Phylogeny  
PAK2 is a Group I p21-activated kinase within the STE20 branch of the human kinome (chetty2022rhofamilygtpase pages 3-4).  
Orthologs are documented in Mus musculus (Pak2), Danio rerio (pak2), Drosophila melanogaster (Pak), Caenorhabditis elegans (pak-1) and Saccharomyces cerevisiae (Ste20) (kumar2017structurebiochemistryand pages 1-3).  
Mammalian PAK2 can replace yeast Ste20 in functional complementation assays, underscoring deep evolutionary conservation (arias‐romero2008ataleof pages 1-3).  
Sequence identity exceeds 88 % in the CRIB domain and 93 % in the catalytic domain when compared with PAK1 and PAK3 (arias‐romero2008ataleof pages 1-3).

Reaction Catalyzed  
ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (zhao2012pakfamilykinases pages 1-3).

Cofactor Requirements  
Catalytic activity is dependent on divalent metal ions, with Mg²⁺ or Mn²⁺ required in vitro (huang2020pak2activatedby pages 12-12).

Substrate Specificity  
Type I PAKs, including PAK2, preferentially phosphorylate serine residues preceded by Arg at −2, another basic residue at −3 and followed by a hydrophobic residue at +1, with larger hydrophobes favoured at +2/+3 (chetty2022rhofamilygtpase pages 3-4).  
This specificity arises from electrostatic pairing of substrate arginines with an acidic pocket adjacent to the catalytic cleft (chetty2022rhofamilygtpase pages 22-25).

Structure  
PAK2 comprises an N-terminal basic segment (1–69), a CDC42/RAC1 interactive binding (CRIB) domain 70–113 overlapping an autoinhibitory domain (AID) 83–149, proline-rich SH3-binding motifs ~150–250 and a C-terminal kinase domain 282–524 (arias‐romero2008ataleof pages 1-3).  
The crystal structure of the kinase domain (PDB 6C5R) and the AlphaFold model AF-Q13177-F1 display a canonical bilobal fold with a conserved Lys-Glu ion pair, correctly positioned αC-helix, DFG-in activation loop and an intact hydrophobic spine (huang2020pak2activatedby pages 12-12).  
Inactive PAK2 forms a trans-autoinhibited dimer in which the AID of one protomer occupies the catalytic cleft of its partner (grebenova2019pak1pak1δ15and pages 1-2).  
Autophosphorylation at Ser141 disengages the AID, stabilising the active conformation (grebenova2019pak1pak1δ15and pages 1-2).  
Thr402 within the activation loop is a secondary autophosphorylation site that maximises catalytic efficiency (kumar2017structurebiochemistryand pages 25-29).  
A flexible inter-domain linker permits the large conformational changes required for dimer dissociation upon activation (chetty2022rhofamilygtpase pages 15-17).

Regulation  
Binding of GTP-loaded CDC42 or RAC1 to the CRIB domain disrupts the autoinhibited dimer and initiates activation-loop autophosphorylation (chetty2022rhofamilygtpase pages 3-4).  
Ser141 autophosphorylation is the principal activation switch (grebenova2019pak1pak1δ15and pages 1-2).  
Thr402 autophosphorylation further enhances enzymatic turnover (kumar2017structurebiochemistryand pages 25-29).  
Additional regulatory sites such as Ser20 and Ser197 are phosphorylated by kinases including PDK1 and AKT and dephosphorylated by PP2A (huang2020pak2activatedby pages 12-12).  
Caspase-3 cleavage at Asp212 during apoptosis generates a constitutively active 34 kDa fragment that amplifies death signalling (grebenova2019pak1pak1δ15and pages 16-17).  
MicroRNAs miR-23b and miR-137 repress PAK2 translation, adding a layer of post-transcriptional control (kumar2017structurebiochemistryand pages 9-11).

Function  
PAK2 is ubiquitously expressed with highest levels in spleen, thymus and fetal brain (huang2020pak2activatedby pages 12-12).  
Pak2 knockout in mice is embryonic lethal, highlighting its essential developmental role (kumar2017structurebiochemistryand pages 9-11).  
Full-length PAK2 promotes survival and motility by phosphorylating MAPK4 and MAPK6, which activate MAPKAPK5 to drive F-actin assembly (huang2020pak2activatedby pages 12-12).  
Phosphorylation of JUN by PAK2 supports EGF-stimulated proliferation (huang2020pak2activatedby pages 12-12).  
Cytoskeletal remodelling involves phosphorylation of LIMK1, histone H4, merlin and paxillin, modulating actin dynamics and adhesion (grebenova2019pak1pak1δ15and pages 1-2).  
Direct phosphorylation of caspase-7 by PAK2 dampens chemotherapy-induced apoptosis (grebenova2019pak1pak1δ15and pages 16-17).  
External stimuli such as transforming growth factor-β, hyperosmotic shock, UV light and ionising radiation activate PAK2 via GTPase-dependent or caspase-dependent mechanisms (grebenova2019pak1pak1δ15and pages 16-17).  
Insulin signalling inhibits PAK2, facilitating GLUT4 translocation in neurons and linking the kinase to metabolic control (kumar2017structurebiochemistryand pages 9-11).  
Proline-rich motifs recruit PIX adaptors to assemble RAC1 activation complexes, conferring spatial specificity to PAK2 signalling (dobrigna2023themolecularbasis pages 6-7).

Inhibitors  
IPA-3 is a covalent allosteric inhibitor targeting the regulatory domain with sub-micromolar potency against PAK2 (grebenova2019pak1pak1δ15and pages 1-2).  
FRAX597 is an ATP-competitive inhibitor that efficiently suppresses PAK2 catalytic activity (grebenova2019pak1pak1δ15and pages 1-2).  
PF-3758309, G-5555 and KPT-9274 are additional small-molecule inhibitors displaying nanomolar activity toward Group I PAKs, including PAK2 (chetty2022rhofamilygtpase pages 22-25).  
A PAK1-selective degrader described by Chow et al. showed limited cross-degradation of PAK2, illustrating avenues for isoform selectivity (chow2022developmentandutility pages 27-28).

Other Comments  
Monoallelic loss-of-function variants such as p.Glu435Lys in PAK2 cause Knobloch syndrome-2 and related neurodevelopmental disorders by haploinsufficiency (dobrigna2023themolecularbasis pages 6-7).  
The p.Glu435Lys mutation is also observed in cancers and perturbs kinase activity and protein interactions, implicating PAK2 in oncogenesis (grebenova2019pak1pak1δ15and pages 1-2).  
Overexpression or hyperactivation of PAK2 drives cellular motility, invasion and chemoresistance in diverse tumour contexts (kumar2017structurebiochemistryand pages 25-29).

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