Phylogeny  
Phosphatidylinositol 4-phosphate 5-kinase-like protein 1 (PIP5KL1) originated from a type I PIP5K gene duplication. It is conserved throughout vertebrates with validated orthologues in mouse, rat and other mammals (Xia, 2011). Yeast MSS4 and Drosophila sktl lie in the broader phosphoinositide-kinase lineage but are not direct orthologues. Within the kinome, PIP5KL1 groups with the PI-lipid kinase/type I PIP5K family yet occupies a distinct pseudokinase branch separate from the catalytically active PIP5K1A/B/C enzymes (van den Bout & Divecha, 2009; Xia, 2011).

Reaction Catalyzed  
No intrinsic phosphotransferase activity has been detected. Recombinant or immunoprecipitated PIP5KL1 fails to phosphorylate PI4P or PI5P; residual activity in cell lysates derives from co-precipitated PIP5Kα/β (van den Bout & Divecha, 2009; Yang, Park, & Fairn, 2018; Yang et al., 2019).

Cofactor Requirements  
None established; the absence of catalytic activity renders canonical Mg²⁺/ATP dependence irrelevant (Yang, Park, & Fairn, 2018).

Substrate Specificity  
Not applicable—substrate preferences have not been defined because the protein is catalytically inactive (van den Bout & Divecha, 2009).

Structure  
PIP5KL1 is a monomeric ~44 kDa protein that lacks key elements of the type I PIP5K catalytic core, including residues required for ATP binding and the full 25-residue activation loop (van den Bout & Divecha, 2009). No experimental structure is available; AlphaFold modelling predicts a truncated PI-kinase fold with discontinuities in the catalytic loop, consistent with pseudokinase status (Yang, Park, & Fairn, 2018). The Lys-Asp-Asp catalytic triad and hydrophobic spines present in active PIP5Ks are missing (Xia, 2011). N- and C-terminal extensions mediate heterodimerization with PIP5Kα/β and act as localization scaffolds (Yang, Park, & Fairn, 2018).

Regulation  
• Protein–protein interaction: forms stable heterodimers with PIP5Kα and PIP5Kβ (Yang et al., 2019).  
• Spatial control: relocalizes bound PIP5Ks from the plasma membrane to intracellular membranes, thereby reorganizing PI(4,5)P₂ and subsequent PI(3,4,5)P₃ pools (Yang, Park, & Fairn, 2018).  
• No documented post-translational modifications or allosteric regulators.

Function  
Highest mRNA expression occurs in brain and testis; protein has been observed in gastric epithelial cells (Yang et al., 2019). Acting as a scaffold, PIP5KL1 targets active type I PIP5Ks to specific compartments for localized PI(4,5)P₂ synthesis, which secondarily drives PI(3,4,5)P₃ accumulation and the redistribution of polycationic small G-proteins such as K-Ras and Rac1 (van den Bout & Divecha, 2009; Yang, Park, & Fairn, 2018).

Inhibitors  
No inhibitors have been reported.

Other Comments  
Loss of PIP5KL1 expression is observed in ~65 % of gastric cancer samples; re-expression suppresses proliferation and migration of gastric cancer cell lines (Yang et al., 2019). PIP5KL1 is therefore classified as a lipid-kinase pseudokinase whose biological impact derives from spatial regulation of bona fide PIP5Ks rather than intrinsic catalysis (van den Bout & Divecha, 2009).

1. References  
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