1. Phylogeny  
   PIM3 belongs to the PIM kinase family, a small but evolutionarily conserved group of serine/threonine protein kinases. Within this family, PIM3 exhibits approximately 70% sequence identity with PIM1 and around 64% with PIM2, underscoring their close evolutionary relationship (korinkova2019roleofpima pages 16-20, zhukova2011pimfamilyof pages 1-2). Unlike many families that show extensive diversification, the PIM kinases are characterized by largely conserved catalytic domains and a relative absence of regulatory regions. The genes encoding these kinases reside on distinct human chromosomes; notably, PIM3 is encoded on chromosome 22 while PIM1 is located on chromosome 6 and PIM2 on the X chromosome (eccleshallUnknownyearpimkinasesin pages 24-27, korinkova2019roleofpima pages 16-20). Phylogenetic studies indicate that the PIM kinase family emerged early in metazoan evolution and has been retained among vertebrates as an essential component of survival and proliferation signaling pathways (narlik‐grassow2014thepimfamily pages 1-4). Their evolutionary conservation suggests that these kinases were part of the ancestral kinase repertoire that preceded the divergence of modern eukaryotes, and they remain part of an evolutionary core set of kinases that include other survival regulators (korinkova2019roleofpima pages 16-20).
2. Reaction Catalyzed  
   PIM3 catalyzes the phosphorylation of target substrates by transferring a phosphate group from ATP to specific serine or threonine residues on protein substrates. The canonical reaction can be represented as:  
     ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺  
   This reaction is fundamental to the regulation of numerous intracellular signaling pathways and is equivalent in chemical terms to the reactions catalyzed by many serine/threonine kinases (warfel2015pimkinase(and pages 4-6).
3. Cofactor Requirements  
   The catalytic activity of PIM3 is dependent on the presence of divalent metal ions, with Mg²⁺ being the principal cofactor required to coordinate ATP binding in the active site. Mg²⁺ facilitates the proper positioning of the ATP molecule, enabling effective phosphoryl transfer during the kinase reaction (malone2020currentperspectiveson pages 6-10).
4. Substrate Specificity  
   PIM3 phosphorylates serine/threonine residues within target proteins by recognizing consensus motifs that are enriched in basic amino acids. Although the most thoroughly characterized motif has been defined for PIM1, it is generally extrapolated to the entire PIM kinase family. In particular, substrates frequently display a motif consisting of multiple basic residues, often described in the literature as a Lys/Arg-rich sequence, for example, in the form K/R-X-X-X-S/T-X (arrouchi2019areviewon pages 2-4, korinkova2019roleofpima pages 16-20). One well-documented target of PIM3-mediated phosphorylation is the pro-apoptotic protein BAD. Phosphorylation of BAD—occurring at serine residues such as Ser112, and in some reports also Ser136 and Ser155—leads to its inactivation via disruption of its binding to anti-apoptotic proteins like Bcl-X(L), thereby promoting cell survival (alvarado2012thepimkinases pages 9-11, korinkova2019roleofpim pages 26-29).
5. Structure  
   PIM3 is a relatively small serine/threonine kinase, with a molecular weight of approximately 34 kDa and a length of roughly 326 amino acids. Its structure is dominated by a central catalytic kinase domain that adopts a bi-lobal fold typical of protein kinases. The N-terminal lobe is composed mostly of β-sheets, whereas the larger C-terminal lobe is predominantly helical. Although no crystal structure for PIM3 has been experimentally resolved to date, high sequence homology with PIM1—all of which has been crystallographically characterized—strongly suggests that PIM3 shares a similar three-dimensional structural organization (choudhury2024pim1kinaseand pages 1-2, karim2023investigatingendothelialcell pages 22-25). A unique feature of the PIM kinases is the presence of an atypical hinge region containing one or more inserted proline residues; in PIM3, this structural insertion is believed to widen the ATP-binding pocket, resulting in a higher Km for ATP relative to other kinases (karim2023investigatingendothelialcell pages 22-25, morwick2010pimkinaseinhibitors pages 1-3). This distinctive architectural element is one of the key determinants used in the design of selective inhibitors for the PIM family.
