1. Phylogeny  
   Serine/threonine‐protein kinase PIM1 belongs to the PIM family of kinases, a group that includes PIM1, PIM2, and PIM3, which are evolutionarily conserved among vertebrates and are found in all mammalian species (zhukova2011pimfamilyof pages 1-2). The PIM kinases share considerable amino acid sequence homology, with PIM1 exhibiting approximately 61% identity with PIM2 and 71% with PIM3; these similarities support a common evolutionary origin dating back to early vertebrate ancestors (atalay2024pim3kinasea pages 1-2, zhukova2011pimfamilyof pages 1-2). Phylogenetic analyses based on the human kinome categorize PIM1 within the calcium/calmodulin‐dependent protein kinase (CaMK) group, although it lacks typical regulatory domains present in other members of this group (arrouchi2019areviewon pages 1-2). In the context of the human kinome assembled by Manning et al., PIM1 is part of an evolutionary core of serine/threonine kinases that have maintained their catalytic domain structure while diverging in regulatory mechanisms (brault2010pimserinethreoninekinases pages 1-2, zhukova2011pimfamilyof pages 1-2).
2. Reaction Catalyzed  
   PIM1 catalyzes the phosphorylation reaction in which the terminal phosphate group from ATP is transferred to the hydroxyl group of serine or threonine residues on target substrates. In a simplified biochemical representation, the reaction is:  
     ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–phospho-(L-serine/threonine) + H⁺  
   This reaction underlies PIM1’s ability to modify various substrates that control cell survival, proliferation, and other oncogenic processes (bullock2005structuralbasisof pages 1-2).
3. Cofactor Requirements  
   Consistent with other serine/threonine kinases, the catalytic activity of PIM1 requires ATP as a phosphate donor and necessitates the presence of divalent metal ions, most notably Mg²⁺, which act as cofactors to stabilize the binding of ATP within the active site and facilitate phosphoryl transfer (chen2019

* pim1kinasea pages 1-2).

