1. Phylogeny  
   Tyrosine‐protein kinase Yes (encoded by YES1) is a member of the Src family kinases, a subgroup within the non‐receptor protein tyrosine kinases. Orthologs of YES1 have been identified in numerous vertebrate species, where the enzyme is highly conserved in both its catalytic domain and modular non‐catalytic regions. YES1 shares a common evolutionary origin with other Src family members such as c‐Src, Fyn, and Fgr, with phylogenetic studies indicating that the Src kinases emerged early in the evolution of metazoans (Manning et al. 2002, Manning et al. 2002). The conservation of core domains—including the N-terminal membrane-targeting SH4 domain, the Unique domain, the SH3 and SH2 domains, and the catalytic kinase (SH1) domain—reflects its common ancestry within the kinome and indicates that YES1 evolved from an ancestral kinase that gave rise to the modern Src family (huang2012generationoffn3 pages 22-27, kook2024emergingrolesof pages 1-2).
2. Reaction Catalyzed  
   YES1 catalyzes a phosphoryl transfer reaction in which the gamma-phosphate group from ATP is transferred to the hydroxyl group of a tyrosine residue on a substrate protein. In chemical terms, the reaction can be written as: ATP + [protein]-L-tyrosine → ADP + [protein]-L-tyrosine-phosphate + H⁺. This enzymatic activity is characteristic of protein tyrosine kinases and underlies the regulation of signal transduction cascades by modifying substrate proteins through phosphorylation (santos2013understandingtheenzymeinhibitor pages 20-25, loris2007exploringstructureand pages 21-24).
3. Cofactor Requirements  
   The catalytic activity of YES1 depends on the binding of ATP as the phosphate donor, and like most protein kinases, its activity is strictly dependent on divalent metal ions. Mg²⁺ is typically required as a cofactor, facilitating the proper positioning of ATP within the active site and the subsequent transfer of the gamma phosphate to the substrate tyrosine (santos2013understandingtheenzymeinhibitor pages 20-25).
4. Substrate Specificity  
   YES1 phosphorylates specific tyrosine residues on target proteins, a specificity that is largely determined by its non-catalytic domains (SH2 and SH3) as well as by interactions with docking motifs present on substrates. Although no single linear consensus motif is universally reported for YES1, the phosphorylation event generally involves the recognition of substrates that display suitable phosphotyrosine binding sites and proline-rich sequences. In some instances, the downstream signaling roles of YES1 have been linked to the phosphorylation of key junctional components (for example, PARD3 during epithelial tight junction assembly) or regulatory proteins such as CTNND1, collapsin response mediator protein 2 (DPYSL2) during T-cell migration, and organic cation transporter OCT2, which leads to enhanced transport activity (kook2024emergingrolesof pages 1-2, summy2001functionaldomaincontributions pages 152-156). Experimental studies using chimeric Src family kinases have also revealed subtle differences in the intrinsic substrate specificity between YES1 and its close paralogs, emphasizing that the non-catalytic domains contribute significantly to the selection of physiological substrates (summy2001functionaldomaincontributions pages 152-156).
5. Structure  
   YES1 is organized in a modular fashion, which is typical of Src family kinases. At the very N-terminus, it contains an SH4 domain that is subject to myristoylation and, in the case of YES1, additional palmitoylation; these lipid modifications are critical for membrane association and the spatial regulation of kinase activity. Immediately following the SH4 domain is the Unique domain, which is less conserved among family members and may serve to fine-tune the functional specificity of YES1. The central portion of the protein contains the SH3 domain, a structural module that adopts a β-barrel fold comprised of approximately 60 amino acids and mediates interactions with proline-rich sequences. Adjacent to it is the SH2 domain, which binds to phosphorylated tyrosine residues within specific amino acid contexts, thereby directing substrate recruitment and the formation of signaling assemblies. The C-terminal part of YES1 encompasses the catalytic kinase domain (SH1 domain), which is bilobed. The smaller N-terminal lobe primarily contributes to ATP binding via an antiparallel β-sheet, whereas the larger C-terminal lobe is responsible for substrate engagement and contains the activation loop. A critical tyrosine residue in the activation loop (Tyr-426 as noted in analogous Src family kinases) must undergo phosphorylation to achieve full catalytic activation, while phosphorylation of a C-terminal regulatory tyrosine (comparable to Tyr-537 in c-Src) promotes an autoinhibited conformation through intramolecular interactions with the SH2 domain (huang2012generationoffn3 pages 22-27, zhao2020scribblesubcellularlocalization pages 18-23).
