FAK

Key References

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Overview

The focal adhesion kinase (FAK) is a cytoplasmic protein tyrosine kinase that distinctly co-localizes with integrins at sites of attachment to their ligands. In cells in culture these sites are manifested as regions of close contact with the underlying substrate called focal adhesions. Attachment of integrins to their extracellular matrix ligands is a major regulatory stimulus for FAK, resulting in its tyrosine phosphorylation and enzymatic activation. Other stimuli, e.g. growth factors, neuropeptides, cytokines, mechanical stimuli, can also induce FAK phosphorylation/activation. FAK associates with a large number of enzymes, adaptor and scaffold proteins and serves both enzymatic and scaffolding roles in the transduction of signals.

FAK is organized into 4 domains. At the N-terminus is a FERM domain, which is found in a number of cytoskeletal and signaling proteins and functions to mediate protein-protein interactions. The central region of FAK contains the catalytic domain. The C-terminal domain of FAK contains two distinct regions. The C-terminal 140 amino acids comprise the focal adhesion targeting (FAT) domain, a four α-helix bundle containing binding sites for paxillin, and functions to localize FAK to focal adhesions. Between the catalytic and FAT domains is a region of undefined structure, containing two proline-rich regions that serve as ligands for the SH3 domains of several signaling proteins.

Upon activation, FAK autophosphorylates creating a docking site for the SH2 domains of a number of signaling molecules, including Src family kinases and phosphatidylinositol 3′-kinase. Src family kinases then promote phosphorylation of FAK on several other tyrosine residues, resulting in maximal FAK catalytic activity and creation of additional binding sites for other proteins. FAK associates with several other proteins that are tyrosine phosphorylated following integrin-dependent adhesion, p130cas and paxillin, and FAK promotes phosphorylation of these substrates.

FAK is an essential gene in the mouse. FAK has been implicated as a downstream signaling molecule that functions in the control of several integrin regulated biological processes, including cell migration, cell survival and cell proliferation. Recent studies have further defined the role of FAK and these cellular functions in a broader biological context. For example, FAK has been implicated in the control of tubule formation by endothelial cells and angiogenesis under certain circumstances in an animal model. Interesting recent findings also suggest that FAK may function in the control of neurite outgrowth and netrin induced axonal guidance. Dysregulation of motility, survival and proliferation is a hallmark of a number of human pathological conditions, e.g. cancer. Aberrant FAK signaling results in altered cellular phenotypes, including increased invasion, growth in soft agar, tumorigenicity and metastasis. Further, FAK is overexpressed in a number of human cancers, suggesting that FAK may play a role in the pathology of this disease.

Pyk2 is a FAK-related kinase sharing the same overall domain structure and approximately 45% sequence identity. In contrast to FAK, which is ubiquitously expressed, Pyk2 is more restricted in its expression, predominantly in epithelial cells, hematopoietic cells and neural tissue. Pyk2 is a nonessential gene as knockout mice are viable. A number of common stimuli, including growth factors, cytokines and cell adhesion regulate FAK and Pyk2. In general, FAK is more strongly activated by cell adhesion whereas Pyk2 is more strongly activated by soluble ligands. Notably, ligands that stimulate elevation of cytoplasmic calcium activate Pyk2. There are a number of common binding partners for FAK and Pyk2, e.g. Src family kinases and paxillin, suggesting some common signaling mechanisms. On the other hand, there are FAK specific ligands, e.g. DCC, and Pyk2 specific ligands, e.g. gelsolin, which play roles in distinct functions of the two kinases. Pyk2 may play important roles in macrophage and osteoclast function.

FAK

Family Members	FAK	Pyk2
Other Names	FAK56 (*D. melanogaster* homolog of FAK/Pyk2), Ptk2 (mouse genomic nomenclature), p125FAK	CAKβ, CADTK, RAFTK, FAK2, Ptk2b
Molecular Weight/ Structural Information	119 kDa (FAKI) 1052 aa (human, mouse), 1055 aa (rat), 1053 aa (avian)	115 kDa 1009 aa (human, mouse, rat)
Isoforms	FAK+ (insert 3 aa after aa 903), FAK+28, 7 (insert 28 aa after aa 391 and 8 aa after aa 433), FAK+28, 6, 7 (insert 6 aa after 28 aa insert of FAK+28,7), FRNK (encodes aa 693-1052)	Pyk2s (aa 739-780 deleted), PRNK (encodes aa 781-1009)
Species	Human, mouse, rat, chicken, frog	Human, mouse, rat
Domain Organization	Proline-rich region, T-Fak paxillin binding sequence contains talin binding sequence, N-terminal domains bind integrin β subunit	Ferm domains
Phosphorylation Sites	Tyr^{397}, Tyr^{407}, Tyr^{576}, Tyr^{577}, Tyr^{861}, Tyr^{925}, Ser^{722}, Ser^{840}, Ser^{843}, Ser^{910}	Tyr^{402}, Tyr^{579}, Tyr^{580}, Tyr^{881}
Tissue Distribution	Ubiquitous, all organs, lymphoid tissue, brain	Some fibroblasts, epithelial cells, brain, hematopoieitic cells
Subcellular Localization	Focal adhesions, cytoplasm	In a few cases in focal adhesions or along stress fibers, most often diffusely cytosolic
Binding Partners/ Associated Proteins	Src family kinases, PI3K, PLCγ, Grb7, Shc, Grb2, SOCS, p130CAS, HEF1, GRAF, ASAP1, Paxillin and related proteins, neogenin, DCC, ezrin, Trio, growth factor receptors, Etk, EphA1, PIAS1, integrins, FIP200, talin, p190RhoGEF, calpain	Src family kinases, ASAP1, p130CAS, HEF1, PRAP, Pap Paxillin and related proteins, gelsolin, Nir family or proteins, FIP200
Upstream Activators	Integrin-dependent cell adhesion, growth factors, neuropeptides, mechanical stimuli	Growth factors, cytokines, Ca^{2+}, nucleotides, membrane depolarization, cell adhesion
Downstream Activation	CAS, Shc, Grb2, PI3K	Nephorocystin, PRAP
Activators	Not known	Not known
Inhibitors	Not known	Not known
Selective Activators	Not known	Not known
Physiological Functions	Cell motility, cell survival, cel proliferation, uptake of pathogenic bacteria, regulate actin cytoskeleton (focal adhesions)	Cell motility, uptake of pathogenic bacteria, bone resorption, regulation of actin cytoskeleton (osteoclast actin ring)
Disease Relevance	Cancer	Not known

Footnotes