## Phylogeny

Orthologous enzymes are found in Saccharomyces cerevisiae (Arg82/Ipk2), Dictyostelium discoideum (IpkA/B), Drosophila melanogaster (IPMK), Arabidopsis thaliana (AtIPMK), Mus musculus (Ipmk) and Homo sapiens (IPMK) (Shears & Wang, 2019, pp. 1–3; Saiardi et al., 2018, pp. 16–21; Unknown Authors, 2009, pp. 18–24).  
Within the kinome, IPMK belongs to the atypical protein kinase class, PDKG-InsPK subfamily of the inositol-phosphate-kinase clade (Shears & Wang, 2019, pp. 3–4).  
Crystal structures show that yeast, plant and human catalytic cores overlay with an RMSD of ~1 Å and share the two-lobe protein-kinase fold characteristic of IP3K and IP6K families (Unknown Authors, 2009, pp. 63–69; Shears & Wang, 2019, pp. 12–17).

## Reaction Catalyzed

Ins(1,4,5)P₃ + ATP ⇌ ADP + Ins(1,3,4,5)P₄ (Sowd et al., 2024, pp. 1–4)  
Ins(1,3,4,5)P₄ + ATP ⇌ ADP + Ins(1,3,4,5,6)P₅ (Sowd et al., 2024, pp. 1–4)  
Ins(1,3,4,6)P₄ + ATP ⇌ ADP + Ins(1,3,4,5,6)P₅ (Unknown Authors, 2003, pp. 14–18)  
PtdIns(4,5)P₂ + ATP ⇌ ADP + PtdIns(3,4,5)P₃ (Malabanan & Blind, 2016, pp. 3–4)

## Cofactor Requirements

Catalysis requires two Mg²⁺ ions that coordinate the nucleotide within the active site (Wang & Shears, 2017, pp. 3–5; Shears & Wang, 2019, pp. 12–17).

## Substrate Specificity

IPMK displays broad specificity for soluble inositol phosphates, with highest turnover of Ins(1,4,5)P₃ and Ins(1,3,4,5)P₄; additional activity is observed toward Ins(1,3,4,6)P₄ and Ins(1,4,5,6)P₄ (Sowd et al., 2024, pp. 1–4; Unknown Authors, 2003, pp. 14–18).  
The enzyme also functions as a lipid 3-kinase for nuclear PtdIns(4,5)P₂ (Malabanan & Blind, 2016, pp. 3–4).  
Substrate discrimination is mediated by an electropositive pocket in the divergent C-lobe; no peptide consensus motif has been identified (Shears & Wang, 2019, pp. 1–3; Malabanan & Blind, 2016, pp. 3–4).

## Structure

Single kinase domain (residues 50–416) composed of an N-lobe β-sheet with αC-helix and an α-helical C-lobe connected by a short hinge (Wang & Shears, 2017, pp. 1–2).  
Representative structures: human IPMK with flavonoid inhibitor (PDB 4O4E, 2.4 Å), yeast IPMK (PDB 2IF8, 2.0 Å) and Arabidopsis IPMK (PDB 4FRF) (Gu et al., 2019, pp. 6–8; Malabanan & Blind, 2016, pp. 9–13).  
Catalytic motifs include VAIK Lys75 (ATP anchoring), HRD Asp144 (catalytic base) and DFG-like Asp385 (Mg²⁺ binding) forming part of the regulatory spine with αC Glu131 (Wang & Shears, 2017, pp. 3–5).  
Activation segment (residues 161–190) contains Tyr191, a glucose-regulated phosphorylation site (Malabanan & Blind, 2016, pp. 9–13).  
Unique “IP loop” and a proline-rich loop reposition basic residues for substrate contact; these inserts are absent from canonical protein kinases (Shears & Wang, 2019, pp. 3–4; Wang & Shears, 2017, pp. 3–5).  
AlphaFold model AF-Q8NFU5-F1 reproduces the two-lobe architecture and IP loop orientation (Shears & Wang, 2019, pp. 3–4).

## Regulation

Post-translational modification: glucose-induced Tyr191 phosphorylation; Y191F abolishes this event without altering catalytic rate. Additional Ser/Thr phosphorylation is detected but unaffected by glucose; the upstream tyrosine kinase is unknown (Bang et al., 2012, pp. 2–4).  
Protein-protein interactions: binding to nuclear receptor SF-1 lowers k\_cat but improves K\_M for PtdIns(4,5)P₂ phosphorylation (Malabanan & Blind, 2016, pp. 9–13). N-terminal residues 1–60 associate with mTORC1, stabilising the complex independently of enzymatic activity (Malabanan & Blind, 2016, pp. 3–4). Phospho-Tyr191 enhances binding to AMPKα2 via regions encoded by exons 4 and 6 (Bang et al., 2012, pp. 2–3).

## Function

Expression: high in intestinal ileum with notable levels in spleen and skeletal muscle; localisation is both nuclear and cytoplasmic, though predominantly nuclear in many cell types (Guha et al., 2020, pp. 6–9; Unknown Authors, 2012, pp. 14–20).  
Biological roles:  
• Epigenetic control—IPMK products Ins(1,4,5,6)P₄, InsP₅ and InsP₆ act as obligatory cofactors for HDAC3; knockout elevates histone H4 acetylation (Sowd et al., 2024, pp. 4–10).  
• Energy sensing—phospho-Tyr191 IPMK binds AMPKα2, affecting Thr172 phosphorylation in a glucose-dependent manner (Bang et al., 2012, pp. 2–3).  
• Nutrient signalling—N-terminal interaction stabilises mTORC1, coupling amino-acid availability to TOR signalling (Malabanan & Blind, 2016, pp. 3–4).  
• Autophagy—required for AMPK-dependent ULK1 activation and transcription of autophagy genes during liver regeneration (Guha et al., 2019, pp. 18–20).  
• Programmed necrosis—InsP₅/InsP₆ produced by IPMK bind MLKL and relieve its auto-inhibition (Malabanan & Blind, 2016, pp. 9–13).  
• Transcriptional scaffolding—yeast Arg82/Ipk2 integrates into the ArgR-Mcm1 complex independently of kinase activity to regulate arginine-responsive genes (Unknown Authors, 2003, pp. 14–18).

## Inhibitors

Flavonoid “UNC7437” (compound 1) inhibits human IPMK with IC₅₀ = 26 ± 1.2 nM; binding mode resolved in PDB 4O4E (Gu et al., 2019, pp. 6–8).  
UNC9750 (compound 15) shows improved mouse pharmacokinetics and lowers cellular InsP₅ at sub-µM concentrations (Zhou et al., 2024, pp. 3–7).

## Other Comments

Global Ipmk knockout in mice is embryonic-lethal with neural-tube defects (Unknown Authors, 2009, pp. 18–24).  
Loss of kinase activity reduces proliferation of PTEN-deficient U251-MG glioblastoma cells (Sowd et al., 2024, pp. 1–4).  
Germline IPMK mutations are linked to small-intestinal carcinoid tumours (Zhou et al., 2024, pp. 27–28).

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