1. Phylogeny  
   Focal adhesion kinase 1 (FAK, gene PTK2, also commonly called FAK1) is an evolutionarily conserved non‐receptor protein tyrosine kinase that is ubiquitously expressed in vertebrate species. Orthologs of FAK are found throughout metazoans, illustrating its fundamental role in the regulation of cell adhesion, migration, and survival. FAK belongs to the non‐receptor tyrosine kinase family and is closely related to its paralog Pyk2, sharing considerable sequence and domain architecture while differing in regulatory nuances and subcellular localization. Comparative analyses of the human kinome consistently place FAK within the integrin‐associated signaling group, emphasizing its central role in translating extracellular matrix cues into intracellular responses (gabarra2002characterizationofan pages 1-2, lu2020progressinthe pages 1-2, nana2019roleoffocal pages 20-21).
2. Reaction Catalyzed  
   FAK catalyzes the transfer of a phosphate group from ATP to specific tyrosine residues on substrate proteins. The chemical reaction can be represented as:  
     ATP + protein–(L-tyrosine) → ADP + protein–(L-tyrosine)-phosphate + H⁺.  
   This phosphorylation reaction is central to its function as it regulates the dynamics of focal adhesion assembly and disassembly by modifying key adaptor and scaffold proteins involved in cell adhesion and migration (gabarra2002characterizationofan pages 1-2, sieg2000fakintegratesgrowthfactor pages 7-8).
3. Cofactor Requirements  
   The catalytic activity of FAK requires the presence of divalent metal ions, with Mg²⁺ serving as an essential cofactor. This ion facilitates the proper coordination of ATP within the kinase domain’s active site and is critical for efficient phosphoryl transfer during the phosphorylation reaction (lu2020progressinthe pages 1-2, goni2014phosphatidylinositol45bisphosphatetriggers pages 10-10).
4. Substrate Specificity  
   FAK exhibits specificity for phosphorylating tyrosine residues on a range of substrate proteins, many of which localize to focal adhesions. A key autophosphorylation event occurs at tyrosine 397 (Y397), which not only activates FAK but also creates a high-affinity binding site for Src family kinases and other SH2 domain-containing proteins. In addition, FAK phosphorylates other sites—including but not limited to Y576, Y577, Y861, and Y925—that modulate interactions with adaptor proteins such as paxillin and p130Cas. These phosphorylation events are crucial for reorganizing the cytoskeleton and promoting dynamic changes in cell adhesion and motility (kanteti2016fakandpaxillin pages 1-3, coq2022newinsightsinto pages 9-9, gabarra2002characterizationofan pages 1-2).
5. Structure  
   FAK is organized into three distinct regions that underpin its multifunctional role. The N-terminal region contains a FERM (4.1, Ezrin, Radixin, Moesin) domain that adopts a cloverleaf structure and is responsible both for mediating interactions with membrane-associated proteins and for autoinhibitory binding to the kinase domain. This autoinhibition helps maintain FAK in an inactive state until relieved by extracellular stimuli. The central portion of FAK is the catalytic kinase domain, which is composed of two lobes—the smaller N-terminal lobe largely consisting of β-sheets and a larger C-terminal lobe primarily of α-helices. Within this domain, the activation loop harbors key tyrosine residues (e.g., Y576 and Y577) whose phosphorylation is essential for maximal kinase activity. An ATP-binding pocket, aided by essential Mg²⁺ ions, is located between these lobes. The C-terminal segment contains the focal adhesion targeting (FAT) domain, a four-helix bundle that directs FAK to focal adhesions by binding to the LD motifs of paxillin and other related proteins. Flanking this domain are several proline-rich regions that contribute additional protein-protein interaction sites, assembling multiprotein signaling complexes at sites of cell-matrix contact (lu2020progressinthe pages 1-2, antoniades2021fakdisplacementfrom pages 21-22, bramicherrier2014fakdimerizationcontrols pages 13-14).
