## Phylogeny

The PIM kinase family is classified within the CAMK (Calcium/calmodulin-dependent protein kinase) group of the human kinome, a classification based on sequence homology and phylogenetic analysis of the kinase catalytic domains (manning2002theproteinkinase pages 1-2, manning2002theproteinkinase pages 2-3, manning2002theproteinkinase pages 3-3, manning2002theproteinkinase pages 6-6, manning2002theproteinkinase pages 7-8).

## Reaction Catalyzed

PIM1 catalyzes the ATP-dependent phosphorylation of serine and threonine residues on substrate proteins (bogusz2017structuralanalysisof pages 1-2, bullock2009crystalstructureof pages 6-7, zhang2018pimkinaseas pages 1-2).

## Cofactor Requirements

PIM1 requires divalent cations, such as Mg2+, for its kinase activity (bogusz2017structuralanalysisof pages 1-2, bullock2009crystalstructureof pages 6-7, iyer2017afunctionalsumomotif pages 12-13).

## Substrate Specificity

PIM1 exhibits a pronounced substrate preference for basic residues, with Arginine (R) at the P-3 position being a defining feature of its substrate specificity (johnson2023anatlasof pages 1-2, johnson2023anatlasof pages 3-4).

## Structure

PIM1 has a bi-lobed kinase fold with an N-terminal lobe (residues 37–122) composed mainly of β-strands and a C-terminal lobe (residues 126–305) that is primarily α-helical (bogusz2017structuralanalysisof pages 1-2, merkel2012pim1kinaseas pages 5-6). The two lobes are connected by a hinge region (residues 123–125) that forms the ATP-binding site, which is flanked by a glycine-rich loop (residues 44–52) and an activation loop (residues 185–204) (bogusz2017structuralanalysisof pages 1-2). Key structural features include the C-helix, DFG motif, and a hydrophobic spine (bullock2009crystalstructureof pages 6-7). A unique structural element is a proline residue (Pro123) in the hinge region, which substitutes for a canonical hydrogen bond donor and alters ATP binding (bogusz2017structuralanalysisof pages 1-2, merkel2012pim1kinaseas pages 5-6, kumar2005crystalstructuresof pages 7-8). PIM1 adopts a constitutively active conformation independent of activation loop phosphorylation (bullock2009crystalstructureof pages 6-7, merkel2012pim1kinaseas pages 5-6).

## Regulation

PIM1 is a constitutively active kinase, with regulation occurring primarily at the levels of transcription and protein stability (bogusz2017structuralanalysisof pages 1-2, unknownauthors2019roleofpim pages 20-23). PIM1 expression is upregulated by cytokines and growth factors via the JAK-STAT and NF-κB signaling pathways (bogusz2017structuralanalysisof pages 1-2). The protein has a short half-life (<5 minutes in normal cells) and its stability is controlled by the ubiquitin-proteasome pathway (merkel2012pim1kinaseas pages 1-2, unknownauthors2019roleofpim pages 20-23). The chaperone protein Hsp90 stabilizes PIM1, while Hsp70 promotes its degradation (merkel2012pim1kinaseas pages 1-2). Protein phosphatase 2A (PP2A) negatively regulates PIM1 by mediating its dephosphorylation, which leads to ubiquitylation and proteasomal degradation (merkel2012pim1kinaseas pages 1-2, nock2023pimkinasesimportant pages 5-6). Autophosphorylation occurs but its effect on activity is unclear, though it may support protein stability (unknownauthors2019roleofpim pages 20-23, nock2023pimkinasesimportant pages 5-6). Phosphorylation at Tyr218 by the tyrosine kinase ETK enhances PIM1 activity (merkel2012pim1kinaseas pages 1-2).

## Function

PIM1 is a proto-oncogene that promotes cell survival and proliferation (bogusz2017structuralanalysisof pages 1-2). It is expressed at low levels in normal tissues but is overexpressed in many cancers, particularly in hematopoietic cells (bogusz2017structuralanalysisof pages 1-2, bullock2009crystalstructureof pages 7-7). A key downstream substrate is the oncoprotein MYC, which PIM1 phosphorylates at serines 62 and 329, leading to its stabilization and increased transcriptional activity (bogusz2017structuralanalysisof pages 1-2, zhang2018pimkinaseas pages 1-2). PIM1 promotes cell survival by phosphorylating and inhibiting pro-apoptotic proteins such as BAD (at Ser112) and MAP3K5 (ASK1) (bullock2009crystalstructureof pages 7-7, merkel2012pim1kinaseas pages 9-10). It also regulates cell cycle progression by phosphorylating substrates including p21Cip1/WAF1, Cdc25A, and histone H3 at serine 10 (bullock2009crystalstructureof pages 7-7, unknownauthors2021altestargetneue pages 421-423). PIM1 influences mTOR signaling by phosphorylating PRAS40 and promotes drug resistance by phosphorylating ABC transporters like BCRP/ABCG2 (merkel2012pim1kinaseas pages 9-10, lee2013crystalstructureof pages 7-7).

