1. Phylogeny  
   HIPK3 is a member of the homeodomain‐interacting protein kinase (HIPK) family, a group of evolutionarily conserved serine/threonine kinases belonging to the CMGC kinase group. It is one of four HIPK isoforms identified in vertebrates (HIPK1–4), and its catalytic domain displays high sequence identity (approximately 87–90%) with that of HIPK1 and HIPK2, while HIPK4 is more divergent in structure and localization (kaltheuner2021abemaciclibisa pages 1-2, laden2015effectoftyrosine pages 1-2). Phylogenetic analyses indicate that the HIPK family can be traced back to a common ancestral kinase, exemplified by the yeast kinase Yak1, from which the vertebrate HIPKs are derived (steinmetz2019drosophilahomeodomaininteractingprotein pages 1-3). In addition, HIPK3 is closely related to the dual‐specificity tyrosine phosphorylation‐regulated kinases (DYRKs), another subgroup within the CMGC family, reinforcing its conserved evolutionary placement within a core set of signaling kinases present in eukaryotes (kaltheuner2021abemaciclibisa pages 1-2, chowdhury2023cmgckinasesin pages 9-10).
2. Reaction Catalyzed  
   HIPK3 catalyzes the transfer of a phosphate group from ATP to target serine and threonine residues on substrate proteins, thereby converting ATP to ADP and generating a phosphorylated protein product along with the release of a proton. This reaction is typical of serine/threonine protein kinases and is represented as follows:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (kaltheuner2021abemaciclibisa pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of HIPK3 is dependent on divalent metal ions, with Mg²⁺ serving as an essential cofactor. The Mg²⁺ ion binds ATP within the active site, thereby promoting the correct positioning of the phosphate group for transfer (kaltheuner2021abemaciclibisa pages 1-2).
4. Substrate Specificity  
   HIPK3 functions as a serine/threonine kinase with substrate specificity that is characteristic of the CMGC kinase family. It phosphorylates numerous proteins involved in transcription regulation and apoptotic signaling. HIPK3 is known to target key transcriptional regulators including the C-terminal domain (CTD) of RNA polymerase II, where phosphorylation occurs primarily on the Ser2 and Ser5 residues within the canonical heptad repeats, and transcription factors such as JUN and RUNX2 (kaltheuner2021abemaciclibisa pages 6-6, kaltheuner2021abemaciclibisa pages 11-12). Moreover, HIPK3 phosphorylates FADD, a critical adaptor protein in the extrinsic apoptotic pathway, which contributes to its role in negatively regulating apoptosis (huang…2010characterizationofhuman pages 1-3). As a member of the CMGC kinase subgroup, HIPK3 is inferred to preferentially phosphorylate serine or threonine residues with adjacent proline residues, reflecting a consensus motif typically observed as S/T-P; supporting studies in Drosophila Hipk demonstrated a consensus motif with serine/threonine residues flanked by proline and basic residues (steinmetz2019drosophilahomeodomaininteractingprotein pages 9-11, hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4).
5. Structure  
   The three-dimensional structure of HIPK3 is characterized by a classical kinase fold that comprises a highly conserved N-terminal catalytic domain and a variable C-terminal region containing regulatory elements. The kinase domain consists of a smaller N-terminal lobe that primarily binds ATP and a larger C-terminal lobe responsible for substrate binding; together, these lobes form the active site (kaltheuner2021abemaciclibisa pages 1-2). A notable structural feature of HIPK3 is the CMGC-specific insert region spanning approximately 78–84 residues located in the C-terminal lobe; this insert is thought to provide a platform for specific protein–protein interactions and to influence substrate selectivity (kaltheuner2021abemaciclibisa pages 4-6, hogg2023functionsofsrpkclkanddyrkkinasesin pages 10-11). The activation loop of HIPK3 is phosphorylated on a conserved tyrosine residue (pY359), a modification that is critical for attaining full catalytic activity as it stabilizes the active conformation of the kinase active site (kaltheuner2021abemaciclibisa pages 11-12). In addition to the catalytic domain, HIPK3 contains a homeodomain-interaction domain (HID) which facilitates its association with homeodomain-containing transcription factors, a PEST-rich domain implicated in proteasomal degradation, and a C-terminal region enriched in serine, glutamine, and alanine residues that is thought to mediate co-factor interactions (laden2015effectoftyrosine pages 1-2, kaltheuner2021abemaciclibisa pages 1-2). The presence of an N-terminal nuclear localization signal ensures that HIPK3 predominantly resides in the nucleus, where it can efficiently interact with its transcriptional substrates (laden2015effectoftyrosine pages 1-2).
