## Phylogeny

Inositol hexakisphosphate kinase 2 (IP6K2) is one of three mammalian isoforms (IP6K1, IP6K2, and IP6K3) belonging to the inositol hexakisphosphate kinase (IP6K) family within the larger inositol polyphosphate kinase superfamily (azevedo2011thesignalingrole pages 1-3, unknownauthors2019discoverysynthesisand pages 35-39, chakraborty2018theinositolpyrophosphate pages 36-37). IP6Ks are classified as atypical kinases, as they possess a unique domain architecture and substrate specificity that places them outside the canonical protein kinome classification established by Manning et al. (chakraborty2018theinositolpyrophosphate pages 39-44, unknownauthors2003functionalstudiesof pages 22-27, shears2019inositolphosphatekinases pages 1-3). The IP6K family is evolutionarily ancient, with orthologs found across eukaryotes, including yeast (*Kcs1*) and the early-diverged protist *Giardia lamblia*, suggesting the family arose from a primordial IP6K precursor (chakraborty2011inositolpyrophosphatesas pages 21-23, wang2014ip6kstructureand pages 1-2, azevedo2011thesignalingrole pages 1-3).

## Reaction Catalyzed

IP6K2 catalyzes the ATP-dependent transfer of the terminal phosphate from ATP to the 5-position of the inositol ring of inositol hexakisphosphate (InsP6), yielding 5-diphosphoinositol pentakisphosphate (5-IP7, also known as 5PP-InsP5 or InsP7) and ADP (chakraborty2011inositolpyrophosphatesas pages 21-23, wang2014ip6kstructureand pages 1-2, azevedo2011thesignalingrole pages 1-3). The enzyme can also phosphorylate inositol pentakisphosphate (IP5) to produce diphosphoinositol tetrakisphosphate (PP-IP4) and possesses a reverse, ATP synthase-like activity, transferring a phosphate from IP7 back to ADP to form ATP (unknownauthors2003functionalstudiesof pages 22-27, azevedo2011thesignalingrole pages 1-3). The kinase exhibits a high Km for ATP of approximately 1 mM (unknownauthors2019discoverysynthesisand pages 43-48).

## Cofactor Requirements

The catalytic activity of IP6K2 requires divalent metal ions, specifically Mg2+, as a cofactor (chakraborty2011inositolpyrophosphatesas pages 21-23, chakraborty2018theinositolpyrophosphate pages 39-44, minini2020thekeyrole pages 10-12).

## Substrate Specificity

The primary substrate for IP6K2 is inositol hexakisphosphate (InsP6) (chakraborty2011inositolpyrophosphatesas pages 21-23, chakraborty2018theinositolpyrophosphate pages 36-37). It shows a 20-fold higher affinity for InsP6 compared to inositol pentakisphosphate (InsP5) (minini2020thekeyrole pages 3-5). IP6K2 also retains vestigial kinase activity toward inositol (1,4,5)-trisphosphate (Ins(1,4,5)P3), which it phosphorylates at the 6-OH position (wang2014ip6kstructureand pages 1-2). In addition to inositol phosphates, protein 4.1N has been identified as a protein substrate (unknownauthors2019discoverysynthesisand pages 35-39). The context provided does not contain information on consensus substrate motifs.

## Structure

IP6K2 belongs to the ATP-grasp fold kinase family (chakraborty2018theinositolpyrophosphate pages 36-37). The structure consists of a variable N-terminal region and a highly conserved C-terminal catalytic region (unknownauthors2003functionalstudiesof pages 22-27, barker2009inositolpyrophosphatesstructure pages 5-7). Structural modeling using AlphaFold (for UniProt Q9UHH9) reveals the organization of the N-terminus and a conserved catalytic domain, which contains isoform-specific regions that mediate selective protein interactions (chakraborty2018theinositolpyrophosphate pages 39-44). The catalytic domain contains a conserved PxxxDxKxG motif for inositol phosphate binding and an essential SSLL tetrapeptide motif required for kinase activity (minini2020thekeyrole pages 3-5, unknownauthors2019discoverysynthesisand pages 23-27, wang2014ip6kstructureand pages 1-2). IP6K2 is predominantly nuclear, a localization facilitated by a bipartite nuclear localization signal (barker2009inositolpyrophosphatesstructure pages 5-7).

