## Phylogeny

Death-associated protein kinase 1 (DAPK1) belongs to a five-member human DAPK family (DAPK1-3, DRAK1-2). Its catalytic domain shares ~80–83 % identity with DAPK2 and DAPK3 and ~50 % with DRAK1/2 (Farag & Roh, 2019). Phylogenetic analysis places DAPK1 in the Ca2+/calmodulin-dependent protein kinase (CAMK) group, specifically on the DMT kinase branch together with myosin light-chain-related and TRIO kinases (Temmerman et al., 2013). Orthologs occur from Caenorhabditis elegans to humans, indicating strong evolutionary conservation (Singh et al., 2016).

## Reaction Catalyzed

ATP + [protein]-L-serine/threonine ⇌ ADP + [protein]-O-phospho-L-serine/threonine (Elbadawy et al., 2018).

## Cofactor Requirements

Mg2+ is essential for catalysis, and Ca2+/calmodulin binding is required for full activation (Farag & Roh, 2019).

## Substrate Specificity

Peptide profiling shows a preference for a basic residue at position –3 relative to the phosphorylation site (Lys or Arg). Met at –2 and Ser at +1 have also been reported (Johnson et al., 2023; Farag & Roh, 2019).

## Structure

DAPK1 is a 1,430–1,431-residue (~160 kDa) multidomain protein. It contains an N-terminal kinase domain (residues 13–267), a Ca2+/CaM autoregulatory segment, 8–10 ankyrin repeats, a cytoskeleton-binding region, two P-loops, ROC-COR GTPase modules, and a C-terminal death domain (Elbadawy et al., 2018; Nair et al., 2013). The kinase domain carries the essential Lys42 in the ATP-binding pocket, adopts a constitutively closed (DFG-in) conformation, and features an HF/LD motif that obviates activation-segment phosphorylation (Temmerman et al., 2013; Singh et al., 2016). Crystal structures of the isolated domain and its CaM complex are available (e.g., PDB 2X0G) (Farag & Roh, 2019).

## Regulation

• Autoinhibition: The Ca2+/CaM autoregulatory domain blocks substrate access; Ca2+/calmodulin binding relieves this inhibition (Singh et al., 2016).  
• Autophosphorylation: Ser308 phosphorylation stabilizes the inhibited state; PP2A-mediated dephosphorylation precedes activation (Farag & Roh, 2019).  
• Additional phosphorylation: ERK-driven Ser735 phosphorylation enhances activity, whereas RSK1/2-directed Ser289 phosphorylation suppresses apoptotic signalling (Farag & Roh, 2019).  
• Nucleotide binding: GTP binding to the ROC domain inhibits kinase activity (Chen et al., 2019).  
• Protein stability: Hsp90 maintains DAPK1 stability; E3 ubiquitin ligases target the ankyrin repeats for proteasomal degradation (Nair et al., 2013).

## Function

DAPK1 is abundantly expressed in brain and lung and acts as a stress-responsive regulator of apoptosis and autophagy (Singh et al., 2016). Upstream activators include IFN-γ, Fas, TNF-α and ER stress (Elbadawy et al., 2018). Reported substrates/interactors include:  
• NR2B (Ser1303) in excitotoxic neuronal injury  
• NDRG2 and tau in neurodegeneration  
• Myosin light chain in cytoskeletal regulation  
• Beclin-1 in autophagy induction  
• Tuberin (TSC2) in mTORC1 signalling  
• MAP1B, ERK, and DAPK3 for apoptotic amplification  
(Elbadawy et al., 2018; Farag & Roh, 2019).

## Inhibitors

Experimental ATP-competitive purine analogues target the kinase domain (Elbadawy et al., 2018). Hsp90 inhibitors tanespimycin and geldanamycin indirectly down-regulate DAPK1 by triggering its proteasomal degradation (Farag & Roh, 2019).

## Other Comments

DAPK1 functions as a tumour suppressor and is frequently silenced through promoter hypermethylation in many cancers; demethylating agents can restore its expression (Farag & Roh, 2019). Dysregulation is implicated in Alzheimer’s disease and post-stroke neuronal damage (Singh et al., 2016). Mutation of Lys42 abolishes catalytic activity (Farag & Roh, 2019).

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