## Phylogeny

Polo-like kinase 1 (PLK1) is the founding and best-characterised member of the eukaryotic Polo-like kinase family of serine/threonine protein kinases. Orthologues are found from yeast (*CDC5/PLO1*) to flies (*polo*) and vertebrates, underscoring deep evolutionary conservation (Kothe et al., 2007; Strebhardt & Ullrich, 2006). Mammals encode five paralogues (PLK1-5), with PLK1 representing the archetype of the PLK branch in the human kinome (Chiappa et al., 2022; Lee et al., 2015).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Weiss & Efferth, 2012; Lee et al., 2015).

## Cofactor Requirements

Catalysis requires a divalent metal ion, typically Mg²⁺ (or Mn²⁺), together with ATP (Cholewa et al., 2013; Schmucker & Sumara, 2014; Park et al., 2017).

## Substrate Specificity

Substrate engagement involves two coordinated determinants:  
• C-terminal Polo-box domain (PBD) docks onto primed phosphopeptides bearing the consensus S-pS/pT-P/X; an optimised sequence is MAGPMQ-S-pT-P-LNGAKK (Elia et al., 2003; Weiss & Efferth, 2012; Chapagai et al., 2025).  
• N-terminal kinase domain phosphorylates sites that typically contain an acidic residue at −2 and Lys/Arg at +3. Alternative motifs such as [E/D]X[S/T][I/L/V/M]X[E] have also been reported (Kothe et al., 2007; Bibi et al., 2013).

## Structure

PLK1 comprises an N-terminal catalytic kinase domain (KD) linked to a C-terminal PBD (Strebhardt & Ullrich, 2006; Chapagai et al., 2025).  
• KD: classical bilobal kinase fold; catalytic Lys82 and activation T-loop containing regulatory Thr210 (Kothe et al., 2007; Lee et al., 2015). Crystal structures include PDB 2OU7, 2OWB and 3FC2.  
• PBD: two polo-box motifs that mediate phosphopeptide binding, autoinhibition and localisation; key residues His538 and Lys540 (Strebhardt & Ullrich, 2006; Chapagai et al., 2025). PBD structure: PDB 3RQ7.  
The two domains are connected by a flexible linker that enables intramolecular autoinhibitory contacts.

## Regulation

Activity is controlled multilayeredly:  
• Activation-loop phosphorylation of Thr210 by Aurora A in complex with Bora at the G2/M transition (Chiappa et al., 2022; Helmke et al., 2016).  
• Autoinhibition: intramolecular KD–PBD interaction suppresses catalysis; binding of the PBD to a phosphorylated docking site relieves this brake (Chiappa et al., 2022; Elia et al., 2003).  
• Transcriptional up-regulation peaks in G2/M and is driven by factors such as p53, pRb, Akt and Myc (Cholewa et al., 2013; Colicino & Hehnly, 2018).

## Function

PLK1 is a master mitotic regulator required from G2 entry through cytokinesis. Key roles include:  
– Phosphorylation of Cdc25C, WEE1 and MYT1 to trigger mitotic entry.  
– Control of centrosome maturation, bipolar spindle assembly, chromosome segregation and cytokinesis (Chiappa et al., 2022).  
– Spatial targeting to centrosomes, kinetochores and the midbody via PBD interaction with proteins such as Bora, Gravin, BubR1 and PRC1 (Colicino & Hehnly, 2018).  
– Participation in DNA-damage responses and negative regulation of p53 (Chiappa et al., 2022; Strebhardt & Ullrich, 2006).

## Inhibitors

Two principal classes have been developed for anticancer therapy:  
• ATP-competitive KD inhibitors – e.g., Volasertib (BI 6727), BI 2536, TAK-960 (Liu et al., 2017; Weiss & Efferth, 2012).  
• PBD-directed inhibitors – e.g., Poloxin; the non-ATP-competitive agent Rigosertib also disrupts PLK1 signalling (McInnes & Wyatt, 2011; Liu et al., 2017).

## Other Comments

PLK1 is frequently overexpressed in diverse tumours and high expression correlates with poor prognosis (Cholewa et al., 2013; Strebhardt & Ullrich, 2006).  
Disease-linked mutations include loss-of-function Lys82Met, constitutively active Thr210Asp and PBD-defective Trp414Phe, which respectively cause mitotic failure, checkpoint override and mis-localisation (Strebhardt & Ullrich, 2006; Chapagai et al., 2025). Dysregulated PLK1 promotes genomic instability and oncogenesis (Cunningham et al., 2020).

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