1. Phylogeny  
   Inositol‑trisphosphate 3‑kinase A (ITPKA) is a member of the inositol phosphate kinase family, a conserved group of enzymes that are present in virtually all metazoans. Within mammals, the family comprises three main isoforms—ITPKA, ITPKB, and ITPKC—with ITPKA sharing a common evolutionary origin with its paralogs. Phylogenetic analyses based on the human kinome have demonstrated that the inositol phosphate kinases form a distinct sub‐group separate from lipid kinases, largely attributable to their unique substrate specificity and regulatory mechanisms. Orthologs of ITPKA can be identified in species ranging from invertebrates such as Drosophila to vertebrates including humans and rodents, indicating its deep evolutionary conservation. This enzyme can be traced back to early eukaryotic ancestors that possessed the basic machinery for inositol phosphate metabolism, and its distribution across the animal kingdom places it within an archetypical branch of Ca²⁺/calmodulin‐regulated kinases. The evolutionary history of ITPKA, as detailed in the literature, implies that the enzyme’s core catalytic and regulatory domains have been maintained throughout evolution, allowing it to integrate calcium signaling with phosphoinositide metabolism in complex multicellular organisms (schell2010inositoltrisphosphate3kinases pages 1-3, windhorst2017inositol145trisphosphate3kinasea(itpka) pages 1-3, xiong2024originevolutionand pages 17-18).
2. Reaction Catalyzed  
   ITPKA catalyzes a specific phosphorylation reaction in which ATP is used as a phosphate donor to modify the inositol ring of its substrate. The reaction involves the phosphorylation of 1D‑myo‑inositol 1,4,5‑trisphosphate (Ins(1,4,5)P₃) at the 3‑hydroxyl position, resulting in the formation of 1D‑myo‑inositol 1,3,4,5‑tetrakisphosphate (Ins(1,3,4,5)P₄) along with the conversion of ATP into ADP and the release of a proton. This highly specific transfer of a phosphate group defines the catalytic function of ITPKA and sets it apart from other kinases that act on lipid substrates (schell2010inositoltrisphosphate3kinases pages 1-3, bennion2009”drosophila”geneticsas pages 88-94).
3. Cofactor Requirements  
   The catalytic activity of ITPKA depends on the presence of essential cofactors. In particular, ATP is required as the donor of the phosphate group in the phosphorylation reaction, and divalent metal ions—most notably magnesium (Mg²⁺)—are indispensable for proper enzymatic function. Mg²⁺ serves to coordinate the ATP substrate and facilitate the correct orientation of both ATP and the inositol phosphate substrate within the active site, thereby optimizing the phosphoryl transfer reaction (wang2014ip6kstructureand pages 11-11, schell2010inositoltrisphosphate3kinases pages 1-3).
4. Substrate Specificity  
   ITPKA exhibits a high degree of substrate specificity, primarily recognizing 1D‑myo‑inositol 1,4,5‑trisphosphate (Ins(1,4,5)P₃) as its substrate. The enzyme specifically targets the 3‑hydroxyl group of the inositol ring, catalyzing its phosphorylation to yield Ins(1,3,4,5)P₄. This selectivity is achieved by a well‐defined binding pocket within the catalytic domain, which contains an elaborated IP lobe that precisely orients the substrate for the phosphoryl transfer reaction. In contrast to more promiscuous kinases that may act on multiple isomers of inositol phosphates, ITPKA’s structural features ensure that its activity is confined mainly to Ins(1,4,5)P₃ (schell2010inositoltrisphosphate3kinases pages 16-18, marquezmonino2024substratepromiscuityof pages 14-15).
