## Phylogeny

PRKDC (DNA-PKcs) is a member of the atypical kinase group and is classified within the Phosphatidylinositol 3-kinase-related kinase (PIKK) family (bartlett2018establishedandemerging pages 1-4, chen2021roleofprkdc pages 1-3, smith1999thednadependentprotein pages 1-2, yue2020dnapkcsamultifaceted pages 1-2). This family also includes other large kinases involved in stress-induced signaling and DNA damage response, such as ATM, ATR, and mTOR, with which DNA-PKcs shares structural and functional similarities (camfield2024secretsofdnapkcs pages 1-2, dylgjeri2022dnapkcsatargetable pages 8-8, smith1999thednadependentprotein pages 1-2). DNA-PKcs is the largest member of the PIKK family (camfield2024secretsofdnapkcs pages 1-2).

Orthologs of PRKDC are conserved in several vertebrate species, including humans, mice, chicken, dog, horse, and amphibians like the toad (bartlett2018establishedandemerging pages 1-4, bartlett2018establishedandemerging pages 4-7). A putative homolog has been identified in the slime mold *Dictyostelium discoideum* (bartlett2018establishedandemerging pages 1-4). However, PRKDC is absent in several common model organisms, including *Caenorhabditis elegans*, *Arabidopsis thaliana*, *Drosophila melanogaster*, and yeast species (bartlett2018establishedandemerging pages 1-4, bartlett2018establishedandemerging pages 4-7).

## Reaction Catalyzed

As a serine/threonine-protein kinase, PRKDC catalyzes the transfer of a phosphate group from ATP to a protein substrate (puustinen2020dnadependentproteinkinase pages 9-9). - ATP + a [protein]-L-serine = ADP + a [protein]-L-serine phosphate (puustinen2020dnadependentproteinkinase pages 9-9). - ATP + a [protein]-L-threonine = ADP + a [protein]-L-threonine phosphate (puustinen2020dnadependentproteinkinase pages 9-9).

## Cofactor Requirements

The catalytic activity of PRKDC is DNA-dependent and requires double-stranded DNA (dsDNA), particularly DNA ends, as a cofactor for activation (bartlett2018establishedandemerging pages 4-7, dylgjeri2022dnapkcsatargetable pages 1-1, puustinen2020dnadependentproteinkinase pages 9-9, smith1999thednadependentprotein pages 1-2, yue2020dnapkcsamultifaceted pages 1-2). The presence of magnesium ions (Mg²⁺) is also required for its kinase activity (chen2021roleofprkdc pages 1-3, dylgjeri2022dnapkcsatargetable pages 1-1, johnson2023anatlasof pages 4-4, puustinen2020dnadependentproteinkinase pages 9-9, smith1999thednadependentprotein pages 1-2, yue2020dnapkcsamultifaceted pages 1-2). Its activity is stimulated more strongly by dsDNA with single-stranded overhangs than by blunt-ended dsDNA (bartlett2018establishedandemerging pages 4-7).

## Substrate Specificity

PRKDC preferentially phosphorylates serine or threonine residues that are immediately followed by a glutamine (Q) residue (johnson2023anatlasof pages 4-4, yue2020dnapkcsamultifaceted pages 1-2). The consensus substrate motif is defined as [S/T]Q (bartlett2018establishedandemerging pages 1-4, johnson2023anatlasof pages 4-4, puustinen2020dnadependentproteinkinase pages 9-9, smith1999thednadependentprotein pages 1-2, yue2020dnapkcsamultifaceted pages 1-2). This substrate specificity is shared with other members of the PIKK family, such as ATM and ATR (bartlett2018establishedandemerging pages 4-7, yue2020dnapkcsamultifaceted pages 1-2). However, PRKDC is also capable of phosphorylating non-SQ/TQ sites, such as serine or threonine followed by leucine or tyrosine, and can phosphorylate substrates that lack a clear consensus sequence, such as the C-terminal domain of RNA polymerase II (dylgjeri2022dnapkcsatargetable pages 3-3).

## Structure

PRKDC is a very large protein of over 4000 amino acids organized into three major structural regions: an N-terminal region, a central Circular Cradle, and a C-terminal Head (chen2021roleofprkdc pages 1-3, sibanda2017dnapkcsstructuresuggests pages 1-5).