6. Regulation  
   The activation and regulation of FAK are modulated by a series of sequential and cooperative events. Autophosphorylation at Y397 is a pivotal early step; this event creates a binding platform for the SH2 domains of Src family kinases. Following recruitment, Src phosphorylates additional tyrosine residues within the kinase domain (notably Y576 and Y577), thereby achieving full catalytic activation. Under basal conditions, the FERM domain binds intramolecularly to the kinase domain, thereby keeping FAK in an autoinhibited conformation. Engagement of integrins by extracellular matrix components or stimulation by growth factors induces conformational changes that displace the FERM domain, relieving autoinhibition and allowing subsequent phosphorylation events to proceed. Furthermore, interactions with focal adhesion proteins such as paxillin and talin refine FAK’s spatial localization and contribute to the temporal regulation of its activity. Additional layers of control are provided by alternative splicing and post-translational modifications including ubiquitination, which further modulate FAK stability and turnover (gabarra2002characterizationofan pages 1-2, lu2020progressinthe pages 17-18, bramicherrier2014fakdimerizationcontrols pages 14-15, coq2022newinsightsinto pages 10-10).
7. Function  
   FAK serves as a central integrator of signals emanating from integrins and growth factor receptors and is essential for various cellular processes. It orchestrates the assembly and disassembly of focal adhesions, thereby regulating cell adhesion, spreading, and migration. By phosphorylating substrates such as paxillin and p130Cas, FAK modulates the reorganization of the actin cytoskeleton, facilitating the formation of cell protrusions and enabling directed cell movement. In addition to its role in motility, FAK is critical for cell cycle progression and proliferation, and it exerts anti-apoptotic effects that contribute to cell survival. During embryonic development, FAK is indispensable for processes such as placental formation, angiogenesis, and cardiomyocyte migration. It also influences neuronal development by regulating axon growth, branching, and synaptogenesis, and it participates in osteoblast differentiation during osteogenesis. The kinase functions not only at the plasma membrane but also within the nucleus, where it impacts the transcription of genes involved in metabolism and survival. In pathological contexts, aberrant upregulation and hyperactivation of FAK are closely linked with cancer progression, invasion, and metastasis. Its role in assembling multisubunit signaling complexes with SRC and other kinases underscores its importance in a broad spectrum of signal transduction pathways that drive tumor aggressiveness (lu2020progressinthe pages 1-2, mierke2013theroleof pages 1-3, kanteti2016fakandpaxillin pages 1-3, antoniades2021fakdisplacementfrom pages 21-22).
8. Other Comments  
   Due to its integral involvement in the regulation of cell migration, adhesion, and survival, FAK has drawn significant attention as a therapeutic target, particularly in oncology. Overexpression and increased kinase activity of FAK have been documented in various malignancies—such as breast, pancreatic, colon, and ovarian cancers—where they correlate with enhanced cell motility, tumor progression, and metastasis. Several experimental small molecule inhibitors have been developed that target the ATP-binding pocket of the kinase domain, including compounds like TAE226, PF-562271, and VS-6063 (defactinib), which have demonstrated efficacy in preclinical models and are currently under clinical investigation. In addition to ATP-competitive inhibitors, research is also directed at disrupting the protein–protein interactions mediated by the FAT domain, such as the binding between FAK and paxillin, to impair focal adhesion signaling. FAK’s central role in integrin and growth factor signaling also makes it a valuable biomarker for disease progression. Although mutations in FAK are less commonly reported than aberrant expression levels, dysregulation of its phosphorylation status has been linked to altered focal adhesion dynamics and dysfunctional cell migration. These characteristics support the continued efforts toward the development of selective FAK inhibitors for use in combination therapies aimed at overcoming drug resistance in tumor cells (lazaro2015﻿focaladhesion pages 35-37, rigiracciolo2021focaladhesionkinase pages 14-15, nana2019roleoffocal pages 20-21).
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