, SCYL2 is required for neuronal viability: knockout mice show degeneration of hippocampal CA3 neurons and early lethality, whereas neuronal SCYL2 restrains excitotoxicity by regulating synaptic NR1 and KA1 glutamate receptor levels (Gingras et al., 2015; Kuliyev et al., 2018).

## Other Comments

Missense mutations in the SCYL2 pseudokinase domain cause neurodevelopmental disorders, presumably by disrupting protein interactions and intracellular trafficking (Unknown authors, 2014; Boudeau et al., 2006). Complete loss of SCYL2 in mice results in severe neurological defects and impaired suckling (Kuliyev et al., 2018).

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