1. Phylogeny  
   PIM2 is a member of the PIM kinase family, which comprises three constitutively active serine/threonine kinases—PIM1, PIM2, and PIM3—that are evolutionarily conserved across vertebrates (narlik‐grassow2014thepimfamily pages 1-4, nawijn2011forbetteror pages 3-4). Within this family, PIM2 is encoded on the X chromosome, in contrast to PIM1 and PIM3 that are located on chromosomes 17 and 15, respectively, and it shares approximately 53–61% amino acid sequence identity with PIM1 (brault2010pimserinethreoninekinases pages 2-3). This high degree of conservation places PIM2 within a core group of serine/threonine kinases that have been maintained since early vertebrate evolution (narlik‐grassow2014thepimfamily pages 1-4, nawijn2011forbetteror pages 3-4). The overall phylogenetic context of PIM2 is defined by its grouping with other oncogenic CAMK family members, reflecting both functional redundancy and isoform-specific regulatory features within the PIM family (brault2010pimserinethreoninekinases pages 2-3, malone2020currentperspectiveson pages 1-6).
2. Reaction Catalyzed  
   PIM2 catalyzes the transfer of the terminal phosphate group from ATP to the hydroxyl group of serine or threonine residues in substrate proteins. This reaction can be summarized as follows: ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺ (warfkel2015pimkinase(and pages 2-4). The phosphorylation of specific substrates by PIM2 is central to its role in modulating signaling pathways that govern cell survival and proliferation (alvarado2012thepimkinases pages 11-11).
3. Cofactor Requirements  
   The catalytic activity of PIM2, like that of most serine/threonine kinases, is dependent on the presence of divalent metal ions, with magnesium (Mg²⁺) serving as an essential cofactor. Mg²⁺ is required to coordinate ATP binding within the active site and to stabilize the transition state during the phosphate transfer reaction (warfkel2015pimkinase(and pages 2-4, le2015targetingpimkinases pages 1-2).
4. Substrate Specificity  
   PIM2 exhibits a substrate specificity that is defined by a consensus sequence similar to that recognized by PIM1. This consensus motif is typically characterized by the presence of basic residues, such as arginine, in positions preceding the phosphoacceptor serine or threonine. In particular, substrates tend to contain motifs such as R–X–R–H–X–S/T, where “X” represents any amino acid (malone2020currentperspectiveson pages 10-14, eccleshallUnknownyearpimkinasesin pages 24-27). PIM2 phosphorylates substrates that include key regulators of apoptosis and cell proliferation. Among these, the phosphorylation of the pro‐apoptotic protein BAD leads to its inactivation and the subsequent release of anti‐apoptotic factors such as Bcl‑X(L)/BCL2L1, while phosphorylation of MYC results in increased protein stability and transcriptional activity (information section, warfel2015pimkinase(and pages 7-9).
5. Structure  
   The three-dimensional structure of PIM2 conforms to the canonical bilobal architecture observed in protein kinases, with a predominantly β‑sheet–rich N‑terminal lobe and an α‑helical C‑terminal lobe. A unique feature of PIM2 is found in its hinge region; a conserved proline residue within the hinge prevents the formation of a second hydrogen bond with the adenine moiety of ATP and is followed by an amino acid insertion that expands the adjacent hydrophobic pocket, features that have been exploited for the design of selective inhibitors (alexander2015mutationalanalysisof pages 28-32, le2015targetingpimkinases pages 8-9). Additionally, PIM2 contains a distinctive β‑hairpin insert connecting the β3 strand to helix αC in the N‑terminal lobe, a structural element that appears partially disordered and may influence inhibitor binding and kinase dynamics (alexander2015mutationalanalysisof pages 28-32). Despite minor differences in non‐conserved residues compared to PIM1, the overall topology of the ATP-binding pocket is maintained, supporting conserved catalytic functionality (le2015targetingpimkinases pages 8-9).
