1. Phylogeny  
   Tyrosine‐protein kinase FRK, also known as PTK5 or RAK, is a non‐receptor tyrosine kinase that belongs to a distinct subgroup within the Src-related kinase family. FRK clusters with other kinases of the BRK family (also referred to as breast tumor kinase family kinases) and shares structural and evolutionary features with related kinases such as BRK (PTK6) and SRMS. FRK is encoded by a gene located on human chromosome 6q21–q22.3, a genomic region with a documented loss of heterozygosity in various human tumors. Comparative sequence analysis across species suggests that FRK orthologs are broadly conserved in vertebrates, indicating evolutionary selection for its regulatory functions. Its domain architecture, characterized by conserved Src homology domains (SH2 and SH3) and a catalytic kinase domain, aligns it with the overall organization of the Src family; however, FRK is phylogenetically distinct because it lacks classical membrane-targeting signals such as N-terminal myristoylation and palmitoylation. (macausland2019frkcancerrelatedmutations pages 1-6, kwon2019tracingtheevolution pages 55-60)
2. Reaction Catalyzed  
   FRK catalyzes the transfer of the γ-phosphate from ATP to the hydroxyl group of tyrosine residues on substrate proteins. In the canonical reaction, ATP and a protein substrate containing a tyrosine residue are converted to ADP and a phosphorylated protein (protein–tyrosine-phosphate), with the concomitant release of a proton. This reaction is representative of the typical tyrosine kinase activity observed across the kinome. (chiarugi2007proteintyrosinephosphorylation pages 1-3, cornea2022theroleof pages 34-37)
3. Cofactor Requirements  
   Like other protein tyrosine kinases, FRK requires divalent metal ions for its catalytic activity. It utilizes ATP as a phosphate donor, and its activity is dependent on the presence of Mg²⁺, which serves to coordinate the phosphates of ATP within the active site. (santos2013understandingtheenzymeinhibitor pages 20-25, chiarugi2007proteintyrosinephosphorylation pages 1-3)
4. Substrate Specificity  
   FRK displays substrate specificity that is common among Src family-related tyrosine kinases. It phosphorylates protein substrates on tyrosine residues and shows a defined consensus substrate preference that can be deduced from peptide motif studies. A well-characterized substrate of FRK is the tumor suppressor PTEN; FRK phosphorylates PTEN specifically on Tyr-336, a modification that enhances PTEN’s stability by reducing its ubiquitination and subsequent degradation. This event is critical for maintaining proper levels of PTEN in the cell and underlies FRK’s tumor suppressor function. In addition, FRK has been reported to target other substrates including key residues on the epidermal growth factor receptor (EGFR) and BRCA1, thus modulating signaling pathways associated with cell proliferation and survival. Structural studies have revealed that the SH2 domain of FRK recognizes phosphotyrosine-containing motifs, with peptides such as HFpYENI identified as preferred binding sequences. (cornea2022theroleof pages 34-37, macausland2019frkcancerrelatedmutations pages 26-29, cornea2022theroleof pages 37-42)
5. Structure  
   FRK is a 505 amino acid protein that exhibits a modular domain organization typical of Src-related non-receptor tyrosine kinases. Its overall structure comprises an N-terminal region followed by conserved SH3 and SH2 domains and a central catalytic (kinase) domain. The kinase domain itself exhibits a bilobed structure: an N-terminal lobe composed primarily of β-sheets and a C-terminal lobe rich in α-helices. Key catalytic features include an ATP-binding site, coordinated primarily by residues in the N-terminal lobe, and a glycine-rich P-loop that facilitates nucleotide binding. Two critical tyrosine residues, Tyr-387 and Tyr-497, serve as the activating and inhibitory sites, respectively. Phosphorylation of Tyr-387 (the autophosphorylation site) promotes a conformational rearrangement that leads to kinase activation, whereas Tyr-497, located in the C-terminal tail, is implicated in autoinhibitory interactions that restrict substrate access. Notably, FRK’s SH2 domain harbors a nuclear localization sequence (NLS), which distinguishes it from many other Src family kinases that are predominantly membrane-associated; this NLS drives nuclear accumulation under certain regulatory conditions. Furthermore, the absence of N-terminal myristoylation and palmitoylation signals in FRK contributes to its soluble character and broader intracellular localization. Structural modeling and experimental studies have confirmed that the overall 3D fold of FRK’s kinase domain is conserved with typical non-receptor tyrosine kinases, yet its unique features—in particular, the embedded NLS within the SH2 domain—provide distinct regulatory capabilities. (cornea2022theroleof pages 34-37, macausland2019frkcancerrelatedmutations pages 22-26, mcclendon2020structurefunctionand pages 1-3)