6. Regulation  
   Regulation of YES1 is achieved through a combination of post-translational modifications and conformational control mediated by its modular domains. Lipid modifications such as myristoylation of the SH4 domain and palmitoylation aid in its targeted localization to the plasma membrane and specific microdomains, ensuring proximity to substrates and regulatory partners. The kinase activity is fine-tuned by phosphorylation events: autophosphorylation within the activation loop (for example, at Tyr-426) enhances activity, whereas phosphorylation of the C-terminal regulatory residue (analogous to the mechanism observed in c-Src) promotes binding of the SH2 domain to the phosphorylated tail, thereby stabilizing the inactive, closed conformation. Additionally, interactions with receptor tyrosine kinases (e.g., EGFR, PDGFR, CSF1R, FGFR) lead to recruitment of YES1 to activated receptors where subsequent phosphorylation of downstream effectors occurs. Allosteric regulation is also mediated via its SH2 and SH3 domains; these domains not only facilitate intermolecular interactions with substrates and adaptor proteins but also contribute to intramolecular contacts that enforce the autoinhibited state in the absence of activating signals (zhao2020scribblesubcellularlocalization pages 18-23, huang2012generationoffn3 pages 22-27, summy2001functionaldomaincontributions pages 152-156).
7. Function  
   YES1 plays multiple roles in cellular physiology through its activity as a non-receptor protein tyrosine kinase. It is involved in the regulation of cell growth and survival as well as the control of apoptosis. YES1 contributes to cell–cell adhesion and the remodeling of the cytoskeleton, thereby influencing processes such as cell migration and differentiation. Following activation by upstream receptor tyrosine kinases—including EGFR, PDGFR, CSF1R, and FGFR—YES1 is recruited to phosphorylated receptors where it becomes activated and transduces signals by phosphorylating a variety of downstream substrates. For example, upon EGFR activation, YES1 phosphorylates PARD3, a modification that favors epithelial tight junction assembly. Additionally, YES1 is implicated in modulating junctional components such as CTNND1 via the stimulation of FYN and FER kinases at cell–cell contacts. In T cells, YES1 phosphorylates collapsin response mediator protein 2 (DPYSL2) following stimulation by CXCL12, thereby promoting migration. YES1 also participates in the CD95L/FASLG signaling pathway and mediates AKT-driven cell migration. Its role in cell cycle control is underscored by the phosphorylation of cyclin-dependent kinase 4 (CDK4), which regulates progression through the G1 phase, while its activity during G2/M progression and cytokinesis further highlights its importance in cell division. Additionally, YES1 phosphorylates organic cation transporter OCT2, resulting in increased transport activity (OpenTargets Search: -YES1, kook2024emergingrolesof pages 1-2, zhao2020scribblesubcellularlocalization pages 18-23).
8. Other Comments  
   YES1 has attracted significant interest as a target in cancer therapy given its involvement in oncogenic signaling pathways, particularly in epithelial tumors such as lung, breast, ovarian, and skin cancers. Its overexpression or amplification has been documented in various human tumors and is often associated with aggressive phenotypes and drug resistance. Inhibitors targeting Src family kinases, such as dasatinib, have been reported to act on YES1, and iterative compound screening methods have identified additional small molecules capable of inhibiting its kinase activity (chiba2017aniterativecompound pages 4-7, kook2024emergingrolesof pages 2-4). While the specificity of available inhibitors for YES1 among members of the Src family can differ, these inhibitors provide opportunities for therapeutic intervention in YES1-driven cancers. No single mutation or disease-specific alteration in YES1 is uniformly reported; however, its dysregulation in cancer underscores its clinical relevance. Resources that compare kinase inhibitor profiles, such as the Chemical Probes portal and related databases, are recommended for further evaluation of compounds targeting YES1.
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