## Phylogeny

PLK2 is a serine/threonine kinase belonging to the Polo-like kinase (PLK) family, which is classified within the CMGC kinase group (johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 7-7). Hierarchical clustering based on amino acid motif selectivity shows that PLK2 is closely related to other mammalian PLKs, including PLK1, PLK3, and PLK4 (johnson2023anatlasof pages 4-5, schoffski2009pololikekinase(plk) pages 1-2). The PLK family is highly conserved evolutionarily across diverse eukaryotes (johnson2023anatlasof pages 4-5, schoffski2009pololikekinase(plk) pages 1-2). Known orthologs include *Plk2* in mouse, the *polo* gene in *Drosophila melanogaster*, and the functional ortholog *Cdc5* in *S. cerevisiae* (bergeron2014invivomodulation pages 7-8, schoffski2009pololikekinase(plk) pages 1-2).

## Reaction Catalyzed

PLK2 catalyzes the ATP-dependent transfer of a gamma-phosphate to a serine or threonine residue on a protein substrate (johnson2023anatlasof pages 2-3, schoffski2009pololikekinase(plk) pages 1-2).

* ATP + [protein]-L-serine = ADP + [protein]-L-serine phosphate
* ATP + [protein]-L-threonine = ADP + [protein]-L-threonine phosphate

## Cofactor Requirements

The catalytic activity of PLK2 requires a divalent metal ion cofactor, such as Mg²⁺ or Mn²⁺, to facilitate ATP binding and catalysis (bergeron2014invivomodulation pages 7-8, schoffski2009pololikekinase(plk) pages 1-2).

## Substrate Specificity

The substrate consensus phosphorylation motif for PLK2 favors a serine or threonine residue, with a preference for acidic residues near the phosphorylation site (weston2021geneticdeletionof pages 12-13). As a member of the PLK family, it may also recognize motifs containing proline residues near the phospho-acceptor site (johnson2023anatlasof pages 2-3). Substrate recognition is mediated by the C-terminal Polo-Box Domain (PBD), which binds to motifs on substrates that have been pre-phosphorylated by a priming kinase (weston2021geneticdeletionof pages 12-13, schoffski2009pololikekinase(plk) pages 1-2, kumar2015plk1targetedinhibitors pages 16-17). The specific amino acid preferences for PLK2 have been defined by position-specific scoring matrices (PSSMs) (johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 9-10).

## Structure

PLK2 consists of an N-terminal serine/threonine kinase domain and a C-terminal Polo-Box Domain (PBD) (weston2021geneticdeletionof pages 12-13, schoffski2009pololikekinase(plk) pages 1-2). The kinase domain contains the catalytic machinery, including an activation (T) loop and DFG motif that are crucial for substrate specificity and activity (johnson2023anatlasof pages 2-3). The PBD is essential for substrate recognition and recruitment, binding to specific phosphopeptide motifs on target proteins (kumar2015plk1targetedinhibitors pages 16-17, schoffski2009pololikekinase(plk) pages 1-2, weston2021geneticdeletionof pages 12-13). The AlphaFold model for PLK2 (Q9NYY3) shows a linear arrangement of the kinase and PBD domains (kumar2015plk1targetedinhibitors pages 16-17, weston2021geneticdeletionof pages 12-13).

## Regulation

PLK2 is regulated by post-translational modifications, including phosphorylation and ubiquitination, which modulate its activity and stability (johnson2023anatlasof pages 2-3). However, a specific activating phosphorylation site in the activation loop for PLK2 is not explicitly detailed in the provided sources (weerdt2006pololikekinasesa pages 7-8, unknownauthorsUnknownyearproteomicanalysisof pages 24-28). PLK2 stability is controlled by ubiquitination, and it is likely degraded via the SCF ubiquitin ligase complex, although the exact mechanism for the endogenous protein remains unclear (weerdt2006pololikekinasesa pages 7-8). The degradation of the related kinase PLK4 is mediated by the SCF^Slimb/β-TrCP E3 ubiquitin ligase complex, which may serve as a paradigm for PLK2 regulation (sillibourne2010pololikekinase4 pages 4-6). Additionally, PLK2 is regulated by acetylation, which protects it from ubiquitin-mediated degradation. The deacetylase SIRT1 controls its acetylation state during G1 phase to permit timely centriole replication (zhang2022pololikekinase2 pages 1-2).

## Function

PLK2 protein levels peak during G1 and early S phase, and it localizes to the centrosomes to regulate centriole duplication (weerdt2006pololikekinasesa pages 3-4, unknownauthors2019plk4regulatescell pages 18-22). This function is critical for the G1/S phase transition and requires a functional Polo-Box Domain (zhang2022pololikekinase2 pages 1-2). Known substrates in this process include centrosomal P4.1-associated protein (CPAP), which it phosphorylates at S589 and S595, and nucleophosmin (NPM1/B23), which it phosphorylates at Ser4 (zhang2022pololikekinase2 pages 2-3).

In post-mitotic neurons, PLK2 is involved in synaptic plasticity through both kinase-dependent and -independent functions (weerdt2006pololikekinasesa pages 3-4, unknownauthors2019plk4regulatescell pages 18-22, zhang2022pololikekinase2 pages 1-2). Its kinase-dependent activity modulates Ras and Rap GTPase signaling by phosphorylating substrates such as RAPGEF2, RASGRF1, SIPA1L1, and SYNGAP1, thereby regulating dendritic spine remodeling (unknownauthors2019plk4regulatescell pages 18-22, zhang2022pololikekinase2 pages 1-2). Kinase-independent functions include acting as a scaffolding protein and interacting with N-ethylmaleimide sensitive factor (NSF) (zhang2022pololikekinase2 pages 1-2, unknownauthors2019plk4regulatescell pages 243-245). PLK2 also phosphorylates alpha-synuclein (SNCA) (weston2021geneticdeletionof pages 12-13).

## Inhibitors

The Polo-like kinase family, including PLK2, is targeted by experimental inhibitors (johnson2023anatlasof pages 2-3). BI 2536 is a known inhibitor of Polo-like kinases (weston2021geneticdeletionof pages 12-13). The compound PPG inhibits PLK2 by targeting its Polo-Box Domain (kumar2015plk1targetedinhibitors pages 16-17).

## Other Comments

Misregulation of PLK2 is associated with pathologies including cancer and neurodegenerative diseases like Parkinson’s disease (johnson2023anatlasof pages 2-3). The phosphorylation of alpha-synuclein at serine-129 by PLK2 is implicated in the pathology of Lewy body disorders, and genetic deletion of PLK2 reduces this modification at presynaptic terminals (weston2021geneticdeletionof pages 12-13).

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