1. Phylogeny  
   Serine/threonine‐protein kinase PAK5 (also referred to as PAK7 or KIAA1264) is a member of the p21‐activated kinase (PAK) family that is assigned to Group II. Group II PAKs, which include PAK4, PAK5, and PAK6, are evolutionarily distinct from Group I PAKs (PAK1–PAK3) and are characterized by a high degree of conservation in their catalytic domains (greater than 75% identity) with divergence in their regulatory regions such that classical autoinhibitory domains found in Group I are absent in Group II members (kichina2010pak1asa pages 17-18). Orthologs of PAK5 can be identified throughout vertebrate species, with evidence indicating that the evolution of this kinase is rooted deeply in the common ancestry of eukaryotes; genomic and phylogenetic analyses classify PAK5 among a core set of kinases conserved since the Last Eukaryotic Common Ancestor (civiero2018paksinthe pages 1-4, rane2014p21activatedkinases pages 11-11). Many studies have established that, although all PAK family members share a common ancestral kinase fold, Group II members have acquired structural and regulatory features that support their specialized roles, particularly in neuronal tissues where PAK5 is predominantly expressed (kichina2010pak1asa pages 17-18, matenia2009thetauof pages 8-9). This evolutionary context underlines a kinome classification in which PAK5 is phylogenetically grouped with PAK4 and PAK6, setting it apart by both its sequence identity and its tissue‐restricted expression profile.
2. Reaction Catalyzed  
   PAK5 catalyzes the transfer of a phosphate group from ATP to serine and threonine residues on protein substrates. In biochemical terms, the reaction can be generalized as follows: ATP + protein - (L‐serine or L‐threonine) → ADP + protein - (L‐serine/threonine)-phosphate + H⁺. This phosphorylation event is central to its role in modulating the activity of several downstream substrates involved in cell signaling pathways such as those that regulate cell survival, cytoskeletal organization, and migration (dummler2009pakproteinkinases pages 1-3).
3. Cofactor Requirements  
   The catalytic activity of PAK5, like that of most serine/threonine kinases, is dependent on the presence of divalent cations. In particular, Mg²⁺ functions as an essential cofactor by coordinating the ATP molecule within the active site and facilitating the phosphotransfer reaction. This requirement for Mg²⁺ is a common feature among protein kinases and is critical for proper enzymatic activity (bagheri2022targetingproteinkinases pages 2-4).
4. Substrate Specificity  
   Group II PAKs, including PAK5, recognize and phosphorylate substrates on serine/threonine residues within specific sequence contexts. Recent efforts employing positional scanning peptide libraries have identified that while Group I PAKs preferentially target peptide motifs with the consensus RRRRRSWYFS, Group II PAKs display a distinct preference for a related motif, RRRRRSWASP (kichina2010pak1asa pages 1-2). This consensus motif reflects the substrate specificity of PAK5 and is indicative of a preference for a cluster of basic residues positioned N-terminal to the phosphoacceptor serine or threonine, followed by a defined hydrophobic region. Through phosphorylation of select substrates, PAK5 influences a variety of cellular processes including cytoskeletal rearrangements and cell survival (dummler2009pakproteinkinases pages 1-3, ye2012paksignalingin pages 2-3).
5. Structure  
   PAK5 is organized into distinct structural domains that underpin its catalytic function and regulatory control. At the N-terminus, PAK5 contains a Cdc42/Rac Interactive Binding (CRIB) domain, which, while capable of binding the small GTPases Cdc42 and Rac1, does not robustly activate the kinase activity as observed with Group I PAKs. Unlike Group I members, PAK5 lacks a classical kinase inhibitory (KI) domain; instead, it is regulated via other mechanisms including autophosphorylation events within the catalytic core. The C-terminal portion of PAK5 comprises the highly conserved kinase domain that features the typical bilobal structure seen in protein kinases. In this fold, an N-terminal lobe, mainly composed of β-sheets, is juxtaposed with a predominantly α-helical C-terminal lobe; key catalytic residues are organized around the ATP-binding cleft and include an activation loop whose phosphorylation is critical for full enzymatic activity (kichina2010pak1asa pages 17-18, thiriet2013cytoplasmicproteinserinethreonine pages 48-51). Although a high-resolution crystal structure specific to PAK5 is not available, homology modeling based on related PAKs suggests that the enzyme possesses a conserved catalytic spine including a C-helix and hydrophobic motifs that facilitate substrate engagement and catalysis. The overall structural organization of PAK5, including its central kinase domain and the flanking regulatory CRIB domain, is reflective of the evolutionary adaptation of Group II PAKs to modulate signaling in neural contexts (civiero2018paksinthe pages 1-4, kichina2010pak1asa pages 17-18).
