## Phylogeny

Homeodomain-interacting protein kinase 3 (HIPK3; also called DYRK6) belongs to the HIPK subfamily (HIPK1-4) of the CMGC group of Ser/Thr protein kinases and clusters phylogenetically with DYRK family members, particularly DYRK1A (Kaltheuner et al., 2021; Agnew et al., 2019). Orthologues are conserved from Drosophila to vertebrates (Kaltheuner et al., 2021; Laden et al., 2015).

## Reaction Catalyzed

ATP + L-seryl/threonyl/tyrosyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl/tyrosyl-[protein] (Kaltheuner et al., 2021; Agnew et al., 2019).

## Cofactor Requirements

Mg²⁺ is required for catalysis (Kaltheuner et al., 2021; Agnew et al., 2019).

## Substrate Specificity

No explicit consensus motif is reported. Consistent with the CMGC group, HIPK3 generally prefers SP/TP contexts (Agnew et al., 2019) and efficiently phosphorylates Ser2 and Ser5 within the heptad repeats of the RNA polymerase II CTD, but not Tyr1 or Thr4 (Kaltheuner et al., 2021).

## Structure

• Crystal structure of the human kinase domain (residues 184–550) resolved at 2.5 Å (PDB 7O7I) shows a classical bilobal fold with an “in” αC-helix and a DFG motif (Kaltheuner et al., 2021).  
• A large CMGC-specific insert (≈ residues 416–493) forms several helices and loops (Kaltheuner et al., 2021; Agnew et al., 2019).  
• The activation loop contains autophosphorylated Tyr359; an R(F/Y)YR motif and salt-bridge network lock the loop in an active conformation even in the apo state (Kaltheuner et al., 2021).  
• Overall domain architecture: N-terminal kinase domain, homeoprotein-interaction domain (HID), PEST/SRS region, autoinhibitory domain (AID), and a C-terminal Ser/Gln/Ala-rich tail (Kaltheuner et al., 2021; Schmitz et al., 2014).  
• Inhibitor-bound structure with abemaciclib is available (PDB 7O7J) (Kaltheuner et al., 2021).

## Regulation

• Intramolecular autophosphorylation on Tyr359 is essential for full activity and yields a constitutively active kinase fold; additional Tyr sites outside the activation loop can also be autophosphorylated (Laden et al., 2015; Kaltheuner et al., 2021).  
• Post-translational modifications—acetylation, ubiquitination, SUMOylation, and caspase cleavage—modulate activity, stability, and localisation (Kaltheuner et al., 2021; Schmitz et al., 2014).  
• SUMO attachment sites and alternative splicing influence interaction with the ubiquitin ligase SIAH1 (Schmitz et al., 2014).  
• Subcellular localisation is variably reported as mainly nuclear or predominantly cytoplasmic; mutation of Tyr359 does not markedly shift localisation (Kaltheuner et al., 2021; Laden et al., 2015).

## Function

HIPK3 acts chiefly in transcriptional regulation within the nucleus. Reported substrates or partners include c-Myc, SPT5, RNA polymerase II (Ser2/Ser5), androgen receptor, and RUNX2 (Kaltheuner et al., 2021; Laden et al., 2015). The kinase participates in stress responses, differentiation, proliferation, and apoptosis, forms nuclear speckles with DCAF7, and may engage in liquid–liquid phase separation (Kaltheuner et al., 2021; Liu et al., 2018).

## Inhibitors

Abemaciclib and the ATP-competitive compound CX-4945 inhibit HIPK3 in vitro; abemaciclib binds the hinge region of the kinase (Kaltheuner et al., 2021; Agnew et al., 2019).

## Other Comments

HIPK3 dysregulation is linked to cancer, chronic fibrosis, type 2 diabetes, and neurodegenerative disorders such as Alzheimer’s and Huntington’s disease. HIPK3-null mice show impaired glucose-stimulated insulin secretion (Agnew et al., 2019; Kaltheuner et al., 2021). In oncology, HIPK3 exhibits both tumour-suppressive and oncogenic properties and serves as a prognostic marker in non-small-cell lung and prostate cancers (Kaltheuner et al., 2021; Liu et al., 2018).

## 9. References

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