## Inhibitors

PIM1 inhibitors are typically ATP-competitive and bind within the ATP pocket in the active conformation of the kinase (merkel2012pim1kinaseas pages 1-2, bogusz2017structuralanalysisof pages 6-7). Known inhibitors that have entered clinical trials include SGI-1776, AZD1208, and LGH447 (zhang2018pimkinaseas pages 1-2, unknownauthors2015mutationalanalysisof pages 28-32). CX-6258 is a potent and selective pan-PIM and Flt-3 inhibitor (bogusz2017structuralanalysisof pages 1-2). Other small molecule inhibitors include imidazo[1,2-b]pyridazines, organoruthenium complexes, and pyridones (bullock2009crystalstructureof pages 7-7, lee2013crystalstructureof pages 7-7). Compounds with off-target activity on PIM1 include the CK2 inhibitor CX-4945, the CDK1 inhibitor Ro-3306, and the PI3K inhibitor LY294002 (bogusz2017structuralanalysisof pages 1-2, unknownauthors2009theroleof pages 109-112).

## Other Comments

PIM1 overexpression is observed in numerous human cancers, including hematopoietic malignancies (acute myeloid and lymphoid leukemia, diffuse large cell lymphoma) and solid tumors (prostate, breast, pancreatic), where it often correlates with poor prognosis and chemoresistance (bogusz2017structuralanalysisof pages 1-2, zhang2018pimkinaseas pages 1-2). PIM1 was first discovered as a Provirus Integration site for Moloney leukemia virus (PIM) and is known to cooperate with MYC to accelerate tumorigenesis (bogusz2017structuralanalysisof pages 1-2). Aberrant somatic hypermutations of PIM1 have been identified in non-Hodgkin’s lymphomas (kumar2005crystalstructuresof pages 8-9). The mild phenotype of PIM1 knockout mice suggests that inhibitors may have an acceptable toxicity profile, making it an attractive therapeutic target (bogusz2017structuralanalysisof pages 1-2).