6. Regulation  
   The regulation of PAK5 occurs via multiple mechanisms that include protein–protein interactions, autophosphorylation, and conformational modulation by GTPase binding. Although PAK5 possesses a CRIB domain that enables binding to small GTPases such as Cdc42 and Rac1, this interaction does not fully relieve autoinhibition in the same robust manner as seen with Group I PAKs. Instead, PAK5 undergoes autophosphorylation at several serine and threonine residues, a post‐translational modification that is integral to its activation (dummler2009pakproteinkinases pages 1-3, kichina2010pak1asa pages 1-2). In addition, PAK5 is subject to regulation by upstream kinases, and it participates in signaling crosstalk with the MARK (microtubule affinity‐regulating kinase) family. Binding of PAK5 to MARK2 results in the inhibition of MARK2’s kinase activity, a regulatory interaction that contributes to microtubule stabilization by preventing MARK2‐mediated phosphorylation events on microtubule‐associated proteins (li2006regulationofthe pages 59-66, li2006regulationofthe pages 87-91). Furthermore, the subcellular localization of PAK5 is regulated in a manner that is dependent on its activation state; active PAK5 promotes dissolution of actin stress fibers and focal adhesions, leading to dynamic reorganization of the cytoskeleton, whereas inactive forms tend to concentrate at specific intracellular sites such as vesicles and the centrosomal area (li2006regulationofthe pages 6-9, sechi2022minorkinaseswith pages 11-13). This constellation of regulatory events, which also includes dephosphorylation by serine/threonine phosphatases, underscores the tight control over PAK5 activity in response to upstream signals and cellular context (rudolph2015inhibitorsofp21activated pages 1-2).
7. Function  
   PAK5 plays a central role in the regulation of several cellular processes by modulating cytoskeletal dynamics, cell migration, and survival signaling. One principal function of PAK5 is its ability to stabilize microtubules through the inhibition of MARK2, thereby preventing the phosphorylation and subsequent detachment of microtubule‐associated proteins. Concurrently, PAK5 destabilizes the F-actin network, which results in the disassembly of stress fibers and focal adhesions. These cytoskeletal modifications facilitate changes in cell morphology and promote the formation of filopodia, contributing to enhanced cell motility (li2006regulationofthe pages 87-91, thiriet2013cytoplasmicproteinserinethreonine pages 48-51). In addition to its role in cytoskeletal regulation, PAK5 phosphorylates key substrates that drive pro-survival and proliferative signaling pathways. For instance, phosphorylation of RAF1 by PAK5 stimulates RAF1 kinase activity, thereby engaging downstream components of the mitogen-activated protein kinase (MAPK) cascade; similarly, phosphorylation of the BCL2 antagonist of cell death (BAD) by PAK5 promotes cell survival by inhibiting apoptotic pathways (dummler2009pakproteinkinases pages 1-3, ye2012paksignalingin pages 2-3). PAK5 also phosphorylates CTNND1 (catenin delta-1), an event that is likely to regulate aspects of cell adhesion and morphology by modulating the cytoskeletal network (kichina2010pak1asa pages 1-2). Expression of PAK5 is predominantly enriched in neuronal tissues, which is consistent with its established roles in neurite outgrowth and synaptic plasticity; this tissue-specific expression pattern differentiates PAK5 from ubiquitously expressed kinases and underscores its importance in neural development and function (kichina2010pak1asa pages 17-18, matenia2009thetauof pages 8-9). These functions place PAK5 at a key nodal point in signal transduction pathways that coordinate cytoskeletal structure, cell migration, and survival responses.
8. Other Comments  
   The identification of small molecule inhibitors for the PAK family has been an area of active research. Although isoform-specific inhibitors for PAK5 have not been as extensively characterized as those for PAK1 or PAK4, several compounds that target p21-activated kinases more broadly have been developed; examples include agents such as FRAX597 and PF-3758309, which exhibit inhibitory activity against multiple PAK isoforms (rudolph2015inhibitorsofp21activated pages 1-2). PAK5 has been implicated in oncogenic processes and may contribute to tumor progression by promoting cell migration, invasion, and resistance to apoptosis. In several cancer types, alterations in PAK family kinase expression and activity correlate with aggressive tumor behavior, although direct disease associations specific to PAK5 require further elucidation (minden2012pak4–6incancer pages 9-9, szczepanowska2009involvementofraccdc42pak pages 8-9). Moreover, the interplay between PAK5 and key regulatory proteins involved in cytoskeletal dynamics and survival signaling suggests that modulation of its activity could have therapeutic potential in contexts where aberrant cell migration and survival contribute to disease pathology. Continued research into the structural details and regulatory mechanisms of PAK5 may yield further insights into the development of more selective inhibitors and targeted therapies.
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