5. Structure  
   The overall three‑dimensional architecture of ITPKA is modular, comprising two main regions with distinct functional roles. At its N‑terminus, ITPKA contains a regulatory domain that includes a calmodulin-binding motif as well as an F‑actin binding region. This N‑terminal domain is responsible for conferring the ability to interact with the actin cytoskeleton, thereby mediating functions that extend beyond mere catalysis and contributing to the shaping of dendritic spine morphology in neuronal cells. The C‑terminal portion of the protein houses the catalytic kinase domain, which adopts a typical kinase fold characterized by an ATP‑binding pocket, an activation segment, and a distinct IP lobe critical for substrate recognition and orientation. High‑resolution crystallographic analyses have revealed that the ATP‑binding site of ITPKA is enclosed and hydrophobic in nature, with key residues forming interactions that stabilize the bound nucleotide and facilitate phosphoryl transfer. Important structural features include a conserved catalytic core with an activation loop and elements such as the C‑helix, which together contribute to aligning catalytic residues in an optimal geometry. The spatial arrangement of these domains enables the enzyme to couple calcium‑regulated activation via calmodulin with substrate phosphorylation, thereby integrating extracellular signals with intracellular Ca²⁺ homeostasis (schell2010inositoltrisphosphate3kinases pages 5-6, schell2010inositoltrisphosphate3kinases pages 6-7, windhorst2017inositol145trisphosphate3kinasea(itpka) pages 1-3, chamberlain2005structuralinsightsinto pages 6-7).
6. Regulation  
   ITPKA is subject to intricate regulatory control mechanisms that modulate its catalytic activity in response to cellular signals. A primary regulatory mechanism involves the binding of calcium‑loaded calmodulin to a distinct motif located within the N‑terminal regulatory domain. This Ca²⁺/calmodulin binding event induces a conformational change that enhances the enzyme’s activity by up to 20‑fold, thereby linking the enzyme’s function directly to cellular Ca²⁺ levels. In addition to calmodulin‑dependent regulation, ITPKA is modulated by phosphorylation events mediated by various protein kinases. Phosphorylation by protein kinase A (PKA) has been observed to activate ITPKA, whereas protein kinase C (PKC) can phosphorylate specific residues (for example, at Ser‑175 in rodent isoforms) to exert an inhibitory effect on its catalytic activity. Furthermore, Ca²⁺/calmodulin‑dependent protein kinase II (CaMKII) phosphorylates ITPKA at distinct sites, resulting in increased Vₘₐₓ and enhanced affinity for Ca²⁺/calmodulin. Proteolytic mechanisms also contribute to the regulation of ITPKA; the enzyme is highly susceptible to cleavage by calcium‑activated proteases such as calpains, particularly at PEST sequences in the N‑terminal region. Such proteolytic events can result in the separation of the actin‑binding domain from the catalytic core, thereby altering both subcellular localization and the functional output of the enzyme (bennion2009”drosophila”geneticsas pages 88-94, schell2010inositoltrisphosphate3kinases pages 6-7, windhorst2017inositol145trisphosphate3kinasea(itpka) pages 8-9).
7. Function  
   The primary function of ITPKA is to regulate intracellular inositol phosphate metabolism and, by extension, calcium homeostasis. By catalyzing the conversion of Ins(1,4,5)P₃ to Ins(1,3,4,5)P₄, ITPKA modulates the duration and spatial propagation of Ca²⁺ signals within the cell. The production of Ins(1,3,4,5)P₄ not only serves to terminate the rapid release of Ca²⁺ from intracellular stores but may also play a role in sustaining longer‐term signaling events by protecting Ins(1,4,5)P₃ from dephosphorylation. In neurons, ITPKA is expressed at high levels—particularly in the brain—and its dual functionality is of special importance. In addition to its kinase activity, the N‑terminal F‑actin‑binding domain facilitates interactions with the cytoskeleton, thereby influencing dendritic spine morphology, synaptic plasticity, and overall neuronal connectivity. Overexpression studies in tumor cell models have implicated ITPKA as an oncogene; aberrantly high levels of ITPKA can augment cell motility through its actin bundling function, contributing to enhanced metastatic potential in cancers such as lung and breast carcinoma. Moreover, by modulating the levels of inositol polyphosphates, ITPKA can indirectly influence the recruitment of PH domain‑containing proteins involved in downstream signaling cascades, which include pathways related to cell growth, proliferation, and apoptosis (schell2010inositoltrisphosphate3kinases pages 5-6, windhorst2017inositol145trisphosphate3kinasea(itpka) pages 9-11, bennion2009”drosophila”geneticsas pages 88-94).
