1. Phylogeny  
   Serine/threonine‐protein kinase PLK4, also known as SAK or STK18, is a member of the Polo‐like kinase (PLK) family and represents the most structurally divergent member within this group. Unlike PLK1–3 that possess tandem Polo‐box domains, PLK4 is characterized by a single, unique Polo‐box domain (often coupled with a cryptic polo‐box element) that distinguishes its evolutionary lineage from its paralogs (garvey2021roleofpololike pages 1-2, long2012smsakthesecond pages 1-2). Orthologs of PLK4 have been identified in multiple eukaryotic organisms including mammals, insects, and amphibians, indicating that its role in centriole duplication and cell cycle regulation is conserved across species (garvey2021roleofpololike pages 1-1, sillibourne2010pololikekinase4 pages 1-2). Phylogenetic analyses based on kinase domain sequences reveal that PLK4 diverged early from a common PLK1-like ancestor, and its evolutionary adaptation is reflected in its unique domain architecture and substrate specificity when compared to other PLK family members (johnson2007pharmacologicalandfunctional pages 1-2, long2012smsakthesecond pages 1-2).
2. Reaction Catalyzed  
   PLK4 catalyzes the transfer of a phosphate group from ATP to specific serine/threonine residues on substrate proteins. In chemical terms, the reaction it catalyzes can be summarized as: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (garvey2021roleofpololike pages 6-6, johnson2007pharmacologicalandfunctional pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of PLK4, like that of most serine/threonine kinases, is dependent on the presence of divalent metal ions. In particular, Mg²⁺ is required as a cofactor to facilitate ATP binding and phosphoryl transfer during the catalytic cycle (johnson2007pharmacologicalandfunctional pages 1-2, lowery2005structureandfunction pages 1-2).
4. Substrate Specificity  
   PLK4 displays a substrate specificity that is critical for its central role in centriole duplication. It phosphorylates proteins that are essential for the initiation and stabilization of procentriole formation. A key substrate is the F-box protein FBXW5, which is phosphorylated on Ser-151 during the G1/S transition; this phosphorylation event inhibits FBXW5’s ability to ubiquitinate SASS6, thereby promoting centriole duplication (garvey2021roleofpololike pages 3-3, garvey2021roleofpololike pages 6-6). In addition, studies employing peptide arrays have defined a consensus motif for PLK4 that is distinct from those of PLK1–3, typically involving a preference for basic residues at the –3 position and hydrophobic residues in the +1 to +2 positions adjacent to the phosphorylated serine/threonine residue (leung2007determinationofthe pages 1-2, johnson2007pharmacologicalandfunctional pages 9-10). This substrate recognition pattern underpins the kinase’s selective phosphorylation of centriole biogenesis proteins such as SASS6, CPAP, CEP135, CCP110, and gamma-tubulin.
5. Structure  
   PLK4 contains an N-terminal catalytic kinase domain that harbors the typical serine/threonine kinase motifs, including a conserved ATP-binding region with a unique Gly–X–Gly–X–Phe–Ala motif that distinguishes it from other kinase families (johnson2007pharmacologicalandfunctional pages 1-2, sillibourne2010pololikekinase4 pages 1-2). Following the catalytic domain, PLK4 possesses a unique, extended central region that has been reported to incorporate sequences necessary for autoinhibition and self-regulation; these may include regions rich in PEST sequences that contribute to its rapid turnover (sillibourne2010pololikekinase4 pages 6-8, weerdt2006pololikekinasesa pages 7-8). The C-terminal region of PLK4 features a single Polo-box domain coupled with an adjacent cryptic Polo-box that mediates homodimerization and dictates its subcellular localization to the centrosome, which is essential for its function in centriole replication (garvey2021roleofpololike pages 1-2, long2012smsakthesecond pages 6-8, park2010poloboxdomaina pages 4-6). In structural models, the kinase domain adopts the classical bilobal architecture with a well-defined activation loop that undergoes autophosphorylation—a key step for activation—and a C-helix that plays a pivotal role in aligning the ATP-binding pocket (johnson2007pharmacologicalandfunctional pages 7-9, lowery2005structureandfunction pages 6-7). Unique to PLK4 is its reduced number of Polo-box repeats compared to other PLKs, which has implications for its substrate targeting and regulation by protein–protein interactions.
