1. Phylogeny  
   cGMP‐dependent protein kinase 1 (PRKG1; also known as PKG1) is a member of the AGC kinase family that is highly conserved throughout eukaryotic evolution. Orthologs of PRKG1 are found in organisms ranging from unicellular eukaryotes to complex mammals, indicating its presence in the ancient kinase core that predates the divergence of major eukaryotic lineages (hofmann2005thebiologyof pages 1-1, arencibia2013agcproteinkinases pages 1-2). In mammals, the PRKG1 gene gives rise to two alternatively spliced isoforms—PKG1α and PKG1β—that share conserved catalytic regions but differ in their N‐terminal sequences, which are critical for subcellular targeting and substrate specificity. PRKG1 belongs to a group of kinases that share evolutionary relationships with other AGC kinases, such as protein kinase A (PKA) and protein kinase C (PKC), and its conservation reflects the essential roles these enzymes play in cellular signaling processes, from vasorelaxation to neuronal function (hofmann2005thebiologyof pages 1-1, arencibia2013agcproteinkinases pages 1-2).
2. Reaction Catalyzed  
   PRKG1 catalyzes the transfer of a phosphate group from ATP to specific serine and threonine residues on its protein substrates. The overall reaction can be summarized as follows:  
   ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺  
   This phosphorylation reaction is fundamental for modulating the activity, localization, and interactions of target proteins within various signaling cascades (hofmann2005thebiologyof pages 1-1).
3. Cofactor Requirements  
   The catalytic activity of PRKG1 is dependent on essential cofactors. In particular, PRKG1 requires Mg²⁺; the divalent magnesium ion is necessary for proper ATP binding and subsequent phosphoryl transfer. In addition, the binding of cyclic guanosine monophosphate (cGMP) to the regulatory domains of PRKG1 is obligatory for its activation. cGMP binding allosterically relieves the autoinhibition exerted by the N-terminal regulatory region, thereby permitting the catalytic domain to engage ATP and substrate proteins (hofmann2020thecgmpsystem pages 24-28, mishra2025cardiaccgmpregulation pages 1-2).
4. Substrate Specificity  
   PRKG1 phosphorylates target proteins on serine/threonine residues, and its substrate preference is characterized by a consensus motif that is enriched in basic residues immediately N-terminal to the phosphorylated residue. In many cases, substrates of PRKG1 contain a motif conforming to a general K/R–K/R–X–S/T sequence. This consensus motif has been observed in key substrates such as vasodilator‐stimulated phosphoprotein (VASP) and others that mediate calcium desensitization in smooth muscle cells (wolfertstetter2013cgmpdependentproteinkinase pages 1-4, roy2021identificationofnovel pages 2-3). High‐throughput kinase profiling experiments have further refined our understanding of PRKG1’s substrate specificity, demonstrating overlapping preferences with other members of the AGC kinase family while maintaining selectivity for cGMP-mediated phosphorylation events (kim2021cyclicnucleotideselectivity pages 1-3).
5. Structure  
   The three-dimensional architecture of PRKG1 is defined by a modular domain organization that underpins its regulatory and catalytic functions. The protein consists of an N-terminal regulatory region that contains a leucine zipper motif; this motif is crucial for homodimerization and for mediating interactions with other cellular proteins. Immediately following the dimerization region is an autoinhibitory segment that, in the absence of cGMP, sterically hinders the catalytic activity by blocking substrate access. Central to PRKG1’s function are the two tandem cyclic nucleotide binding (CNB) domains that exhibit differential binding affinities for cGMP; these domains serve as allosteric switches that, upon nucleotide binding, induce a conformational rearrangement which displaces the autoinhibitory region from the catalytic cleft (hofmann2005thebiologyof pages 1-1, kim2021cyclicnucleotideselectivity pages 1-3). The C-terminal catalytic domain, which harbors the conserved ATP-binding pocket, activation loop, hydrophobic spine, and C-helix, is responsible for phosphoryl transfer and substrate recognition. Structural studies, including crystallographic analyses and computational models from AlphaFold, confirm that cGMP binding triggers the release of the autoinhibitory sequence and aligns the catalytic residues in an optimal configuration for ATP binding and phosphoryl transfer (hofmann2020thecgmpsystem pages 24-28, kim2021cyclicnucleotideselectivity pages 3-4, wolfertstetter2013cgmpdependentproteinkinase pages 7-10).
