1. Phylogeny  
   PXK, also referred to as Slob, is classified among protein kinase‐like nonenzymatic homologues (PKLNKs) and is characterized by the presence of an N‐terminal Phox homology (PX) domain and a C‐terminal kinase‐like domain that lacks key catalytic residues. Its domain organization is evolutionarily conserved across higher eukaryotes including humans, mice, rats, and Drosophila, indicating that its ancestral origin can be traced to early eukaryotic signaling modules (vaughn2015pxkandlupus pages 31-36, anamika2009classificationofnonenzymatic pages 15-16). Although typical protein kinases catalyze the transfer of a phosphate group, PXK lacks the conserved catalytic amino acids found in active kinases and thus is regarded as a pseudokinase. The PX domain found in PXK is a conserved module found in many sorting nexin family proteins and is implicated in phosphoinositide binding and membrane trafficking, situations in which these domains have been maintained throughout evolution (vaughn2015pxkandlupus pages 165-170, anamika2009classificationofnonenzymatic pages 7-9). Its sequence conservation and orthologous relationships with kinases in model organisms have led to its assignment within a subgroup of the kinome that remained structurally similar to canonical kinases while losing catalytic function, consistent with the evolutionary models described for kinase-like proteins (anamika2009classificationofnonenzymatic pages 2-3).
2. Reaction Catalyzed  
   The reaction normally catalyzed by a serine/threonine kinase—in the presence of an appropriate substrate—is the transfer of a phosphate group from ATP to the hydroxyl group of a serine or threonine residue, producing ADP and a phosphorylated substrate along with a proton. For PXK, however, due to the absence of essential catalytic residues, no intrinsic kinase activity has been detected; consequently, PXK is not known to catalyze a phosphoryl transfer reaction under physiological conditions, and thus no reaction in which ATP is consumed and ADP is generated has been assigned to this protein (vaughn2015pxkandlupus pages 31-36, anamika2009classificationofnonenzymatic pages 2-3).
3. Cofactor Requirements  
   In serine/threonine kinases that are enzymatically active, the catalytic reaction typically requires Mg²⁺ as a cofactor to coordinate the binding of ATP and facilitate phosphoryl transfer. Although PXK is classified in a kinase‐like family, its lack of catalytic activity means that its function does not depend on Mg²⁺ as a cofactor for a phosphotransfer reaction. Nonetheless, if PXK were to operate as a classical kinase, Mg²⁺ would be required (vaughn2015pxkandlupus pages 31-36).
4. Substrate Specificity  
   Active serine/threonine kinases generally exhibit substrate specificity defined by consensus motifs, such as an RxRxxp[ST] motif, which guide the selection of target proteins for phosphorylation. For PXK, no consensus substrate motif has been established, and no specific substrate phosphorylation event has been reliably assigned. Despite its structural similarity to other kinases, PXK functions primarily as a noncatalytic regulatory protein, and its substrate specificity in terms of phosphotransfer cannot be defined on the basis of available data (vaughn2015pxkandlupus pages 31-36, anamika2009classificationofnonenzymatic pages 7-9).
5. Structure  
   PXK’s architecture is defined by a bipartite domain organization. At its N-terminus, it contains a Phox homology (PX) domain that is structurally responsible for binding phosphoinositides and for targeting the protein to specific membrane compartments. This PX domain is evolutionarily conserved among proteins that regulate membrane trafficking and receptor endocytosis (vaughn2015pxkandlupus pages 165-170, anamika2009classificationofnonenzymatic pages 15-16). The C-terminal region of PXK displays sequence similarity to serine/threonine kinases; however, it lacks several key residues that are required for catalytic phosphotransfer, consistent with its classification as a pseudokinase (vaughn2015pxkandlupus pages 31-36, anamika2009classificationofnonenzymatic pages 2-3).  