8. Other Comments  
   Selective inhibition of ITPKA has been an area of active investigation due to its involvement in both calcium signaling and actin cytoskeletal regulation. Small‑molecule inhibitors, such as BIP‑4, have been identified that target the Ins(1,4,5)P₃‑binding pocket within the kinase domain. However, these inhibitors are specific to the enzymatic function and do not affect the protein’s actin bundling activity, which represents an additional functional facet of ITPKA that currently lacks targeted inhibitory compounds. Overexpression of ITPKA has been documented in various solid tumors and is associated with oncogenic progression; moreover, alterations in gene body methylation have been proposed as early biomarkers of tumor malignancy linked to ITPKA expression. Although the majority of research on ITPKA has focused on its roles in the central nervous system, evidence also suggests potential contributions to immune cell signaling, an aspect underscored by functional studies on related isoforms within the ITPK family (windhorst2017inositol145trisphosphate3kinasea(itpka) pages 8-9, ribeiro2017institutonacionalde pages 50-51).
9. References  
   [1] schell2010inositoltrisphosphate3kinases pages 1-3. Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. Cellular and Molecular Life Sciences, 67:1755-1778, Jan 2010, doi:10.1007/s00018-009-0238-5.  
   [2] schell2010inositoltrisphosphate3kinases pages 16-18. Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. Cellular and Molecular Life Sciences, 67:1755-1778, Jan 2010, doi:10.1007/s00018-009-0238-5.  
   [3] schell2010inositoltrisphosphate3kinases pages 5-6. Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. Cellular and Molecular Life Sciences, 67:1755-1778, Jan 2010, doi:10.1007/s00018-009-0238-5.  
   [4] schell2010inositoltrisphosphate3kinases pages 6-7. Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. Cellular and Molecular Life Sciences, 67:1755-1778, Jan 2010, doi:10.1007/s00018-009-0238-5.  
   [5] windhorst2017inositol145trisphosphate3kinasea(itpka) pages 1-3. Inositol-1,4,5-trisphosphate 3-kinase-A (ITPKA) is frequently over-expressed and functions as an oncogene in several tumor types. Biochemical Pharmacology, 137:1-9, Aug 2017, doi:10.1016/j.bcp.2017.03.023.  
   [6] windhorst2017inositol145trisphosphate3kinasea(itpka) pages 8-9. Inositol-1,4,5-trisphosphate 3-kinase-A (ITPKA) is frequently over-expressed and functions as an oncogene in several tumor types. Biochemical Pharmacology, 137:1-9, Aug 2017, doi:10.1016/j.bcp.2017.03.023.  
   [7] marquezmonino2024substratepromiscuityof pages 14-15. Substrate promiscuity of inositol 1,4,5-trisphosphate kinase driven by structurally-modified ligands and active site plasticity. Nature Communications, Feb 2024, doi:10.1038/s41467-024-45917-5.  
   [8] xiong2024originevolutionand pages 17-18. Origin, evolution, and diversification of inositol 1,4,5-trisphosphate 3-kinases in plants and animals. BMC Genomics, Apr 2024, doi:10.1186/s12864-024-10257-7.  
   [9] chamberlain2005structuralinsightsinto pages 6-7. Structural insights into enzyme regulation for inositol 1,4,5-trisphosphate 3-kinase B. Biochemistry, 44:14486-14493, Nov 2005, doi:10.1021/bi051256q.  
