1. Phylogeny  
   Inositol‐trisphosphate 3‐kinase C (ITPKC), also known as Inositol‐1,4,5‐trisphosphate 3‐kinase C, is a member of the inositol phosphate kinase family that is evolutionarily conserved among metazoans. ITPKC belongs to a kinase subfamily that includes two paralogues, ITPKA and ITPKB, which share a well‐conserved C‐terminal catalytic domain while differing in their N‐terminal regulatory regions. Phylogenetic analyses based on domain conservation and sequence homology indicate that the catalytic core of ITPKs emerged in the early history of eukaryotes, with orthologs present in all mammalian species and additional representatives identified in other vertebrate lineages. The evolutionary trajectory of these kinases appears to mirror the development of inositol phosphate signaling mechanisms, in which the need for precise modulation of calcium release via inositol phosphates became critical. Comparative studies have traced the emergence of these enzymes to the common ancestor of animals and fungi, demonstrating that while the overall catalytic machinery is highly conserved, significant divergence exists in regulatory domains that likely contribute to tissue‐ and context‐specific functions (chamberlain2005structuralinsightsinto pages 1-2, xiong2024originevolutionand pages 1-2).
2. Reaction Catalyzed  
   The primary reaction catalyzed by ITPKC is the ATP‐dependent phosphorylation of 1D‐myo‐inositol 1,4,5‐trisphosphate (InsP3) to produce 1D‐myo‐inositol 1,3,4,5‐tetrakisphosphate (InsP4). The reaction can be summarized as follows:  
     ATP + Ins(1,4,5)P3 → ADP + Ins(1,3,4,5)P4 + H⁺  
   In addition, by similarity to its enzymatic repertoire, ITPKC is thought to also phosphorylate inositol 2,4,5‐triphosphate to yield inositol 2,4,5,6‐tetraphosphate. This conversion plays a vital role in reducing the levels of Ins(1,4,5)P3 available for calcium mobilization from internal stores, thereby modulating downstream calcium‐dependent signaling events (chamberlain2005structuralinsightsinto pages 1-2, onouchi2008itpkcfunctionalpolymorphism pages 4-5).
3. Cofactor Requirements  
   The catalytic activity of ITPKC, like many kinases, is dependent on the presence of divalent metal ions. In vitro studies have demonstrated that magnesium ions (Mg²⁺) are required as an essential cofactor for efficient ATP binding and optimal phosphotransferase activity. Magnesium ions serve to stabilize the negative charges of the phosphate groups of ATP during the catalytic process, ensuring proper orientation of the substrate within the enzyme’s active site (chamberlain2005structuralinsightsinto pages 1-2).
4. Substrate Specificity  
   ITPKC exhibits a high degree of substrate specificity toward its inositol phosphate substrates. The enzyme preferentially recognizes 1D‐myo‐inositol 1,4,5‐trisphosphate and catalyzes its phosphorylation at the 3‐hydroxyl position to produce Ins(1,3,4,5)P4. This high substrate specificity is conferred by the shape and charge distribution of the catalytic pocket, which is configured to tightly accommodate the inositol ring decorated by phosphates at positions 1, 4, and 5. Structural studies have identified key residues—such as a conserved tryptophan (e.g., Trp666) and a histidine (e.g., His672)—that form part of the substrate‐binding site and participate in orienting the substrate for efficient phosphotransfer (chamberlain2005structuralinsightsinto pages 6-7, marquezmonino2024substratepromiscuityof pages 14-15). Although the principal substrate is Ins(1,4,5)P3, there is also evidence by similarity that ITPKC can phosphorylate inositol 2,4,5‐triphosphate, generating inositol 2,4,5,6‐tetraphosphate. These features underscore the enzyme’s role as a gatekeeper in the inositol phosphate signaling cascade, ensuring the generation of specific signaling molecules through tight substrate discrimination (chamberlain2005structuralinsightsinto pages 1-2, marquezmonino2024substratepromiscuityof pages 14-15).
5. Structure  
   The three‐dimensional structure of ITPKC is characterized by a modular organization in which the protein is divided into distinct functional regions. The C‐terminal catalytic domain possesses a protein kinase–like fold comprising two lobes: an N‐lobe and a C‐lobe, which together form the active site cleft responsible for ATP binding and phosphate transfer. Notably, structural analyses have revealed that the ATP‐binding site within ITPKC is more enclosed and hydrophobic compared to related isoforms, a feature that is critical for its catalytic efficiency. Within this domain, key catalytic residues have been identified. For example, the catalytic pocket contains a conserved lysine residue that interacts directly with the phosphates of ATP, while adjacent to this site lies Trp666, a residue that acts as a gating element by mimicking ATP substrate binding in the absence of calmodulin, thereby maintaining the enzyme in a low‐activity state until appropriate activation occurs (chamberlain2005structuralinsightsinto pages 6-7).

In addition to the catalytic domain, ITPKC contains a divergent N‐terminal region that encompasses regulatory sequences. This region includes a membrane anchoring domain that plays a role in subcellular localization, and a putative PEST sequence that may serve as a signal for proteolytic degradation. Structural data indicate that the catalytic domain of ITPKC can form homodimers through an intermolecular antiparallel β‐sheet, a configuration that is mediated by the calmodulin‐binding region. This dimerization is thought to be part of a regulatory mechanism that influences enzyme activity. Combined, these structural features—conserved catalytic motifs, regulatory autoinhibitory elements, and dimerization interfaces—provide a framework for understanding how ITPKC integrates catalytic function with regulatory control (chamberlain2005structuralinsightsinto pages 1-2, chamberlain2005structuralinsightsinto pages 8-8, whitfield2023diversificationinthe pages 4-7).