6. Regulation  
   PLK4 is subject to a multi-layered regulatory mechanism that ensures precise control over centriole duplication. One principal regulatory mechanism involves autophosphorylation, wherein PLK4 phosphorylates residues within an internal degron region often associated with PEST motifs; this autophosphorylation marks the kinase for recognition by the SCF-βTrCP ubiquitin ligase complex, leading to its proteasomal degradation (sillibourne2010pololikekinase4 pages 6-8, klebba2015autoinhibitionandrelief pages 5-6). Additionally, PLK4 can engage in autoinhibition through its interdomain linker (L1), a mechanism that is relieved upon homodimerization mediated by its cryptic Polo-box domain; this conformational shift facilitates activation via autophosphorylation of its activation loop (klebba2015autoinhibitionandrelief pages 5-6, long2012smsakthesecond pages 6-8). PLK4 also phosphorylates FBXW5 on Ser-151 during the G1/S phase; this modification prevents FBXW5 from ubiquitinating SASS6, thereby stabilizing centriole biogenesis factors (garvey2021roleofpololike pages 3-3, garvey2021roleofpololike pages 6-6). Transcriptional regulation plays a role as well; PLK4 expression is under tight cell cycle–dependent control, with mRNA levels rising during the S phase and mitosis and declining during G1, and its transcription may be negatively regulated by p53 (garvey2021roleofpololike pages 1-1, weerdt2006pololikekinasesa pages 8-9). These layers of regulation ensure that PLK4 activity is confined to specific time windows within the cell cycle, thus preventing aberrant centrosome duplication that could lead to genomic instability.
7. Function  
   The primary function of PLK4 is to orchestrate centriole duplication by triggering the formation of a procentriole on the surface of the parental centriole. By phosphorylating key substrates, PLK4 initiates and stabilizes the recruitment of centriole biogenesis proteins such as SASS6, CPAP, CCP110, CEP135, and gamma-tubulin, which are essential for building a functional centriole (garvey2021roleofpololike pages 1-1, garvey2021roleofpololike pages 3-3). Under normal physiological conditions, this tightly controlled process ensures that centriole duplication occurs only once per cell cycle, which is critical for maintaining genomic stability during cell division (sillibourne2010pololikekinase4 pages 8-8, press2019roleforpololike pages 1-1). In addition to its canonical function in centriole duplication, PLK4 is involved in alternative pathways of centriole biogenesis; it plays a role in deuterosome-mediated centriole amplification in multiciliated cells, permitting the generation of over 100 centrioles required for the formation of motile cilia (long2012smsakthesecond pages 2-3). Furthermore, during trophoblast differentiation, PLK4 phosphorylates the transcription factor HAND1, thereby disrupting its interaction with MDFIC and leading to HAND1 activation, a process implicated in the differentiation of trophoblast cells (garvey2021roleofpololike pages 1-1, long2012smsakthesecond pages 2-3). Through these roles, PLK4 not only ensures correct centrosome replication and normal mitotic progression but also impacts broader developmental processes. Overexpression of PLK4 has been shown to induce centrosome amplification, which is a frequent phenomenon in many tumors and correlates with genomic instability and tumorigenesis (garvey2021roleofpololike pages 1-1, garvey2021roleofpololike pages 3-3).
8. Other Comments  
   A number of small-molecule inhibitors that target PLK4 have been developed with the aim of suppressing aberrant centriole duplication and, consequently, tumorigenesis. Notable among these are compounds such as centrinone-B, YLT-11, and CFI-400945, an orally available ATP-competitive inhibitor with low nanomolar potency against PLK4; these inhibitors disrupt normal PLK4 function, leading to mitotic defects and polyploidy in cancer cells (garvey2021roleofpololike pages 6-6, liu2015targetingpololikekinases pages 8-9). Inhibition of PLK4 is being investigated as a therapeutic strategy in epithelial cancers where centrosome amplification is prevalent, and preclinical studies have demonstrated significant anti-tumor efficacy upon PLK4 inhibition (garvey2021roleofpololike pages 1-1, garvey2021roleofpololike pages 3-3). Additionally, disease associations for PLK4 stem from its central role in centrosome duplication; dysregulation, whether through overexpression or mutations that alter its regulatory autophosphorylation and turnover, has been linked to genomic instability and tumor development (strebhardt2010multifacetedpololikekinases pages 8-9, johnson2007pharmacologicalandfunctional pages 7-9). Although specific disease-related mutations are not detailed in the available literature, the tight regulation of PLK4 underscores its importance in maintaining cell division fidelity, and its perturbation is considered a hallmark in several cancers. Moreover, the multifaceted roles of PLK4 extend to specialized cellular processes such as deuterosome-mediated centriole amplification in multiciliated cells and trophoblast cell differentiation, highlighting its broader significance in developmental biology in addition to cancer pathology (long2012smsakthesecond pages 2-3, garvey2021roleofpololike pages 1-1). Despite the progress in inhibitor development, challenges remain with regard to achieving absolute selectivity given the structural divergence between PLK4 and its PLK family counterparts, underscoring the need for ongoing research into the precise structural features and regulatory mechanisms governing PLK4 function (johnson2007pharmacologicalandfunctional pages 7-9, klebba2015autoinhibitionandrelief pages 9-9).

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