   [10] chamberlain2005structuralinsightsinto pages 8-8. Structural insights into enzyme regulation for inositol 1,4,5-trisphosphate 3-kinase B. Biochemistry, 44:14486-14493, Nov 2005, doi:10.1021/bi051256q.  
   [11] wang2014ip6kstructureand pages 11-11. IP6K structure and the molecular determinants of catalytic specificity in an inositol phosphate kinase family. Nature Communications, Jun 2014, doi:10.1038/ncomms5178.  
   [12] whitfield2023diversificationinthe pages 18-19. Diversification in the inositol tris/tetrakisphosphate kinase (ITPK) family: crystal structure and enzymology of the outlier AtITPK4. Biochemical Journal, 480:433-453, Mar 2023, doi:10.1042/bcj20220579.

References

1. (bennion2009”drosophila”geneticsas pages 88-94): Janis M. Bennion. “drosophila” genetics as a tool in the search for novel components of the s6 kinase signaling pathway. Unknown journal, 2009. URL: https://doi.org/10.5451/unibas-005042278, doi:10.5451/unibas-005042278. This article has 0 citations.
2. (marquezmonino2024substratepromiscuityof pages 14-15): M. A. Márquez-Moñino, R. Ortega-García, H. Whitfield, Andrew M. Riley, L. Infantes, Shane W Garrett, Megan L. Shipton, Charles A. Brearley, Barry V L Potter, and Beatriz González. Substrate promiscuity of inositol 1,4,5-trisphosphate kinase driven by structurally-modified ligands and active site plasticity. Nature Communications, Feb 2024. URL: https://doi.org/10.1038/s41467-024-45917-5, doi:10.1038/s41467-024-45917-5. This article has 3 citations and is from a highest quality peer-reviewed journal.
3. (schell2010inositoltrisphosphate3kinases pages 1-3): Michael J. Schell. Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. Cellular and Molecular Life Sciences, 67:1755-1778, Jan 2010. URL: https://doi.org/10.1007/s00018-009-0238-5, doi:10.1007/s00018-009-0238-5. This article has 42 citations and is from a domain leading peer-reviewed journal.
4. (schell2010inositoltrisphosphate3kinases pages 16-18): Michael J. Schell. Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. Cellular and Molecular Life Sciences, 67:1755-1778, Jan 2010. URL: https://doi.org/10.1007/s00018-009-0238-5, doi:10.1007/s00018-009-0238-5. This article has 42 citations and is from a domain leading peer-reviewed journal.
5. (schell2010inositoltrisphosphate3kinases pages 5-6): Michael J. Schell. Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. Cellular and Molecular Life Sciences, 67:1755-1778, Jan 2010. URL: https://doi.org/10.1007/s00018-009-0238-5, doi:10.1007/s00018-009-0238-5. This article has 42 citations and is from a domain leading peer-reviewed journal.
6. (schell2010inositoltrisphosphate3kinases pages 6-7): Michael J. Schell. Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. Cellular and Molecular Life Sciences, 67:1755-1778, Jan 2010. URL: https://doi.org/10.1007/s00018-009-0238-5, doi:10.1007/s00018-009-0238-5. This article has 42 citations and is from a domain leading peer-reviewed journal.
7. (windhorst2017inositol145trisphosphate3kinasea(itpka) pages 1-3): Sabine Windhorst, Kai Song, and Adi F. Gazdar. Inositol-1,4,5-trisphosphate 3-kinase-a (itpka) is frequently over-expressed and functions as an oncogene in several tumor types. Biochemical Pharmacology, 137:1-9, Aug 2017. URL: https://doi.org/10.1016/j.bcp.2017.03.023, doi:10.1016/j.bcp.2017.03.023. This article has 33 citations and is from a domain leading peer-reviewed journal.