6. Regulation  
   The activity of PRKG1 is tightly regulated by allosteric mechanisms, ensuring that its kinase activity is precisely controlled in response to changes in cellular cGMP levels. In its basal state, the autoinhibitory domain of PRKG1 interacts with the catalytic domain, maintaining the enzyme in an inactive conformation. Binding of cGMP to the two CNB domains leads to substantial conformational rearrangements that displace the autoinhibitory segment, thereby activating the catalytic domain for substrate phosphorylation (hofmann2005thebiologyof pages 1-1, hofmann2006functionofcgmpdependent pages 1-2). Furthermore, autophosphorylation of PRKG1 has been observed in experimental systems; such phosphorylation events can enhance the basal activity of the enzyme and prime it for downstream signaling (wolfertstetter2013cgmpdependentproteinkinase pages 7-10). PRKG1 is also regulated indirectly by nitric oxide (NO), which, upon binding to soluble guanylyl cyclase, increases intracellular cGMP levels. This NO-mediated cascade provides a mechanism for the fine‐tuning of PRKG1 activity in response to external stimuli, thereby integrating PRKG1 into larger signaling networks that control smooth muscle relaxation, platelet inhibition, and neuronal function (mishra2025cardiaccgmpregulation pages 1-2, hofmann2020thecgmpsystem pages 24-28). In addition to these physiological regulatory mechanisms, selective pharmacological inhibitors—such as cyclic nucleotide analogs that compete for the cGMP-binding sites (e.g., Rp-8-Br-PET-cGMPS)—have been employed in research to selectively modulate PRKG1 activity without affecting other cyclic nucleotide-dependent kinases (wolfertstetter2013cgmpdependentproteinkinase pages 13-16, potter2006natriureticpeptidestheir pages 11-11).
7. Function  
   PRKG1 is a pivotal enzyme that mediates the effects of nitric oxide (NO)/cGMP signaling across multiple tissues. In vascular smooth muscle, PRKG1 phosphorylates a variety of substrates that lead to a decrease in intracellular free calcium and a reduction in the sensitivity of contractile proteins to Ca²⁺. These phosphorylation events result in smooth muscle relaxation and are essential for the vasodilatory effects of NO, thereby contributing to the regulation of blood pressure and vascular tone (hofmann2005thebiologyof pages 2-3, potter2006natriureticpeptidestheir pages 11-11). In platelets, PRKG1 plays a critical role in inhibiting activation and adhesion, which is instrumental in maintaining hemostatic balance and preventing unwarranted thrombus formation (hofmann2005thebiologyof pages 2-3). Within the cardiac context, PRKG1 modulates cardiac contractility and has been implicated in protective signaling pathways that counteract pathological hypertrophy; such effects are partly mediated through the modulation of intracellular calcium handling and the inhibition of pro-hypertrophic signaling cascades (mishra2025cardiaccgmpregulation pages 1-2, hofmann2020thecgmpsystem pages 24-28). In the central nervous system, PRKG1 is expressed in brain regions including the hippocampus and cerebellum and is involved in diverse processes such as axon guidance, synaptic plasticity, circadian rhythm regulation, and nociception. This role is facilitated by the phosphorylation of key proteins involved in intracellular calcium dynamics and gene expression, including transcription factors like CREB (hofmann2005thebiologyof pages 2-3, roy2021identificationofnovel pages 2-3). Collectively, the functions of PRKG1 span the regulation of smooth muscle tone, platelet function, cardiac performance, and neuronal signaling; these diverse roles underscore its importance as a central mediator of NO/cGMP-dependent signaling pathways (wolfertstetter2013cgmpdependentproteinkinase pages 1-4, mishra2025cardiaccgmpregulation pages 1-2).
8. Other Comments  
   Selective inhibition of PRKG1 has attracted substantial interest due to its central role in modulating vital physiological processes and its emerging implications in disease pathogenesis. Experimental inhibitors such as Rp-8-Br-PET-cGMPS and Rp-8-pCPT-cGMPS have been developed to selectively target the cGMP-binding domain of PRKG1, thereby preventing its activation without perturbing the activity of related kinases like PKA (wolfertstetter2013cgmpdependentproteinkinase pages 13-16, potter2006natriureticpeptidestheir pages 11-11). Dysregulation of PRKG1 activity has been implicated in several disease conditions, including hypertension and vascular disorders—stemming from its role in smooth muscle relaxation—as well as in platelet dysfunction. In addition, aberrantly elevated cGMP levels leading to PRKG1 overactivation have been linked to pathologies in the central nervous system, such as defects in synaptic plasticity and photoreceptor degeneration observed in inherited retinal degenerations (hofmann2005thebiologyof pages 2-3, mishra2025cardiaccgmpregulation pages 1-2, roy2021identificationofnovel pages 2-3). High‐throughput phosphoproteomic and kinase activity profiling studies have expanded the known substrate repertoire of PRKG1, thereby enhancing our understanding of its involvement in intracellular signaling networks and providing novel opportunities for therapeutic intervention in diseases ranging from cardiovascular dysfunction to neurodegenerative disorders (roy2024integrativekinaseactivity pages 119-121, kim2021cyclicnucleotideselectivity pages 1-3). These advances underscore the therapeutic potential of modulating PRKG1 activity in a variety of clinical settings.
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