1. Phylogeny  
   Serine/threonine‐protein kinase PLK2, also known as SNK, belongs to the Polo‐like kinase (Plk) family—a group of highly conserved serine/threonine kinases defined by an N‐terminal catalytic kinase domain and one or more C‐terminal Polo‐box domains (PBDs) responsible for phosphopeptide binding and substrate targeting (carcer2011fromplk1to pages 3-4). Comparative genomic analyses reveal that PLK2 is present predominantly in bilaterian animals and is absent from several simpler model organisms, a distribution that reflects its emergence during later stages of eukaryotic evolution. Phylogenetically, the expansion of the Plk family in vertebrates involved gene duplication events that yielded PLK2 alongside close relatives such as PLK3 and PLK5, while PLK1 and PLK4 appear as distinct subfamilies with specialized functions (carcer2011fromplk1to pages 3-4, weerdt2006pololikekinasesa pages 3-4). The kinase domain of PLK2 exhibits high sequence similarity to those of PLK1 and PLK3, indicating that PLK2 shares a common evolutionary origin with these kinases; this relationship is underscored by consensus motifs required for ATP binding and catalytic function (johnson2007pharmacologicalandfunctional pages 2-3, carcer2011fromplk1to pages 1-3).
2. Reaction Catalyzed  
   PLK2 catalyzes the transfer of a phosphate group from ATP to serine or threonine residues on target proteins. The reaction can be summarized by the classical kinase equation: ATP + [protein]-(L‑serine or L‑threonine) → ADP + [protein]-(L‑serine/threonine)-phosphate + H⁺. This phosphoryl transfer reaction is central to regulating the activity and function of numerous substrates involved in cell cycle progression, centriole duplication, and synaptic signaling (carcer2011fromplk1to pages 6-8, johnson2007pharmacologicalandfunctional pages 1-2).
3. Cofactor Requirements  
   The enzymatic activity of PLK2 is dependent on divalent metal ions, with Mg²⁺ being the essential cofactor. Mg²⁺ ions coordinate with ATP in the active site, thereby facilitating the proper positioning of the phosphate groups for efficient phosphoryl transfer to target serine/threonine residues (carcer2011fromplk1to pages 3-4, johnson2007pharmacologicalandfunctional pages 11-12).
4. Substrate Specificity  
   PLK2 phosphorylates a diverse set of substrates that are critical for both cell cycle regulation and synaptic signaling. Experimentally validated substrates include CPAP—a protein essential for centriole duplication—as well as NPM1, RAPGEF2, RASGRF1, SNCA (α-synuclein), SIPA1L1, and SYNGAP1. Consistent with the modus operandi of Polo‐like kinases, PLK2 shows a distinct substrate specificity that relies on the prior phosphorylation of the substrate by other kinases; its Polo‐box domain recognizes phosphoserine/threonine-containing motifs. Detailed peptide library screenings have demonstrated that PLK2 preferentially phosphorylates serine or threonine residues in substrates that are flanked by acidic residues; for example, residues positioned at –6 and at positions +5 to +7 relative to the phosphorylation site contribute to substrate recognition (johnson2007pharmacologicalandfunctional pages 3-6, mbefo2010phosphorylationofsynucleins pages 12-13, liu2015targetingpololikekinases pages 6-8). In vitro kinase assays further support that PLK2’s consensus substrate motif is comparable to that of its close homolog PLK3, although subtle differences in amino acid preferences may underlie its unique functional interactions in centrosome biology and synaptic plasticity (johnson2007pharmacologicalandfunctional pages 9-10).
5. Structure  
   PLK2 is organized into two major domains: an N-terminal serine/threonine kinase domain and a C-terminal Polo‐box domain (PBD) composed of two tandem polo boxes. The kinase domain adopts the typical bi-lobal structure seen in serine/threonine kinases, with a smaller N-terminal lobe that primarily participates in ATP binding and a larger C-terminal lobe that contains the catalytic machinery. Key structural features within this domain include the glycine-rich loop, which stabilizes ATP binding, and the activation loop (T-loop) where phosphorylation at a conserved threonine residue is critical for full catalytic activity (carcer2011fromplk1to pages 3-4, lowery2005structureandfunction pages 1-2). The ATP-binding pocket, including a highly conserved lysine residue, is essential for anchoring ATP via a network of hydrogen bonds and electrostatic interactions.  
   The C-terminal PBD of PLK2 is responsible for substrate recognition and subcellular localization. Each Polo-box exhibits a β-sheet core flanked by α-helices, forming a structure that creates a shallow groove specifically designed to bind phosphopeptide motifs that are generated by prior phosphorylation events. This binding governs the spatial targeting of PLK2 to specific cellular locales, such as centrosomes, and permits a secondary layer of regulation of its kinase activity (carcer2011fromplk1to pages 3-4, lowery2005structureandfunction pages 7-9, weerdt2006pololikekinasesa pages 7-8, lampkin2010targetingpololikekinase pages 1-3). Additionally, structural models based on homologous proteins, such as PLK1, indicate that PLK2 contains a hydrophobic spine and a correctly positioned C-helix in the kinase domain that are necessary for the stabilization of its active conformation. Although high-resolution crystal structures of PLK2 are not yet available, homology modeling using PLK1 as a template has provided important insights into the overall domain architecture and key regulatory elements that control its enzymatic function (johnson2007pharmacologicalandfunctional pages 6-7, lowery2005structureandfunction pages 4-5).
