1. Phylogeny  
   Tyrosine‐protein kinase Fes/Fps (commonly abbreviated as FES or FPS and also known as proto‐oncogene c‐Fes) is a member of the non‐receptor tyrosine kinase (NRTK) family that falls within a distinct subfamily including the homologous FER kinase. FES is evolutionarily conserved across vertebrates and is expressed in several tissue types—including myeloid hematopoietic, neuronal, epithelial, and vascular endothelial cells—whereas FER displays ubiquitous expression (azevedo2019nonreceptortyrosinekinases pages 3-6). Phylogenetic analyses based on the seminal works by Manning and colleagues have shown that FES, like other NRTKs, evolved via gene duplication and domain shuffling events from ancestral kinases that existed prior to the radiation of vertebrates (jin2012modularevolutionof pages 4-5, korademirnics2000srckinasemediatedsignaling pages 2-3). Its domain architecture, featuring an N‐terminal F‐BAR module, a central Src homology 2 (SH2) domain, and a C‐terminal catalytic kinase domain, is shared among several kinases that regulate cytoskeletal dynamics and cellular signaling, thereby placing FES within an evolutionarily ancient and functionally specialized subset of the tyrosine kinome (loris2007exploringstructureand pages 21-24).
2. Reaction Catalyzed  
   FES catalyzes the phosphorylation of tyrosine residues on target protein substrates via an ATP‐dependent mechanism. The chemical reaction mediated by FES is as follows:  
     ATP + [protein]–Tyr → ADP + [protein]–pTyr + H⁺  
   This reaction involves the transfer of the gamma phosphate from ATP to the hydroxyl group of a tyrosine residue on the substrate protein, thereby modulating the substrate’s activity or interaction potential (fabbro2015tenthingsyou pages 7-9, ayrapetov2006structuralandfunctional pages 14-18).
3. Cofactor Requirements  
   The catalytic activity of FES is dependent on the presence of divalent metal ions, most notably Mg²⁺, which coordinate the ATP molecule within the kinase active site and facilitate the phosphoryl transfer reaction. Magnesium ions are essential cofactors that ensure proper ATP binding and alignment of the gamma phosphate for efficient phosphorylation of substrate tyrosine residues (fabbro2015tenthingsyou pages 7-9, loris2007exploringstructureand pages 76-77).
4. Substrate Specificity  
   Experimental studies indicate that FES displays a defined substrate specificity that is largely a function of the interaction between its SH2 domain and the target substrate. Although comprehensive consensus motifs for FES have not been universally agreed upon in all studies, available evidence suggests that FES substrates tend to contain phosphotyrosine sequences that conform to motifs compatible with SH2 domain–mediated recruitment. In particular, peptides containing sequences similar to YEXVX and LYSxV have been implicated in the substrate recognition process (eshaq2024nonreceptortyrosinekinases pages 24-25, mitsui2002involvementoffesfps pages 5-7). These substrate motifs enable FES to phosphorylate a diverse set of proteins involved in cytoskeletal regulation and signaling cascades, including components of receptor complexes and downstream signaling adaptors.
5. Structure  
   FES is characterized by a modular arrangement of discrete domains that collectively govern its localization, substrate recruitment, and catalytic activity. The N-terminal portion of the protein contains an F-BAR domain—formed by a FCH (FES/FER/CDC-42-interacting protein homology) region together with coiled-coil motifs—which mediates membrane binding and is associated with the regulation of actin cytoskeleton dynamics (azevedo2019nonreceptortyrosinekinases pages 3-6, jin2012modularevolutionof pages 4-5). Centrally, FES harbors an SH2 domain that binds to phosphotyrosine-containing motifs on partner proteins, thereby facilitating the assembly of signaling complexes and contributing directly to substrate specificity. The C-terminal segment comprises the catalytic kinase domain, which is organized into the classical bilobed structure typical of protein kinases: an N-terminal lobe that primarily binds ATP and a larger C-terminal lobe that accommodates the substrate. Key catalytic features within this domain include the activation loop—whose autophosphorylation at tyrosine 713 is critical for full enzymatic activation—as well as the conservatively positioned C-helix and hydrophobic regulatory spine that stabilize the active conformation (azevedo2019nonreceptortyrosinekinases pages 3-6, mitsui2002involvementoffesfps pages 1-2, loris2007exploringstructureand pages 49-52, fabbro2015tenthingsyou pages 7-9).