1. Regulation  
   ITPKC is subject to a variety of regulatory mechanisms that modulate its catalytic activity in response to intracellular signals. A principal mode of regulation is mediated by calcium and calmodulin. In the presence of elevated intracellular Ca²⁺ concentrations, calmodulin (CaM) binds to ITPKC near the catalytic domain, resulting in a dramatic (approximately 20‐fold) stimulation of enzyme activity. This Ca²⁺/CaM binding is critical for relieving the autoinhibitory effect of an internal helix that mimics ATP binding in the absence of calmodulin; mutations in the pivotal tryptophan residue within this helix have been shown to lead to enzyme hyperactivity (chamberlain2005structuralinsightsinto pages 1-2, chamberlain2005structuralinsightsinto pages 6-7).

Moreover, the N‐terminal region of ITPKC, which contains a PEST sequence, may be targeted for proteolytic cleavage by calpain. Under conditions where calpain activity is elevated, such as during certain Ca²⁺‐dependent processes, proteolytic cleavage can release a catalytic fragment from the membrane-bound pool of ITPKC. However, Ca²⁺/CaM binding appears to protect the enzyme from such cleavage, thereby contributing to the fine‐tuning of its activity (chamberlain2005structuralinsightsinto pages 1-2).

Additional regulatory input may result from post‐translational modifications including phosphorylation by other protein kinases such as protein kinase A (PKA), protein kinase C (PKC), and calmodulin‐dependent kinase II (CaMKII). Although specific phosphorylation sites on ITPKC have not been exhaustively detailed in the currently available literature, such modifications are recognized to affect catalytic activity, protein stability, and subcellular localization in related inositol phosphate kinases (shears2004howversatileare pages 8-9). Together, these mechanisms—calcium/calmodulin activation, protection against proteolytic cleavage, and potential phosphorylation events—constitute an elaborate regulatory network that adjusts ITPKC activity in response to cellular calcium fluxes and various signaling cues.

1. Function  
   The primary biological role of ITPKC is to modulate intracellular calcium homeostasis through its enzymatic activity on inositol phosphates. By catalyzing the conversion of Ins(1,4,5)P3 to Ins(1,3,4,5)P4, ITPKC functions as an essential negative regulator of calcium signaling. In specific cellular contexts, the reduction of Ins(1,4,5)P3 levels results in decreased calcium release from the endoplasmic reticulum via IP3 receptors, thereby fine‐tuning calcium‐dependent processes. Structural and genetic studies in mice have demonstrated that loss of ITPKC activity causes defects in T-cell development, particularly arresting T-cell maturation at the CD4⁺ CD8⁺ double-positive stage, which underscores its critical role in immune system development (chamberlain2005structuralinsightsinto pages 1-2).

In humans, genetic polymorphisms in the ITPKC gene, including functional single nucleotide polymorphisms located in noncoding regions, have been associated with an increased susceptibility to Kawasaki disease and coronary artery aneurysm formation. These studies implicate ITPKC as a negative regulator of T-cell receptor (TCR) signaling by modulating the Ca²⁺/NFAT signaling pathway, thereby influencing cytokine expression profiles and immune responses (onouchi2008itpkcfunctionalpolymorphism pages 3-4, onouchi2008itpkcfunctionalpolymorphism pages 4-5).

ITPKC is ubiquitously expressed, with particularly high mRNA and protein levels detected in tissues such as brain, heart, lung, testis, and thymus. The isoform‐specific differences, especially in the N‐terminal regulatory domains, may contribute to divergent subcellular localizations and tissue‐specific functions. Through its regulation of inositol phosphate levels, ITPKC integrates extracellular cues—such as antigen receptor activation in lymphocytes—with intracellular calcium flux, modulating downstream signaling pathways including those mediated by Ras/Erk and NFAT. Thus, ITPKC plays a crucial role not only in the acute regulation of calcium release but also in long‐term processes like immune cell maturation and inflammatory responses (chamberlain2005structuralinsightsinto pages 1-2, onouchi2008itpkcfunctionalpolymorphism pages 3-4, marquezmonino2024substratepromiscuityof pages 14-15).

1. Other Comments  
   Current research into ITPKC has revealed its significance in human disease, particularly in the context of immune and inflammatory disorders. The association of functional polymorphisms in ITPKC with Kawasaki disease has generated considerable interest in this enzyme as a potential biomarker and therapeutic target; for example, the SNPs that reduce ITPKC expression are correlated with more severe coronary complications (onouchi2008itpkcfunctionalpolymorphism pages 3-4, onouchi2008itpkcfunctionalpolymorphism pages 4-5). Despite these findings, there are as yet no widely accepted small molecule inhibitors that selectively target ITPKC. However, the unique structural features of its catalytic domain and regulatory mechanisms, including Ca²⁺/CaM‐dependent activation and autoinhibitory elements, suggest that the development of specific inhibitors is feasible. The search for such pharmacological agents is supported by studies in related kinases where selective inhibitors have been characterized (marquezmonino2024substratepromiscuityof pages 1-2). Additionally, further elucidation of post‐translational modifications and allosteric regulation in ITPKC may provide alternative strategies for therapeutic intervention.
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