1. Phylogeny  
   PBK/TOPK is a 322–amino acid serine/threonine kinase that belongs to the MAPKK‐like family and occupies an evolutionary position between MAP2K1 and MAP2K7. (albony2021…ofthe pages 12-15) It is conserved across vertebrate species, with orthologs present in mammals, amphibians, and fish, as indicated by its conserved kinase domain observed in proliferating neural progenitor cells. (dougherty2005pbktopkaproliferating pages 3-4) Within the kinome, PBK/TOPK is grouped with mitotic kinases that regulate cell‐cycle progression, and its restricted expression in testis and activated lymphoid cells underscores its specialized evolutionary role. (park2006pdzbindingkinasetlakcelloriginated pages 1-2)
2. Reaction Catalyzed  
   PBK/TOPK catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of serine or threonine residues on substrate proteins. (albony2021…ofthe pages 12-15) In enzymatic terms, the reaction can be written as: ATP + [protein]–OH → ADP + [protein]–O‑phosphate + H⁺. (Information)
3. Cofactor Requirements  
   As with most serine/threonine kinases, PBK/TOPK requires Mg²⁺ ions as a cofactor to coordinate the phosphates of ATP during catalysis. (albony2021…ofthe pages 12-15)
4. Substrate Specificity  
   PBK/TOPK phosphorylates substrates that include the MAP kinase p38, thereby modulating p38 signaling during mitosis. (albony2021…ofthe pages 109-112) It also recognizes consensus sequences similar to the conserved TGEKP motif found in C2H2 zinc finger proteins, as evidenced by phosphopeptide analyses that identified sites on substrates such as FUBP1 (phosphorylated at Thr229) and ADNP (phosphorylated at Ser98). (albony2021…ofthe pages 89-94, albony2021…ofthe pages 97-100) Additional substrates reported in the literature include histone H3 (phosphorylated at Ser10) and histone H2AX (phosphorylated at Ser139), underscoring its role in chromatin and DNA damage‐related signaling. (park2006pdzbindingkinasetlakcelloriginated pages 1-2, zhu2006topkphosphorylationof pages 7-9)
5. Structure  
   The 3D structure of PBK/TOPK is defined by a central catalytic domain that adopts the typical bilobal fold of serine/threonine kinases—a smaller N-terminal lobe primarily composed of β-strands and a larger C-terminal lobe rich in α-helices (comprised of approximately 6 β–strands and 14 α–helices as revealed by crystallographic studies, PDB accession 5j0A). (albony2021…ofthe pages 12-15) A distinctive feature is its C-terminal PDZ-binding motif, typically characterized by a T/SXV sequence, which mediates interactions with PDZ domain–containing proteins such as the human homolog of Drosophila Discs-large (hDlg). (park2006pdzbindingkinasetlakcelloriginated pages 1-2) In addition, PBK/TOPK contains several phosphorylation sites within the regulatory regions—including Thr9, T24, Ser32, and Ser59—that are targets for upstream kinases and are critical for its activation and function during mitosis. (huang2021pbktopkaneffective pages 2-4)
6. Regulation  
   PBK/TOPK is regulated in a highly cell cycle–dependent manner, with its activity being confined predominantly to the G2/M phase. (albony2021…ofthe pages 112-116) Activation of PBK/TOPK requires phosphorylation by the CDK1/cyclin B complex, most notably at Thr9, which is essential for its kinase activity during mitosis. (dougherty2005pbktopkaproliferating pages 5-7) In addition, phosphorylation at tyrosine residues such as Tyr74 and Tyr272 by Src family kinases further modulates its enzymatic activity. (albony2021…ofthe pages 116-119) Post‐translational modifications including autophosphorylation and ubiquitination—mediated by proteins like CHFR—regulate its stability and may influence substrate interactions. (park2006pdzbindingkinasetlakcelloriginated pages 8-9) Moreover, upon phosphorylation, PBK/TOPK forms a complex with TP53, an event that leads to TP53 destabilization and attenuation of the G2/M checkpoint during doxorubicin-induced DNA damage. (Information, albony2021…ofthe pages 116-119)
7. Function  
   PBK/TOPK plays a pivotal role in mitosis by phosphorylating key substrates such as the MAP kinase p38, histone H3, and other regulators of cell division. (albony2021…ofthe pages 109-112) Its activity is confined largely to mitotically active cells, and it is expressed in activated lymphoid cells, testis, fetal tissues, and proliferative neural progenitors—as evidenced by its detection in neurogenic regions of the central nervous system. (dougherty2005pbktopkaproliferating pages 2-3, park2006pdzbindingkinasetlakcelloriginated pages 1-2) In cancer cells, PBK/TOPK is markedly overexpressed and contributes to enhanced cell proliferation, oncogenic transformation, and cytokinesis. (bagheri2022targetingproteinkinases pages 9-11, lei2015pbktopkexpressioncorrelates pages 7-8) Furthermore, by forming a complex with TP53 upon its phosphorylation, PBK/TOPK reduces TP53 stability, resulting in an attenuated G2/M checkpoint during DNA damage; this activity is important under conditions of doxorubicin-induced stress and may contribute to tumor cell survival. (Information, zlobec2010prognosticandpredictive pages 10-10, albony2021…ofthe pages 97-100) Its expression pattern and kinase activity render it a valuable biomarker and a potential therapeutic target in various cancers. (park2006pdzbindingkinasetlakcelloriginated pages 1-2, dougherty2005pbktopkaproliferating pages 7-8)
8. Other Comments  
   Multiple small-molecule inhibitors of PBK/TOPK have been identified in preclinical studies, including HI-TOPK-032, OTS514, and OTS964, which have demonstrated the ability to suppress tumor growth in vitro and in vivo. (huang2021pbktopkaneffective pages 10-11, huang2021pbktopkaneffective pages 16-17) Its characterization as a cancer/testis antigen—given its restricted expression in normal adult tissues aside from testis and fetal tissues—further emphasizes its clinical relevance as a therapeutic target in oncology. (park2006pdzbindingkinasetlakcelloriginated pages 1-2, lei2015pbktopkexpressioncorrelates pages 7-8) PBK/TOPK has also been implicated in radiosensitivity modulation, as studies in melanoma models have linked its activity to resistance against apoptosis under arsenite-induced stress. (pirovano2016topkasa pages 102-108, zhu2006topkphosphorylationof pages 7-9) Additionally, its regulation by interleukin-6 signaling has been observed in multiple myeloma cells, suggesting roles in inflammatory responses in certain cancer contexts. (ota2020novelinterleukin6inducible pages 11-13) Because of its central role in promoting mitotic progression and its involvement in TP53 destabilization, PBK/TOPK is increasingly being considered for targeted combination therapies aimed at overcoming cell cycle checkpoint deficiencies in tumors. (albony2021…ofthe pages 116-119, zhong2022choosingkinaseinhibitors pages 18-19)

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