6. Regulation  
   PIM3 is constitutively active owing to its lack of regulatory or autoinhibitory domains; thus, its enzymatic activity is largely governed by the levels of protein expression rather than by classical phosphorylation-dependent activation events. Transcriptional regulation plays a dominant role in controlling PIM3 abundance, with cytokine signaling—particularly through the JAK/STAT pathway—serving as a major driving force; transcription factors such as STAT3, STAT5, and Ets-1 directly bind the promoter regions of PIM genes to upregulate their expression (choudhury2024pim1kinaseand pages 25-26, korinkova2019roleofpim pages 16-20). At the post-transcriptional level, the mRNA encoding PIM3 contains several destabilizing AU-rich elements in its 3′ untranslated region, contributing to a short mRNA half-life and tight regulation of protein synthesis (narlik‐grassow2014thepimfamily pages 4-6). In addition, protein stability is regulated by molecular chaperones; HSP90 has been shown to stabilize PIM kinases, thereby protecting them from proteasomal degradation, while HSP70 promotes their recognition by the ubiquitin–proteasome system (morwick2010pimkinaseinhibitors pages 17-18). Furthermore, dephosphorylation events mediated by phosphatases such as PP2A contribute to the turnover of PIM3 by triggering ubiquitination (choudhury2024pim1kinaseand pages 25-26).
7. Function  
   PIM3 functions as a proto-oncogene and exerts its influence through a variety of pro-survival and proliferative mechanisms. Its kinase activity is central to the prevention of apoptosis and the promotion of cell survival. One of the best characterized functions of PIM3 is the phosphorylation of the pro-apoptotic protein BAD; this phosphorylation disrupts BAD’s association with anti-apoptotic proteins like Bcl-X(L), thereby inhibiting the apoptotic cascade and promoting cell survival (alvarado2012thepimkinases pages 9-11, korinkova2019roleofpim pages 26-29). In addition to its anti-apoptotic role, PIM3 also contributes to cell cycle progression by regulating the phosphorylation state of key cell cycle regulators, and it enhances protein synthesis by promoting cap-dependent translation. PIM3 modulates the transcriptional activity of oncogenes such as MYC, contributing to transcriptional regulation in malignant cells (choudhury2024pim1kinaseand pages 22-23). Beyond these oncogenic functions, PIM3 influences energy metabolism through the regulation of AMP-activated protein kinase (AMPK) activity and by modulating the levels of metabolic coactivators such as PPARGC1A. Moreover, it exerts negative regulatory control on insulin secretion by interfering with the activation of MAPK1/3 (ERK1/2) via SOCS6, linking its activity to both neoplastic and metabolic signaling pathways (alvarado2012thepimkinases pages 9-11, choudhury2024pim1kinaseand pages 22-23, korinkova2019roleofpima pages 29-31). PIM3 expression is detected predominantly in tissues including the kidney, breast, brain, and various endoderm-derived organs, and its overexpression has been documented in several types of solid tumors such as pancreatic, hepatocellular, and gastric carcinomas (brault2010pimserinethreoninekinases pages 6-7, korinkova2019roleofpim pages 29-31).
8. Other Comments  
   Several small-molecule inhibitors have been developed to target the PIM kinase family, with many of these compounds exhibiting pan-PIM activity that includes inhibition of PIM3. Notable examples include compounds such as SGI-1776 and AZD1208, which are in various stages of preclinical and clinical evaluation; these inhibitors target the conserved ATP-binding pocket of the PIM kinases, exploiting the unique structural features—such as the widened hinge region—to achieve selectivity (le2015targetingpimkinases pages 13-15, morwick2010pimkinaseinhibitors pages 19-20). To date, specific mutations in PIM3 that affect its catalytic activity or inhibitor sensitivity have not been extensively characterized; the pathological role of PIM3 is largely attributable to its dysregulated expression in cancer cells rather than to recurrent activating mutations (alvarado2012thepimkinases pages 11-11, narlik‐grassow2014thepimfamily pages 1-4). In addition to its role in oncogenesis, the ability of PIM3 to regulate insulin secretion and cellular energy metabolism suggests potential implications for metabolic disorders, though the primary focus of current research remains on its contributions to tumorigenesis. The distinct structural features of PIM3 compared with many other kinases, particularly the atypical conformation of its ATP-binding site, have sparked targeted drug discovery efforts, as these features provide an opportunity for the design of selective inhibitors that may overcome issues of cross-reactivity with other kinases (karim2023investigatingendothelialcell pages 22-25, morwick2010pimkinaseinhibitors pages 18-19).
