## Phylogeny

• Orthologs are documented in Homo sapiens, Rattus norvegicus, Mus musculus and Drosophila melanogaster, whereas homologues are absent from Caenorhabditis elegans and Saccharomyces cerevisiae (takeuchi2010characterizationofpxk pages 3-4).  
• PXK groups within the PX-serine/threonine kinase subfamily of the protein-kinase-like (PKL) superfamily and is classified as a pseudokinase owing to degeneration of the β3 VAIK Lys and catalytic HRD Asp motifs (teasdale2012insightsintothe pages 4-5).  
• Comparative analyses align PXK with other PX-domain kinases such as SGK3 and RPK118 that combine lipid-sensing PX modules with catalytically inactive kinase folds (teasdale2012insightsintothe pages 4-5).  
• Large-scale surveys of the human kinome list PXK among ~50 pseudokinases lacking both the β3 Lys and HXD catalytic Asp residues (unknownauthors2014biochemicalanalysisof pages 29-33).

## Reaction Catalyzed

ATP + protein-L-OH ⇌ ADP + protein-L-O-PO₃²⁻; however, PXK lacks measurable kinase activity in vitro or in cells (takeuchi2010characterizationofpxk pages 4-7).

## Cofactor Requirements

No divalent-metal or other cofactor requirement has been reported because catalytic activity is undetectable (takeuchi2010characterizationofpxk pages 4-7).

## Substrate Specificity

Not determined; the absence of catalytic activity precludes definition of a phosphorylation consensus motif (takeuchi2010characterizationofpxk pages 4-7).

## Structure

• Domain architecture: N-terminal PX domain → central protein-kinase-like domain → proline-rich segment containing a PXXP motif → C-terminal WH2 actin-binding domain (takeuchi2010characterizationofpxk pages 10-11).  
• PX domain: binds PtdIns(3)P through basic residues R54/R55; the R54Q/R55Q double mutant abolishes endosomal targeting (takeuchi2010characterizationofpxk pages 3-4).  
• Kinase-like domain: the canonical VAIK Lys is replaced and the HRD Asp is mutated; no autophosphorylation is detected after PKA or PKC treatment, confirming pseudokinase status (takeuchi2010characterizationofpxk pages 4-7).  
• WH2 domain: conserved basic residues mediate G-actin binding; their mutation eliminates actin interaction (takeuchi2010characterizationofpxk pages 4-7).  
• Fold assignment: sequence homology places the kinase-like region within the PKL superfamily defined by structural surveys of typical and atypical kinases (scheeff2005structuralevolutionof pages 12-13).  
• Structural data: no crystal or NMR structure is available; current knowledge derives from sequence analysis and domain prediction (scheeff2005structuralevolutionof pages 5-7).  
• Oligomeric state: no evidence for homo-oligomerization (takeuchi2010characterizationofpxk pages 10-11).

## Regulation

• Membrane recruitment is PI3K-dependent; PI3K inhibition with wortmannin abolishes PXK endosomal localisation (takeuchi2010characterizationofpxk pages 10-11).  
• Post-translational modifications: none reported; phosphorylation assays do not activate the kinase-like domain (takeuchi2010characterizationofpxk pages 4-7).

## Function

• Tissue distribution: highly expressed in brain, heart, skeletal muscle, placenta and peripheral blood lymphocytes with lower ubiquitous expression elsewhere (takeuchi2010characterizationofpxk pages 3-4).  
• Subcellular localisation: predominates on early endosomes (≈62 % overlap with EEA1), with lesser presence on transferrin receptor-positive compartments (≈38 %) and lysosomes (≈12 %) (takeuchi2010characterizationofpxk pages 4-7).  
• Endocytic trafficking: promotes ligand-induced EGFR ubiquitination, accelerates EGFR internalisation and drives endolysosomal degradation without direct EGFR binding (takeuchi2010characterizationofpxk pages 11-12).  
• Cytoskeletal interface: binds G-actin via the WH2 domain; actin binding is dispensable for EGFR trafficking but implicates PXK in broader cytoskeletal reorganisation (takeuchi2010characterizationofpxk pages 10-11).  
• Ion-transport modulation: directly interacts with Na,K-ATPase β1 and β3 subunits, consistent with the alias “Modulator of Na,K-ATPase” (teasdale2012insightsintothe pages 34-35).  
• Upstream regulator: PtdIns(3)P production by class III PI3K controls PXK membrane targeting (takeuchi2010characterizationofpxk pages 10-11).

## Inhibitors

No PXK-selective inhibitors have been reported in the literature surveyed.

## Other Comments

• Genomic locus: PXK resides on chromosome 3p14.3 (takeuchi2010characterizationofpxk pages 3-4).  
• Disease association: the SNP rs6445972 in PXK shows strong linkage to systemic lupus erythematosus (takeuchi2010characterizationofpxk pages 11-12).

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