1. Phylogeny  
   Homeodomain‐interacting protein kinase 1 (HIPK1, gene KIAA0630; also known as MYAK and NBAK2) belongs to a highly conserved family of serine/threonine kinases that function in transcription regulation and stress‐responsive signaling. HIPK1 is a member of the HIPK subfamily within the CMGC group of kinases, an assemblage that also includes CDKs, MAP kinases, GSK3 and CLK kinases. Based on sequence comparisons, HIPK1 shares high catalytic domain homology (~87–93% identity) with HIPK2 and HIPK3, while HIPK4 is more divergent and found only in mammals. Orthologs of HIPK1 are identifiable across vertebrate species, and a single homolog, dHipk, is present in Drosophila melanogaster, which underlines the deep evolutionary conservation of these kinases from invertebrates to mammals (kinsey2022usingtransgenicdrosophila pages 15-19, isono2006overlappingrolesfor pages 1-2). Gene duplication events that led to the emergence of multiple HIPK paralogs occurred early in vertebrate evolution, establishing a family of kinases that have conserved catalytic properties as well as specialized regulatory and substrate‐interaction domains (schmitz2014integrationofstress pages 1-2, kondo2003characterizationofcells pages 1-2).
2. Reaction Catalyzed  
   HIPK1 catalyzes a phosphorylation reaction in which a phosphate group from ATP is transferred to specific serine or threonine residues on substrate proteins. In chemical terms, the reaction can be summarized as follows:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This reaction underlies the kinase’s ability to modulate the function of its target proteins through phosphorylation, thereby affecting various cellular processes (kaltheuner2021abemaciclibisa pages 2-4, ecsedy2003homeodomaininteractingproteinkinase pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of HIPK1 is dependent on divalent cations. In particular, Mg²⁺ acts as a critical cofactor by coordinating ATP binding within the kinase domain and facilitating the transfer of the phosphate group to substrate proteins. This requirement for Mg²⁺ is characteristic of many serine/threonine kinases within the CMGC kinase family (laden2015effectoftyrosine pages 1-2).
4. Substrate Specificity  
   HIPK1 exhibits substrate specificity for serine/threonine residues within proteins that are involved in transcriptional regulation and stress responses. Notably, HIPK1 phosphorylates the nuclear protein DAXX in response to cellular stress, an event that mediates DAXX translocation from the nucleus to the cytoplasm. It also phosphorylates the transcription factor MYB, thereby inactivating its transcriptional activity. In addition, HIPK1 phosphorylates PAGE4 at threonine 51, a modification that is critical for potentiating the transcriptional activator properties of PAGE4. Although a precise consensus motif for HIPK1 has not been completely defined, the substrate specificity is consistent with that of related HIPK family members and appears to favor serine/threonine residues in regulatory contexts (ecsedy2003homeodomaininteractingproteinkinase pages 1-2, wong2020decodingnutrientsensing pages 45-49, laden2015effectoftyrosine pages 1-2).
5. Structure  
   HIPK1 comprises a modular structure characterized by a highly conserved N-terminal kinase domain and extended C-terminal regions that facilitate regulatory interactions. The kinase domain is responsible for both autophosphorylation (including on a conserved tyrosine residue in the activation loop) and for substrate phosphorylation on serine/threonine residues. This dual-specificity activity is aligned with the structural attributes observed in related members of the DYRK family within the CMGC kinome. In addition to its catalytic domain, HIPK1 contains a homeodomain-interacting region that enables it to function as a transcriptional corepressor, binding directly to homeodomain transcription factors. The C-terminal region is enriched in proline, glutamic acid, serine, and threonine residues and includes PEST sequences that are implicated in the regulation of protein stability. Furthermore, post-translational modifications such as ubiquitin-like SUMO-1 conjugation are important for mediating its nuclear targeting and for maintaining its localization within discrete nuclear bodies (giraud2004us11ofherpes pages 1-2, huang…characterizationofhuman pages 1-3, kinsey2022usingtransgenicdrosophila pages 15-19, laden2015effectoftyrosine pages 1-2).
6. Regulation  
   The activity and localization of HIPK1 are tightly regulated by multiple post-translational modification mechanisms. Autophosphorylation on a conserved activation-loop tyrosine residue is essential for full kinase activity, a mechanism that is shared with other HIPK family members and reflective of dual-specificity phosphorylation processes (laden2015effectoftyrosine pages 1-2, kaltheuner2021abemaciclibisa pages 2-4). In addition, covalent modification by SUMO-1 plays a significant role in mediating nuclear targeting, ensuring that HIPK1 is concentrated within nuclear bodies where it can effectively regulate transcription. A further layer of regulation is provided by extrinsic stress signals. Under basal conditions, HIPK1 suppresses MAP3K5-JNK activation; however, in the presence of tumor necrosis factor (TNF), HIPK1 undergoes translocation from the nucleus to the cytoplasm. This translocation is associated with the derepression of nuclear MAP3K5-JNK signaling, which promotes apoptotic pathways. These regulatory events illustrate the integration of post-translational modifications and dynamic subcellular localization in modulating HIPK1’s functions (giraud2004us11ofherpes pages 1-2, matt2016thednadamageinduced pages 8-9, isono2006overlappingrolesfor pages 1-2).
7. Function  
   HIPK1 plays multiple roles in cellular physiology, with its activity primarily centered on the regulation of transcription and the mediation of stress responses. As a transcriptional corepressor, HIPK1 interacts with homeodomain transcription factors to modulate gene expression. It phosphorylates DAXX, thereby facilitating the translocation of DAXX from the nucleus to the cytoplasm under stress conditions. In parallel, HIPK1 phosphorylates the transcription factor MYB, leading to its inactivation. These phosphorylation events directly influence cell survival and apoptotic pathways. Additionally, HIPK1 prevents MAP3K5-JNK activation in the absence of TNF, contributing to the maintenance of basal cell proliferation. Upon TNF stimulation, HIPK1 is translocated from the nucleus to the cytoplasm, a process that derepresses nuclear MAP3K5-JNK signaling and culminates in the promotion of apoptosis. Beyond its role in stress signaling, HIPK1 is involved in developmental processes such as the regulation of eye size, lens formation, and retinal lamination during late embryogenesis. It further contributes to angiogenesis and erythroid differentiation, and it has been implicated in the pathogenesis of malignant squamous cell tumors. The phosphorylation of PAGE4 at threonine 51 by HIPK1 is also critical for modulating the function of PAGE4 as a transcriptional activator, underscoring the kinase’s role in fine-tuning transcriptional outputs (ecsedy2003homeodomaininteractingproteinkinase pages 1-2, kondo2003characterizationofcells pages 1-2, isono2006overlappingrolesfor pages 1-2, matt2016thednadamageinduced pages 8-9, stefek2025biologyandpharmacological pages 1-3).
8. Other Comments  
   To date, specific inhibitors that selectively target HIPK1 have not been broadly characterized; however, pharmacological intervention strategies aimed at modulating the activity of HIPK family kinases are under active investigation. HIPK1’s involvement in a range of cellular processes—including transcription regulation, stress response, apoptosis, and developmental patterning—suggests that dysregulation of its activity may contribute to disease progression, including malignant transformation in squamous cell tumors. Although notable disease-associated mutations in HIPK1 have not been explicitly documented in the available literature, its role in mediating TNF-dependent signaling and in anti-oxidative stress responses highlights its potential as a therapeutic target in conditions where these pathways are disrupted (stefek2025biologyandpharmacological pages 1-3, isono2006overlappingrolesfor pages 1-2).

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