## Phylogeny

Death-associated protein kinase 1 (DAPK1) is a member of the DAPK family, which includes DAPK2 (DRP-1), DAPK3 (ZIPK), DRAK1, and DRAK2 (elbadawy2018novelfunctionsof pages 1-3, chen2019deathassociatedproteinkinase pages 2-3, makgoo2023theroleof pages 2-5). The catalytic domain of DAPK1 shares approximately 80-83% sequence identity with DAPK2 and DAPK3, and around 50% identity with DRAK1 and DRAK2 (farag2019death‐associatedproteinkinase pages 2-4, elbadawy2018novelfunctionsof pages 1-3, unknownauthors2009controlofdapk1 pages 19-24). Phylogenetic analyses based on the work of Manning et al. classify DAPK1 within the calcium/calmodulin-dependent protein kinase (CAMK) group of the human kinome (unknownauthors2009controlofdapk1 pages 13-19, farag2019death‐associatedproteinkinase pages 28-30, temmerman2013structuralandfunctional pages 1-2). Specifically, it belongs to a distinct branch of CAMKs known as the DMT kinase family, which also includes myosin light-chain-related kinases (MLCKs) and triple functional domain (TRIO) kinases (temmerman2013structuralandfunctional pages 1-2). Orthologs of DAPK1 are conserved across species from C. elegans to humans (singh2016deathassociatedprotein pages 2-4, farag2019death‐associatedproteinkinase pages 28-30).

## Reaction Catalyzed

As a serine/threonine kinase, DAPK1 catalyzes the transfer of the γ-phosphate group from ATP to the hydroxyl group of serine or threonine residues on a protein substrate (elbadawy2018novelfunctionsof pages 1-3, farag2019death‐associatedproteinkinase pages 2-4). ATP + [a protein]-L-serine/threonine = ADP + [a protein]-O-phospho-L-serine/threonine (elbadawy2018novelfunctionsof pages 1-3, farag2019death‐associatedproteinkinase pages 4-6, singh2016deathassociatedprotein pages 1-2).

## Cofactor Requirements

The kinase activity of DAPK1 requires Mg2+ as a cofactor for ATP coordination (elbadawy2018novelfunctionsof pages 1-3, farag2019death‐associatedproteinkinase pages 2-4, kim2019deathassociatedproteinkinase pages 1-3). Activation of the enzyme is also dependent on Ca2+/calmodulin (CaM) binding (farag2019death‐associatedproteinkinase pages 2-4, elbadawy2018novelfunctionsof pages 1-3).

## Substrate Specificity

The provided sources present contradictory information regarding the DAPK1 consensus substrate motif as determined by Johnson et al. (2023). One source states the motif shows a preference for lysine (K) at position -3, methionine (M) at position -2, and serine (S) at position +1 relative to the phosphorylation site (johnson2023anatlasof pages 4-4). However, multiple other sources report a preference for an arginine (Arg, R) residue at the -3 position, with one of these sources explicitly attributing this finding to the Johnson et al. (2023) study (unknownauthors2009controlofdapk1 pages 13-19, elbadawy2018novelfunctionsof pages 1-3, farag2019death‐associatedproteinkinase pages 4-6, singh2016deathassociatedprotein pages 1-2, you2024mechanismofdapk1 pages 3-4).

## Structure

DAPK1 is a large, 160 kDa multi-domain protein of 1430-1431 amino acids (farag2019death‐associatedproteinkinase pages 2-4, you2024mechanismofdapk1 pages 1-3, nair2013deathassociatedprotein pages 3-7). Its architecture comprises an N-terminal catalytic kinase domain (residues 13-267), a Ca2+/CaM-binding autoregulatory domain, eight to ten ankyrin repeats, a cytoskeleton binding domain, two P-loops, ROC and COR domains, and a C-terminal death domain (elbadawy2018novelfunctionsof pages 1-3, singh2016deathassociatedprotein pages 2-4, chen2019deathassociatedproteinkinase pages 2-3, nair2013deathassociatedprotein pages 1-3). The kinase domain has a typical bilobal architecture and contains a critical lysine residue at position 42 (Lys42) in the ATP-binding site that is essential for its phosphotransfer activity (farag2019death‐associatedproteinkinase pages 2-4, kim2019deathassociatedproteinkinase pages 1-3). DAPK1’s catalytic domain assumes a constitutively active ‘closed’ conformation (DFG-in) and does not require activation segment phosphorylation (singh2016deathassociatedprotein pages 2-4, farag2019death‐associatedproteinkinase pages 6-9, unknownauthors2020definingtheproximal pages 18-21). This is due to the substitution of the typical HRD motif with an HF/LD motif that maintains the active state via a local hydrophobic core (temmerman2013structuralandfunctional pages 1-2, singh2016deathassociatedprotein pages 2-4). Multiple crystal structures exist for the catalytic domain, including one bound to CaM (PDB: 2X0G) (farag2019death‐associatedproteinkinase pages 2-4).

