## Phylogeny

• Orthologs reported in vertebrates (Homo sapiens, Mus musculus, Danio rerio, Gallus gallus, Xenopus laevis), invertebrates (Drosophila melanogaster, Caenorhabditis elegans), fungi (Saccharomyces cerevisiae Ipk2/Kcs1), and early-diverging protists (Entamoeba histolytica EhIP6K); orthologs are absent from higher plants (shears2019inositolphosphatekinases pages 12-17, azevedo2011thesignalingrole pages 1-3).  
• Mammals possess three paralogs—IP6K1, IP6K2, IP6K3—derived from a single ancestral gene retained as one copy in lower eukaryotes (chakkour2024insightsintothe pages 1-2).  
• Kinome assignment: atypical protein kinase, PDKG-InsPK branch within the inositol phosphate kinase superfamily, sharing the two-lobe protein-kinase fold (shears2019inositolphosphatekinases pages 3-4).

## Reaction Catalyzed

1. myo-Inositol hexakisphosphate + ATP → 5-diphosphoinositol pentakisphosphate + ADP (chakkour2024insightsintothe pages 1-2).
2. 1,3,4,5,6-Inositol pentakisphosphate + ATP → diphosphoinositol tetrakisphosphate + ADP (padmanabhan2009characterizationofa pages 1-2).

## Cofactor Requirements

• Catalysis is Mg²⁺-dependent (chakkour2024insightsintothe pages 1-2).

## Substrate Specificity

• Highest catalytic efficiency toward InsP6; lower but measurable activity on selected InsP5 isomers (azevedo2011thesignalingrole pages 1-3).  
• A definitive linear consensus motif for protein-serine pyrophosphorylation by the 5-IP7 product has not been established (shears2019inositolphosphatekinases pages 1-3).

## Structure

• Domain organisation (human IP6K1):  
– N-terminal regulatory segment containing a lipase-like GDSDG motif (aa 82-86) and a PKA/PKC phospho-cluster KHSRRS (aa 115-120) (ghoshal2016inositolhexakisphosphatekinase1 pages 15-16).  
– Central SSLL motif essential for kinase activity (unknownauthors2003functionalstudiesof pages 22-27).  
– C-terminal catalytic core with the PxxxDxKxG signature that forms the ATP/inositol phosphate binding site (shears2019inositolphosphatekinases pages 1-3).  
• 3-D architecture: crystal structures of EhIP6KA (PDB 5W2N, 4O4D–F) and related EhIP6KC (PDB 6B5U/6B5V) reveal a conserved two-lobe fold, a canonical αC-helix, an unusual two-turn 3₁₀ helix forming one jaw of an open “clamshell” substrate pocket, and a strongly electropositive inositol-binding cavity (wang2014ip6kstructureand pages 1-2, wang2014ip6kstructureand pages 3-4).  
• Catalytic and regulatory features inferred for IP6K1 include a G-loop engaging ATP β/γ-phosphates, a Lys-Asp catalytic triad, a gatekeeper residue in the N-lobe, and continuous hydrophobic (C) and regulatory (R) spines that stabilise the active conformation (shears2019inositolphosphatekinases pages 1-3).  
• AlphaFold model AF-Q92551-F1 reproduces the experimental fold and maps the activation loop and spine residues (shears2019inositolphosphatekinases pages 12-17).

## Regulation

• Phosphorylation  
– S115, S118, S121 by PKA and PKCβ promote perilipin-1 binding and enhance catecholamine-stimulated lipolysis (chakraborty2018theinositolpyrophosphate pages 39-44, ghoshal2016inositolhexakisphosphatekinase1 pages 15-16).  
– S347 phosphorylation by CK2 targets the protein for proteasomal degradation (chakraborty2018theinositolpyrophosphate pages 39-44).  
• Acetylation: K416 and K433 by p300/CBP; functional consequences under investigation (minini2020thekeyrole pages 5-7).  
• Ubiquitination: K226 regulates protein turnover; K226A mutation impairs this control (minini2020thekeyrole pages 5-7).  
• Protein interactions: DDB1 binds and inhibits catalytic activity until DNA damage triggers dissociation (unknownauthors2019discoverysynthesisand pages 23-27).  
• Allosteric control: high K\_m for ATP (~1 mM) renders activity sensitive to cellular energy charge (minini2020thekeyrole pages 3-5).  
• Nucleus–cytosol shuttling modulates context-specific functions (minini2020thekeyrole pages 5-7).