**Domain Organization:** - **N-terminal Solenoid/Cradle:** The extensive N-terminal region (residues 1-2801) is composed of α-helical HEAT repeats and armadillo domains arranged into a solenoid that forms a hollow, double-ring or cradle shape (baretic2019structuralinsightsinto pages 2-3, bartlett2018establishedandemerging pages 4-7, sibanda2017dnapkcsstructuresuggests pages 10-14). This region creates a central channel or cavity for binding dsDNA and mediates interaction with the Ku70/80 heterodimer (bartlett2018establishedandemerging pages 4-7, chen2021roleofprkdc pages 1-3). It can be subdivided into an N-terminal unit (residues 1-892) and a Circular Cradle unit (residues 893-2801) (baretic2019structuralinsightsinto pages 2-3, sibanda2017dnapkcsstructuresuggests pages 10-14). - **C-terminal Head:** The C-terminal Head (residues 2802-4128) contains the catalytic and regulatory domains (baretic2019structuralinsightsinto pages 2-3, sibanda2017dnapkcsstructuresuggests pages 10-14). This includes the FAT (FRAP-ATM-TRRAP) domain, the kinase domain (KD), the FRB (FKBP12-rapamycin binding) domain, the Lst8 binding element (LBE), the PIKK regulatory domain (PRD), and the C-terminal FAT (FATC) domain (baretic2019structuralinsightsinto pages 2-3, dylgjeri2022dnapkcsatargetable pages 1-1). The FAT and FATC domains form an α-solenoid structure that surrounds and clamps the kinase domain, contributing to restricted access to the active site (bartlett2018establishedandemerging pages 7-9, sibanda2017dnapkcsstructuresuggests pages 1-5). - **Kinase Domain (KD):** The KD is bilobal, comprising a small N-terminal lobe and a larger C-terminal lobe separated by a flexible hinge, and shares structural features with other PIKKs like mTOR (bartlett2018establishedandemerging pages 4-7, bartlett2018establishedandemerging pages 7-9, sibanda2017dnapkcsstructuresuggests pages 1-5). It contains conserved motifs such as a P-loop, catalytic loop, and activation loop (sibanda2017dnapkcsstructuresuggests pages 1-5, sibanda2017dnapkcsstructuresuggests pages 14-19). - **FRB Domain:** A unique FRB-like domain inserts into the N-terminal lobe of the kinase domain and is thought to act as a gatekeeper, regulating substrate access to the active site (bartlett2018establishedandemerging pages 7-9, camfield2024secretsofdnapkcs pages 1-2).

The overall structure has been resolved by cryo-EM and X-ray crystallography, revealing the arrangement of these domains (baretic2019structuralinsightsinto pages 2-3, bartlett2018establishedandemerging pages 4-7).

## Regulation

The kinase activity of PRKDC is tightly regulated through allosteric mechanisms, protein-protein interactions, and post-translational modifications (PTMs).

**Allosteric Regulation:** PRKDC kinase activity is allosterically activated upon recruitment to DSBs by the Ku70/80 heterodimer (baretic2019structuralinsightsinto pages 2-3, bartlett2018establishedandemerging pages 4-7). The C-terminal tail of Ku80 binds directly to PRKDC, inducing conformational changes in the HEAT repeat domains (bartlett2018establishedandemerging pages 7-9, jette2015thednadependentprotein pages 6-9). This remodels the catalytic cleft, in part by moving the FRB domain, to allow increased access to the active site (bartlett2018establishedandemerging pages 7-9).

**Post-Translational Modifications:** - **Autophosphorylation:** Upon activation, PRKDC undergoes extensive autophosphorylation on serine and threonine residues located within distinct regulatory regions, most notably the PQR and ABCDE clusters (baretic2019structuralinsightsinto pages 2-3, bartlett2018establishedandemerging pages 1-4, sibanda2017dnapkcsstructuresuggests pages 10-14). Key sites include S2056 (within the PQR cluster) and T2609 (within the ABCDE cluster) (bartlett2018establishedandemerging pages 9-12, camfield2024secretsofdnapkcs pages 1-2, williams2008cryoemstructureof pages 1-2). These phosphorylation events induce further conformational changes that regulate kinase activity and facilitate the disassembly of PRKDC from DNA ends, allowing access for downstream repair factors (baretic2019structuralinsightsinto pages 6-7, bartlett2018establishedandemerging pages 7-9, bartlett2018establishedandemerging pages 9-12). - **Phosphorylation by other kinases:** PRKDC is also phosphorylated by other kinases, including ATM, ATR, and AKT, which modulates its activity (dylgjeri2022dnapkcsatargetable pages 3-3, yue2020dnapkcsamultifaceted pages 1-2). - **Other PTMs:** PRKDC is subject to other PTMs that contribute to its regulation, including PARylation, acetylation, ubiquitylation, neddylation, nitrosylation, and glycosylation (dylgjeri2022dnapkcsatargetable pages 3-3).