6. Regulation  
   The regulation of PLK2 activity is multifactorial, involving both transcriptional and post-translational mechanisms. As a serum-inducible kinase, PLK2 gene expression is rapidly upregulated in response to extracellular mitogenic stimuli, a feature that classifies it as an immediate early gene. This induction is further modulated by tumor suppressor pathways, notably through p53-dependent mechanisms, which link PLK2 expression to cellular responses to DNA damage and genotoxic stress (carcer2011fromplk1to pages 3-4, weerdt2006pololikekinasesa pages 8-9).  
   At the post-translational level, full activation of PLK2 requires phosphorylation within its activation loop. This phosphorylation event, which may be mediated by upstream kinases or by autophosphorylation, alleviates autoinhibitory intramolecular interactions between the kinase domain and the PBD. Such modifications are essential for achieving the conformational changes required for catalytic activity (johnson2007pharmacologicalandfunctional pages 10-11, liu2015targetingpololikekinases pages 8-9).  
   Moreover, the PBD not only mediates substrate binding but also plays a role in regulating PLK2’s subcellular localization. By binding to phosphorylated target sequences on substrates or scaffold proteins, the PBD directs PLK2 to centrosomes, synaptic sites, or other subcellular compartments where its substrates are concentrated. This local recruitment is critical for centriole duplication during the G1/S transition and for the dynamic remodeling of synapses in neuronal cells (carcer2011fromplk1to pages 4-6, liu2015targetingpololikekinases pages 9-10). In addition, PLK2 engages in kinase-independent regulatory interactions. Notably, its binding to NSF (N-ethylmaleimide-sensitive factor) interferes with NSF’s interaction with the GRIA2 subunit of AMPA receptors, thereby modulating synaptic transmission independent of direct phosphorylation (liu2015targetingpololikekinases pages 9-10).
7. Function  
   PLK2 functions as a tumor suppressor kinase with pivotal roles in both proliferative and non-proliferative contexts. In the realm of cell cycle regulation, PLK2 is critically involved in the G1/S phase transition. It ensures proper centrosome duplication by phosphorylating substrates such as CPAP and NPM1; defects in this process can lead to aberrant centriole numbers and genomic instability (carcer2011fromplk1to pages 3-4, weerdt2006pololikekinasesa pages 8-9).  
   In addition to its well‐documented role in cell division, PLK2 has emerged as an essential regulator of synaptic plasticity and memory. In neuronal cells, PLK2 modulates Ras and Rap signaling pathways through the phosphorylation of multiple substrates. It phosphorylates the Ras activator RASGRF1 and the Rap inhibitor SIPA1L1, which targets these proteins for proteasomal degradation. Conversely, PLK2 phosphorylates the Rap activator RAPGEF2 and the Ras inhibitor SYNGAP1, thereby enhancing their activity. These combined actions fine-tune signaling cascades that are crucial for overactivity-dependent spine remodeling and synaptic homeostasis (carcer2011fromplk1to pages 4-6, mbefo2010phosphorylationofsynucleins pages 12-13).  
   Furthermore, PLK2 phosphorylates SNCA (α-synuclein), linking it to pathways that regulate neuronal function and synaptic integrity. In addition to its catalytic role, PLK2 exerts kinase-independent effects by interacting with NSF, which in turn disrupts the functional association between NSF and the AMPA receptor subunit GRIA2. This interaction promotes a rapid reduction in AMPAR-mediated synaptic currents, a process that is instrumental in the modulation of long-term depression (LTD) in neurons (johnson2007pharmacologicalandfunctional pages 13-13, liu2015targetingpololikekinases pages 6-8).  
   PLK2 is expressed in a broad range of tissues. It is prominently found in proliferative tissues such as the testis and in various cell types within the central nervous system, particularly in cortical neurons where it participates in activity-dependent synaptic remodeling (carcer2011fromplk1to pages 4-6, weerdt2006pololikekinasesa pages 8-9). The dual role of PLK2 in controlling centrosome duplication and modulating synaptic signaling underpins its function as a tumor suppressor and as a key regulator of neuronal plasticity.
8. Other Comments  
   While extensive efforts in drug discovery have primarily focused on PLK1 due to its prominent mitotic functions, several ATP-competitive inhibitors—such as volasertib, BI2536, and GSK461364A—have been developed that target the conserved ATP‐binding pocket of Plk family members. These compounds, although designed for PLK1, often inhibit PLK2 to a lesser extent due to the high degree of conservation in the catalytic domain (liu2015targetingpololikekinases pages 6-8, schoffski2009pololikekinase(plk) pages 2-4). In contrast, inhibitors that target the Polo-box domain represent an emerging strategy for achieving isoform selectivity; for instance, peptidomimetic compounds under development aim to disrupt PBD-mediated protein–protein interactions, potentially offering a route to selectively modulate PLK2 function (stafford2022developmentofpeptidomimetic pages 119-123).  
   Epigenetic alterations leading to the silencing of the PLK2 gene have been documented in certain hematological malignancies, supporting its role as a tumor suppressor (weerdt2006pololikekinasesa pages 8-9, carcer2011fromplk1to pages 8-9). Furthermore, animal models lacking PLK2 exhibit defects in centriole duplication and abnormal synaptic homeostasis, although these models remain viable. Such findings underscore the nonredundant contributions of PLK2 to both cell cycle control and neural function. Consequently, further understanding of PLK2’s regulatory networks—including both its kinase-dependent activities and its non-catalytic roles—is imperative for the development of targeted therapeutics against cancers and neurological disorders linked to dysregulated Plk signaling (carcer2011fromplk1to pages 3-4, liu2015targetingpololikekinases pages 9-10, weerdt2006pololikekinasesa pages 8-9).

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