References

1. (bogusz2017structuralanalysisof pages 1-2): Jozefina Bogusz, Karol Zrubek, Krzysztof P. Rembacz, Przemyslaw Grudnik, Przemyslaw Golik, Malgorzata Romanowska, Benedykt Wladyka, and Grzegorz Dubin. Structural analysis of pim1 kinase complexes with atp-competitive inhibitors. Scientific Reports, Oct 2017. URL: https://doi.org/10.1038/s41598-017-13557-z, doi:10.1038/s41598-017-13557-z. This article has 36 citations and is from a poor quality or predatory journal.
2. (bullock2009crystalstructureof pages 6-7): Alex N. Bullock, Santina Russo, Ann Amos, Nicholas Pagano, Howard Bregman, Judit É. Debreczeni, Wen Hwa Lee, Frank von Delft, Eric Meggers, and Stefan Knapp. Crystal structure of the pim2 kinase in complex with an organoruthenium inhibitor. PLoS ONE, 4:e7112, Oct 2009. URL: https://doi.org/10.1371/journal.pone.0007112, doi:10.1371/journal.pone.0007112. This article has 114 citations and is from a peer-reviewed journal.
3. (bullock2009crystalstructureof pages 7-7): Alex N. Bullock, Santina Russo, Ann Amos, Nicholas Pagano, Howard Bregman, Judit É. Debreczeni, Wen Hwa Lee, Frank von Delft, Eric Meggers, and Stefan Knapp. Crystal structure of the pim2 kinase in complex with an organoruthenium inhibitor. PLoS ONE, 4:e7112, Oct 2009. URL: https://doi.org/10.1371/journal.pone.0007112, doi:10.1371/journal.pone.0007112. This article has 114 citations and is from a peer-reviewed journal.
4. (iyer2017afunctionalsumomotif pages 12-13): R. S. Iyer, L. Chatham, R. Sleigh, and D. Meek. A functional sumo-motif in the active site of pim1 promotes its degradation via rnf4, and stimulates protein kinase activity. Scientific Reports, Jun 2017. URL: https://doi.org/10.1038/s41598-017-03775-w, doi:10.1038/s41598-017-03775-w. This article has 17 citations and is from a poor quality or predatory journal.
5. (johnson2023anatlasof pages 1-2): Jared L. Johnson, Tomer M. Yaron, Emily M. Huntsman, Alexander Kerelsky, Junho Song, Amit Regev, Ting-Yu Lin, Katarina Liberatore, Daniel M. Cizin, Benjamin M. Cohen, Neil Vasan, Yilun Ma, Konstantin Krismer, Jaylissa Torres Robles, Bert van de Kooij, Anne E. van Vlimmeren, Nicole Andrée-Busch, Norbert F. Käufer, Maxim V. Dorovkov, Alexey G. Ryazanov, Yuichiro Takagi, Edward R. Kastenhuber, Marcus D. Goncalves, Benjamin D. Hopkins, Olivier Elemento, Dylan J. Taatjes, Alexandre Maucuer, Akio Yamashita, Alexei Degterev, Mohamed Uduman, Jingyi Lu, Sean D. Landry, Bin Zhang, Ian Cossentino, Rune Linding, John Blenis, Peter V. Hornbeck, Benjamin E. Turk, Michael B. Yaffe, and Lewis C. Cantley. An atlas of substrate specificities for the human serine/threonine kinome. Nature, 613:759-766, Jan 2023. URL: https://doi.org/10.1038/s41586-022-05575-3, doi:10.1038/s41586-022-05575-3. This article has 446 citations and is from a highest quality peer-reviewed journal.
6. (johnson2023anatlasof pages 3-4): Jared L. Johnson, Tomer M. Yaron, Emily M. Huntsman, Alexander Kerelsky, Junho Song, Amit Regev, Ting-Yu Lin, Katarina Liberatore, Daniel M. Cizin, Benjamin M. Cohen, Neil Vasan, Yilun Ma, Konstantin Krismer, Jaylissa Torres Robles, Bert van de Kooij, Anne E. van Vlimmeren, Nicole Andrée-Busch, Norbert F. Käufer, Maxim V. Dorovkov, Alexey G. Ryazanov, Yuichiro Takagi, Edward R. Kastenhuber, Marcus D. Goncalves, Benjamin D. Hopkins, Olivier Elemento, Dylan J. Taatjes, Alexandre Maucuer, Akio Yamashita, Alexei Degterev, Mohamed Uduman, Jingyi Lu, Sean D. Landry, Bin Zhang, Ian Cossentino, Rune Linding, John Blenis, Peter V. Hornbeck, Benjamin E. Turk, Michael B. Yaffe, and Lewis C. Cantley. An atlas of substrate specificities for the human serine/threonine kinome. Nature, 613:759-766, Jan 2023. URL: https://doi.org/10.1038/s41586-022-05575-3, doi:10.1038/s41586-022-05575-3. This article has 446 citations and is from a highest quality peer-reviewed journal.
7. (kumar2005crystalstructuresof pages 7-8): Abhinav Kumar, V. Mandiyan, Yoshihisa Suzuki, Chao Zhang, J. Rice, J. Tsai, D. Artis, P. Ibrahim, and R. Bremer. Crystal structures of proto-oncogene kinase pim1: a target of aberrant somatic hypermutations in diffuse large cell lymphoma. Journal of molecular biology, 348 1:183-93, Apr 2005. URL: https://doi.org/10.1016/j.jmb.2005.02.039, doi:10.1016/j.jmb.2005.02.039. This article has 198 citations and is from a domain leading peer-reviewed journal.
8. (kumar2005crystalstructuresof pages 8-9): Abhinav Kumar, V. Mandiyan, Yoshihisa Suzuki, Chao Zhang, J. Rice, J. Tsai, D. Artis, P. Ibrahim, and R. Bremer. Crystal structures of proto-oncogene kinase pim1: a target of aberrant somatic hypermutations in diffuse large cell lymphoma. Journal of molecular biology, 348 1:183-93, Apr 2005. URL: https://doi.org/10.1016/j.jmb.2005.02.039, doi:10.1016/j.jmb.2005.02.039. This article has 198 citations and is from a domain leading peer-reviewed journal.
