## Phylogeny

• Member of the STE20 family, Group II PAK sub-family together with PAK4 and PAK5; Group II kinases share ≈75 % identity within the catalytic domain and diverge from Group I PAKs by lacking the canonical autoinhibitory domain (eswaran2008unpakingtheclass pages 1-2, jaffer2002p21activatedkinasesthree pages 1-3).  
• Mouse ortholog Pak6: targeted disruption causes learning and locomotor defects, indicating functional conservation in vertebrates (goyette2019detectionofthe pages 10-13).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr → ADP + protein-O-phospho-L-Ser/Thr (jha20123dstructureanalysis pages 1-2).

## Cofactor Requirements

Catalytic activity requires divalent cations; biochemical assays employ 10 mM MgCl₂ and 1 mM MnCl₂ (gao2013substrateandinhibitor pages 2-3).

## Substrate Specificity

• Positional-scanning peptide libraries define a preference for basic residues at −3/−2 and a hydrophobic residue at +1 relative to the phosphoacceptor, identical to other Group II PAKs (gao2013substrateandinhibitor pages 2-3).  
• Documented cellular substrates include the androgen receptor DNA-binding domain, ESR1, PACSIN1, 14-3-3γ and BAD (schrantz2004mechanismofp21activated pages 1-1, gao2013substrateandinhibitor pages 1-2, iannotta2024pak6rescuespathogenic pages 1-4, kaur2008increasedpak6expression pages 1-2).

## Structure

• Domain organisation: N-terminal CRIB (≈aa 10-47), central proline-rich segment containing a pseudosubstrate sequence centred on Pro52, C-terminal kinase domain (aa 383-674) (jaffer2002p21activatedkinasesthree pages 1-3, gao2013substrateandinhibitor pages 2-3).  
• High-resolution crystal structures of the kinase domain solved at 1.4 Å with PF-3758309 and 1.95 Å with sunitinib adopt an active DFG-in configuration (gao2013substrateandinhibitor pages 7-8).  
• Phosphorylated kinase domain structure (PDB 2C305) shows an ordered activation loop and intact regulatory spine with <0.2 Å RMSD among phosphorylated forms (jha20123dstructureanalysis pages 1-2).  
• CRIB–Cdc42 co-crystal reveals the small-GTPase interaction interface (jha20123dstructureanalysis pages 9-9).  
• A serine replaces the conserved catalytic-loop asparagine; S→N substitution constitutively activates the enzyme (jaffer2002p21activatedkinasesthree pages 1-3).  
• Melanoma-associated mutation P52L in the pseudosubstrate segment disrupts autoinhibition and enhances kinase activity (gao2013substrateandinhibitor pages 8-9).

## Regulation

• Intramolecular pseudosubstrate autoinhibition maintains basal control; P52L relieves this inhibition (gao2013substrateandinhibitor pages 8-9).  
• GTP-bound Cdc42/Rac1 binds the CRIB domain to drive relocalisation without markedly increasing catalytic output (jaffer2002p21activatedkinasesthree pages 1-3, eswaran2008unpakingtheclass pages 1-2).  
• Activation by the MAP2K6–p38 MAPK cascade via phosphorylation (goyette2019detectionofthe pages 10-13, kaur2008increasedpak6expression pages 1-2).  
• Negative regulation through association with PP1B and POPX1/POPX2 phosphatases (kaur2008increasedpak6expression pages 7-7).  
• Constitutive autophosphorylation detected in recombinant preparations indicates basal phosphorylation (gao2013substrateandinhibitor pages 1-2).

## Function

• Expression enriched in brain, testis, prostate, kidney and placenta; localises to cytoplasm and nucleus in prostate cells (jaffer2002p21activatedkinasesthree pages 1-3, kaur2008increasedpak6expression pages 5-6).  
• Localises to centrosomes and the primary cilium; required for ciliogenesis and centrosomal cohesion (iannotta2024pak6rescuespathogenic pages 1-4).  
• Directly interacts with the androgen receptor via an FXXFF motif; phosphorylation of the AR DNA-binding domain suppresses AR-dependent transcription (kaur2008increasedpak6expression pages 1-2, schrantz2004mechanismofp21activated pages 1-1).  
• Inhibits ESR1-mediated transcription (goyette2019detectionofthe pages 10-13).  
• Forms complexes with IQGAP1 at cell–cell adhesions, influencing adhesion dynamics (goyette2019detectionofthe pages 10-13).  
• Phosphorylates 14-3-3 proteins, reducing LRRK2 activity and rescuing G2019S LRRK2-linked ciliogenesis defects (iannotta2024pak6rescuespathogenic pages 1-4, iannotta2024pak6rescuespathogenic pages 6-7).  
• Phosphorylates BAD, contributing to apoptosis resistance (kaur2008increasedpak6expression pages 1-2).  
• Over-expression correlates with enhanced motility and chemoresistance to 5-fluorouracil in colorectal cancer cells (goyette2019detectionofthe pages 10-13).

## Inhibitors

• PF-3758309: ATP-competitive inhibitor originally developed for PAK4; co-crystallised with PAK6 at 1.4 Å resolution (gao2013substrateandinhibitor pages 1-2).  
• Sunitinib: multi-target tyrosine kinase inhibitor; co-crystallised with PAK6 at 1.95 Å (gao2013substrateandinhibitor pages 7-8).

## Other Comments

• Up-regulated in primary, metastatic and androgen-independent prostate cancers (kaur2008increasedpak6expression pages 1-2).  
• High expression predicts poor response to 5-fluorouracil chemotherapy in colon cancer (goyette2019detectionofthe pages 10-13).  
• Pak6-null mice display deficits in learning and locomotion (goyette2019detectionofthe pages 10-13).  
• Melanoma-associated P52L mutation enhances kinase activity via loss of pseudosubstrate autoinhibition (gao2013substrateandinhibitor pages 7-8).

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