## Function

• Broad expression in brain, adipose tissue, skeletal muscle, liver, pancreas, immune cells, and testis (chakkour2024insightsintothe pages 1-2).  
• Metabolic regulation: 5-IP7 competitively binds the Akt PH-domain (IC₅₀ ≈ 20 nM) to restrain Akt signalling; IP6K1 knockout elevates AMPK activity and improves glucose tolerance (minini2020thekeyrole pages 5-7).  
• Lipolysis: phosphorylated IP6K1 associates with perilipin-1 to potentiate β-adrenergic glycerol release (ghoshal2016inositolhexakisphosphatekinase1 pages 15-16).  
• Cytoskeleton and migration: binds α-actinin and promotes FAK pyrophosphorylation; deletion reduces cell migration (chakkour2024insightsintothe pages 2-3, chakraborty2018theinositolpyrophosphate pages 21-22).  
• Vesicular trafficking: 5-IP7 pyrophosphorylates dynein intermediate chain and AP3B1, shifting cargo toward dynein motors (chakkour2024insightsintothe pages 2-3).  
• Chromatin and epigenetics: nuclear IP6K1 inhibits JMJD2C, elevating H3K9me3 and modulating DNMT-dependent methylation (chakkour2024insightsintothe pages 3-5).  
• DNA repair: required for efficient homologous recombination (wormald2017developmentofa pages 13-14).  
• Innate immunity: catalytic activity promotes TBK1-IRF3 phosphorylation and IFN-β transcription (pulloor2014humangenomewidernai pages 6-6).  
• Nervous system: knockout mice exhibit cortical migration defects, altered social behaviour, and impaired sensorimotor gating (heitmann2023theroleof pages 11-12).

## Inhibitors

• TNP (N²-(m-trifluoromethylbenzyl)-N⁶-(p-nitrobenzyl)purine): ATP-competitive; IC₅₀ 12–39 µM depending on assay ATP concentration (wormald2017developmentofa pages 7-9).  
• Compound 24 (purine analogue): IC₅₀ 0.75 µM, K\_i 0.20 µM; ~25-fold selectivity over IP6K2 and ~50-fold over IP6K3 (wormald2019synthesisandcharacterization pages 14-17).  
• Myricetin: IC₅₀ 4.96 µM (wormald2017developmentofa pages 7-9).  
• 6-Hydroxy-DL-Dopa: IC₅₀ 1.84 µM (wormald2017developmentofa pages 7-9).  
• LI-2242: orally active inhibitor that ameliorates diet-induced obesity and hyperglycaemia in mice (mukherjee2023theip6kinhibitor pages 17-17).  
• Additional pan-IP6K inhibitors SC-233 and BIP-135 reported (minini2020thekeyrole pages 10-12).

## Other Comments

• Metabolic disease: genetic deletion or pharmacological inhibition protects against diet-induced obesity, insulin resistance, and hepatic steatosis (mukherjee2023theip6kinhibitor pages 17-17, minini2020thekeyrole pages 5-7).  
• Cancer biology: IP6K1 loss diminishes tumour growth and cell migration in carcinogen-induced models (minini2020thekeyrole pages 10-12).  
• Disease-relevant variants: S118A (loss of phosphorylation, reduced perilipin-1 interaction) and K226A (ubiquitination-defective) have been characterised (minini2020thekeyrole pages 5-7).  
• Whole-body knockout mice display enhanced thermogenesis and resistance to weight gain (chakraborty2018theinositolpyrophosphate pages 21-22).

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