6. Regulation  
   HIPK3 is regulated through multiple post-translational modifications that modulate its catalytic activity, stability, and subcellular localization. Autophosphorylation on a conserved tyrosine residue within the activation loop (pY359) is an essential mechanism for kinase activation, rendering the enzyme constitutively active under basal conditions (kaltheuner2021abemaciclibisa pages 1-2, saul2013hipk2kinaseactivity pages 1-2). In addition to autophosphorylation, HIPK3 undergoes further phosphorylation on serine/threonine residues which may influence its interaction with substrates and regulatory proteins (kaltheuner2021abemaciclibisa pages 6-6). Ubiquitination and sumoylation are additional layers of regulation that affect HIPK3 protein stability and nuclear speckle localization; for instance, modifications by ubiquitin ligases and SUMO-conjugating enzymes can target HIPK3 for proteasomal degradation or alter its interaction with co-repressors (stefek2025biologyandpharmacological pages 1-3, hogg2023functionsofsrpkclkanddyrkkinasesin pages 19-21). Furthermore, interactions with regulatory proteins such as DCAF7 and other co-factors contribute to fine-tuning HIPK3 activity, although the precise molecular mechanisms have not been delineated in full detail (kaltheuner2021abemaciclibisa pages 11-12). These regulatory events collectively ensure that HIPK3 activity is appropriately modulated in response to cellular signaling dynamics.
7. Function  
   HIPK3 plays a multifaceted role in cellular signaling, with primary functions centered on transcription regulation, apoptosis modulation, and steroidogenic gene expression. In the nucleus, HIPK3 phosphorylates critical transcription regulators such as the carboxy-terminal domain of RNA polymerase II, which influences transcriptional initiation and elongation (kaltheuner2021abemaciclibisa pages 6-6). It also phosphorylates transcription factors including JUN and RUNX2, thereby contributing to the regulation of gene expression programs that govern cell proliferation and differentiation (kaltheuner2021abemaciclibisa pages 11-12, huang…2010characterizationofhuman pages 1-3). In the context of apoptosis, HIPK3 negatively regulates cell death by phosphorylating FADD, a key adaptor protein in the extrinsic apoptotic pathway, which may lead to altered outcomes in apoptotic signaling cascades (huang…2010characterizationofhuman pages 1-3, laden2015effectoftyrosine pages 1-2). Additionally, HIPK3 enhances androgen receptor-mediated transcription by functioning as a transcriptional activator and has been implicated in the phosphorylation of NR5A1; the latter activates SF1 and thereby upregulates steroidogenic gene expression upon stimulation of the cAMP signaling pathway (kaltheuner2021abemaciclibisa pages 1-2, adeyelu2023kinfamsdenovoclassification pages 19-20). In osteoblasts, HIPK3 supports osteogenic differentiation by phosphorylating RUNX2, which synergizes with co-repressors such as SPEN/MINT to activate the osteocalcin FGF-responsive element (OCFRE) and promote bone formation (kaltheuner2021abemaciclibisa pages 11-12, huang…2010characterizationofhuman pages 6-9). Moreover, HIPK3 has been shown to modulate autophagy and huntingtin protein levels in models of Huntington’s disease, indicating its involvement in cellular stress responses and neurodegenerative pathways (fu2018hipk3modulatesautophagy pages 6-7). Collectively, these functions underline HIPK3’s central role in directing cell fate decisions by integrating signals from transcriptional, apoptotic, and metabolic pathways (stefek2025biologyandpharmacological pages 1-3, hogg2023functionsofsrpkclkanddyrkkinasesin pages 10-11).
8. Other Comments  
   Several small-molecule inhibitors have been identified that target HIPK family members and are reported to inhibit HIPK3. Abemaciclib, an FDA-approved CDK4/6 inhibitor, has been shown to inhibit HIPK3 with an IC50 of approximately 467 nM, indicating potential off-target effects that may contribute to its therapeutic profile (kaltheuner2021abemaciclibisa pages 8-9). In addition, inhibitors based on the furo[3,2-b]pyridine scaffold, such as MU135 and MU1787, have been developed with reported IC50 values in the nanomolar range (stefek2025biologyandpharmacological pages 7-9). Beyond inhibitor development, HIPK3 dysregulation has been associated with a number of disease states. Altered HIPK3 expression and activity have been implicated in the progression of various cancers, including clear cell renal cell carcinoma, esophageal squamous cell carcinoma, and colorectal cancer, and it is considered a potential biomarker in these contexts (stefek2025biologyandpharmacological pages 13-13, stefek2025biologyandpharmacological pages 5-6). Moreover, its role in promoting androgen receptor-mediated transcription and steroidogenic gene expression links HIPK3 to disorders of steroidogenesis and metabolic dysfunction. HIPK3’s involvement in the modulation of autophagy further implicates it in neurodegenerative diseases such as Huntington’s disease (fu2018hipk3modulatesautophagy pages 6-7). These aspects make HIPK3 an attractive target for therapeutic interventions and warrant further investigation into isoform‐selective inhibitors to dissect its precise biological contributions.
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