1. Phylogeny  
   Death-associated protein kinase 2 (DAPK2) is a member of the death-associated protein kinase family that comprises DAPK1, DAPK2, DAPK3, and the related DRAK kinases. The catalytic domain of DAPK2 shows approximately 80% sequence identity with those of DAPK1 and DAPK3, whereas the DRAK kinases exhibit lower similarity, indicating that DAPK2 is evolutionarily closely related to its family counterparts (elbadawy2018novelfunctionsof pages 1-3, kawai1999deathassociatedproteinkinase pages 1-2). Orthologs of DAPK2 have been identified in a broad array of vertebrate species, supporting the notion that the gene emerged early in the evolution of complex eukaryotes and is part of an evolutionarily conserved signaling module among Ca²⁺/calmodulin (CaM)-dependent serine/threonine kinases (farag2019death‐associatedproteinkinase pages 2-4). In phylogenetic terms, DAPK2 is classified within the Ca²⁺/CaM-dependent kinase group, and its conservation across mammalian species underscores its fundamental role in cellular homeostasis and programmed cell death processes (kawai1999deathassociatedproteinkinase pages 1-2).
2. Reaction Catalyzed  
   DAPK2 catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of serine or threonine residues in substrate proteins. In doing so, the general reaction can be represented as follows:  
     ATP + [protein] – OH → ADP + [protein] – O‑phosphate + H⁺  
   This reaction is characteristic of serine/threonine kinases and enables DAPK2 to modulate the activity, stability, and interactions of target proteins through reversible phosphorylation (elbadawy2018novelfunctionsof pages 12-14, kawai1999deathassociatedproteinkinase pages 7-8).
3. Cofactor Requirements  
   The enzymatic activity of DAPK2 is dependent on the binding of calcium and calmodulin, which are essential for relieving autoinhibition by the CaM regulatory domain. In addition, as with most kinases, the catalytic process requires the presence of divalent metal ions—most commonly magnesium (Mg²⁺)—to facilitate ATP binding and the subsequent phosphoryl transfer reaction (elbadawy2018novelfunctionsof pages 1-3, farag2019death‐associatedproteinkinase pages 2-4, kawai1999deathassociatedproteinkinase pages 1-2).
4. Substrate Specificity  
   DAPK2 displays substrate specificity for serine/threonine residues within proteins that are involved in controlling cytoskeletal dynamics and cell death pathways. Experimentally, DAPK2 has been shown to phosphorylate the regulatory light chain (MLC) of myosin, implicating it in the regulation of membrane blebbing during apoptotic processes (kawai1999deathassociatedproteinkinase pages 7-8). In addition, DAPK2 is capable of phosphorylating other members of the DAPK family, suggesting an inter-kinase regulatory cascade within this family (elbadawy2018novelfunctionsof pages 3-5). Although no explicit consensus substrate motif has been firmly established, the high degree of conservation in the catalytic domain with DAPK1 implies that DAPK2 preferentially recognizes motifs similar to those of its relatives, phosphorylating serine/threonine residues within a context that may include basic amino acids favoring substrate binding (shiloh2018noncanonicalactivationof pages 12-13, shiloh2019ser289phosphorylationactivates pages 1-2).
5. Structure  
   The overall structure of DAPK2 is organized into distinct domains that underlie both its catalytic function and regulatory features. At the N-terminus, the protein contains a canonical kinase domain that comprises 11 conserved subdomains typically arranged in a bilobal fashion. The smaller N-terminal lobe consists mainly of five β-sheets and a single αC-helix, while the larger C-terminal lobe is predominantly α-helical; these lobes are connected by a short and flexible hinge region, which is critical for accommodating conformational changes during catalysis (patel2011structureofthe pages 1-4, elbadawy2018novelfunctionsof pages 1-3). Adjacent to the kinase domain lies a CaM-binding autoregulatory domain of approximately 42 residues. In the autoinhibited state, this domain interacts with the catalytic cleft, thereby blocking substrate access. This inhibition is relieved upon binding of Ca²⁺/CaM, which induces a conformational rearrangement that exposes the active site (kawai1999deathassociatedproteinkinase pages 4-6). Unique to DAPK2 among its family members is a short 40-residue C-terminal tail that does not share sequence homology with other proteins. This tail mediates homodimerization, an important allosteric mechanism that further regulates kinase activity by influencing CaM binding and positioning of the catalytic elements (elbadawy2018novelfunctionsof pages 12-14, farag2019death‐associatedproteinkinase pages 4-6). The highly conserved lysine residue within the ATP-binding pocket is essential for phosphotransfer activity and has been demonstrated to be critical for catalytic function, as evidenced by loss-of-function mutations (kawai1999deathassociatedproteinkinase pages 2-4, kim2019deathassociatedproteinkinase pages 12-14). Collectively, the structural organization of DAPK2—as derived from X-ray crystallography and modeled structures using resources such as AlphaFold—displays the characteristic features of serine/threonine kinases while incorporating unique regulatory motifs that differentiate it from other family members (elbadawy2018novelfunctionsof pages 1-3, patel2011structureofthe pages 1-4).