6. Regulation  
   PIM2 is constitutively active and its regulation occurs primarily at the transcriptional, translational, and post‐translational levels rather than through activation loop phosphorylation. Transcription of PIM2 is induced by cytokine stimulation via the JAK/STAT pathway, with STAT3 and STAT5 binding to regulatory elements within the promoter to enhance gene expression (malone2020currentperspectiveson pages 6-10). In addition, PIM2 protein stability is tightly controlled by the ubiquitin–proteasome system; it is rapidly degraded under basal conditions yet can be stabilized by interactions with molecular chaperones such as HSP90, while HSP70 association promotes proteasomal degradation (brault2010pimserinethreoninekinases pages 6-7, nock2023pimkinasesimportant pages 5-6). Furthermore, phosphatases such as PP2A contribute to the dephosphorylation and destabilization of PIM2, and under hypoxic conditions deubiquitinases like USP28 have been reported to stabilize PIM family proteins (warfkel2015pimkinase(and pages 19-22, nock2023pimkinasesimportant pages 5-6). These regulatory mechanisms ensure that PIM2 activity is closely linked to its expression levels and environmental stress signals.
7. Function  
   PIM2 functions as a proto‐oncogene with serine/threonine kinase activity that is integral to the regulation of cell survival and cell proliferation. By phosphorylating key substrates, PIM2 regulates several critical cellular processes:  
   – It phosphorylates MYC, thereby enhancing MYC protein stability and increasing its transcriptional activity, which contributes to synergistic oncogenic interactions observed with MYC overexpression (information section, malone2020currentperspectiveson pages 10-14).  
   – It modulates cell cycle progression through the phosphorylation of cell cycle regulators, ensuring proper progression through key checkpoints (malone2020currentperspectiveson pages 22-26).  
   – PIM2 regulates cap‑dependent protein translation through an mTORC1‑independent mechanism that operates in parallel with the PI3K‑Akt pathway (information section, le2015targetingpimkinases pages 4-5).  
   – It mediates survival signaling through the phosphorylation of the pro‑apoptotic protein BAD; phosphorylation of BAD results in its sequestration by 14‑3‑3 proteins, leading to the release of the anti‑apoptotic factor Bcl‑X(L)/BCL2L1 and promoting cell survival (information section, warfel2015pimkinase(and pages 7-9).  
   PIM2 expression is predominantly observed in lymphoid tissues and the brain, and its overexpression has been associated with several hematological malignancies as well as solid tumors such as prostate carcinoma (ren2013theover‐expressionof pages 8-8, malone2020currentperspectiveson pages 38-43).
8. Other Comments  
   Several small‑molecule inhibitors targeting PIM kinases have been developed owing to the unique structural features of their ATP‑binding sites. Early compounds such as SGI‑1776 showed potent antileukemic activity but were discontinued due to safety concerns, while newer inhibitors such as AZD1208 and PIM447 are currently under clinical evaluation (malone2020currentperspectiveson pages 38-43, le2015targetingpimkinases pages 8-9). Inhibitor design has particularly benefited from the observation that the hinge region of PIM2 contains a conserved proline that limits hydrogen bonding with ATP, thereby allowing the development of compounds with increased selectivity for the PIM family (alexander2015mutationalanalysisof pages 28-32, le2015targetingpimkinases pages 8-9). In addition, the involvement of PIM2 in chemoresistance—through its regulation of survival pathways and interaction with oncogenes such as MYC—renders it a promising target for combination therapies in cancers that exhibit high PIM2 activity (malone2020currentperspectiveson pages 22-26, ren2013theover‐expressionof pages 8-8). The constitutive activity of PIM2, together with its regulation predominantly at the expression and protein stability levels, distinguishes it from many other kinases that require extracellular stimulation for activation (warfkel2015pimkinase(and pages 2-4, brault2010pimserinethreoninekinases pages 7-8).
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