1. Phylogeny  
   Serine/threonine‐protein kinase PAK1 belongs to the p21‐activated kinase (PAK) family, which encompasses six mammalian isoforms divided into two groups: Group I (PAK1, PAK2, and PAK3) and Group II (PAK4, PAK5, and PAK6) (crawford2012p21activatedkinaseinhibitors pages 1-2). PAK1, as a member of Group I PAKs, is highly conserved among vertebrates and has orthologs present across diverse eukaryotic species, indicating that its evolutionary origins can be traced to an ancestral set of kinases predating the divergence of animals and fungi (dummler2009pakproteinkinases pages 1-3, pacheco2010groupip21activated pages 1-2). Its classification within the STE20 family of kinases further underscores its phylogenetic relationship with other Rho‐effector kinases, which are collectively involved in regulating cytoskeletal dynamics and signal transduction in multiple organisms (zhao2012pakfamilykinases pages 1-2).
2. Reaction Catalyzed  
   PAK1 is an ATP‐dependent serine/threonine kinase that catalyzes the transfer of a phosphate group from ATP to a hydroxyl group on the serine or threonine residue of a substrate protein, converting ATP to ADP and yielding a phosphorylated protein along with the release of a proton (crawford2012p21activatedkinaseinhibitors pages 1-2, yao2020p21activatedkinase1 pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of PAK1, like many other serine/threonine kinases, is dependent on the presence of divalent metal ions. In particular, Mg²⁺ is required as a cofactor for proper positioning of ATP within the active site to facilitate the phosphoryl transfer reaction (dummler2009pakproteinkinases pages 1-3, yao2020p21activatedkinase1 pages 1-2).
4. Substrate Specificity  
   PAK1 phosphorylates serine and threonine residues within a variety of substrates that regulate cellular cytoskeletal dynamics and signal transduction. Studies indicate that PAK1 exhibits a substrate preference for motifs in which basic residues (arginine or lysine) occur upstream of the phosphoacceptor residue, yielding a recognition sequence that is often described as (R/K)(R/K)X(S/T) (dummler2009pakproteinkinases pages 10-11, kichina2010pak1asa pages 5-7). This relatively broad consensus helps PAK1 to target a diverse set of substrates including cytoskeletal regulatory proteins, kinases, and components related to apoptotic signaling.
5. Structure  
   PAK1 is organized into two major regions: an N‐terminal regulatory region and a C‐terminal catalytic domain. The N‐terminal region contains the p21-binding domain (PBD), which overlaps with an autoinhibitory domain (AID) that maintains the kinase in a low‐activity state through intramolecular and trans‐inhibitory interactions; this region also includes several proline-rich motifs that mediate binding to SH3 domain–containing adapter proteins (crawford2012p21activatedkinaseinhibitors pages 1-2, pacheco2010groupip21activated pages 1-2). The C‐terminal catalytic domain is characterized by the typical bilobed kinase fold, with a smaller N-lobe and a larger C-lobe that together form the ATP-binding cleft. A key structural element is the activation loop, which contains the critical residue Thr423; autophosphorylation of Thr423 is essential for shifting PAK1 into an active conformation (kichina2010pak1asa pages 27-30, lei2005theactiveconformation pages 1-2). High-resolution structural studies and crystallographic analyses have revealed that in its inactive form, PAK1 exists as a dimer where the AID from one monomer interacts with the catalytic domain of the other, thereby preventing access of ATP to the active site; binding of activated Cdc42 or Rac1 disrupts this dimerization and promotes a conformational change that releases the autoinhibitory constraints (manser2005pakandother pages 2-4, kichina2010pak1asa pages 2-4).
6. Regulation  
   PAK1 is regulated primarily through an allosteric mechanism triggered by its interaction with active (GTP-bound) forms of small Rho-family GTPases, namely Cdc42 and Rac1, which bind to the combined CRIB/PBD region in the N-terminal regulatory domain. This binding event disrupts the autoinhibitory dimeric configuration, facilitating autophosphorylation at Thr423 and additional residues (such as Ser144) that further amplify its catalytic activity (kichina2010pak1asa pages 4-5, somanath2023targetingp21activatedkinase1 pages 5-6). Additional layers of regulation involve phosphorylation by upstream kinases such as PDK1 and Akt, which modify specific serine residues (for example, Ser21 in PAK1) affecting its interaction with adapter proteins like Nck and Grb2 (eswaran2012molecularpathwaystargeting pages 10-11, kichina2010pak1asa pages 4-5). Negative regulation is achieved by dephosphorylation through serine/threonine phosphatases such as PP2A and POPX family phosphatases that remove activating phosphate groups from the activation loop; furthermore, chemical inhibitors like IPA-3 exert allosteric inhibition by binding covalently to cysteine residues in the regulatory domain, thereby preventing the conformational changes required for activation (deacon2008anisoformselectivesmallmolecule pages 1-2, rane2014p21activatedkinases pages 2-5).
7. Function  
   PAK1 functions as a critical effector kinase within multiple intracellular signaling pathways that are initiated by integrins and receptor-type kinases. It plays an essential role in the regulation of cytoskeletal dynamics by orchestrating the reorganization of actin filaments, which in turn affects cell adhesion, migration, and the formation of focal adhesion complexes; this is achieved in part through phosphorylation of substrates such as myosin light chain kinase (MLCK) and LIM kinase, leading to modifications in actin stress fibers and lamellipodia formation (crawford2012p21activatedkinaseinhibitors pages 1-2, dummler2009pakproteinkinases pages 1-3). Additionally, PAK1 phosphorylates and inactivates pro-apoptotic proteins such as BAD, thereby providing a cell-survival signal that protects against apoptosis. By linking Rho GTPase activation to the c-Jun N-terminal kinase (JNK) MAP kinase cascade, PAK1 serves as a key mediator that relays signals from small GTPases (Cdc42 and Rac1) to downstream kinases including MAP2K1, thus influencing proliferation and differentiation (crawford2012p21activatedkinaseinhibitors pages 1-2, eswaran2012molecularpathwaystargeting pages 4-5). In addition to its role in cytoskeletal remodeling, PAK1 also participates in vesicle-mediated transport processes, mitotic progression, and gene expression regulation, thereby affecting a wide range of cellular processes that contribute to normal physiology and oncogenic transformation (yeo2015theroleof pages 28-33, somanath2023targetingp21activatedkinase1 pages 2-3).
8. Other Comments  
   A number of small-molecule inhibitors have been developed targeting PAK1, including ATP-competitive compounds as well as allosteric inhibitors like IPA-3, which binds to the regulatory region and prevents GTPase-mediated activation; these compounds are being explored in preclinical studies for their ability to attenuate tumor cell proliferation, migration, and survival (rudolph2015inhibitorsofp21activated pages 1-2, yao2020p21activatedkinase1 pages 18-21). PAK1 is frequently overexpressed or hyperactivated in various cancers—such as breast, ovarian, colorectal, and hepatocellular carcinomas—and its dysregulation is associated with enhanced cell migration, invasion, and resistance to apoptosis, making it a promising therapeutic target (crawford2012p21activatedkinaseinhibitors pages 1-2, yeo2015theroleof pages 28-33, somanath2023targetingp21activatedkinase1 pages 2-3). Although specific disease-causing mutations in PAK1 are not prominently reported, its aberrant expression and kinase activity are implicated in oncogenic signaling networks. The development of more selective inhibitors continues to be a major focus, as researchers aim to overcome challenges associated with targeting a kinase that possesses a highly conserved catalytic domain among its family members (rane2014p21activatedkinases pages 9-10, yao2020p21activatedkinase1 pages 22-23).
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