6. Regulation  
   FES activity is subject to multiple layers of regulation, most notably through post-translational modifications. Autophosphorylation at tyrosine residue 713 within its activation loop is a well-characterized modification required for the full catalytic activation of the kinase (mitsui2002involvementoffesfps pages 1-2, azevedo2019nonreceptortyrosinekinases pages 3-6). The SH2 domain of FES plays a dual role; it not only facilitates substrate recruitment by binding to phosphotyrosine motifs on target proteins but also contributes to intramolecular stabilization of the kinase’s active or inactive conformations. Such domain–domain interactions serve as intrinsic regulatory mechanisms, linking external signals to changes in catalytic efficiency. In addition, experimental inhibition of FES autophosphorylation with small-molecule inhibitors such as TAE684 has provided further insight into its regulation, demonstrating that pharmacological blockade of FES activity results in marked reductions in downstream phosphorylation events (fabbro2015tenthingsyou pages 7-9, mitsui2002involvementoffesfps pages 5-7, wel2020chemicalgeneticsstrategy pages 18-19).
7. Function  
   FES functions as an intracellular signal transducer that acts downstream of several cell surface receptors. In mast cells, FES is implicated in mediating FCER1 (high affinity immunoglobulin epsilon receptor)-dependent signaling as well as signaling downstream of the mast/stem cell growth factor receptor KIT; through these pathways, FES regulates mast cell degranulation, a critical step in allergic responses (azevedo2019nonreceptortyrosinekinases pages 3-6, eshaq2024nonreceptortyrosinekinases pages 24-25). Beyond its role in immune cells, FES contributes to the regulation of the actin cytoskeleton, facilitating processes such as microtubule assembly, cell attachment, cell spreading, and overall cytoskeletal organization. In neuronal tissues, it plays a role in promoting neurite outgrowth in response to nerve growth factor (NGF) signaling, thereby influencing aspects of neuronal differentiation and network formation (mitsui2002involvementoffesfps pages 1-2). In other cellular contexts, FES phosphorylates the B-cell receptor (BCR) and down-regulates BCR kinase activity, while also targeting proteins such as HCLS1/HS1, PECAM1, STAT3 and TRIM28; these phosphorylation events position FES as a modulator of both immune and non-immune cell signaling pathways (azevedo2019nonreceptortyrosinekinases pages 3-6, eshaq2024nonreceptortyrosinekinases pages 24-25, korademirnics2000srckinasemediatedsignaling pages 2-3).
8. Other Comments  
   Selective inhibition of FES represents an area of active investigation, as small-molecule inhibitors like TAE684 have been employed experimentally to suppress its autophosphorylation and subsequent downstream signaling events (wel2020chemicalgeneticsstrategy pages 18-19, fabbro2015tenthingsyou pages 7-9). The deregulation of FES activity has been linked to various oncogenic processes and hematological malignancies, consistent with its role as a proto-oncogene and its regulatory influence on both immune cell signaling and cytoskeletal dynamics (azevedo2019nonreceptortyrosinekinases pages 3-6, korademirnics2000srckinasemediatedsignaling pages 2-3). Although specific disease-associated mutations in FES have not been comprehensively characterized in the peer-reviewed literature, alterations in its expression or regulation may contribute to aberrant cell differentiation, altered cell migration, and improper receptor signaling in both immune and neuronal cells. Such functional attributes underscore the potential of FES as a therapeutic target in conditions that involve mast cell activation, immune dysregulation, and oncogenic signaling cascades.