9. References

References

1. (alvarado2012thepimkinases pages 9-11): Yesid Alvarado, Francis J Giles, and Ronan T Swords. The pim kinases in hematological cancers. Expert Review of Hematology, 5:81-96, Feb 2012. URL: https://doi.org/10.1586/ehm.11.69, doi:10.1586/ehm.11.69. This article has 95 citations and is from a peer-reviewed journal.
2. (korinkova2019roleofpim pages 16-20): K Kořínková. Role of pim oncogenes in the biology and chemoresistance of aggressive lymphomas. Unknown journal, 2019.
3. (warfel2015pimkinase(and pages 4-6): Noel A. Warfel and Andrew S. Kraft. Pim kinase (and akt) biology and signaling in tumors. Pharmacology & Therapeutics, 151:41-49, Jul 2015. URL: https://doi.org/10.1016/j.pharmthera.2015.03.001, doi:10.1016/j.pharmthera.2015.03.001. This article has 227 citations.
4. (arrouchi2019areviewon pages 2-4): Housna Arrouchi, Wiame Lakhlili, and Azeddine Ibrahimi. A review on pim kinases in tumors. Bioinformation, 15:40-45, Jan 2019. URL: https://doi.org/10.6026/97320630015040, doi:10.6026/97320630015040. This article has 35 citations.
5. (brault2010pimserinethreoninekinases pages 6-7): L. Brault, C. Gasser, F. Bracher, K. Huber, S. Knapp, and J. Schwaller. Pim serine/threonine kinases in the pathogenesis and therapy of hematologic malignancies and solid cancers. Haematologica, 95:1004-1015, Feb 2010. URL: https://doi.org/10.3324/haematol.2009.017079, doi:10.3324/haematol.2009.017079. This article has 446 citations.
6. (choudhury2024pim1kinaseand pages 22-23): Rituparna Choudhury, Chandan Kumar Bahadi, Ipsa Pratibimbita Ray, Pragyanshree Dash, Isha Pattanaik, Suman Mishra, Soumya R. Mohapatra, Srinivas Patnaik, and Kumar Nikhil. Pim1 kinase and its diverse substrate in solid tumors. Cell Communication and Signaling, Nov 2024. URL: https://doi.org/10.1186/s12964-024-01898-y, doi:10.1186/s12964-024-01898-y. This article has 3 citations and is from a peer-reviewed journal.
7. (choudhury2024pim1kinaseand pages 25-26): Rituparna Choudhury, Chandan Kumar Bahadi, Ipsa Pratibimbita Ray, Pragyanshree Dash, Isha Pattanaik, Suman Mishra, Soumya R. Mohapatra, Srinivas Patnaik, and Kumar Nikhil. Pim1 kinase and its diverse substrate in solid tumors. Cell Communication and Signaling, Nov 2024. URL: https://doi.org/10.1186/s12964-024-01898-y, doi:10.1186/s12964-024-01898-y. This article has 3 citations and is from a peer-reviewed journal.
8. (eccleshallUnknownyearpimkinasesin pages 24-27): W Eccleshall. Pim kinases in luminal a breast cancer. Unknown journal, Unknown year.
9. (karim2023investigatingendothelialcell pages 22-25): E Karim. Investigating endothelial cell pim kinase as a novel anti-thrombotic target. Unknown journal, 2023.
10. (korinkova2019roleofpim pages 26-29): K Kořínková. Role of pim oncogenes in the biology and chemoresistance of aggressive lymphomas. Unknown journal, 2019.
11. (korinkova2019roleofpim pages 29-31): K Kořínková. Role of pim oncogenes in the biology and chemoresistance of aggressive lymphomas. Unknown journal, 2019.
12. (korinkova2019roleofpima pages 16-20): K Kořínková. Role of pim oncogenes in the biology and chemoresistance of aggressive lymphomas. Unknown journal, 2019.
13. (korinkova2019roleofpima pages 29-31): K Kořínková. Role of pim oncogenes in the biology and chemoresistance of aggressive lymphomas. Unknown journal, 2019.
14. (le2015targetingpimkinases pages 13-15): Bich Thuy Le, Malika Kumarasiri, Julian RJ Adams, Mingfeng Yu, Robert Milne, Matthew J Sykes, and Shudong Wang. Targeting pim kinases for cancer treatment: opportunities and challenges. Future medicinal chemistry, 7 1:35-53, Jan 2015. URL: https://doi.org/10.4155/fmc.14.145, doi:10.4155/fmc.14.145. This article has 55 citations and is from a peer-reviewed journal.
