1. Phylogeny  
   SCYL1, also known as N-terminal kinase‐like protein (NTKL) and by alternate names such as CVAK90, GKLP, TAPK, TEIF, and TRAP, belongs to the Scy1‐like family of kinase‐related proteins that are conserved across eukaryotes. Orthologs of SCYL1 have been identified in multiple mammalian species as well as in organisms as divergent as yeast, underscoring its ancient evolutionary origin and placement within a regulatory arm of the kinome (Burman2009characterizationofmolecules pages 80-84, Burman2009characterizationofmoleculesa pages 80-84). Although the domain architecture of SCYL1 is reminiscent of conventional serine/threonine kinases, it lacks essential catalytic residues—such as the key aspartic acid in the catalytic loop—that are indispensable for phosphotransferase activity; this deficit categorizes SCYL1 as a pseudokinase (Burman2009characterizationofmoleculesa pages 84-88, Niranjan2014functionalcharacterizationof pages 27-30). Moreover, SCYL1 is evolutionarily related to other members of the Scyl family, including SCYL2 and SCYL3—with the more distantly related CVAK104 (Scyl1-like 2) serving as a point of reference for the divergence of catalytic properties in this group—and thus occupies a distinct branch in the serine/threonine kinase superfamily as defined in classical kinome analyses (Jung2017scyl2genesare pages 11-15, Burman2009characterizationofmoleculesd pages 80-84).
2. Reaction Catalyzed  
   Conventional protein kinases catalyze the transfer of a phosphate group from ATP to specific serine or threonine residues on substrate proteins, as represented by the reaction: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(phospho-L-serine/threonine) + H⁺. In contrast, SCYL1 has been classified as a pseudokinase because extensive in vitro assays have failed to detect any phosphorylation of common substrates such as myelin basic protein, histones, or casein, and no auto-phosphorylation has been observed under conditions that typically support kinase activity (Burman2009characterizationofmolecules pages 80-84, Falcenberg2013sutentsensitivekinasesas pages 94-100).
3. Cofactor Requirements  
   Active serine/threonine kinases generally require divalent metal ions, most notably Mg²⁺, as cofactors to coordinate ATP binding and facilitate phosphoryl transfer. In biochemical assays performed with SCYL1, reactions were conducted in the presence of Mg²⁺; however, SCYL1 did not exhibit any measurable catalytic activity even when this cofactor was available. Thus, while Mg²⁺ is a standard requirement for catalytic kinases, no specific cofactor dependency has been established for SCYL1 in relation to any detectable catalytic function (Falcenberg2013sutentsensitivekinasesasa pages 94-100, Burman2009characterizationofmoleculesd pages 80-84).
4. Substrate Specificity  
   A number of serine/threonine kinases show defined substrate preferences, often recognizing phosphorylation motifs such as RxRxx[pS/pT]. Nevertheless, SCYL1—being a pseudokinase—has not been shown to phosphorylate any substrates. High-throughput peptide library screenings using fluorescein-labeled peptides and ADP detection assays with protein substrates (including histone mixtures, myelin basic protein, and casein) failed to identify any consensus motif or phosphorylation event attributable to SCYL1, and hence no substrate specificity has been established for this protein (Falcenberg2013sutentsensitivekinasesasa pages 94-100, Burman2009characterizationofmoleculesa pages 80-84).
5. Structure  
   SCYL1 displays a modular architecture that is characteristic of many pseudokinases. Its N-terminal region is composed of a kinase-like domain that adopts the typical bilobal fold found in serine/threonine kinases; however, the absence of key catalytic residues in this domain renders it inactive with respect to phosphoryl transfer. The longest isoform encompasses 806 amino acids and has an approximate molecular weight of 89 kDa (Burman2009characterizationofmoleculesb pages 80-84). Beyond the kinase-like domain, SCYL1 contains a C-terminal region that harbors several HEAT repeats and a coiled-coil domain. The HEAT repeats are predicted to form elongated, flexible solenoid structures that facilitate protein–protein interactions and oligomerization; experimental evidence has demonstrated that SCYL1 can form oligomeric complexes, with assemblies ranging from trimers to pentamers (Hamlin2015interactionofproteinsb pages 55-59, Summerfeldt…2015scyl1scaffoldsclass pages 38-44). A particularly notable structural feature is the presence of a C-terminal dibasic motif with the amino acid sequence RKLD-COO⁻, which resembles the canonical KKXX endoplasmic reticulum (ER) retrieval signals. This motif is critical for the binding of SCYL1 to the coatomer (COPI) complex, a function essential for its role in retrograde trafficking between the Golgi apparatus and the ER (Burman2009characterizationofmoleculesd pages 84-88, Burman2009characterizationofmoleculesc pages 88-92). Overall, while the canonical kinase fold is retained in the N-terminal region, the lack of catalytic residues and the presence of extensive protein–protein interaction domains underscore SCYL1’s role as a regulatory scaffold rather than an active enzyme (Hamlin2015interactionofproteinsc pages 38-44, Summerfeldt…2015scyl1scaffoldsclassa pages 38-44).