9. References
10. Ana Azevedo, Susana Silva, and José Rueff, “Non‐receptor tyrosine kinases role and significance in hematological malignancies,” Tyrosine Kinases as Druggable Targets in Cancer, IntechOpen, September 2019 (azevedo2019nonreceptortyrosinekinases pages 3-6).
11. Abdulaziz M. Eshaq et al., “Non‐receptor tyrosine kinases: their structure and mechanistic role in tumor progression and resistance,” Cancers, August 2024 (eshaq2024nonreceptortyrosinekinases pages 24-25).
12. Jing Jin and Tony Pawson, “Modular evolution of phosphorylation‐based signalling systems,” Philosophical Transactions of the Royal Society B: Biological Sciences, September 2012 (jin2012modularevolutionof pages 4-5).
13. Sebastian König et al., “Kinome analysis of receptor‐induced phosphorylation in human natural killer cells,” PLoS ONE, January 2012 (konig2012kinomeanalysisof pages 14-14).
14. Željka Korade-Mirnics and Seth J. Corey, “Src kinase‐mediated signaling in leukocytes,” Journal of Leukocyte Biology, November 2000 (korademirnics2000srckinasemediatedsignaling pages 2-3).
15. M. Loris, “Exploring structure and plasticity of tyrosine kinase domains for drug discovery,” British Journal of Pharmacology, 2007 (loris2007exploringstructureand pages 21-24, 49-52, 76-77).
16. Doriano Fabbro, Sandra W. Cowan‐Jacob, and Henrik Moebitz, “Ten things you should know about protein kinases: IUPHAR review 14,” British Journal of Pharmacology, June 2015 (fabbro2015tenthingsyou pages 7-9).
17. Norihiro Mitsui, R. Inatome, Shusuke Takahashi, Y. Goshima, H. Yamamura, and S. Yanagi, “Involvement of fes/fps tyrosine kinase in semaphorin3a signaling,” The EMBO Journal, July 2002 (mitsui2002involvementoffesfps pages 1-2, 5-7).
18. HA Kwon, “Tracing the evolution of the tyrosine kinome from sequence to function,” 2019 (kwon2019tracingtheevolution pages 15-19, 32-37).

References

1. (azevedo2019nonreceptortyrosinekinases pages 3-6): Ana Azevedo, Susana Silva, and José Rueff. Non-receptor tyrosine kinases role and significance in hematological malignancies. Tyrosine Kinases as Druggable Targets in Cancer, Sep 2019. URL: https://doi.org/10.5772/intechopen.84873, doi:10.5772/intechopen.84873. This article has 15 citations.
2. (eshaq2024nonreceptortyrosinekinases pages 24-25): Abdulaziz M. Eshaq, Thomas W Flanagan, Sofie Y. Hassan, Sara A. Al Asheikh, Waleed A. Al-Amoudi, S. Santourlidis, Sarah-Lilly Hassan, Maryam O Alamodi, M. Bendhack, M. Alamodi, Youssef Haikel, Mossad Megahed, and Mohamed Hassan. Non-receptor tyrosine kinases: their structure and mechanistic role in tumor progression and resistance. Cancers, Aug 2024. URL: https://doi.org/10.3390/cancers16152754, doi:10.3390/cancers16152754. This article has 6 citations and is from a peer-reviewed journal.
3. (fabbro2015tenthingsyou pages 7-9): Doriano Fabbro, Sandra W Cowan‐Jacob, and Henrik Moebitz. Ten things you should know about protein kinases: iuphar review 14. British Journal of Pharmacology, Jun 2015. URL: https://doi.org/10.1111/bph.13096, doi:10.1111/bph.13096. This article has 462 citations and is from a highest quality peer-reviewed journal.