9. (lee2013crystalstructureof pages 7-7): Sang Jae Lee, Byeong-Gu Han, Jea-Won Cho, Jang-Sik Choi, Jaekyoo Lee, Ho-Juhn Song, Jong Sung Koh, and Byung Il Lee. Crystal structure of pim1 kinase in complex with a pyrido[4,3-d]pyrimidine derivative suggests a unique binding mode. PLoS ONE, 8:e70358, Jul 2013. URL: https://doi.org/10.1371/journal.pone.0070358, doi:10.1371/journal.pone.0070358. This article has 16 citations and is from a peer-reviewed journal.
10. (manning2002theproteinkinase pages 1-2): G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam. The protein kinase complement of the human genome. Science, 298:1912-1934, Dec 2002. URL: https://doi.org/10.1126/science.1075762, doi:10.1126/science.1075762. This article has 10728 citations and is from a highest quality peer-reviewed journal.
11. (manning2002theproteinkinase pages 2-3): G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam. The protein kinase complement of the human genome. Science, 298:1912-1934, Dec 2002. URL: https://doi.org/10.1126/science.1075762, doi:10.1126/science.1075762. This article has 10728 citations and is from a highest quality peer-reviewed journal.
12. (manning2002theproteinkinase pages 3-3): G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam. The protein kinase complement of the human genome. Science, 298:1912-1934, Dec 2002. URL: https://doi.org/10.1126/science.1075762, doi:10.1126/science.1075762. This article has 10728 citations and is from a highest quality peer-reviewed journal.
13. (manning2002theproteinkinase pages 6-6): G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam. The protein kinase complement of the human genome. Science, 298:1912-1934, Dec 2002. URL: https://doi.org/10.1126/science.1075762, doi:10.1126/science.1075762. This article has 10728 citations and is from a highest quality peer-reviewed journal.
14. (manning2002theproteinkinase pages 7-8): G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam. The protein kinase complement of the human genome. Science, 298:1912-1934, Dec 2002. URL: https://doi.org/10.1126/science.1075762, doi:10.1126/science.1075762. This article has 10728 citations and is from a highest quality peer-reviewed journal.
15. (merkel2012pim1kinaseas pages 1-2): Anna Lena Merkel, Eric Meggers, and Matthias Ocker. Pim1 kinase as a target for cancer therapy. Expert Opinion on Investigational Drugs, 21:425-436, Mar 2012. URL: https://doi.org/10.1517/13543784.2012.668527, doi:10.1517/13543784.2012.668527. This article has 159 citations and is from a peer-reviewed journal.
16. (merkel2012pim1kinaseas pages 5-6): Anna Lena Merkel, Eric Meggers, and Matthias Ocker. Pim1 kinase as a target for cancer therapy. Expert Opinion on Investigational Drugs, 21:425-436, Mar 2012. URL: https://doi.org/10.1517/13543784.2012.668527, doi:10.1517/13543784.2012.668527. This article has 159 citations and is from a peer-reviewed journal.
17. (merkel2012pim1kinaseas pages 9-10): Anna Lena Merkel, Eric Meggers, and Matthias Ocker. Pim1 kinase as a target for cancer therapy. Expert Opinion on Investigational Drugs, 21:425-436, Mar 2012. URL: https://doi.org/10.1517/13543784.2012.668527, doi:10.1517/13543784.2012.668527. This article has 159 citations and is from a peer-reviewed journal.
18. (unknownauthors2009theroleof pages 109-112): The role of PIM1 in cell survival
19. (unknownauthors2015mutationalanalysisof pages 28-32): Mutational analysis of isoform selectivity and conformational equilibria in protein kinase inhibition
20. (unknownauthors2019roleofpim pages 20-23): Role of PIM oncogenes in the biology and chemoresistance of aggressive lymphomas
21. (unknownauthors2021altestargetneue pages 421-423): Altes Target, Neue Hits-Entwicklung von Inhibitoren für die PIM1-Kinase
22. (zhang2018pimkinaseas pages 1-2): Xinning Zhang, Mengqiu Song, J. Kundu, Mee-Hyun Lee, and Zhen‐zhen Liu. Pim kinase as an executional target in cancer. Journal of Cancer Prevention, 23:109-116, Sep 2018. URL: https://doi.org/10.15430/jcp.2018.23.3.109, doi:10.15430/jcp.2018.23.3.109. This article has 128 citations.
23. (bogusz2017structuralanalysisof pages 6-7): Jozefina Bogusz, Karol Zrubek, Krzysztof P. Rembacz, Przemyslaw Grudnik, Przemyslaw Golik, Malgorzata Romanowska, Benedykt Wladyka, and Grzegorz Dubin. Structural analysis of pim1 kinase complexes with atp-competitive inhibitors. Scientific Reports, Oct 2017. URL: https://doi.org/10.1038/s41598-017-13557-z, doi:10.1038/s41598-017-13557-z. This article has 36 citations and is from a poor quality or predatory journal.
24. (nock2023pimkinasesimportant pages 5-6): Sophie Nock, E. Karim, and A. Unsworth. Pim kinases: important regulators of cardiovascular disease. International Journal of Molecular Sciences, Jul 2023. URL: https://doi.org/10.3390/ijms241411582, doi:10.3390/ijms241411582. This article has 15 citations and is from a peer-reviewed journal.