## Regulation

IP6K2 activity and stability are regulated by post-translational modifications and protein interactions. Phosphorylation by casein kinase 2 (CK2) targets IP6K2 for proteasomal degradation, thereby reducing its stability and pro-apoptotic function (chakraborty2011inositolpyrophosphatesas pages 21-23, chakraborty2018theinositolpyrophosphate pages 39-44, unknownauthors2019discoverysynthesisand pages 35-39). While protein kinase A (PKA) and protein kinase C (PKC) regulate the IP6K1 isoform, their regulation of IP6K2 is not described or is considered less relevant (chakraborty2018theinositolpyrophosphate pages 39-44). Similarly, direct phosphorylation of IP6K2 by mTOR is not detailed in the provided context (chakraborty2018theinositolpyrophosphate pages 39-44). IP6K2 is a client protein of the molecular chaperone HSP90; the binding of HSP90 inhibits its catalytic activity (chakraborty2011inositolpyrophosphatesas pages 21-23, chakraborty2018theinositolpyrophosphate pages 17-19). Apoptotic stimuli stabilize and activate IP6K2 and promote its translocation into the nucleus (chakraborty2011inositolpyrophosphatesas pages 21-23).

## Function

IP6K2 is expressed in various mammalian tissues, including high levels in the brain (cerebellar granule and Purkinje cells), testis, breast, thymus, colon, adipose tissue, and prostate (chakraborty2018theinositolpyrophosphate pages 17-19, unknownauthors2019discoverysynthesisand pages 35-39, minini2020thekeyrole pages 3-5, unknownauthors2022theinositolpyrophosphates pages 23-28).

IP6K2 interacts with the tumor suppressor p53 in the nucleus, augmenting its apoptotic function (chakraborty2011inositolpyrophosphatesas pages 21-23, chakraborty2018theinositolpyrophosphate pages 17-19). Other interacting partners include TNF receptor-associated factor-2 (TRAF2), protein 4.1N, the kinase LKB1, and creatine kinase-B (chakraborty2018theinositolpyrophosphate pages 39-44, unknownauthors2019discoverysynthesisand pages 35-39, minini2020thekeyrole pages 10-12, unknownauthors2022theinositolpyrophosphates pages 23-28). The product of IP6K2 activity, 5-IP7, can activate protein kinase CK2 (minini2020thekeyrole pages 3-5).

IP6K2 plays a primary role in promoting apoptosis and is involved in DNA repair pathways, where it can stabilize DNA-PKcs and ATM (chakraborty2011inositolpyrophosphatesas pages 21-23, wang2014ip6kstructureand pages 1-2, unknownauthors2022theinositolpyrophosphates pages 23-28). Overexpression of IP6K2 enhances apoptosis induced by stimuli like γ-irradiation and cisplatin (minini2020thekeyrole pages 10-12, chakraborty2018theinositolpyrophosphate pages 17-19). It is also essential for neuronal migration and synapse formation in the brain (unknownauthors2019discoverysynthesisand pages 35-39). Additional functions include regulating epithelial-mesenchymal transition (EMT) via interaction with LKB1, vesicle trafficking, autophagy, and cellular energy dynamics (minini2020thekeyrole pages 10-12, chakraborty2011inositolpyrophosphatesas pages 21-23, unknownauthors2003functionalstudiesof pages 22-27, unknownauthors2022theinositolpyrophosphates pages 23-28).

## Inhibitors

The ATP-competitive molecule N2-(m-trifluorobenzyl)-N6-(p-nitrobenzyl)purine (TNP) is a known pan-IP6K inhibitor that also targets IP6K2, although it has off-target effects (minini2020thekeyrole pages 10-12, unknownauthors2019discoverysynthesisand pages 43-48). Other non-selective inhibitors that target IP6K1 and may also affect IP6K2 include phenylarsine oxide (PAO), U73122, and LY294002 (unknownauthors2019discoverysynthesisand pages 23-27).

## Other Comments

IP6K2 has an alternative name, PiUS (P(i)-uptake stimulator) (unknownauthors2003functionalstudiesof pages 22-27). The protein has a dual, context-dependent role in cancer. Deletion of IP6K2 increases susceptibility to carcinogen-induced tumors, yet it can also promote metastasis by enabling invasive phenotypes (minini2020thekeyrole pages 10-12, wang2014ip6kstructureand pages 1-2). IP6K2 is also implicated in the pathogenesis of Huntington’s disease through increased production of 5PP-IP5 (unknownauthors2019discoverysynthesisand pages 23-27). IP6K2 knockout mice show improved survival after ionizing radiation, highlighting the protein’s pro-apoptotic role in response to DNA damage (chakraborty2018theinositolpyrophosphate pages 17-19).