1. Substrate Specificity  
   PIM1 exhibits a defined substrate specificity that is characterized by a consensus recognition motif enriched in basic amino acids. Typically, substrates phosphorylated by PIM1 contain sequences with multiple lysine (K) or arginine (R) residues preceding a serine/threonine target; for example, motifs such as (K/R)-(K/R)-(R/L)-S/T-X have been described (arrouchi2019areviewon pages 2-4). This preference for basic residues in close proximity to the phosphorylation site underpins its ability to regulate proteins involved in apoptosis and cell cycle progression, such as the pro-apoptotic protein BAD and transcription factors like MYC (brault2010pimserinethreoninekinases pages 9-10, arrouchi2019areviewon pages 2-4).
2. Structure  
   PIM1 shares the typical bilobal architecture common to serine/threonine kinases, featuring an N-terminal lobe primarily composed of β-sheets and a C-terminal lobe dominated by α-helices (bullock2005structuralbasisof pages 1-2, lee2013crystalstructureof pages 1-2). Central to its structure is the kinase domain, which includes a glycine-rich loop (G-loop) that interacts with the phosphate groups of ATP and a conserved catalytic loop that supports phosphotransfer activity (lee2013crystalstructureof pages 4-7). A unique structural hallmark of PIM1 is its atypical hinge region; the presence of a proline residue (commonly identified as Pro123) within this region precludes the formation of a second hydrogen bond with ATP, resulting in a distinct ATP-binding mode that has been exploited for selective inhibitor design (bullock2005structuralbasisof pages 9-10, lee2013crystalstructureof pages 4-7). Additionally, PIM1 is expressed in two major isoforms—a shorter 34 kDa variant and a longer 44 kDa variant generated via alternative translation initiation—with the larger isoform containing an extended N-terminal region that is implicated in directing subcellular localization, such as targeting to the plasma membrane (nock2023pimkinasesimportant pages 5-6). The overall 3D organization, as revealed by crystallographic studies, underscores the constitutively active nature of PIM1, with its structure being pre-organized for catalysis without the need for activation loop phosphorylation (lee2013crystalstructureof pages 7-7, bullock2005structuralbasisof pages 9-10).
3. Regulation  
   Unlike many kinases that require regulatory phosphorylation events for activation, PIM1 is constitutively active owing to the presence of an acidic residue in its activation loop that mimics the phosphorylated state (malone2020currentperspectiveson pages 6-10). Regulation of PIM1 occurs predominantly at the transcriptional and translational levels, with its expression being induced by cytokine signaling via the JAK/STAT pathway; transcription factors such as STAT3 and STAT5 bind directly to the PIM1 promoter to upregulate its expression in response to growth factors and cytokines (arrouchi2019areviewon pages 1-2, warfel2015pimkinase(and pages 2-4). In addition, the stability of the PIM1 protein is tightly controlled post-translationally through mechanisms that include ubiquitination and subsequent proteasomal degradation; chaperone proteins such as HSP90 can bind to PIM1 and protect it from degradation, whereas association with HSP70 facilitates its ubiquitination and turnover (malone2020currentperspectiveson pages 6-10, magnuson2010whytargetpim1 pages 8-10). Autophosphorylation events have been reported to occur, although they do not play a central role in activation, and modifications by other kinases such as ETK (which phosphorylates a tyrosine residue) may enhance PIM1 activity further (choudhury2024pim1kinaseand pages 1-2, warfel2015pimkinase(and pages 2-4).
4. Function  
   PIM1 functions as a proto‐oncogene and plays a pivotal role in regulating cell survival, proliferation, and apoptosis, processes that collectively contribute to tumorigenesis. One of its key functional roles is the stabilization of the MYC oncoprotein through phosphorylation, which prevents MYC degradation and enhances its transcriptional activity; this synergistic interaction between PIM1 and MYC is a critical driver of oncogenic transformation (alvarado2012thepimkinases pages 11-11, warfel2015pimkinase(and pages 7-9). Moreover, PIM1 phosphorylates the pro-apoptotic protein BAD at specific serine residues, leading to its sequestration by 14-3-3 proteins and the subsequent release of anti-apoptotic proteins such as Bcl-X(L)/BCL2L1, thereby promoting cell survival (alvarado2012thepimkinases pages 11-11, arrouchi2019areviewon pages 1-2). In addition to modulating apoptosis, PIM1 influences cell cycle progression by phosphorylating regulators that control key checkpoints, which further supports its role in facilitating uncontrolled proliferation in cancer cells (brault2010pimserinethreoninekinases pages 9-10, arrouchi2019areviewon pages 2-4). The kinase’s broad substrate specificity enables it to impact multiple signaling cascades; its ability to phosphorylate transcription factors, pro-apoptotic mediators, and cell cycle inhibitors integrates survival signals that confer a selective growth advantage to tumor cells (choudhury2024pim1kinaseand pages 22-23, word from warfel2015pimkinase(and pages 7-9). Elevated expression of PIM1 has been observed in diverse malignancies, including hematologic cancers such as leukemia and lymphoma, as well as in solid tumors like prostate, gastric, and head and neck cancers, highlighting its clinical relevance as a biomarker of poor prognosis and a promising target for therapeutic intervention (magnuson2010whytargetpim1 pages 1-2, wu2021pimkinasesin pages 10-11).
5. Other Comments  
   A number of small molecule inhibitors have been developed to target PIM1, reflecting its central role in oncogenic signaling and its potential as a therapeutic target in cancer. Notable inhibitors include ATP-competitive compounds such as SGI-1776, AZD1208, and PIM447, which have shown efficacy in preclinical models and, in some cases, have been evaluated in early clinical trials (le2015targetingpimkinases pages 1-2, malone2020currentperspectiveson pages 22-26). Despite the development of multiple PIM kinase inhibitors, challenges persist regarding isoform specificity among PIM1, PIM2, and PIM3, as well as potential off-target effects resulting from the conserved nature of their ATP-binding sites (le2015targetingpimkinases pages 13-15, malone2020currentperspectiveson pages 10-14). PIM1 overexpression is closely associated with chemoresistance in several tumor types; its ability to facilitate survival signaling through phosphorylation of key substrates like BAD, MAP3K5, and FOXO3 underscores the rationale for targeting PIM1 in combination therapies to overcome drug resistance (alvarado2012thepimkinases pages 11-11, warfel2015pimkinase(and pages 7-9). In addition, the unique structural features of PIM1, particularly its atypical hinge region, provide a foundation for the design of highly selective inhibitors that may minimize collateral inhibition of other kinases (lee2013crystalstructureof pages 4-7, bullock2005structuralbasisof pages 9-10). Furthermore, PIM1’s role in modulating the activity of oncogenic transcription factors such as MYC and in controlling cell cycle progression makes it an attractive candidate for combination strategies with other targeted therapies, including those aimed at the PI3K/Akt/mTOR signaling axis (warfel2015pimkinase(and pages 7-9, wu2021pimkinasesin pages 2-4). Finally, ongoing clinical investigations continue to evaluate the therapeutic potential of PIM kinase inhibition in various malignancies, thereby reinforcing the importance of this kinase as both a biomarker and a drug target (magnuson2010whytargetpim1 pages 18-18, wu2021pimkinasesin pages 10-11).

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