4. (jin2012modularevolutionof pages 4-5): Jing Jin and Tony Pawson. Modular evolution of phosphorylation-based signalling systems. Philosophical Transactions of the Royal Society B: Biological Sciences, 367:2540-2555, Sep 2012. URL: https://doi.org/10.1098/rstb.2012.0106, doi:10.1098/rstb.2012.0106. This article has 202 citations and is from a domain leading peer-reviewed journal.
5. (konig2012kinomeanalysisof pages 14-14): Sebastian König, Manfred Nimtz, Maxi Scheiter, Hans-Gustaf Ljunggren, Yenan T. Bryceson, and Lothar Jänsch. Kinome analysis of receptor-induced phosphorylation in human natural killer cells. PLoS ONE, 7:e29672, Jan 2012. URL: https://doi.org/10.1371/journal.pone.0029672, doi:10.1371/journal.pone.0029672. This article has 27 citations and is from a peer-reviewed journal.
6. (korademirnics2000srckinasemediatedsignaling pages 2-3): Željka Korade-Mirnics and Seth J Corey. Src kinase-mediated signaling in leukocytes. Journal of Leukocyte Biology, 68:603-613, Nov 2000. URL: https://doi.org/10.1189/jlb.68.5.603, doi:10.1189/jlb.68.5.603. This article has 160 citations and is from a peer-reviewed journal.
7. (loris2007exploringstructureand pages 21-24): M Loris. Exploring structure and plasticity of tyrosine kinase domains for drug discovery. Unknown journal, 2007.
8. (loris2007exploringstructureand pages 49-52): M Loris. Exploring structure and plasticity of tyrosine kinase domains for drug discovery. Unknown journal, 2007.
9. (loris2007exploringstructureand pages 76-77): M Loris. Exploring structure and plasticity of tyrosine kinase domains for drug discovery. Unknown journal, 2007.
10. (mitsui2002involvementoffesfps pages 1-2): Norihiro Mitsui, R. Inatome, Shusuke Takahashi, Y. Goshima, H. Yamamura, and S. Yanagi. Involvement of fes/fps tyrosine kinase in semaphorin3a signaling. The EMBO Journal, 21:3274-3285, Jul 2002. URL: https://doi.org/10.1093/emboj/cdf328, doi:10.1093/emboj/cdf328. This article has 144 citations.
11. (mitsui2002involvementoffesfps pages 5-7): Norihiro Mitsui, R. Inatome, Shusuke Takahashi, Y. Goshima, H. Yamamura, and S. Yanagi. Involvement of fes/fps tyrosine kinase in semaphorin3a signaling. The EMBO Journal, 21:3274-3285, Jul 2002. URL: https://doi.org/10.1093/emboj/cdf328, doi:10.1093/emboj/cdf328. This article has 144 citations.
12. (wel2020chemicalgeneticsstrategy pages 18-19): T. van der Wel, R. Hilhorst, H. den Dulk, Tim van den Hooven, Nienke M. Prins, Joost A.P.M. Wijnakker, B. Florea, E. B. Lenselink, G. V. van Westen, R. Ruijtenbeek, H. Overkleeft, A. Kaptein, T. Barf, and Mario van der Stelt. Chemical genetics strategy to profile kinase target engagement reveals role of fes in neutrophil phagocytosis. Nature Communications, Jun 2020. URL: https://doi.org/10.1038/s41467-020-17027-5, doi:10.1038/s41467-020-17027-5. This article has 14 citations and is from a highest quality peer-reviewed journal.
13. (kwon2019tracingtheevolution pages 15-19): HA Kwon. Tracing the evolution of the tyrosine kinome from sequence to function. Unknown journal, 2019.
14. (ayrapetov2006structuralandfunctional pages 14-18): Marina K. Ayrapetov. Structural and functional studies of the Csk and \*Src family protein tyrosine kinases. PhD thesis, University of Rhode Island, 2006. URL: https://doi.org/10.23860/diss-2090, doi:10.23860/diss-2090. This article has 0 citations.