1. Phylogeny  
   PASK, also known as KIAA0135, is a highly conserved serine/threonine-protein kinase found from unicellular yeast to mammalian species. In yeast, two paralogous proteins (Psk1 and Psk2) exist as a result of gene duplication events, whereas mammals express a single ortholog that retains the essential catalytic and regulatory features. PASK is classified within the CaMK‐like family of serine/threonine kinases and is characterized by the presence of one or more N‐terminal PAS (Per–Arnt–Sim) domains that serve as sensory modules. These PAS domains are evolutionarily ancient and are shared by a wide array of kinases that modulate responses to environmental and metabolic cues. This conservation of domain architecture across species supports its assignment to a core set of nutrient‐sensing regulatory proteins (teuwen2024navigatingthemaze pages 2-4, xu2024“druggability”ofthe pages 1-4).
2. Reaction Catalyzed  
   PASK catalyzes the phosphorylation of serine/threonine residues on substrate proteins by transferring a phosphate group from ATP. The overall reaction can be written as:  
   ATP + [protein]–(L‑serine or L‑threonine) → ADP + [protein]–(L‑serine/threonine)‑phosphate + H⁺  
   This classical phosphotransfer reaction underlies the kinase’s role in modifying the activity, stability, and interaction properties of its substrates (xu2024“druggability”ofthe pages 1-4).
3. Cofactor Requirements  
   The enzymatic activity of PASK is dependent on the presence of divalent metal ions. In common with other serine/threonine kinases, PASK requires Mg²⁺ to promote ATP binding and facilitate the phosphotransfer reaction. Such cofactor dependency is typical for kinases within the CaMK-like family and is essential for efficient catalysis (xu2024“druggability”ofthe pages 1-4).
4. Substrate Specificity  
   PASK phosphorylates substrate proteins at serine or threonine residues and is involved in regulating key processes in energy homeostasis and protein translation. Notable substrates include eukaryotic elongation factor 1 alpha 1 (EEF1A1), glycogen synthase 1 (GYS1), pancreatic and duodenal homeobox 1 (PDX1), and ribosomal protein S6 (RPS6). Phosphorylation of GYS1 leads to its inactivation, thereby downregulating glycogen synthesis, while modification of EEF1A1 and RPS6 is associated with enhanced translation efficiency. Although a defined consensus sequence has not been fully established in the cited literature, these substrate targets highlight PASK’s role in integrating nutrient and metabolic signals through selective phosphorylation events (teuwen2024navigatingthemaze pages 21-22, xu2024“druggability”ofthe pages 15-18).
5. Structure  
   PASK is composed of a multi‐domain architecture that integrates sensory and catalytic functions. The N-terminal region harbors one or more PAS domains that adopt the classical PAS fold—a central five‐stranded antiparallel β-sheet interspersed with α-helices—and these domains are connected by flexible linker regions. Structural analysis, including predictions from AlphaFold and molecular dynamics simulations, suggests that PASK contains at least three PAS domains (PAS1, PAS2, and PAS3). PAS3, in particular, has been modeled as a domain that may form from non-contiguous sequence segments and features a hydrophobic binding cavity that is considered a potential druggable hotspot. Downstream of the regulatory PAS modules is the C‐terminal kinase domain, which exhibits the conserved catalytic motifs common to serine/threonine kinases such as the activation loop, the C‑helix, and hydrophobic spines critical for substrate phosphorylation. An additional regulatory element, sometimes referred to as the PAS-C domain, is formed through the association of a PAS fold with a PAS-associated C-terminal (PAC) motif; this composite regulatory module is thought to mediate conformational changes required for full kinase activation. These structural features collectively enable PASK to integrate external and internal signals by coupling ligand-induced alterations in the PAS domains to modulations in catalytic activity (xu2024“druggability”ofthe pages 12-15, xu2024“druggability”ofthe pages 8-11).
6. Regulation  
   The activity of PASK is tightly regulated by its modular structure, which couples environmental sensing to catalytic activation. Under basal conditions, the intramolecular interaction between the PAS domains and the catalytic domain exerts an autoinhibitory effect, thereby limiting kinase activity. Binding of small molecules or metabolites to the PAS domains is proposed to induce conformational changes, relieving this autoinhibition and permitting full kinase activation. In addition, post-translational modifications, including multisite phosphorylation events, have been implicated in regulating the structural dynamics of PASK. These modifications are believed to be mediated, in part, by upstream nutrient-sensing kinases such as mTORC1 and AMPK, which adjust PASK activity in response to the cellular metabolic state. Such regulatory events may promote quaternary structural remodeling by, for example, facilitating the assembly of the PAS-C domain with the kinase domain, thereby aligning critical catalytic residues within the activation loop (xu2024“druggability”ofthe pages 15-18, xu2024“druggability”ofthe pages 12-15).
7. Function  
   PASK functions as an integrator of metabolic cues and plays a central role in energy homeostasis and protein translation. It phosphorylates key substrates that are involved in the regulation of glycogen metabolism and protein synthesis. For instance, by phosphorylating GYS1, PASK leads to the downregulation of glycogen synthesis in response to nutritional signals. In pancreatic beta cells, PASK may contribute to glucose-stimulated insulin production through the phosphorylation of PDX1, while its activity on other substrates such as RPS6 and EEF1A1 enhances translational efficiency in response to energetic demands. PASK expression is observed in metabolically active tissues, including the liver, pancreas, and muscle, and expression studies in mouse models have revealed high mRNA levels in testicular germ cells. This tissue-specific expression pattern underscores its role in coordinating cellular energy status with the regulation of anabolic processes such as protein synthesis and glycogen storage (katschinski2003targeteddisruptionof pages 1-2, teuwen2024navigatingthemaze pages 21-22).
8. Other Comments  
   Recent computational studies have identified several druggable sites within the PAS domains of PASK, making them attractive targets for pharmacological intervention in metabolic and liver disorders. In particular, high-throughput in silico screening and molecular dynamics simulations have revealed that the ligand-binding cavities within the PAS domains, including the structurally unique PAS3 domain, may be amenable to small molecule modulation. Such studies have also suggested that clinically used compounds, including metformin, might interact with these domains and thereby influence PASK’s regulatory interactions. From a disease perspective, alterations in PASK activity have been associated with dysregulation of insulin secretion and abnormal glycogen metabolism, conditions that are relevant to type 2 diabetes and other metabolic syndromes. Although knockout studies in mice indicate that loss of PASK (PASKIN) does not cause overt developmental defects, its role in fine-tuning metabolic responses positions it as a promising target for therapeutic development (teuwen2024navigatingthemaze pages 21-22, xu2024“druggability”ofthe pages 6-8, xu2024“druggability”ofthe pages 12-15).
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