Phylogeny  
PEAK1 belongs to the New Kinase Family 3 (NKF3) pseudokinases, clustering with PEAK2/Pragmin and PEAK3 (Ha & Boggon, 2018; Hou et al., 2021). It shares >45 % sequence identity across the kinase fold with PEAK2 (Ha & Boggon, 2018). Phylogenetic analyses indicate that a PEAK1/PEAK2 gene-duplication occurred after divergence from the PEAK3 lineage early in vertebrate evolution (Ounoughene et al., 2021). Orthologues are present in Mus musculus (Peak1) and Danio rerio (peak1a/peak1b), underscoring conservation within vertebrates (Wang et al., 2010; Yang et al., 2024). Because of its extensive low-complexity N-terminus, PEAK1 was initially omitted from the first human kinome survey but is now classified in the “Other/atypical” kinase group (Lopez et al., 2019).

Reaction Catalyzed  
ATP + protein → ADP + phosphoprotein; however, neither nucleotide binding nor catalytic turnover has been detected (Ha & Boggon, 2018).

Cofactor Requirements  
No divalent‐metal requirement has been reported, consistent with the absence of measurable catalytic activity (Ha & Boggon, 2018).

Substrate Specificity  
Large-scale kinase substrate profiling reports no intrinsic kinase activity and thus no consensus phosphorylation motif (Hou et al., 2021). Early in-vitro assays noted only weak autophosphorylation and low-level phosphorylation of myelin basic protein without motif definition (Wang et al., 2010).

Structure  
PEAK1 comprises an N-terminal low-complexity segment (~ residues 1–1200) enriched in SH2/SH3 docking motifs, a central split-helical dimerisation (SHED) module, and a C-terminal pseudokinase domain (residues 1330–1664) (Ha & Boggon, 2018; Wang et al., 2010). The crystal structure (PDB 6FJ3) reveals a canonical bilobal kinase fold with an occluded nucleotide pocket. Catalytic motifs are degenerate (HRD → HCD; DFG → NFL), the αC helix is displaced, and both catalytic and regulatory spines are disrupted (Ha & Boggon, 2018). The SHED forms an “XL” four-helix bundle that buries ~ 1900 Å² to mediate obligate dimerisation (Ha & Boggon, 2018). Despite loss of catalytic residues, the pseudokinase core aligns most closely with RET and Aurora A kinase structures (Ha & Boggon, 2018).

Regulation  
• Tyrosine phosphorylation  
– Y665, Y635 and Y1188 by Src; Y797 by Abl (Hou et al., 2021; Wang et al., 2010; Kelber & Klemke, 2010; Agajanian et al., 2015).  
• Ser/Thr phosphorylation  
– S779 and T783 by ERK (Wang et al., 2010).  
– Multiple sites by CaMK2 following binding to an R297-L301-R303 motif (Yang et al., 2024).  
• Dephosphorylation by the phosphatase PTPN12 (Hou et al., 2021).  
• Oligomerisation through the SHED domain (homo- or heterodimers with other NKF3 members) is required for signalling (Ha & Boggon, 2018; Hou et al., 2021).

Function  
PEAK1 is broadly expressed, with highest levels in brain, kidney and spleen (Wang et al., 2010; Ounoughene et al., 2021). Acting as a scaffolding pseudokinase, it regulates cytoskeletal organisation, focal-adhesion turnover, cell spreading and migration (Ha & Boggon, 2018; Kelber & Klemke, 2010). EGFR and selected integrins drive Src-dependent phosphorylation of PEAK1, initiating signalling (Hou et al., 2021). Reported interactors include Src family kinases, Grb2, Shc1, Csk, Crk/CrkL, Paxillin, p130Cas, FAK, ASAP1, PYK2, CaMK2 isoforms and 14-3-3 proteins (Hou et al., 2021; Yang et al., 2024; Kelber & Klemke, 2010). Downstream pathways comprise the Src–p130Cas–Crk–Paxillin axis, Ras/MAPK via Grb2, an EGFR/Src/ErbB2 amplification loop, JAK1/STAT3 signalling, and a PEAK1–Ca²⁺/CaMK2 feed-forward circuit that promotes migration and invasion (Kelber & Klemke, 2010; Patel et al., 2020; Tactacan et al., 2015; Yang et al., 2024).

Other Comments  
PEAK1 is overexpressed in breast, colon (> 80 % of lesions), lung and pancreatic cancers (Kelber & Klemke, 2010; Hou et al., 2021; Patel et al., 2020). High co-expression with CAMK2D correlates with poor prognosis in triple-negative breast cancer (Yang et al., 2024). Overexpression promotes epithelial–mesenchymal transition, whereas knock-down drives mesenchymal–epithelial transition (Hou et al., 2021).

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