8. (windhorst2017inositol145trisphosphate3kinasea(itpka) pages 8-9): Sabine Windhorst, Kai Song, and Adi F. Gazdar. Inositol-1,4,5-trisphosphate 3-kinase-a (itpka) is frequently over-expressed and functions as an oncogene in several tumor types. Biochemical Pharmacology, 137:1-9, Aug 2017. URL: https://doi.org/10.1016/j.bcp.2017.03.023, doi:10.1016/j.bcp.2017.03.023. This article has 33 citations and is from a domain leading peer-reviewed journal.
9. (chamberlain2005structuralinsightsinto pages 6-7): Philip P. Chamberlain, Mark L. Sandberg, Karsten Sauer, Michael P. Cooke, Scott A. Lesley, and Glen Spraggon. Structural insights into enzyme regulation for inositol 1,4,5-trisphosphate 3-kinase b. Biochemistry, 44 44:14486-93, Nov 2005. URL: https://doi.org/10.1021/bi051256q, doi:10.1021/bi051256q. This article has 27 citations and is from a peer-reviewed journal.
10. (chamberlain2005structuralinsightsinto pages 8-8): Philip P. Chamberlain, Mark L. Sandberg, Karsten Sauer, Michael P. Cooke, Scott A. Lesley, and Glen Spraggon. Structural insights into enzyme regulation for inositol 1,4,5-trisphosphate 3-kinase b. Biochemistry, 44 44:14486-93, Nov 2005. URL: https://doi.org/10.1021/bi051256q, doi:10.1021/bi051256q. This article has 27 citations and is from a peer-reviewed journal.
11. (wang2014ip6kstructureand pages 11-11): Huanchen Wang, E. DeRose, R. London, and S. Shears. Ip6k structure and the molecular determinants of catalytic specificity in an inositol phosphate kinase family. Nature Communications, Jun 2014. URL: https://doi.org/10.1038/ncomms5178, doi:10.1038/ncomms5178. This article has 70 citations and is from a highest quality peer-reviewed journal.
12. (whitfield2023diversificationinthe pages 18-19): Hayley L. Whitfield, Sining He, Yinghong Gu, Colleen Sprigg, Hui-Fen Kuo, Tzyy-Jen Chiou, Andrew M. Riley, Barry V.L. Potter, Andrew M. Hemmings, and Charles A. Brearley. Diversification in the inositol tris/tetrakisphosphate kinase (itpk) family: crystal structure and enzymology of the outlieratitpk4. Biochemical Journal, 480:433-453, Mar 2023. URL: https://doi.org/10.1042/bcj20220579, doi:10.1042/bcj20220579. This article has 9 citations and is from a domain leading peer-reviewed journal.
13. (windhorst2017inositol145trisphosphate3kinasea(itpka) pages 9-11): Sabine Windhorst, Kai Song, and Adi F. Gazdar. Inositol-1,4,5-trisphosphate 3-kinase-a (itpka) is frequently over-expressed and functions as an oncogene in several tumor types. Biochemical Pharmacology, 137:1-9, Aug 2017. URL: https://doi.org/10.1016/j.bcp.2017.03.023, doi:10.1016/j.bcp.2017.03.023. This article has 33 citations and is from a domain leading peer-reviewed journal.
14. (ribeiro2017institutonacionalde pages 50-51): GDEO RIBEIRO B DE INOSITOL, PEME DE. Instituto nacional de pesquisas da amazônia–inpa programa de pós-graduação em genética, conservação e biologia …. Unknown journal, 2017.
15. (xiong2024originevolutionand pages 17-18): Tao Xiong, Zai-Bao Zhang, Tianyu Fan, Fan Ye, and Ziyi Ye. Origin, evolution, and diversification of inositol 1,4,5-trisphosphate 3-kinases in plants and animals. BMC Genomics, Apr 2024. URL: https://doi.org/10.1186/s12864-024-10257-7, doi:10.1186/s12864-024-10257-7. This article has 1 citations and is from a peer-reviewed journal.