6. Regulation  
   SCYL1 functions predominantly as a non‐catalytic regulatory protein, and its activity is controlled through mechanisms that govern its subcellular localization and interaction with components of the vesicular trafficking machinery. Regulation of SCYL1 is mediated primarily by its association with the COPI coat proteins; specifically, the C-terminal RKLD motif facilitates direct binding to key subunits of the coatomer complex, thereby localizing SCYL1 to the ER–Golgi intermediate compartment and the cis-Golgi, where COPI‐mediated budding and retrograde trafficking occur (Burman2009characterizationofmoleculesd pages 80-84, Burman2009characterizationofmoleculesc pages 80-84). Experimental knockdown studies using RNA interference have shown that reduction in SCYL1 levels leads to a specific defect in the COPI‐dependent retrograde transport of cargo such as the KDEL receptor, indicating that its expression is critical for maintaining normal trafficking dynamics (Burman2009characterizationofmoleculesa pages 80-84, Burman2009characterizationofmoleculesd pages 80-84). Additionally, the capacity of SCYL1 to oligomerize via its HEAT repeats appears to enhance its binding affinity for COPI components, suggesting that oligomerization constitutes a further regulatory mechanism over its scaffolding function (Hamlin2015interactionofproteinsb pages 55-59, Summerfeldt…2015scyl1scaffoldsclass pages 55-59). No definitive post‐translational modifications—such as phosphorylation or ubiquitination—that modulate SCYL1’s activity have been reported in the available literature (Burman2009characterizationofmolecules pages 80-84, Falcenberg2013sutentsensitivekinasesasa pages 94-100).
7. Function  
   SCYL1 plays a pivotal role in the regulation of COPI-mediated retrograde protein trafficking between the Golgi apparatus and the endoplasmic reticulum. By binding to coatomer subunits such as βCOP and αCOP via its C-terminal RKLD motif, SCYL1 facilitates the retrieval of key proteins including the KDEL receptor from the Golgi to the ER, thereby contributing to the maintenance of Golgi apparatus morphology and homeostasis (Burman2009characterizationofmoleculesa pages 80-84, Burman2009characterizationofmoleculesd pages 80-84). Functional disruptions of SCYL1—demonstrated by RNA interference experiments—lead to specific defects in retrograde transport while leaving anterograde trafficking relatively unaffected, highlighting its specialized role in vesicle coat function (Burman2009characterizationofmoleculesa pages 80-84, Burman2009characterizationofmoleculesc pages 80-84). In vivo, mutations in SCYL1 are associated with severe neurodegenerative phenotypes as observed in the muscle deficient (mdf) mouse model, which exhibits progressive motor neuron degeneration and cerebellar atrophy; this establishes a physiological link between SCYL1 function and neuronal health (Burman2009characterizationofmoleculesd pages 136-139, Burman2009characterizationofmoleculesa pages 80-84). In addition, splice variants such as NTKL have been reported to localize to centrosomes during mitosis, implicating SCYL1 in additional aspects of cell division and organelle dynamics (Burman2009characterizationofmoleculesa pages 84-88, Hamlin2015interactionofproteinsa pages 38-44).
8. Other Comments  
   Currently, no highly specific enzymatic inhibitors for SCYL1 have been described. Notably, treatment with the multi-kinase inhibitor sunitinib has been shown to reduce SCYL1 mRNA levels in certain cellular models, although direct inhibition of SCYL1’s (non-existent) kinase activity has not been demonstrated; this observation is of potential therapeutic relevance in contexts such as anti-diabetic therapy, wherein SCYL1 expression has been implicated (Falcenberg2013sutentsensitivekinasesasa pages 89-94, Falcenberg2013sutentsensitivekinasesasa pages 94-100). Disease associations for SCYL1 are significant; mutations in the SCYL1 gene result in the muscle deficient (mdf) phenotype in mice, characterized by progressive neurodegeneration affecting motor neurons and cerebellar structures (Burman2009characterizationofmoleculesd pages 136-139, Burman2009characterizationofmoleculesa pages 80-84). Furthermore, alterations in the function of SCYL1’s interacting partner, Scyl1BP1, have been linked to Gerodermia Osteoplastica, a disorder manifesting as premature skin and bone aging (Burman2009characterizationofmoleculesa pages 80-84, Burman2009characterizationofmoleculesd pages 136-139).
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