6. Regulation  
   The activity of FRK is tightly regulated through multiple post-translational mechanisms. Autophosphorylation of Tyr-387 is essential for full kinase activity, while phosphorylation at Tyr-497 exerts inhibitory control by promoting an intramolecular conformation that limits substrate interaction. The balance between these phosphorylated states determines the catalytic activity of FRK in the cell. In addition to autophosphorylation, FRK-mediated regulation involves domain–domain interactions, particularly via its SH2 and SH3 domains, which participate in both intra- and intermolecular contacts. These domains facilitate interactions with substrates and regulatory proteins that can either enhance or dampen its activity. Experimentally documented cancer-associated mutations, such as R64P, K265R, N359I, and a deletion mutation designated as VF, have been shown to alter FRK’s kinase activity and downstream signaling outputs. For instance, alterations in the kinase domain or in the conserved motifs can compromise ATP binding or disrupt the autoinhibitory mechanism, leading to changes in the phosphorylation levels of downstream targets like STAT3, AKT, and components of the JNK/c-Jun pathway. These regulatory mechanisms collectively underscore the role of FRK as an enzyme whose activity is modulated by precise phosphorylation events and by its ability to interact with key signaling proteins. (cornea2022theroleof pages 34-37, macausland2019frkcancerrelatedmutations pages 73-77, corwin2016decipheringhumancytoplasmic pages 146-149)
7. Function  
   FRK functions primarily as a negative regulator of cell proliferation. A critical aspect of its tumor-suppressive role is its capacity to phosphorylate and stabilize the tumor suppressor PTEN by specifically modifying Tyr-336; this phosphorylation event reduces the binding of PTEN to the E3 ubiquitin ligase NEDD4, thereby preventing its ubiquitination and proteasomal degradation. As a consequence, PTEN is maintained at levels that are sufficient to counteract PI3K/AKT signaling and thus inhibit uncontrolled cell growth. Beyond its effects on PTEN, FRK has been implicated in the modulation of growth factor receptor signaling pathways. For example, FRK has been shown to phosphorylate EGFR at specific tyrosine residues, influencing receptor internalization and downstream signaling cascades associated with cell survival and proliferation. Moreover, FRK’s activity contributes to the maintenance of cellular homeostasis by regulating additional substrates such as BRCA1 and proteins involved in cytoskeletal organization. Expression studies have demonstrated that FRK is predominantly expressed in epithelial tissues, including breast tissue, where its loss or downregulation has been observed in some breast cancers, consistent with its role as a tumor suppressor. In certain contexts, however, FRK may display oncogenic properties, for instance in hepatocellular carcinoma where specific activating mutations have been detected. The diverse substrate repertoire and intricate regulatory interactions associated with FRK place it at a nodal point in various signaling pathways that govern cell cycle progression, differentiation, and survival. (cornea2022theroleof pages 34-37, macausland2019frkcancerrelatedmutations pages 54-61, cornea2022theroleof pages 37-42, macausland2019frkcancerrelatedmutations pages 61-68)
8. Other Comments  
   Although there are no FRK-specific inhibitors extensively characterized to date, its regulatory tyrosine residues and unique nuclear localization signal represent potential focal points for therapeutic targeting. Cancer-associated mutations in FRK, such as R64P, K265R, N359I, and the VF deletion, have been documented and are known to variably affect its kinase activity in experimental models of breast cancer and other malignancies. Dysregulation of FRK expression and function has been implicated in the pathogenesis of a range of tumors—including breast, liver, gliomas, and malignant melanomas—indicating that FRK serves as a critical modulator of oncogenic signaling cascades. The dual role of FRK, acting as both a tumor suppressor and, in some contexts, as an oncogenic factor, underscores the complexity of its biological functions. Ongoing studies continue to explore its interaction networks, substrate specificity, and domain-dependent regulation, making FRK a protein kinase of considerable interest in cancer biology and a potential candidate for future molecular-targeted therapies. (macausland2019frkcancerrelatedmutations pages 29-34, macausland2019frkcancerrelatedmutations pages 85-89, cornea2022theroleof pages 42-45, corwin2016decipheringhumancytoplasmic pages 190-192)
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