1. Phylogeny  
   PLK5, encoded by the PLK5 (or PLK5P) gene and identified by UniProt ID Q496M5, is a member of the Polo‐like kinase family that comprises PLK1 to PLK5. (carcer2011plk5apolo pages 1-2)  
   Unlike PLK1–PLK4—which harbor fully functional serine/threonine kinase domains required for canonical phosphorylation reactions—human PLK5 features a truncated kinase domain due to a premature stop codon that renders it catalytically inactive. (carcer2011plk5apolo pages 12-13)  
   Phylogenetic analyses position PLK5 as evolving from the PLK2 subfamily; however, its sequence divergence is pronounced, suggesting an adaptation toward non‐enzymatic roles primarily in differentiated, post‐mitotic tissues such as those of the central nervous system. (malumbres2011physiologicalrelevanceof pages 6-7)  
   Orthologs of PLK5 have been identified across multiple mammalian species, consistent with an evolutionarily conserved function that is tightly linked to neuronal differentiation and stress responses in specialized tissues. (carcer2011plk5apolo pages 1-2)
2. Reaction Catalyzed  
   PLK5 is classified as an inactive serine/threonine protein kinase and does not catalyze the phosphorylation of substrate proteins. (carcer2011plk5apolo pages 1-2)  
   While active members of the PLK family execute the reaction ATP + [protein]–(L-serine/threonine) → ADP + [protein]–phospho(L-serine/threonine) + H⁺, PLK5 lacks the key catalytic residues necessary for this reaction, and no robust phosphorylation activity has been detected. (xu2017pololikekinase3 pages 1-2)
3. Cofactor Requirements  
   Traditional serine/threonine kinases require divalent metal ions such as Mg²⁺ for optimal ATP binding and phosphoryl-transfer; however, due to the inactive nature of its kinase domain, PLK5 does not exhibit a defined cofactor requirement. (carcer2011plk5apolo pages 1-2)
4. Substrate Specificity  
   Because PLK5 is catalytically inactive, it does not phosphorylate substrates and, as such, a consensus substrate motif (e.g., an RxRxx[S/T] sequence) has not been established for this kinase. (carcer2011plk5apolo pages 2-2)  
   Instead, any substrate recognition by PLK5 is hypothesized to be mediated by its preserved polo-box domain, which governs protein–protein interactions rather than classical enzymatic substrate specificity. (carcer2011plk5apolo pages 2-3)
5. Structure  
   Human PLK5, with a total length of approximately 336 amino acids, exhibits a severely truncated kinase domain that lacks many of the structural motifs essential for catalytic activity. (carcer2011plk5apolo pages 12-13)  
   The protein is expressed as a shorter isoform—approximately 40 kDa in size—in which the canonical kinase domain is disrupted, and the remaining protein primarily consists of the interdomain linker and an intact polo-box domain responsible for mediating substrate binding and subcellular localization. (carcer2011plk5apolo pages 14-15)  
   Predictions based on structural modeling indicate that PLK5 can be divided into an N-terminal pseudo-kinase domain (roughly residues 1–81), a flexible interdomain linker spanning residues 82–150, and a C-terminal polo-box domain covering residues 151–336. (wyatt2024insightsintothe pages 3-7)  
   The loss of critical catalytic elements—such as the ATP-binding pocket, activation loop phosphorylation site, and other residues normally required for phosphoryl-transfer—is a defining structural feature that accounts for its inactivity, while the preserved polo-box domain retains a typical fold that facilitates phosphopeptide binding. (schmucker2014moleculardynamicsof pages 2-3)  
   Additional structural analysis suggests that PLK5 does not form the elaborate autoinhibited conformation typical of active kinases, largely because key regulatory elements such as the C-helix and hydrophobic spine are either absent or highly altered in its truncated kinase region. (carcer2011plk5apolo pages 3-3)
6. Regulation  
   Regulation of PLK5 occurs predominantly at the transcriptional level; its expression is modulated by epigenetic mechanisms, with promoter hypermethylation being frequently observed in brain tumors such as glioblastoma. (carcer2011plk5apolo pages 14-15)  
   Expression studies indicate that PLK5 levels are elevated in quiescent or differentiated neuronal cells and tend to be downregulated in actively proliferating cells, consistent with its specialized role in non-dividing tissues. (carcer2011plk5apolo pages 5-6)  
   In addition, cellular stress signals, including DNA damage, influence PLK5 expression, implicating its involvement in stress response pathways despite its lack of catalytic signaling activity. (goroshchuk2020targetingpololikekinase pages 59-63)  
   Current evidence does not demonstrate significant post-translational modifications such as additional phosphorylation or ubiquitination events on PLK5 that impact its regulatory function; its regulation appears to be largely dictated by genomic and transcriptional controls. (ha2012mitotickinasesand pages 10-11)
7. Function  
   PLK5 plays an important biological role in neuronal differentiation, being primarily expressed in the adult brain where it influences neurite outgrowth and the establishment of proper neuronal morphology. (carcer2011plk5apolo pages 1-2)  
   Experimental studies have demonstrated that overexpression of PLK5 can induce a G1 cell cycle arrest, suggesting that its activity, despite being non-catalytic, contributes to the regulation of cell cycle progression in a manner that may be independent of classical enzymatic activity. (carcer2011plk5apolo pages 3-5)  
   In addition to its role in neural differentiation, PLK5 is implicated as a tumor suppressor in glioblastoma; loss or epigenetic silencing of the PLK5 gene correlates with enhanced tumor cell proliferation and reduced apoptotic responses in neoplastic tissues originating from the central nervous system. (carcer2011plk5apolo pages 8-9)  
   Moreover, PLK5 has been linked to cellular stress response mechanisms, potentially participating in pathways activated upon DNA damage, although the exact downstream effectors and interaction partners remain to be fully elucidated. (xu2017pololikekinase3 pages 4-5)
8. Other Comments  
   PLK5 is associated with a tumor suppressor function in neural tissues, as its reduced expression or promoter hypermethylation has been documented in aggressive brain tumors, notably glioblastoma. (carcer2011plk5apolo pages 14-15)  
   No selective small-molecule inhibitors have been specifically developed for PLK5 due to its inactive catalytic nature and the consequent focus on designing inhibitors against active PLK family members such as PLK1. (stratmann2019

* pololikekinase1 pages 1-2)  
  The unique structural organization of PLK5, characterized by a truncated kinase domain alongside a functional polo-box domain, underscores its specialization in non-enzymatic, scaffolding, or regulatory roles that are distinct from those of its catalytically active counterparts. (kressin2021modellingthefunctions pages 8-10)  
  Furthermore, the absence of conventional catalytic activity in PLK5 poses challenges for traditional kinase inhibitor design strategies, thereby shifting the focus toward understanding its protein–protein interactions and epigenetic regulation for potential therapeutic modulation in diseases such as glioblastoma and disorders of neuronal development. (dzamko2014parkinsonâ€™sdiseaseimplicatedkinases pages 1-2)

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