## Phylogeny

The protein is encoded in Homo sapiens and has an ortholog in Mus musculus, indicating conservation across mammals (Jacobsen & Murphy, 2017; Thiriet, 2013). It belongs to the AGC group, ribosomal S6 kinase (RSK) family that arose by gene-fusion events generating tandem kinase domains (Manning et al., 2002). Because its N-terminal kinase-like region is catalytically impaired and preceded by a phox homology (PX) lipid-binding module, it is further classified among vesicle-associated pseudokinases (Jacobsen & Murphy, 2017).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] (Thiriet, 2013).  
Note: Structural analyses indicate that the N-terminal domain is catalytically inactive and functions mainly as a scaffold (Jacobsen & Murphy, 2017).

## Cofactor Requirements

No divalent-metal or other cofactor requirement has been reported (Jacobsen & Murphy, 2017).

## Substrate Specificity

Confirmed substrates are ribosomal protein S6 and translation initiation factor eIF4B; a consensus phosphorylation motif has not been defined (Thiriet, 2013).

## Structure

The protein comprises an N-terminal PX domain that binds phosphatidylinositol-3-phosphate (PI3P) via three conserved lipid-contact sites (Kervin & Overduin, 2021), followed by two sequential kinase-like domains:  
• C-terminal CaMK-related domain that activates the upstream AGC-related domain (Thiriet, 2013).  
• N-terminal AGC-related domain with degenerate catalytic motifs, explaining loss of enzymatic activity (Jacobsen & Murphy, 2017).  
No crystallographic structure is available; current models are homology-based (Kervin & Overduin, 2021).

## Regulation

• ERK1/2 phosphorylate six sites in the C-terminal domain, after which autophosphorylation creates a PDK1 docking site that promotes activation of the N-terminal domain (Thiriet, 2013).  
• Protein phosphatase PP2Cδ removes these activating phosphates (Thiriet, 2013).  
• PX-dependent binding to PI3P recruits the protein to early endosomes; release from the membrane terminates signalling (Jacobsen & Murphy, 2017).

## Function

Highly expressed in brain, lung, kidney, liver, pancreas, skeletal muscle, spleen and thymus (Thiriet, 2013). It is cytosolic at rest and relocates to PI3P-rich early endosomes via its PX domain (Jacobsen & Murphy, 2017). Binding partners include sphingosine kinase-1, PI3P and the antioxidant enzyme PRDX3, the latter being recruited to endosomes (Thiriet, 2013). Upstream regulators are ERK1/2 and PDK1, whereas downstream targets comprise ribosomal protein S6, eIF4B, and pro-apoptotic proteins BAD and DAPK (Thiriet, 2013). Collectively, the kinase integrates Ras–ERK signalling with sphingosine-1-phosphate pathways and early endosomal trafficking (Jacobsen & Murphy, 2017; Thiriet, 2013).

## Other Comments

The gene is co-amplified with 4EBP1 on chromosome 11q13 in breast cancer; high expression correlates with poor prognosis and elevated Akt/mTOR activity (Karlsson et al., 2015). Knock-down in ZR751 breast-cancer cells increases S6K1 and the mTORC1 component Raptor, suggesting compensatory feedback within the mTOR pathway (Karlsson et al., 2015).

## 9. References

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