   Structural predictions, including those generated by AlphaFold, support the presence of a canonical bilobal kinase fold in the C-terminal domain with an N-lobe rich in β-sheets and a larger C-lobe dominated by α-helices, similar to active kinases, but with an altered active site that precludes effective ATP binding and phosphotransfer. Key structural features such as the activation loop, the hydrophobic spine, and the C-helix are discernible; however, the classical DFG and HRD motifs are not conserved in a functionally active manner. In this domain, the loss of the catalytic aspartate is particularly notable, underscoring the protein’s probable role in regulatory scaffolding rather than enzymatic activity (vaughn2015pxkandlupus pages 31-36, anamika2009classificationofnonenzymatic pages 7-9, zacharchenko2023pk1fromdrosophila pages 1-2).
6. Regulation  
   Regulatory control of PXK is achieved primarily through mechanisms that govern its subcellular localization and protein–protein interactions rather than by modulating catalytic activity. Several studies indicate that multiple splice isoforms of PXK are produced, which differ in their expression patterns and subcellular localization within cells (vaughn2015pxkandlupus pages 165-170). The PX domain mediates membrane association by binding to specific phosphoinositides, and its membrane-targeting function is likely further regulated by its conformational state. In immune cells, PXK has been implicated in the modulation of receptor internalization processes, with genetic variants altering its function, although these variants do not appear to affect overall protein expression levels (vaughn2015pxkandlupus pages 108-113, vaughn2015pxkandlupus pages 83-90). Despite its classification within a kinase-like family, no post-translational modifications—such as autophosphorylation—that lead to modulated catalytic activity have been conclusively identified for PXK. Instead, its regulation appears to depend on alternative splicing and possibly on interactions with other protein partners that are critical for its role in receptor trafficking and membrane dynamics (vaughn2015pxkandlupus pages 31-36).
7. Function  
   PXK has been functionally linked through genetic and biochemical studies to the modulation of membrane receptor dynamics. According to the information provided, PXK binds to and modulates brain Na,K-ATPase subunits ATP1B1 and ATP1B3. This interaction is proposed to play a role in the regulation of electrical excitability and synaptic transmission in neuronal tissues (Information section). In addition, studies have documented the involvement of PXK in endocytic trafficking pathways. In immune cells, particularly B cells, PXK has been shown to colocalize with cell surface receptors and to influence receptor internalization kinetics, which implicates it in the control of receptor-mediated signaling processes that are relevant to pathways in autoimmune conditions such as systemic lupus erythematosus (vaughn2015lupusriskvariants pages 1-2, vaughn2015pxkandlupus pages 90-95).  
   PXK is widely expressed, with notable levels in brain tissue as well as in peripheral blood cells, suggesting that it may have distinct roles in neuronal function and immune regulation. Despite being annotated as a serine/threonine kinase-like protein, its lack of demonstrable catalytic activity indicates that its primary biological function is regulatory, likely by scaffolding or serving as a mediator in protein–protein interaction networks that control receptor trafficking events (vaughn2015pxkandlupus pages 31-36, vaughn2015lupusriskvariants pages 12-12).
8. Other Comments  
   PXK is also known under the synonym “Slob” and has been referred to in several studies that examine its nonenzymatic regulatory roles. Genome-wide association studies have identified the PXK locus as a risk factor for systemic lupus erythematosus and other autoimmune diseases; these studies report that risk variants correlate with alterations in receptor internalization dynamics in B cells (vaughn2015lupusriskvariants pages 1-2, vaughn2015pxkandlupus pages 108-113). Such genetic associations underscore its potential involvement in the modulation of immune signaling, although the primary reported function in the provided information relates to Na,K-ATPase modulation in the brain. There are no reported selective inhibitors developed against PXK and no determined catalytic activity suggesting that conventional small-molecule inhibition targeting kinase active sites is not applicable to this protein. Disease associations have been highlighted in the context of autoimmunity as well as in the regulation of neuronal excitability, with the extent of its contribution being under active investigation. Furthermore, data from domain classification studies indicate that PX domain-containing PKLNKs are evolutionarily repurposed from active kinases to serve primarily scaffolding and regulatory roles (anamika2009classificationofnonenzymatic pages 15-16).
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