## Function

PRKDC is a multifunctional kinase that is abundantly expressed in human cells and plays a central role in maintaining genomic stability (yue2020dnapkcsamultifaceted pages 1-2).

**Signaling Pathways and Biological Roles:** - **DNA Repair:** The primary function of PRKDC is as a molecular sensor for DNA damage and a key component of the non-homologous end joining (NHEJ) pathway for repairing DNA double-strand breaks (DSBs) (bartlett2018establishedandemerging pages 1-4, chen2021roleofprkdc pages 1-3, yue2020dnapkcsamultifaceted pages 1-2). It forms the DNA-PK holoenzyme with the Ku70/80 heterodimer, which recruits PRKDC to DSBs (wu2024themultifacetedfunctions pages 1-2). DNA-PKcs then acts as a scaffold to protect DNA ends and recruit other NHEJ factors (chen2021roleofprkdc pages 1-3). - **V(D)J Recombination:** PRKDC is essential for V(D)J recombination, the process that generates immune receptor diversity in developing B and T lymphocytes (bartlett2018establishedandemerging pages 1-4, wu2024themultifacetedfunctions pages 1-2). This function requires the activation of the nuclease Artemis (bartlett2018establishedandemerging pages 9-12). - **Other Cellular Processes:** PRKDC also participates in other cellular processes, including the regulation of transcription, mitosis, cell migration, and autophagy (bartlett2018establishedandemerging pages 1-4, puustinen2020dnadependentproteinkinase pages 9-9, yang2020beyonddnarepair pages 11-14).

**Substrates and Interacting Partners:** - **Ku70/80:** Forms the DNA-PK holoenzyme with PRKDC and recruits it to DNA ends (baretic2019structuralinsightsinto pages 2-3). - **Artemis (DCLRE1C):** A key substrate whose nuclease activity is activated by PRKDC-mediated phosphorylation, which is critical for processing DNA hairpins during V(D)J recombination and some forms of NHEJ (bartlett2018establishedandemerging pages 9-12, matsumoto2022developmentandevolution pages 2-4, wu2024themultifacetedfunctions pages 1-2). - **XRCC4:** A substrate that works with DNA ligase IV to facilitate the final ligation step of NHEJ (bartlett2018establishedandemerging pages 1-4, chen2021roleofprkdc pages 1-3, wu2024themultifacetedfunctions pages 1-2). - **Other substrates:** Known substrates include histone H2AX, XLF, p53, Ku70/80, hsp90, and RNA polymerase II (bartlett2018establishedandemerging pages 4-7, bartlett2018establishedandemerging pages 9-12, chen2021roleofprkdc pages 1-3).

## Inhibitors

Several small molecule inhibitors targeting the kinase activity of PRKDC have been developed for experimental and therapeutic use (wu2024themultifacetedfunctions pages 1-2). These include the PI3K/PIKK family inhibitors wortmannin and LY294002 (unknownauthors1999dnadependentproteinkinase pages 1-4). More selective inhibitors include NU-7441, VX-984, AZD7648, and M3814 (pepetinib) (bartlett2018establishedandemerging pages 1-4, wu2024themultifacetedfunctions pages 1-2). Dual DNA-PKcs/mTOR inhibitors such as CC-115 also exist (bartlett2018establishedandemerging pages 1-4).

## Other Comments

Mutations or deficiencies in the *PRKDC* gene are associated with human diseases, primarily due to impaired DNA repair and V(D)J recombination (bartlett2018establishedandemerging pages 1-4).

* **Severe Combined Immunodeficiency (SCID):** Loss-of-function mutations in *PRKDC* cause a form of SCID characterized by impaired lymphocyte development, radiosensitivity, and genomic instability (bartlett2018establishedandemerging pages 1-4, matsumoto2022developmentandevolution pages 2-4, wu2024themultifacetedfunctions pages 1-2). For example, a patient with homozygous or compound heterozygous mutations, including an A3574V substitution and an exon 16 deletion, presented with SCID and profound neurological abnormalities, including cortical disorganization (woodbine2013prkdcmutationsin pages 7-8). These mutations drastically reduce or ablate kinase activity (woodbine2013prkdcmutationsin pages 7-8).
* **Cancer:** As a key regulator of genome stability, dysfunction of PRKDC is linked to increased cancer risk (bartlett2018establishedandemerging pages 1-4). Its inhibition is being explored as a therapeutic strategy to sensitize tumors to DNA-damaging therapies like radiation and chemotherapy (chen2021roleofprkdc pages 1-3, wu2024themultifacetedfunctions pages 1-2).

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