## Phylogeny

Tyrosine-protein kinase FRK (PTK5/RAK) is a soluble, non-receptor member of the BRK subfamily that is evolutionarily linked to Src-family kinases. Orthologues occur throughout vertebrates, and comparative analyses trace its ancestry to early metazoans (Superti-Furga, 1995; Martellucci, 2020). In contrast with classical Src kinases, FRK lacks N-terminal myristoylation and palmitoylation signals and instead contains a nuclear-localisation signal within its SH2 domain, reflecting a phylogenetic divergence that favours cytosolic and nuclear distribution.

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine + H⁺ (Fan, 2015).

## Cofactor Requirements

Mg²⁺ is required for ATP coordination and phosphoryl transfer (Byeon, 2012; Martellucci, 2020).

## Substrate Specificity

Best-characterised substrate is PTEN, phosphorylated at Tyr336, which blocks its ubiquitination and degradation. FRK also targets components of the EGFR complex and BRCA1. A consensus motif (e.g., HFpYENI) with defined amino-acid preferences has been identified (Jimura, 2021; Siveen, 2018).

## Structure

The 505-residue protein comprises an N-terminal SH3 domain, an SH2 domain containing an NLS, and a C-terminal kinase (SH1) domain. Key residues include Lys262 (ATP binding), Tyr387 (activation-loop autophosphorylation) and Tyr497 (C-terminal inhibitory site). Absence of lipid-anchoring motifs distinguishes FRK from membrane-bound Src kinases. Predicted 3-D models preserve the canonical bilobed kinase fold with a conserved regulatory spine (Superti-Furga, 1995; McClendon, 2020).

## Regulation

Activity is enhanced by autophosphorylation of Tyr387 and suppressed by phosphorylation of Tyr497, which promotes an intramolecular SH2-tail interaction that locks the kinase in an inactive conformation. SH2-mediated binding to phosphotyrosine ligands and the embedded NLS modulate subcellular localisation, adding further regulatory control (Byeon, 2012; McClendon, 2020; Martellucci, 2020).

## Function

FRK acts as a tumour-suppressive tyrosine kinase that stabilises PTEN and thereby constrains PI3K/AKT signalling. Additional substrates (EGFR, BRCA1) link FRK to regulation of receptor internalisation, genomic stability and pathways such as STAT3 and JNK. Expression is prominent in epithelial tissues, including breast epithelium, and loss or mutation of FRK correlates with breast carcinoma, glioma and other malignancies (Jimura, 2021; Martellucci, 2020; Park, 2021; Siveen, 2018).

## Inhibitors

No highly selective FRK inhibitors are yet available, although compounds active against Src-family kinases are expected to inhibit FRK. Structural insights are guiding early-stage inhibitor design (Martellucci, 2020; Park, 2021).

## Other Comments

Cancer-associated mutations (e.g., R64P, K265R, N359I, and a VF deletion) variably alter FRK activity, underscoring its context-dependent tumour-suppressive or oncogenic roles. The soluble cytoplasmic/nuclear distribution suggests a broader substrate repertoire than membrane-anchored Src kinases (Neul, 2016; Siveen, 2018).

## References

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