## Regulation

DAPK1 is regulated by an autoinhibitory mechanism in which its Ca2+/CaM autoregulatory domain occludes the catalytic cleft, blocking substrate access (farag2019death‐associatedproteinkinase pages 6-9, singh2016deathassociatedprotein pages 2-4). This inhibition is relieved by the binding of Ca2+/calmodulin (farag2019death‐associatedproteinkinase pages 6-9). Autophosphorylation at Ser308 within this autoregulatory domain stabilizes the autoinhibited state and reduces CaM binding affinity (elbadawy2018novelfunctionsof pages 1-3, farag2019death‐associatedproteinkinase pages 6-9). Full activation is a two-step process requiring dephosphorylation of Ser308, which can be performed by phosphatases like PP2A, followed by Ca2+/CaM binding (farag2019death‐associatedproteinkinase pages 10-12, you2024mechanismofdapk1 pages 3-4, unknownauthors2009controlofdapk1 pages 19-24). Other phosphorylation sites also modulate activity; phosphorylation at Ser735 by ERK enhances kinase activity, while phosphorylation at Ser289 by RSK1/2 inhibits its apoptotic function (farag2019death‐associatedproteinkinase pages 10-12, farag2019death‐associatedproteinkinase pages 6-9). Intramolecular regulation also occurs via the ROC-COR domains; GTP binding to the ROC domain suppresses kinase activity (chen2019deathassociatedproteinkinase pages 2-3, unknownauthors2020definingtheproximal pages 18-21). DAPK1 stability is maintained through its interaction with the chaperone Hsp90, and its degradation is mediated by the ubiquitin-proteasome pathway via E3 ubiquitin ligases that bind its ankyrin repeats (farag2019death‐associatedproteinkinase pages 28-30, nair2013deathassociatedprotein pages 3-7).

## Function

DAPK1 is a stress-responsive kinase primarily expressed in the brain and lungs that plays a central role in regulating apoptosis and autophagy (unknownauthors2009controlofdapk1 pages 19-24, elbadawy2018novelfunctionsof pages 3-5, singh2016deathassociatedprotein pages 1-2). Upstream signals that activate DAPK1 include IFN-γ, Fas, TNF-α, and ER stress (elbadawy2018novelfunctionsof pages 1-3). It interacts with and phosphorylates numerous downstream targets, including the NMDA receptor subunit NR2B (at Ser-1303) in neuronal injury, NDRG2 and tau in neurodegeneration, myosin light chain (MLC) in cytoskeleton regulation, Beclin-1 (BECN1) in autophagy induction, and tuberin (TSC2) in mTORC1 signaling (elbadawy2018novelfunctionsof pages 3-5, farag2019death‐associatedproteinkinase pages 2-4, singh2016deathassociatedprotein pages 2-4, nair2013deathassociatedprotein pages 3-7). DAPK1 also interacts with microtubule-associated protein MAP1B and ERK, and forms complexes with DAPK3 (ZIPK) to amplify apoptotic signals (farag2019death‐associatedproteinkinase pages 10-12, elbadawy2018novelfunctionsof pages 1-3).

## Inhibitors

Several experimental small molecule inhibitors targeting DAPK1 have been developed, including purine analogs that target the catalytic domain (elbadawy2018novelfunctionsof pages 15-16, singh2016deathassociatedprotein pages 1-2). Additionally, Hsp90 inhibitors such as tanespimycin and geldanamycin can indirectly inhibit DAPK1 by causing its proteasomal degradation (farag2019death‐associatedproteinkinase pages 4-6).

## Other Comments

DAPK1 functions as a tumor suppressor, and its expression is frequently silenced in a wide range of cancers, including lymphomas, leukemias, and solid tumors of the lung, colon, and breast, via promoter hypermethylation (farag2019death‐associatedproteinkinase pages 10-12, elbadawy2018novelfunctionsof pages 3-5, unknownauthors2009controlofdapk1 pages 19-24). Restoration of DAPK1 expression using pharmacological demethylating agents can enhance antitumor activity (farag2019death‐associatedproteinkinase pages 10-12). Dysregulation of DAPK1 is also implicated in neurodegenerative diseases like Alzheimer’s disease and neuronal injury after stroke (elbadawy2018novelfunctionsof pages 3-5, singh2016deathassociatedprotein pages 1-2). Disease-associated mutations that affect DAPK1 function have been reported; for instance, mutation of the catalytically essential Lys42 residue abolishes kinase activity (farag2019death‐associatedproteinkinase pages 4-6).

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