References

1. (chakraborty2011inositolpyrophosphatesas pages 21-23): Anutosh Chakraborty, Seyun Kim, and Solomon H. Snyder. Inositol pyrophosphates as mammalian cell signals. Science Signaling, 4:re1-re1, Aug 2011. URL: https://doi.org/10.1126/scisignal.2001958, doi:10.1126/scisignal.2001958. This article has 182 citations and is from a domain leading peer-reviewed journal.
2. (chakraborty2018theinositolpyrophosphate pages 39-44): Anutosh Chakraborty. The inositol pyrophosphate pathway in health and diseases. Biological Reviews, May 2018. URL: https://doi.org/10.1111/brv.12392, doi:10.1111/brv.12392. This article has 112 citations and is from a domain leading peer-reviewed journal.
3. (minini2020thekeyrole pages 10-12): Mirko Minini, Alice Senni, Vittorio Unfer, and Mariano Bizzarri. The key role of ip6k: a novel target for anticancer treatments? Molecules, 25:4401, Sep 2020. URL: https://doi.org/10.3390/molecules25194401, doi:10.3390/molecules25194401. This article has 25 citations and is from a peer-reviewed journal.
4. (unknownauthors2019discoverysynthesisand pages 35-39): DISCOVERY, SYNTHESIS, AND CHARACTERIZATION OF PURINE BASED ISOFORM SELECTIVE INHIBITORS OF INOSITOL HEXAKISPHOSPHATE KINASE 1
5. (unknownauthors2019discoverysynthesisand pages 43-48): DISCOVERY, SYNTHESIS, AND CHARACTERIZATION OF PURINE BASED ISOFORM SELECTIVE INHIBITORS OF INOSITOL HEXAKISPHOSPHATE KINASE 1
6. (wang2014ip6kstructureand pages 1-2): Huanchen Wang, Eugene F. DeRose, Robert E. London, and Stephen B. 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 71 citations and is from a highest quality peer-reviewed journal.
7. (chakraborty2018theinositolpyrophosphate pages 17-19): Anutosh Chakraborty. The inositol pyrophosphate pathway in health and diseases. Biological Reviews, May 2018. URL: https://doi.org/10.1111/brv.12392, doi:10.1111/brv.12392. This article has 112 citations and is from a domain leading peer-reviewed journal.
8. (chakraborty2018theinositolpyrophosphate pages 36-37): Anutosh Chakraborty. The inositol pyrophosphate pathway in health and diseases. Biological Reviews, May 2018. URL: https://doi.org/10.1111/brv.12392, doi:10.1111/brv.12392. This article has 112 citations and is from a domain leading peer-reviewed journal.
9. (minini2020thekeyrole pages 3-5): Mirko Minini, Alice Senni, Vittorio Unfer, and Mariano Bizzarri. The key role of ip6k: a novel target for anticancer treatments? Molecules, 25:4401, Sep 2020. URL: https://doi.org/10.3390/molecules25194401, doi:10.3390/molecules25194401. This article has 25 citations and is from a peer-reviewed journal.
10. (unknownauthors2003functionalstudiesof pages 22-27): Functional studies of type I inositol hexakisphosphate kinase and its role in cell signaling
11. (unknownauthors2019discoverysynthesisand pages 23-27): DISCOVERY, SYNTHESIS, AND CHARACTERIZATION OF PURINE BASED ISOFORM SELECTIVE INHIBITORS OF INOSITOL HEXAKISPHOSPHATE KINASE 1
12. (unknownauthors2022theinositolpyrophosphates pages 23-28): The inositol pyrophosphates are essential for the development of mammals
13. (azevedo2011thesignalingrole pages 1-3): Cristina Azevedo, Zsolt Szijgyarto, and Adolfo Saiardi. The signaling role of inositol hexakisphosphate kinases (ip6ks). Advances in enzyme regulation, 51 1:74-82, Dec 2011. URL: https://doi.org/10.1016/j.advenzreg.2010.08.003, doi:10.1016/j.advenzreg.2010.08.003. This article has 21 citations.
14. (barker2009inositolpyrophosphatesstructure pages 5-7): Christopher John Barker, Christopher Illies, Gian Carlo Gaboardi, and Per-Olof Berggren. Inositol pyrophosphates: structure, enzymology and function. Cellular and Molecular Life Sciences, 66:3851-3871, Aug 2009. URL: https://doi.org/10.1007/s00018-009-0115-2, doi:10.1007/s00018-009-0115-2. This article has 117 citations and is from a domain leading peer-reviewed journal.
15. (shears2019inositolphosphatekinases pages 1-3): Stephen B. Shears and Huanchen Wang. Inositol phosphate kinases: expanding the biological significance of the universal core of the protein kinase fold. Advances in Biological Regulation, 71:118-127, Jan 2019. URL: https://doi.org/10.1016/j.jbior.2018.10.006, doi:10.1016/j.jbior.2018.10.006. This article has 42 citations and is from a peer-reviewed journal.