15. (malone2020currentperspectiveson pages 6-10): Tom Malone, Lea Schäfer, Nathalie Simon, Susan Heavey, Sinead Cuffe, Stephen Finn, Gillian Moore, and Kathy Gately. Current perspectives on targeting pim kinases to overcome mechanisms of drug resistance and immune evasion in cancer. Pharmacology & Therapeutics, 207:107454, Mar 2020. URL: https://doi.org/10.1016/j.pharmthera.2019.107454, doi:10.1016/j.pharmthera.2019.107454. This article has 36 citations.
16. (morwick2010pimkinaseinhibitors pages 1-3): Tina Morwick. Pim kinase inhibitors: a survey of the patent literature. Expert Opinion on Therapeutic Patents, 20:193-212, Jan 2010. URL: https://doi.org/10.1517/13543770903496442, doi:10.1517/13543770903496442. This article has 84 citations and is from a peer-reviewed journal.
17. (morwick2010pimkinaseinhibitors pages 18-19): Tina Morwick. Pim kinase inhibitors: a survey of the patent literature. Expert Opinion on Therapeutic Patents, 20:193-212, Jan 2010. URL: https://doi.org/10.1517/13543770903496442, doi:10.1517/13543770903496442. This article has 84 citations and is from a peer-reviewed journal.
18. (morwick2010pimkinaseinhibitors pages 19-20): Tina Morwick. Pim kinase inhibitors: a survey of the patent literature. Expert Opinion on Therapeutic Patents, 20:193-212, Jan 2010. URL: https://doi.org/10.1517/13543770903496442, doi:10.1517/13543770903496442. This article has 84 citations and is from a peer-reviewed journal.
19. (narlik‐grassow2014thepimfamily pages 1-4): Maja Narlik‐Grassow, Carmen Blanco‐Aparicio, and Amancio Carnero. The pim family of serine/threonine kinases in cancer. Medicinal Research Reviews, Jan 2014. URL: https://doi.org/10.1002/med.21284, doi:10.1002/med.21284. This article has 252 citations and is from a domain leading peer-reviewed journal.
20. (narlik‐grassow2014thepimfamily pages 4-6): Maja Narlik‐Grassow, Carmen Blanco‐Aparicio, and Amancio Carnero. The pim family of serine/threonine kinases in cancer. Medicinal Research Reviews, Jan 2014. URL: https://doi.org/10.1002/med.21284, doi:10.1002/med.21284. This article has 252 citations and is from a domain leading peer-reviewed journal.
21. (zhukova2011pimfamilyof pages 1-2): Yu. N. Zhukova, M. G. Alekseeva, N. V. Zakharevich, A. A. Shtil, and V. N. Danilenko. Pim family of protein kinases: structure, functions, and roles in hematopoietic malignancies. Molecular Biology, 45:695-703, Oct 2011. URL: https://doi.org/10.1134/s0026893311040170, doi:10.1134/s0026893311040170. This article has 30 citations and is from a peer-reviewed journal.
22. (alvarado2012thepimkinases pages 11-11): Yesid Alvarado, Francis J Giles, and Ronan T Swords. The pim kinases in hematological cancers. Expert Review of Hematology, 5:81-96, Feb 2012. URL: https://doi.org/10.1586/ehm.11.69, doi:10.1586/ehm.11.69. This article has 95 citations and is from a peer-reviewed journal.
23. (choudhury2024pim1kinaseand pages 1-2): Rituparna Choudhury, Chandan Kumar Bahadi, Ipsa Pratibimbita Ray, Pragyanshree Dash, Isha Pattanaik, Suman Mishra, Soumya R. Mohapatra, Srinivas Patnaik, and Kumar Nikhil. Pim1 kinase and its diverse substrate in solid tumors. Cell Communication and Signaling, Nov 2024. URL: https://doi.org/10.1186/s12964-024-01898-y, doi:10.1186/s12964-024-01898-y. This article has 3 citations and is from a peer-reviewed journal.
24. (morwick2010pimkinaseinhibitors pages 17-18): Tina Morwick. Pim kinase inhibitors: a survey of the patent literature. Expert Opinion on Therapeutic Patents, 20:193-212, Jan 2010. URL: https://doi.org/10.1517/13543770903496442, doi:10.1517/13543770903496442. This article has 84 citations and is from a peer-reviewed journal.