6. Regulation  
   The activity of DAPK2 is finely tuned by multiple regulatory mechanisms that involve post-translational modifications and protein–protein interactions. A primary mode of regulation is via Ca²⁺/calmodulin binding to the autoregulatory domain; under basal conditions, the autoinhibitory conformation is maintained by interaction of this domain with the catalytic cleft, with autophosphorylation at sites such as Ser318 reinforcing the inactive state (elbadawy2018novelfunctionsof pages 1-3, kawai1999deathassociatedproteinkinase pages 4-6). Activation occurs when a rise in intracellular calcium enables CaM binding, which displaces the autoregulatory domain, thereby exposing the active site for substrate phosphorylation. In addition to this canonical mechanism, DAPK2 can be activated independently of CaM binding by phosphorylation at alternative sites. For instance, phosphorylation at Ser299 by cyclic guanosine monophosphate (cGMP)-dependent protein kinase I enhances DAPK2 activity in a CaM-independent manner (elbadawy2018novelfunctionsof pages 12-14, farag2019death‐associatedproteinkinase pages 6-9). Moreover, non-canonical activation via phosphorylation at Ser289, mediated by AMP-activated protein kinase (AMPK), has been documented and links metabolic stress to autophagy induction by DAPK2 (shiloh2019ser289phosphorylationactivates pages 1-2, shiloh2018noncanonicalactivationof pages 12-13). The unique C-terminal tail further contributes to regulatory control through homodimerization, a process that modulates the affinity for CaM by generating a low-affinity binding site within the catalytic domain (elbadawy2018novelfunctionsof pages 12-14, farag2019death‐associatedproteinkinase pages 6-9). Another level of regulation is provided by the binding of 14-3-3 scaffold proteins to phosphorylated motifs, such as those that include Thr369 in the C-terminal region. This interaction, which can be promoted by phosphorylation events occurring through protein kinase B (Akt) or other kinases, stabilizes the autoinhibited dimeric form and protects inhibitory phosphorylation sites from dephosphorylation (horvath20211433proteinsinactivate pages 1-2, farag2019death‐associatedproteinkinase pages 9-10, yuasa2015suppressionofdeathassociated pages 6-6). Finally, interactions with molecular chaperones such as HSP90 contribute to the stabilization of DAPK2 levels by preventing proteasomal degradation, thus integrating chaperone-mediated quality control into the regulatory network (farag2019death‐associatedproteinkinase pages 4-6).
7. Function  
   DAPK2 plays a multifaceted role in transducing cellular signals that regulate programmed cell death and autophagy. As a Ca²⁺/CaM-dependent serine/threonine kinase, it is directly involved in phosphorylation events that trigger both type I apoptotic (caspase-dependent) and type II autophagic (caspase-independent) cell death pathways. In several cellular contexts, DAPK2 acts as a mediator of anoikis and serves as a suppressor of β-catenin-dependent anchorage-independent growth, especially in malignant epithelial cells, thereby contributing to tumor suppression (elbadawy2018novelfunctionsof pages 12-14, kawai1999deathassociatedproteinkinase pages 1-2). DAPK2 is also implicated in the regulation of granulocytic maturation and motility. For example, it modulates granulocytic motility by controlling cell spreading and polarization, functions that are critical for the proper immune response (farag2019death‐associatedproteinkinase pages 2-4, elbadawy2018novelfunctionsof pages 12-14). In apoptotic signaling, DAPK2 phosphorylates substrates such as the myosin light chain (MLC), which is important for membrane blebbing – a key morphological feature of apoptosis (kawai1999deathassociatedproteinkinase pages 7-8). Furthermore, DAPK2 has been shown to phosphorylate other DAPK family members, thereby establishing a kinase hierarchy that may fine-tune the cellular response to stress and death signals (elbadawy2018novelfunctionsof pages 3-5). In the context of autophagy, emerging evidence indicates that DAPK2 phosphorylates essential regulators of the autophagic machinery, including Beclin-1, thereby contributing to the dissociation of Beclin-1 from its inhibitor Bcl-XL and promoting autophagosomal formation (shiloh2018noncanonicalactivationof pages 12-13, shiloh2019ser289phosphorylationactivates pages 1-2). Collectively, these functions underscore the role of DAPK2 as a critical node in cellular decision-making processes that govern survival, apoptotic cell death, and autophagic response in both normal and disease settings.
8. Other Comments  
   Several pharmacological aspects have been explored in relation to DAPK2 due to its involvement in cell death pathways and potential tumor suppressor functions. Inhibitors originally developed against DAPK family members—such as FDA-approved agents including nintedanib, abemaciclib, and alectinib—have been tested for their ability to inhibit DAPK2 activity and exhibit comparable inhibitory potency across DAPK1, DAPK2, and DAPK3 (farag2019death‐associatedproteinkinase pages 26-28, farag2019death‐associatedproteinkinase pages 19-22). These compounds, although not exclusively selective for DAPK2, suggest that therapeutic strategies targeting the catalytic domain may be applicable to modulate DAPK2 activity in pathological conditions. With respect to disease associations, DAPK2 is implicated in cancers—especially of hematopoietic origin—where its pro-apoptotic activity contributes to tumor suppression by sensitizing cells to death stimuli. In addition, its regulatory influence on oxidative stress, as reflected in its ability to preserve mitochondrial function and regulate reactive oxygen species (ROS) production, positions DAPK2 as a potential target in diseases characterized by oxidative imbalance (elbadawy2018novelfunctionsof pages 14-15, farag2019death‐associatedproteinkinase pages 30-31). Although less extensively studied than DAPK1, DAPK2’s involvement in granulocytic maturation and motility further supports its significance in immune cell functions and inflammatory responses. Overall, while selective inhibitors specifically designed for DAPK2 are currently lacking, the cross-reactivity of available kinase modulators and expanding knowledge of its functional roles continue to drive interest in the development of novel therapeutic agents aimed at DAPK2-related signaling pathways.
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