## Phylogeny

Inositol-1,4,5-trisphosphate 3-kinase A (ITPKA) belongs to the inositol polyphosphate kinase (IPK) family and clusters within the atypical protein kinase (aPK) group of the lipid-kinase-like branch of the group 1 protein kinase superfamily (González et al., 2004; Schell, 2010). IP3Ks arose before the divergence of fungi, plants and animals and are conserved across metazoans, with functional homologues in C. elegans and Drosophila (Schell, 2010; Xiong et al., 2024). Although structurally related to phosphoinositide 3-kinases, ITPKA is functionally distinct because it phosphorylates soluble inositol phosphates rather than membrane phosphoinositides (Schell, 2010; Windhorst et al., 2017).

## Reaction Catalyzed

ATP + 1D-myo-inositol 1,4,5-trisphosphate ⇌ ADP + 1D-myo-inositol 1,3,4,5-tetrakisphosphate (Schell, 2010).  
ITPKA also transfers the γ-phosphate of ATP to Ser29 of the protein substrate PYCR1 (Luo et al., 2024).

## Cofactor Requirements

Catalysis requires Mg²⁺ or Mn²⁺ as divalent metal cofactors (Márquez-Moñino et al., 2024; Zhang et al., 2023).

## Substrate Specificity

• High specificity for Ins(1,4,5)P₃, phosphorylating the 3-OH exclusively; no activity toward phosphoinositide lipids (Schell, 2010; Márquez-Moñino et al., 2024).  
• Selectivity is conferred by a four-helix “IP lobe” insertion that forms a positively charged pocket for the inositol phosphate (González et al., 2004; Schell, 2010).  
• Protein substrate: PYCR1 (Ser29) (Luo et al., 2024).  
• Consensus peptide-array data are unavailable because ITPKA is not a canonical protein kinase (González et al., 2004; Windhorst et al., 2017; Xiong et al., 2024).

## Structure

• 461-residue homodimer (Zhang et al., 2023).  
• N-terminal actin-binding domain (1–52); 3-D structure unresolved (Schell, 2010; Windhorst et al., 2017).  
• C-terminal IPK catalytic domain (245–455); crystal structure solved (PDB 1W2F). Key catalytic residue Lys264 (Zhang et al., 2023).  
• Lacks canonical protein-kinase features (C-helix, hydrophobic spine, DFG catalytic loop) but retains an activation-segment motif (ID416FG) that orients ATP (González et al., 2004).  
• Unique four-helix insertion in the C-lobe accommodates Ins(1,4,5)P₃ (González et al., 2004).

## Regulation

• Phosphorylation: PKA, PKC and Ca²⁺/CaM-dependent protein kinase II (CaMKII) modify ITPKA; CaMKII phosphorylation increases V\_max and Ca²⁺/CaM affinity (Schell, 2010; Zhang et al., 2023).  
• Ca²⁺/Calmodulin: reports are conflicting—some describe direct CaM activation, whereas others state mammalian ITPKA lacks a CaM-binding domain (Schell, 2010; Xiong et al., 2024).  
• Proteolysis: Ca²⁺-regulated calpains cleave ITPKA, separating targeting and catalytic modules but leaving the catalytic fragment active (Schell, 2010).

## Function

Expression: Highly enriched in neurons (forebrain principal neurons, cerebellar Purkinje cells, dendritic spines) and detected in myeloid precursors (Schell, 2010; Unknown Authors, 2010).  
Interacting partners and upstream regulators: F-actin, calmodulin, PKA, PKC, CaMKII, RASA3, Ras, Rap, Rac and protein substrate PYCR1 (Schell, 2010; Xiong et al., 2024; Luo et al., 2024).  
Signalling: Terminates Ins(1,4,5)P₃-mediated Ca²⁺ release by generating Ins(1,3,4,5)P₄ and modulates Ras/Rap GTPase pathways (Schell, 2010).  
Biological roles: Regulates synaptic plasticity, learning/memory and dendritic-spine morphology; bundles F-actin to remodel the cytoskeleton and enhance cell motility; phosphorylation of PYCR1 promotes glioma growth and invasion (Schell, 2010; Zhang et al., 2023; Luo et al., 2024).

## Inhibitors

Purine-based inhibitors have been described; the best characterised are BIP-4 (IC₅₀ ≈ 157 nM, competitive) and BAMB-4 (IC₅₀ ≈ 20 µM, mixed) (Márquez-Moñino et al., 2024; Zhang et al., 2023; Unknown Authors, 2010).

## Other Comments

ITPKA acts as an oncogene—over-expression drives motility, invasion and metastasis in glioblastoma and lung adenocarcinoma (Márquez-Moñino et al., 2024; Windhorst et al., 2017; Luo et al., 2024). Dysregulation is also linked to Alzheimer’s disease and Kawasaki disease (Schell, 2010; Xiong et al., 2024). Somatic mutation frequency is low (~1.1 %), with missense/truncating variants clustered in the catalytic domain; alterations in CaM- or F-actin-binding sites change activity or localisation (Schell, 2010; Zhang et al., 2023).

## 9. References

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